hacettepe medical journal

A QUARTERLY PUBLICATION **VOLUME 19 / NO. 1 / JANUARY 1986**

PUBLISHED BY HACETTEPE SCIENCE CENTER FOUNDATION

SUBSCRIPTION RATES

TURKEY :	Annual subscription (four issues forming one volume including postage)	2.500 TL.
	Special annual rate for students, interns and residents	1.000 TL.
	Single issue (including postage)	750 TL.
FOREIGN :	Annual subscription (including postage)	$ 25.00 or 75 D.M.
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HACETTEPE TIP DERGİSİ/HACETTEPE MEDICAL JOURNAL
HACETTEPE ÜNİVERSİTESİ TIP FAKÜLTESİ DEKANLIĞI
HACETTEPE-ANKARA

Printed by
Hacettepe University Press
Printing Division

VOLUME 19 / NO. 1 / JANUARY 1986

hacettepe medical journal

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Hacettepe Medical Journal
Volume 19 / No. 1 / January 1986 / pp. 1 – 6

Fluorescein Method in Determining the Borders of Intestinal Ischemia and Comparison of the Fluorescein Method and Standard Clinical Criteria with Histopathological Border

Ferit Bernay, M.D. / Naci Gürses, M.D.*****

Summary

This study was undertaken to compare methods of fluorescein and standard clinical criteria (color, visible peristaltism, visible or palpable mesenteric pulsation and experience of the surgeon in the evoluation of the ischemic border) in determining the border of intestinal ischemia. In 34 ischemic intestinal segments obtained from 10 rabbits, ischemic borders determined by the two methods mentioned above were compared with each other in regard to the histopathological ischemic border. Statistically significant differences were found between standart clinical criteria and fluorescein methods. As a result, fluorescein method was found to be more sensitive, specific and predictive than the standart clinical criteria in determining the ischemic intestinal border.

Key Words: Fluoresceine, Intestinal ischemia.

* This study was undertaken in the Pediatric Surgery Department of Ondokuzmayıs University School of Medicine, Samsun, Turkey.
** Resident of Pediatric Surgery, School of Medicine.
*** Associate Professor of Pediatric Surgery, School of Medicine.

Introduction

Ischemia in the gastrointestinal system may occur due to various causes. Patients who have intestinal ischemia are usually operated on with the diagnosis of acute abdomen and required surgical intervention for the ischemic segment which is determined by standart clinical criteria.

Intestinal blood supply and border of ischemia must be accurately determined in these patients and in the operations such as intrathoraxic transplantation of colon for esophageal replacement and abdomino-perineal pull through. Errors in determining the ischemic border may result in serious complications and mortality. The ischemic intestinal borders are determined by standard clinical criteria in almost all surgical clinics. Standard Clinical Criteria (SCC) are; color, visible peristaltism, visible or palpable mesenteric pulsation. In addition, the experience of the surgeon in the evaluation of the ischemic intestinal segment is critical.[1] These criteria are varied due to different evaluations of the surgeons. Although there are some studies[2, 3] claiming that the ischemic border is much better demonstrated by the doppler ultrasound technique, an experienced physician is required to apply and interpert this method.

Recently the fluorescein technique which was first applied in 1942 by Lange and Body[4] in determining the intestinal ischemia, has been frequently applied in the intestinal vascular pathologies as it is easily applied and is claimed to be successful in surgical practice.[1, 3, 5, 6] In spite of the reported successful results of this technique, the number of studies undertaken of compare standard clinical criteria and this technique in determining the ischemic intestinal segment accurately are insuffucient.

This study was undertaken to compare SSC and fluorescein methods in determining the border of intestinal ischemia. These two methods were applied to 34 ischemic intestinal segments in 10 rabbits and the results were compared with each other in regard to the histopathological border of the ischemic segment.

Materials and Methods

This study was performed on 10 New Zealand white rabbits whose weights ranged from 2200-2700 gm. Under ketamine hydrochloride anesthesia administred intramuscularly with a dose of 20 mq/kg, an abdominal vertical incision was made after preoperative preperation. Aorta and Vena Cava inferior were both cannulated with a polyethylene catheter (0.8 x 1.4 mm) at the level of iliac bifurcation and arterial blood pressure was traced utilizing mercury blood pressure manometry throu-

ghout the operation. Ringer lactate solution was administered through the venous catheter with an estimated dose of 100 cc/kg/ 24 hour. Three intestinal segments in six rabbits and four in four rabbits with a length varying between 10-15 cm were devascularized by dividing all their marginal and mesenteric blood vessels. The intestine was replaced into the abdominal cavity and after four hours it was inspected by another surgeon in regard to SCC and probable ischemic borders which were later marked with a black silk suture. After administering fluorescein with a dose of 20 mg/kg through the venous catheter, the room was darkened and borders of ischemia were determined by fluorescein fluorescence using Wood's lights at different intervals (5-20 minutes). These ischemic borders were marked with a white silk suture. Rabbits were then sacrificed and the ischemic intestinal segments containing the marked sutures and adjacent viable intestinal tissues were excised for histopathological investigation. Sections prepared with one centimeter intervals from the viable part to the ischemic region in every intestinal segment were stained with hematoksilen eosin. Subsequently, histopathological changes were investigated under the light microscope and the intestinal segment from which the ischemic changes was started was accepted as the ischemic border.

As the sections were marked by the fluoresceine and SCC methods their distance from the zone of histopathological ischemic border was expressed in centimeters, and it was detected whether they exist in the viable or in the ischemic intestinal segment and duly recorded. Later, the findings in each group were compared statistically by using Khi-square and Student's 't' test.

In the histopathological investigation of ischemic segments, it was observed that only the mucosal layer was affected by ischemia as opposed to the muscular and sero-muscular layer which appeared normal at the end of four hours.

No changes were detected at the ischemic border observed at different intervals (5 and 20 minutes later) using fluoresceine. 22 of 34 ischemic borders determined by fluoresceine method correlated to the histopathological border. The distance to the histopathological ischemia border was one centimeter in nine and longer than one centimeter in three of the remaning 12 ischemic borders. Only one of them was found to be in the ischemic part, one centimeter from the histopathological border (Figure 1).

One ischemic border established by SCC method in 34 segments was found to be corralated with the histopathologic ischemic border.

The distance to the histopathological ischemic border was longer than one centimeter in 23 of the remaining 33 ischemic borders. 22 of the ischemic borders determined by SCC method were found to be in the viable segment and 11 in the ischemic side in 33 ischemic borders (Figure 1).

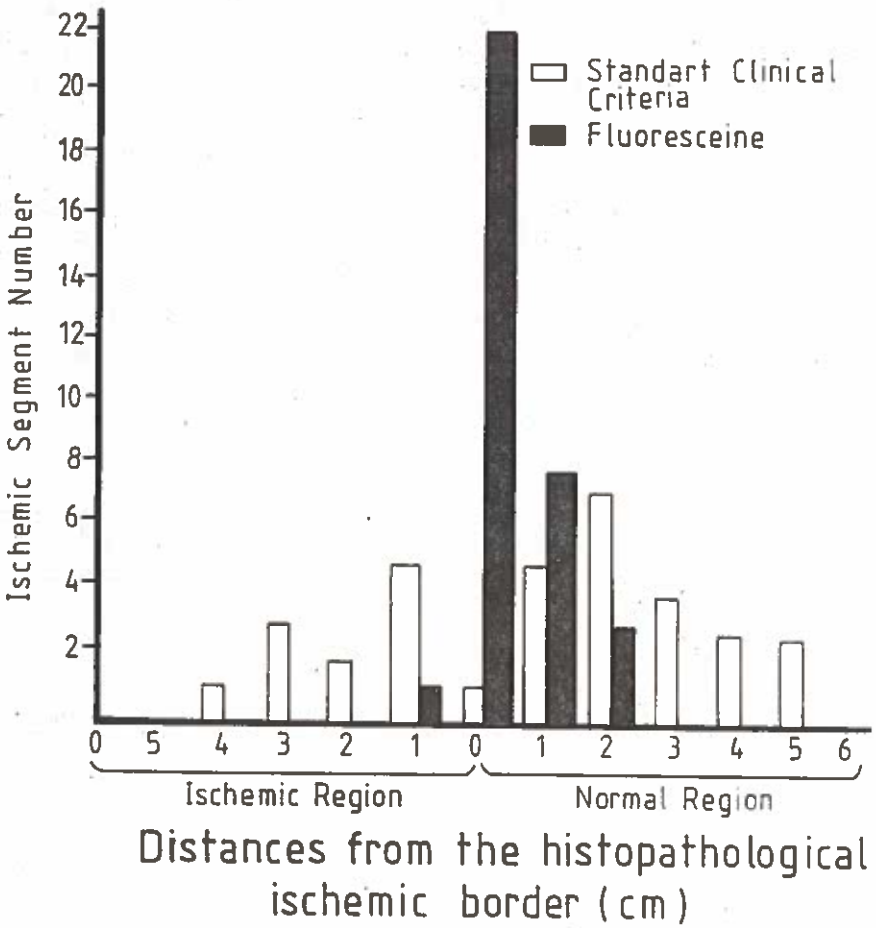

Figure 1
The borders determined by fluorescein and SCC by the histopathologic ischemic border.

The statistical analysis by using Khi-square method based on the histopathological ischemic border in two groups comprising SCC and fluoresceine revealed significant differences ($P < 0.001$, Table I).

The sensitivity, specificity and predicitive value per-cents determined in two groups were statistically compared with each other by

using Student's 't' test and significant differences were found (Table II). Fluoresceine method was found to be more sensitive, spesific and predictive than the SCC method.

TABLE I

IDENTIFICATION OF ISCHEMIC BORDERS IN GROUPS

Distance to the histopathologic iscemic border	Fluoresceine method	Standart clinical criteria	Total cases
Within the border	22	1	23
Within one centimeter	9	10	19
More than one centimeter	3	23	26

$X^2 = 34.874 \quad P < 0.001$

TABLE II

COMPARISON OF TWO METHODS IN REGARD TO SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUE

Method	Number of segments	Sensitivity (%)	Specificity (%)	Predictive value (%)
Fluorescein	34	97	68	64
S C C	34	68	35	3
		$P < 0.01$	$P < 0.01$	$P < 0.01$

Discussion

The ischemic border of the intestine must be determined accurately during intrathoraxic transplantation of colon for esophageal replacement and abdominoperineal pull through operations and in the ischemic lesions of the gastrointestinal system. The accurate determination of the ischemic border is important from the standpoint of patient survival. As it was observed in our study and in accordance with the findings of other studies,[3, 7] a constant period is required for the intestinal ischemic changes to appear histopathologically. In this study, it was found that changes only in the mucosal layer occured after four hours in the ischemic period. For this reason it is clearly evident that determining the ischemic border during operations with short duration is quite difficult. SCC have been commonly used to determine the ischemic border during abdominal operations.[1, 3, 6] According to these criteria it can be stated that determining the ischemic border largely depends on the observer and different evaluations can be made by different observers. Apart from this the most important problem encountered in this method is the requirement of a deriod for the appearence of the ischemia. As this method seems not to

be reliable in operations with short duration, a second operation is required. However, the number of such second operations must be limited, lest they endanger patient life.

Our study, which determined the ischemic intestinal border with 97 % sensitivity, 68 % specificity and 64 % predictive value using the fluoresceine method indicate that this method is more reliable and accurate than the SCC method in intestinal ischemia with short duration. Our findings are in accordance with the results of the other studies.[1,3,6]

Small sections of prepared intestine, even a few centimeters, may be of critical importance in the abdominoperineal operations performed in Hirschprung disease and intrathoraxic transplantation of colon for esophageal replacement. For determining the ischemic border of intestine the method which is going to be applied by the surgeon has to fullfil some requirements. These are; determining the ischemic border accurately in ischemia with short duration, getting fast results without harmful effects on the patient.

Based on our findings and other study results, it was concluded that the fluoresceine method is much more reliable and accurate than the SCC method in the evaluation of the ischemia with short duration.

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The Determination of Serum Estradiol Testosterone and Progesterone Levels in Acute Myocardial Infarction Using Radioimmuno-Assay Method

Seydi V. Aksüt, M.D.* / Gönül Aksüt, Ph.D. / Aydın Karamehmetoğlu, M.D.*** / Şevket Uğurlu, M.D.*** / Coşkun Bekdik, M.D.**** / Erdem Oram, M.D.*******

Summary

The levels of serum estradiol, testosterone and progesterone were determined in 13 cases of acute myocardial infarction; a stress group of thirteen, thirteen cases of unstable angina and fifteen normal subjects, all of whom were middle-aged men. The patients were of 24 to 56 years of age, the average being 40,4 years.

It was found that the level of serum estradiol in acute myocardial infarction and unstable angina had risen significantly in contrast to the normal group. No difference was found between the normal and the stress groups.

The level of testosterone was found to be significantly lower in acute myocardial infarction and unstable angina than in the normal group. Progesterone had risen only in acute myocardial infarction. The ratio of estradiol-testosterone was found to have considerably risen in the acute phase of acute myocardial infarction. Although this ratio had increased

* Fellow in Hacettepe University Medical Faculty Depertment of Cardiology Ankara, Turkey.
** Research Fellow in same Faculty Department of Nuclear Medicine.
*** Professor in same Faculty Department of Cardiology.
**** Professor, the Chief of Nuclear Medicine in same Faculty.
***** Professor, the Chief of Internal Medicine in same Faculty.

in unstable angina, it was not of statistical significance. No difference was found between the stress and normal groups.

Key Words: Acute myocardial infarction, Unstable Angina, Estradiol, Testosterone, and Progesterone.

Introduction

Various studies have shown that the levels of serum estradiol and estrone are high in middle-aged men with acute myocardial infarction.[1-5] However, serum levels of testosterone, androstenedione and dihydrotestosterone were not elevated in acute myocardial infarction. It was, therefore, claimed that hyperestrogenemia could be a risk factor in middle-aged men for myocardial infarction. Studies on men who had been given estrogens have revealed findings to support the view that estrogen could be a risk factor in men.

The incidence of reinfarction is higher in survivors of myocardial infarction who were given estrogens than the same age group who did not receive estrogens during the treatment of myocardial infarction. The rate of re-infarction has a positive correlation with the dose of estrogene.[6,7] In addition, the rate of mortality in cardiovascular diseases increased in cases where estrogen was given for the treatment of prostate carcinoma.[8] The relation between estrogens and myocardial infarction in women is more complex. The incidence of myocardial infarction in premenopausal women is significantly lower than in men of the same age group.[9]

Both bilateral oophorectomy and early menopause are associated with an increased risk of premature ischemic heart disease.[10-12] As a result of these relations the theory was introduced that women were protected against myocardial infarction by estrogens. However, the risk of myocardial infarction increased in young women who used oral contraceptives which contain estrogen.[13,14] This is especially true if other risk factors also exist.[15]

Therefore, the relation between estrogen and myocardial infarction is not clear. If estrogen is a risk factor for myocardial infarction, then its pathophysiology should be considered separately for each sex. It has been also stated that the level of serum estradiol rises in the acute phase of acute myocardial infarction.[17]

Levels of serum testosterone in the acute phase of acute myocardial infarction have not been investigated. Levels of serum testosterone in cases of coronary heart disease have been studied by various researchers

but the results are of a contradictory nature. In some studies, little or no difference was found between cases of coronary heart disease and normal groups.[3, 4, 5, 16, 18, 19] Another research also shown that the level of serum testosterone is lower in men who have had myocardial infarction.[20] The aim of this study is to determine serum estradiol, testosterone and progesterone levels in middle-aged male patients in the early phase of acute myocardial infarction. In reviewing the medical literature, it is observed that only the estradiol levels have been studied in the early phase of acute myocardial infarction but testosterone, progesterone and estradiol levels have not been studied simultaneously. We studied the levels of these three hormones simultaneously. Another difference between the above mentioned studies and ours is the determination of unstable angina group. Other studies defined unstable angina by electrocardiography and the history of the patients only, but we performed coronary angiography in addition to electrocardiography and the history of the patients. It is well known that coronary angiography is the most predictive method in determination of these cases.

Materials and Methods

Four patient groups have been selected for this study. There was no difference between the groups in age, height and weight.

Group 1: Patients with myocardial infarction (acute phase). There were 13 patients in this group between 30 to 56 years of age, the average being 47,9. The diagnosis of acute myocardial infarction was based on the case history, electrocardiographic and serum creatine phosphokinase (CPK) levels.

Group 2: Patients with unstable angina:

There were 13 patients of 29 to 52 years of age in this group and the average was 39.4 years. All these patients were hospitalized in the coronary care unit and suffered from myocardial ischemia electrocardiographically. However, myocardial infarction was not found electrocardiographically and enzymatically.

Survivors of myocardial infarction were not included in this group. The patients were chosen in order to find out whether the levels of serum estradiol, testosterone and progesterone could change in ischemia without infarction. Coronary angiography was employed in eleven cases. In ten of these, considerable stenoses was found angiographically. One patient had anterolateral and inferior ischemia and ST-T depression but his coronary angiography was normal.

Group 3: Patients hospitalized in the intensive care unit without coronary artery disease, liver and kidney disease but for other reasons (Stress group)

In this group there were 13 patients aging from 24 to 55 with an average of 33,3 years. They were in the intensive care unit for various reasons but did not have coronary artery disease liver and kidney disease, in their case histories, electrocardiographies and blood tests. These patients were chosen in order to investigate the effects of physical and emotional stress of severe medical illness on the sex hormone levels.

Group 4: Control group (Normal subjecsts):

This group consisted of subjects who came to the cardiology (out-patient) unit with non-specific complaints but who were found to be normal and with outcoronary artery or other diseases from the standpoint of their case history and means of EKG, CPK and treadmil tests.

In this group there were 15 normal subjects between the ages of 24 to 54 years, the average being 39.

All diseases that affect hormone levels (for example, liver and kidney disease) were excluded from all groups.

Blood Samples: Blood samples were taken from each patient of the first three groups on three consecutive days starting with hospitalization. Blood samples were taken from the normal group only once.

Assay Methods: Serum estradiol, testosterone and progesterone levels were determined by means of the radioimmunoassay method. Eir-ria kits were used to determine estradiol levels of which the normal values were 15-45 pq/ml and the intraassay and interassay coefficients of variation were 9,7 % and 9,2 % respectively. For the determination of testosterone, Mallinckrodt Diagnositica GmbH kits were used with the normal range 3-14 ng/ml and the intra assay and interassay coefficients of variation were respectively 4,6 % and 5,5 %. To determine serum progesterone levels, Coat-A Count kits provided from Diagnostic Products Corporation with the normal values 0,0-0,4 ng/ml and its intraassay and interassay coefficients of variation were 7,5 % and 6,6 % respectively.

Other Indicies: The levels of total serum creatine phosphokinase were studied for three days immediately after hospitalization. Its normal values were 22-269 IÜ/L. These levels were determined using Astra-8, automated stat/Routine analyzer method.

Statistical Analyses: In order to find out whether the difference between the groups was significant consistency test and the Z test based on the average were used.

Results

Estradiol Results: The levels of serum estradiol in the acute phase of acute myocardial infarction and unstable angina were found to be significantly higher than of the normal group (67,4 $\pm$ 0,9 pg/ml, 64,1 $\pm$ 1,0 pg/ml versus 31,8 $\pm$ 0,2 pg/ml and $P < 0,05$). No difference was found between acute myocardial infarction and unstable angina (67,4 $\pm$ 0,9 pg/ml versus 64,1 $\pm$ pg/ml and $P > 0,05$). No difference was observed between the stress and normal groups (33,1 $\pm$ 0,4 pg/ml versus 31.8 $\pm$ 0,2 pg/ml and $P > 0,05$).

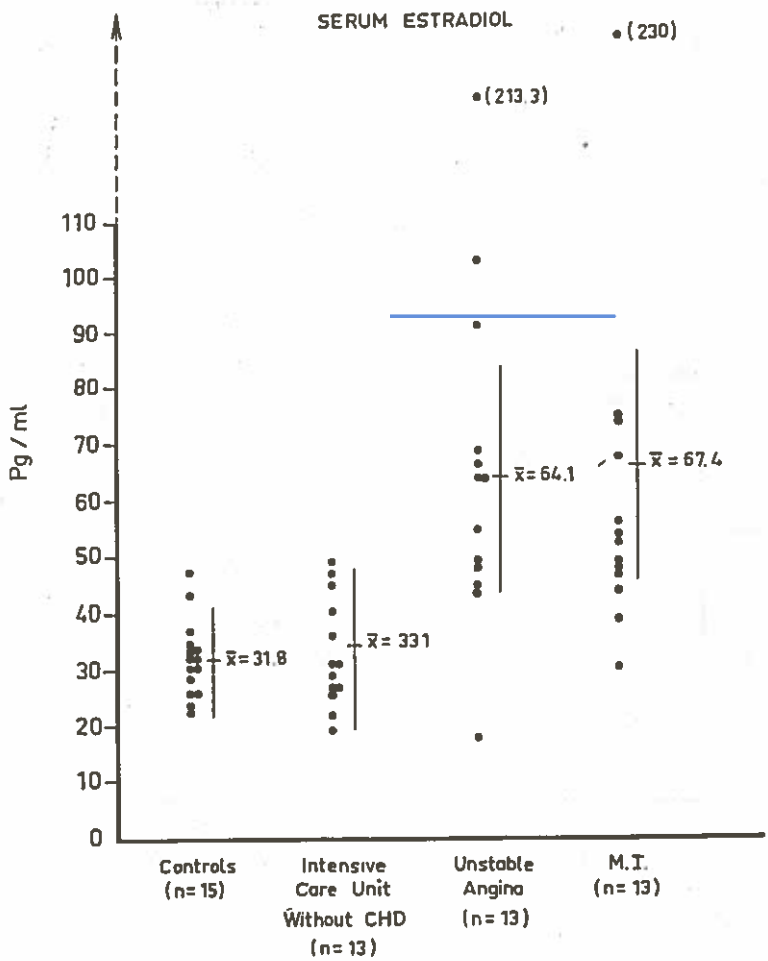

Figure 1

Distribution of Serum Estradiol Levels.

Hence, a significant difference was recorded between the average levels of serum estradiol in groups with coronary heart disease and those without, (Figure 1). It was interesting that some serum estradiol values in acute myocardial infarction and unstable angina were as high as 340, 310, 275 pg/ml. In our lab. normal value is 10-35 pg/ml. These differences in estradiol levels are supposed to be biological variations. Estradiol levels have increased in 3 patients on the second and third day, but decreased in eight and nine patients on the second and third day respectively.

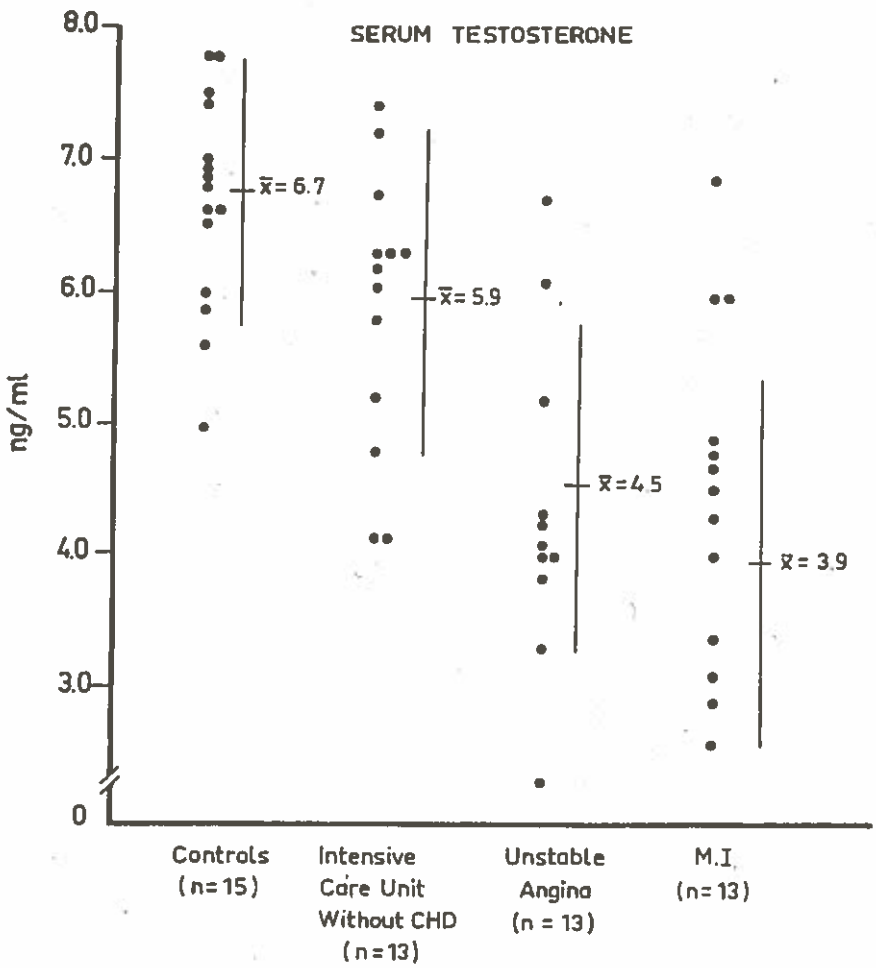

Figure 2
Distribution of Serum Testosterone Levels.

Testosterone Results: The levels of serum testosterone in the acute phase of acute myocardial infarction and unstable angina were found to be considerably lower than of the normal group (3,9 $\pm$ 0,4 ng/ml, 4,5 $\pm$ 0,3 ng/ml versus 6,7 $\pm$ 0,2 ng/ml and $P < 0,05$). In other words, the levels of serum testosterone in coronary heart disease were found to be considerably lower than in the normal group. However, no difference was recorded between the stress and normal groups (5,9 $\pm$ 0,1 ng/ml versus 6,7 $\pm$ 0,2 ng/ml and $P > 0,05$), (Figure 2).

Progesterone Results: The levels of serum progesterone in acute phase of acute myocardial infarction were considerably higher than in the normal group (1,737 ng/ml versus 0,375 ng/ml). A small increase was observed in unstable angina but this had no statistical significance.

Estradiol/Testosterone Ratio (E/T): This ratio was higher in acute stage of acute myocardial infarction and unstable angina than in the normal group. However, no difference was found between the stress and normal groups. Table I.

TABLE I
ESTRADIOL/TESTOSTERONE RATIO (E/T)

	Mean (E/T)
Acute Myocardial Infarction (Group I)	17,06
Unstable Angina (Group II)	16,72
Stress Group (Group III)	8,61
Normal (Group IV)	5

Discussion

This study reveals that although the levels of serum estradiol rise significantly in coronary heart disease, the same values are found to be normal in patients without coronary heart disease but hospitalized for various acute illnesses. Similar results were obtained by various other researchers.[3, 4, 5, 17]

In this study, we did not investigate the levels of serum estrone, because a previous study has shown that the level of estrone increases due to stress and is not peculiar to coronary heart disease. The authors have also stated that the levels of serum estradiol increase only in coronary heart diseases and not related to stress.[17]

Estradiol is three times as biologically active as estrone and a biological relation may be considered between estradiol and coronary heart

diseases. That this biological relation can appear due to the increase of adrenergic activity in various cardiac disease has been clearly defined.[21] Estrogens increase adrenergic activity by means of many physiological effects. Estradiol may have the following specific effects:

a) It increases adrenergic neurotransmitters synthesis.[22, 23]

b) It inhibits the enzymatic degradation of adrenergic neurotransmitters.[24, 25, 26]

c) It potentializes the synaptic activity of the adrenergic neurotransmitters.[27]

In clinical studies, estrogens cause electroencephalographical changes similar to norepinephrine and amphetamine.[28]

Heightened adrenergic stimulation secondary to the rise in estradiol levels increases the demand for myocardial oxygen and causes pain due to myocardial ischemia. It has been difficult for us to determine whether the levels of estradiol rise in pre-acute myocardial infarction. However, the fact that the level of estradiol is high immediately after acute myocardial infarction and unstable angina suggests that the level of estradiol increases prior to acute myocardial infarction. The major source of estradiol in men consists of the aromatization of testosterone in muscle and adipose tissues. To a lesser degree it is also made up of direct secretion from testes and estrone. Estradiol is not produced due to stress.[29, 30] Therefore the rise in the level of serum estradiol in coronary heart diseases cannot be related to stress. Although estradiol increases due to obesity have been reported, these rises are very low and our cases were not obese.

Thus, obesity cannot explain the rise of estradiol in our cases. The rise of estradiol in our patients can be attributed to aromatization of testosterone to estradiol in muscle and adipose tissues although the source of the rise in aromatization is unknown.[31]

In vitro studies show that the elevation is probably due to the increase of aromatization in muscle and adiposes of testosterone to estrone and estradiol by norepinephrine. In other words, adrenergic stimulation may play a role in aromatization and the production of estradiol.

It has been shown that the levels of serum norepinephrine increase in acute myocardial infarction and angina pectoris.[32]

This in turn stimulates aromatization and increases the formation of estradiol.

In this study, the levels of serum testosterone and progesterone which are also considered to be risk factors in coronary heart diseases have been studied.[33] We have found that the levels of serum testosterone in the acute phase of acute myocardial infarction and unstable angina are significantly lower than in the normal group. The research carried out in 1976 by Poggi et al. supports our results.[20] The fall in the levels of testosterone may be due to the patient's age. The older the patient, the lower is the level of testosterone and higher is the risk of heart diseases.[34]

However, our patients belong to the middle-aged group. Secondly, the decrease of testosterone may be related to the heightened aromatization from testosterone to estradiol as a result of increased neuroadrenergic activity during acute myocardial infarction. Another finding which supports this theory is the fact the rate of E/T was higher than in the normal group.

However, we still have contradictory information on the level of serum testosterone in coronary heart diseases. Some other studies claim that there is no significant difference in the levels of serum testosterone.[16, 33]

In the case of our patients the levels of serum progesterone rose only in the acute phase of acute myocardial infarction.

Although it was found to be high in stress and unstable angina group this was not considered to be of statistical importance. This rise may be related to stress.

Conclusion; Today the role of sex hormones in coronary heart disease and acute myocardial infarction is still not clear. But as the number of our cases was not sufficient, widescale and controlled epidemiological studies must be carried out for a more specific conclusion.

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Hacettepe Medical Journal
Volume 19 / No. 1 / January 1986 / pp. 19 – 24

Reconstruction of Hypoplastic Pulmonary Arteries in Tetralogy of Fallot

Coşkun İkizler, M.D.* / Sait Aşlamacı, M.D. / Ali Yener, M.D.** / Atılay Taşdelen, M.D.*** / Fatih Yorulmaz, M.D.******

Summary

Patch enlargement of the hypoplastic pulmonary arteries in three patients with tetralogy of Fallot is presented. The obstruction was relieved by widening of the pulmonary branches and bifurcation plasty with porcine pericardial patch. A valved conduit was used in one patient. Post-repair right ventricular and left ventricular peak pressure ratios were at a reasonable level. There is no operative mortality.

Key Words: Right ventricular outflow tractus, Pulmonary hypoplasia, Pulmonary bifurcation plasty.

Introduction

Since the first successful repair of tetralogy of Fallot, many improvements have been made in the surgical management of this disorder. The surgical procedures for correction of this anomaly lead to restoration not only of the hemodynamics of the heart but beyond that, of the continuity between the right ventricle and the distal pulmonary arteries without significant pressure gradient. High pressure gradient, due to distal obstruction of pulmonary arteries, deteriorates the function of the right ventricle.[1, 2, 3] Therefore, reconstruction of right ventricle

* Associate Professor of Thoracic and Cardiovascular Surgery, Gazi University, Faculty of Medicine, Ankara, Turkey.

** Assistant Professor of Thoracic and Cardiovascular Surgery, Gazi University, Faculty of Medicine.

*** Specialist in the same Department.

**** Research Fellow in the same Department.

outflow must consist of widening outflow tract and main pulmonary artery as well as bifurcation, with right and left branches if necessary.[4]

This report describes the successful surgical reconstruction of hypoplastic pulmonary bifurcation and the right and left pulmonary arteries in three patients with tetralogy of Fallot.

Materials and Methods

Between Jan 1984-May 1985 fifteen patients with tetralogy of Fallot underwent surgical repair at Gazi University Medical School. Primary total correction was the method of choice for all patients who needed surgical repair over 2 years. There was no operative mortality.

In three patients with total correction, the hypoplastic pulmonary bifurcation and stenosis of the main pulmonary branches were corrected by patch plasty. The age and weight distribution is shown in Table I.

Operative procedure: The operations were performed with cardiopulmonary bypass. Moderate systemic hypotherima wa sused in all patients (26°C). Myocardial protection was provided by cold K^+ cardioplegia.

TABLE I

AGE AND WEIGHT DISTRIBUTION OF THE PATIENTS

Case No	Age	Weight
1	8 yr.	25 kg.
2	5 yr.	16 kg.
3	7 yr.	18 kg.

Because of severe pulmonary hypoplasia, the continuity between right ventricle to distal pulmonary artery was established by an Ionescu Shiley valved conduit in the first case.

The pulmonary artery was divided at the side of the bifurcation. Then, separate longitudinal incisions was made both on the right and left pulmonary branches. The distal end of the conduit was tailored "T" shape. First, the posterior wall of the conduit and the pulmonary bifurcation was sutured. Then the anterior wall and the stenotic pulmonary branches were widened by using porcine pericardial patch (Polystan) (Figure 1).

In the remaining two patients, a woven dacron patch was sutured to the edges of the right ventriculotomy incision up to the pulmonary valve ring. Then porcine pericardium beginning from there and extend-

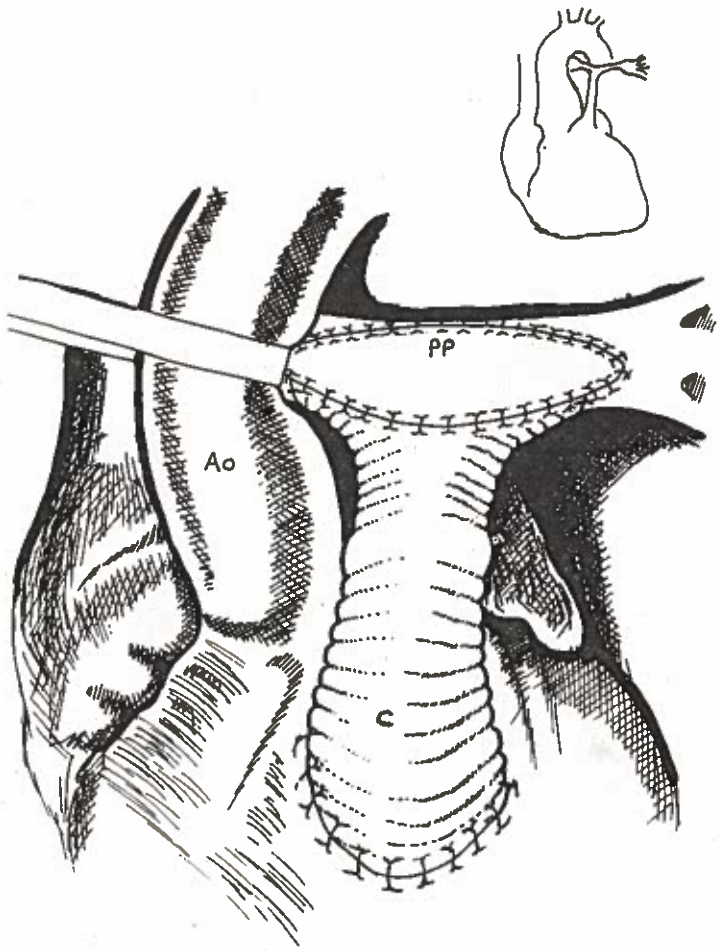

Figure 1

The continuity between right ventricle to pulmonary artery was established with a valved conduit in the first case. The pulmonary bifurcation was enlarged with porcine pericardium. The schematic illustration in the upper schema demonstrates the pre-operative anatomy. Ao: Aorta, PP: Porcine pericardial patch, C: Valved Conduit.

ing to both the right and the left pulmonary arteries beyond to the obstruction was used to correct the hypoplasia of the bifurcation and the pulmonary branches (Figure 2).

The ventricular septal defect (VSD) was closed by sewing a knitted dacron patch with a continuous polyproplene suture. During closure, the base of the septal leaflet was used at the posteroinferior portion of the VSD, because this method avoids damage to the conduction system.

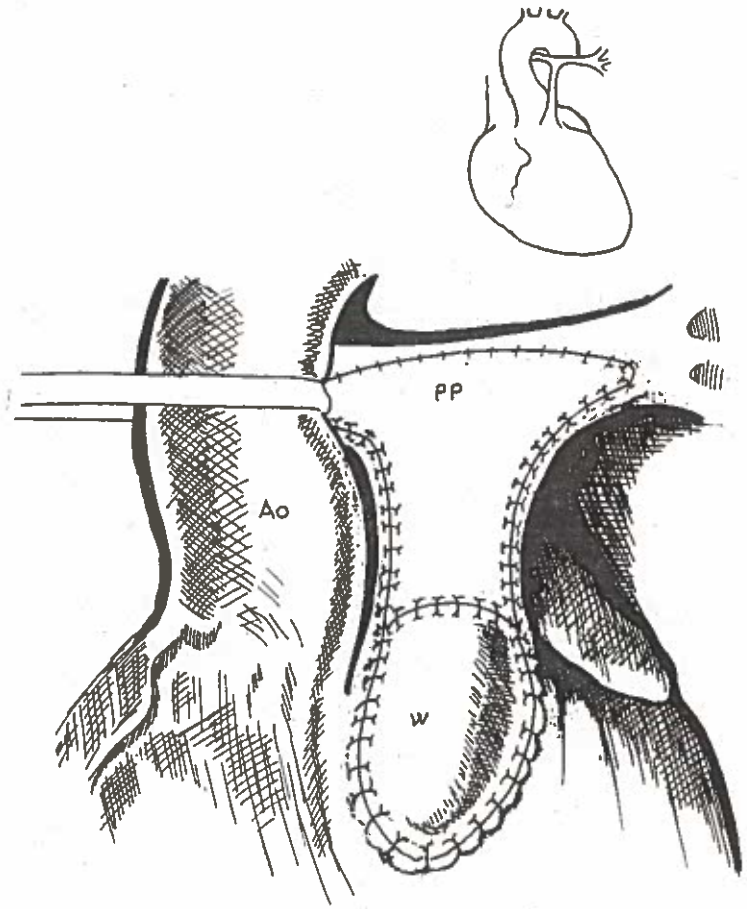

Figure 2
Right ventricular outflow and pulmonary bifurcation construction was done with a dacron patch and porcine pericardium in the remaining two patients. Smilar Pre-operative anatomy of the two patients is shown in the upper schema. Ao: Aorta, PP: Porcine pericardial patch, W: Woven patch.

Systolic pressures in the right and the left ventricles were measured. Post-repair $P_{RV/LV}$ were at a reasonable level.

Results

There were no surgical deaths. Only the case where the pulmonary continuity repaired with a valved conduit received catecholamine infusion for 6 hours after the operation.

The peak systolic pressure in the right ventricle decreased after termination of extracorporeal circulation and during the early post-

operative period. In of the two patients the right ventricular and the systemic pressures were measured hourly further during the postoperative course. Table II summarizes the pressure values.

TABLE II

POST-REPAIR PEAK PRESSURE RATIOS OF THE RIGHT AND LEFT VENTRICLE

$P_{RV/LV}$	First case	Second case	Third case
During operation	0,39	0,55	0,60
2 hours later	–	0,49	0,48

There were no late deaths and conduction disturbances, The results of one year follow up of the three patients are excellent. They have no symptoms, no restriction in activity and no need for medication. Their functional status belong to class I according to New York Heart Association.

Discussion

Total correction of tetralogy of Fallot can be performed with an operative mortality of less than 10 %.[5] By examining the currently available data we realised that the most important risk factor after surgical repair is the residual pulmonary stenosis.[4, 6, 7] It is well known that transannular patch enlargement is necessary in the hypoplastic pulmonary valve ring and arteries. Moreover, the small calibre in main pulmonary artery stenosis of the right or left pulmonary arteries or both are independent risk factors.[6, 8] In such cases surgical technique must also include widening of these vessels. A valved external conduit combined with bifurcation plasty, we belive, should be employed only if the main pulmonary artery is too small for appropriate correction.

Young age also is a risk factor.[6] Although, some authors have reported reasonably good results in infants,[9] we would advise a palliative shunt and later repair in infants less than 2 years. Often, but not always, shunt procedure increases the diameter of the pulmonary valve annulus and it does not grow proportionally.[10]

If significant anatomical residual stenosis still exists after complete repair in cases which pulmonary arteries are small, the $P_{RV/LV}$ will be high.[6, 7] A ratio higher than 0.8 is the most important cause of early death. However, using a transannular patch extending to the both right and left pulmonary artery can neutralize this risk factor. Kirklin et al., stated a way of estimating the size of the right and left pulmonary artery

preoperatively.[6] When these vessels are too small and diffusely affected, a primary repair should be avoided. Stenosis at the origin of the left and right pulmonary arteries can be corrected by appropriate surgical procedures such as we perform.

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Hacettepe Medical Journal
Volume 19 / No. 1 / January 1986 / pp. 25 – 29

Evaluation of Lower Urinary Tract Injuries and Their Association with Fractures of the Bony Pelvis

Ferruh Şimşek M.D.* / Ali Gökalp M.D. / Celal Bulut M.D.*****

Summary

In the last eight years 71 patients with pelvic fractures had been diagnosed and we have investigated the relationship between urological injuries and these fractures. A total of 26 lower urinary tract lesions were evaluated with their late results and prognosis. The rate of lower urinary tract lesions in pelvic fractures was 31%. It is recommended that urological evaluation in these fractures should be stressed.

Key Words: Lower urinary tract injuries, fractures of the bony pelvis.

Introduction

Although lower urinary tract injuries are quite infrequent, their occurrence seems to be rising in our country due to the dramatic increase in traffic accidents. Fracture of the bony pelvis is a well recognised etiological factor. 5-10 % of patients with pelvic fractures display an extraperitoneal rupture of the bladder.[1] On the other hand, 95 % of the bladder ruptures and 90 % of the posterior urethral injuries are associated with pelvic fractures.[1,2] Therefore, urological assessment is vital in a patient with pelvic fracture, only then can lower urinary tract injuries be ruled out.

* Assistant Professor of Urology, Cumhuriyet University, Faculty of Medicine, Sivas, Turkey.
** Associate Professor of Urology, Cumhuriyet University, Faculty of Medicine.
*** Chief Resident in Urology, Cumhuriyet University, Faculty of Medicine.

Other factors which cause bladder and urethral injuries are blunt and penetrating trauma, straddle injuries or iatrogenic trauma.[2, 3] Straddle type injuries usually result with urethral injuries inferior to the urogenital diaphragm.

Materials and Method

A review of 71 cases with pelvic fractures diagnosed in the Orthopedics and Urology Departments of Cumhuriyet University, Faculty of Medicine between 1978 and 1985 is done. Urological and radiological evaluations are made on every patient and the records of 22 patients with lower urinary tract injuries due to fracture of the bony pelvis and four others due to causes other than pelvic fracture are investigated. The surgical interventions, results and the prognoses of the patients are discussed.

Results

The patients with pelvic fractures were between the ages of 11 and 54. There were 52 males and 19 females. Traffic accidents were the cause of 84.5 % of the fractures.

22 lower urinary tract injuries were diagnosed in 71 pelvic fractures with retrograde urethrography, cystography and I. V. P. Four other lower tract injuries were free of pelvic fractures, three were with bladder ruptures and one was with iatrogenic anterior urethral rupture. Two of these three bladder ruptures were caused by a sharp blow on the abdomen and one was caused by a gunshot wound (Table I).

TABLE I
TYPES OF LESIONS SEEN IN 26 PATIENTS WITH LOWER URINARY TRACT INJURIES

Type of Injury	No of Patients
Bladder Injuries	
Extraperitoneal	6
Intraperitoneal	2
Combined	2
Bladder and urethral injuries	6
Urethral Injuries	
Complete	4
Incomplete	6
Total	26

Among the 26 injury cases, 23 were male (88.5 %) and three were female (11.5 %). One woman had a bladder rupture, the other a combined bladder and urethral injury and the third one had urethral injury.

The diagnosis of the lower urinary tract injury was made according to the localization and extravasation of the radioopaque material and its passage to the bladder during the radiological evaluation (Figures 1, 2).

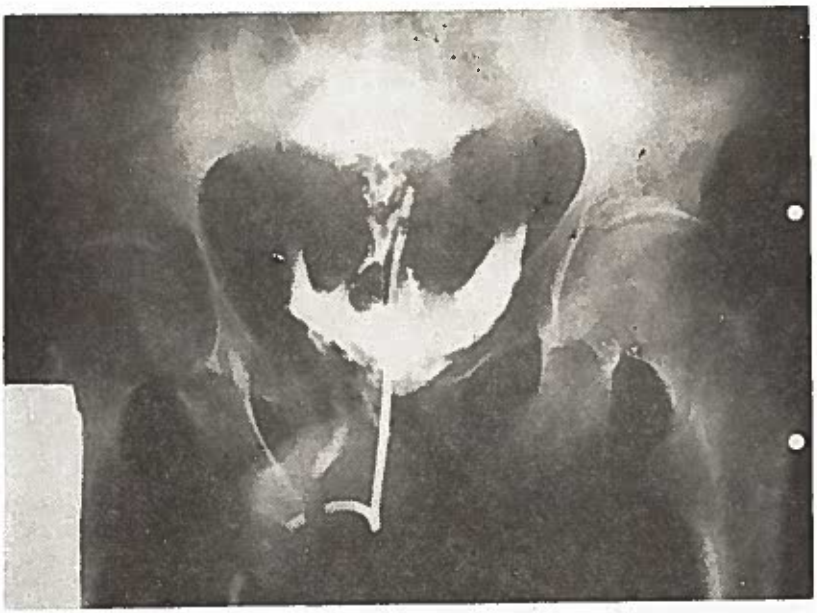

Figure 1
Cystographic appearance of a bladder rupture.

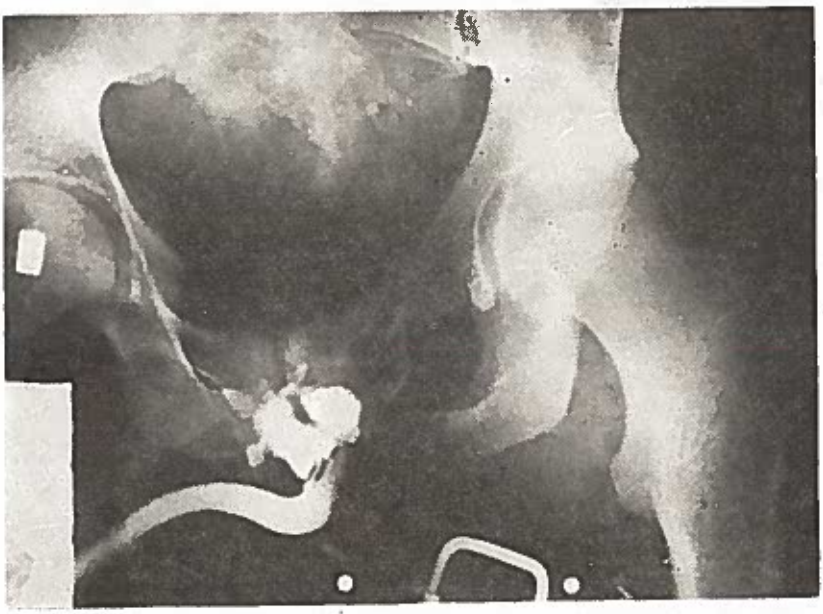

Figure 2
Posterior urethral rupture in retrograde urethrography.

The major symptom was inability to void in 10 patients (31.2 %), and gross hematuria in 5 (19.2 %).

All 26 patients had undergone immediate surgical intervention. In the bladder ruptures, the defects were closed and the perivesical areas were drained promptly. Laparotomies in 12 patients revealed ileum perforation in one and meso defects and hemorrhage in the other two. Rail-road catheterization and suprapubic cystostomy was applied in 13 of the 16 urethral injuries and suprapubic cystostomy in three.

Two patients out of 26 died of hemorrhagic shock (7.7 %).

The average follow-up of the bladder ruptures was eight months and radiographic controls revealed normal urinary tracts.

12 of the 16 urethral injuries were followed and the follow-up period was between four months to two years. Urethral strictures developed in 10 of these patients (83.3 %), Periodic urethral dilations were applied to these patients after which normal voiding with adequate projection and caliber of the urinary stream could be maintained in eight. The other two were referred for urethroplasty.

Discussion

The unfortunate increase in traffic accidents in our country in recent years has become the major reason for the fractures of the bony pelvis and lower urinary tract injuries. Our district's (Sivas) share among these casualties is quite large, since it happens to be on one of the main international highway routes. In fact, 84.5 % of the pelvic fractures seen in our hospital is due to traffic accidents. The rate of 31 % of lower urinary tract injuries in these fractures indicates the necessity of immediate and emergent urological evaluation of these patients. In fact, pelvic fractures were responsible for 22 out of 26 urinary injuries (84.6 %). Similar results are also reported in various studies.[4, 5]

In our study, gross hematuria was the major complaint in 31.2 % of the patients and inability to void in 38.5 %. These figures clearly demonstrate the necessity of radiographic evaluation even in the absence of those major symptoms. For this purpose, the first step should be the retrograde urethrography for confirming the integrity of the urethra and lack of extravasation. No attempt should be made to pass a catheter to the bladder at this stage which otherwise will convert an incomplete urethral rupture into a complete one.[5, 6] If the urethra is intact, then cystographic evaluation may be done. I. V. P. is not performed routinely but done in selected patients when indicated.

In our series, 16 bladder ruptures were repaired and 13 laparotomies were performed, 23.1 % of which revealed intraabdominal injuries. Therefore, we confirm that laparotomy is a very important part of the whole procedure especially in the management of intraperitoneal ruptures.

13 out of 16 patients with urethral injuries were catheterized in a rail-road fashion in order to realign the urethra. In three other patients catheterization was unsuccessful due to extensive periurethral abcess formation, two of whom had been admitted late for one of whom had diffuse perineal hematoma and hemorrhage. Only suprapubic cystostomy was applied to these patients. Realignement of urethral ends along with appropriate urinary diversions during the first operation is the treatment of choice in many centers and this is the most popular method in urethral injuries.[7,8] Though, some other authors prefer cystostomy drainage only in immediate surgery and anastomose the ruptured urethra electively a few months later. They claim that the success of the anastomosis will be greater in an enviroment free of edema, hemorrhage and urinary extravasation.[7,9]

The most prominent late complication after a urethral injury is stricture formation. In our series, the rate of urethral strictures was found to be 83.3 % and the majority of them were managed with dilations only. Two long strictures necessitated urethroplasty.

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Hacettepe Medical Journal
Volume 19 / No. 1 / January 1986 / pp. 31 - 34

A Bullet Embolus to the Right Ventricle Via the Right Brachial Vein

Coşkun İkizler, M.D.* / Ali Yener, M.D.**
Sait Aşlamacı, M.D. / Rüstem Olga, M.D.*** /**
İlhan Paşaoğlu, M.D.** / Aydın Aytaç, M.D.*******

Summary

A case of a bullet injury and migration via the brachial vein to the right heart cavity is presented, The patient was operated on successfully using an extra-corporeal circulation and the bullet was taken out from the heart. The patient was discharged on the twelfth post operative day.

Key Words: Bullet embolus, Bullet migration.

Introduction

In injuries caused by bullets, the bullet can sometimes be found in unpredictable parts of the body. The direction of a high velocity bullet is changed when it strikes the bones or the soft tissues and it may be localized in an uncommon site. It is very rate to find a bullet that settles down in the right ventricle by migrating through periperal veins. We have been able to find only 55 such cases in the literature but were unable to find a single case in which the bullet has entered through the

* Associate Professor, the Department of Cardiovascular Surgery, Gazi University Medical School, Ankara-Turkey.

** Assistant Professor, the Department of Cardiovascular Surgery Gazi University Medical School.

*** Associate Professor, İstanbul University Cerrahpaşa Medical School Haseki Cardiovascular Unit.

**** Associate Professor, the Department of Cardiovascular Surgery, Hacettepe University Medical School.

***** Professor, Cardiovascular Surgery İstanbul University Haseki Cardiovascular Unit.

upper extremity veins and migrated int othe right ventricle of the heart. The femoral, iliac, pelvic, hepatic, vena cava inferior, vena cava superior and jugular veins are the sites of entry of the bullet in previous cases.

Case Report

A 14 year old boy was admitted to the pediatric emergency department of the Hacettepe Medical Center on November II, 1976. His main complaint was pain in the right arm. The patient had been shot four days before his admission. During the physical examination it was found that he had some echimosis and haemotoma in the right arm at the medial head of the triceps. There was a well-healed hole at the same site. The X-ray of the right arm and the shoulder revealed no fractures (in the bones) Heart rate was 90/min., A.P: 130/90 mmHg., temperature was 36.5 C, Hb level 13.80 gr %, White blood cells were 7000 mm per cubic.

In the antero-posterior chest X-ray a bullet was seen on the heart shadow at the left side of the midline (Figure 1). In the X-ray taken laterally the bullet was seen directly behind the xiphoid. There were no other injuries in the thoracic bones and soft tissues.

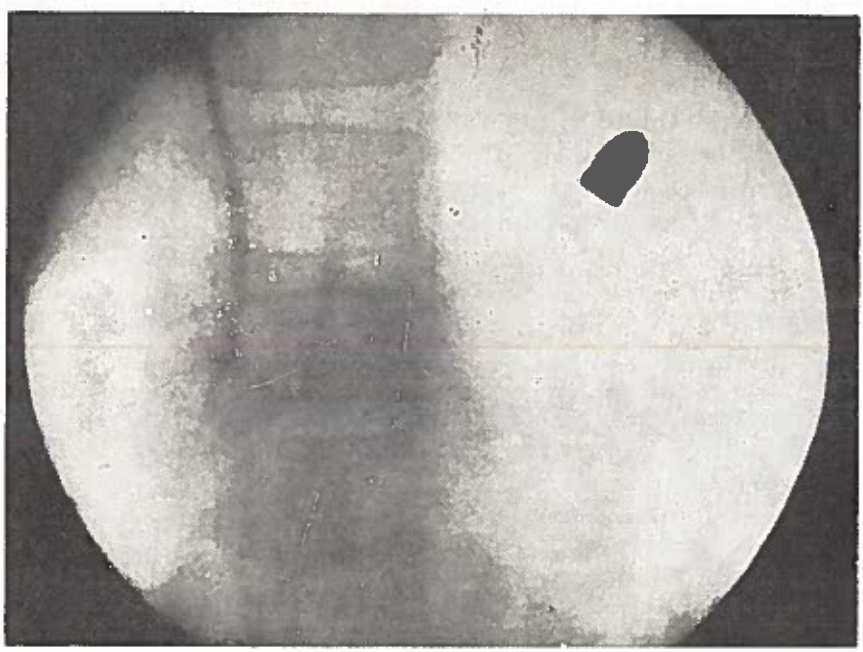

Figure 1

In the flouroscopic examination, the bullet was seen on the diaphragm and moved on, syncronized with the contraction of the heart. The cardiac synthigraphy did not reveal any pathology.

The patient was taken to the operating room on November 19, 1976. Median sternotomy was performed and the pericardium was opened. The pericardial sac was normal. By palpation, the bullet was felt in the right heart at the apex. A new X-ray was taken. The bullet had moved to the tricuspid valve. After that both the aorta and vena cava were cannulated and a bypass was performed. Immediately the pulmonary artery was totally clamped. The aorta was calmped and the right atrium was opened. After retraction of the tricuspid valve the bullet was seen just below the tricuspid (Figure 2). The bullet was taken out and the atrium was sewn. The patient's postoperative course was uneventful and he was discharged twelve days after the operation.

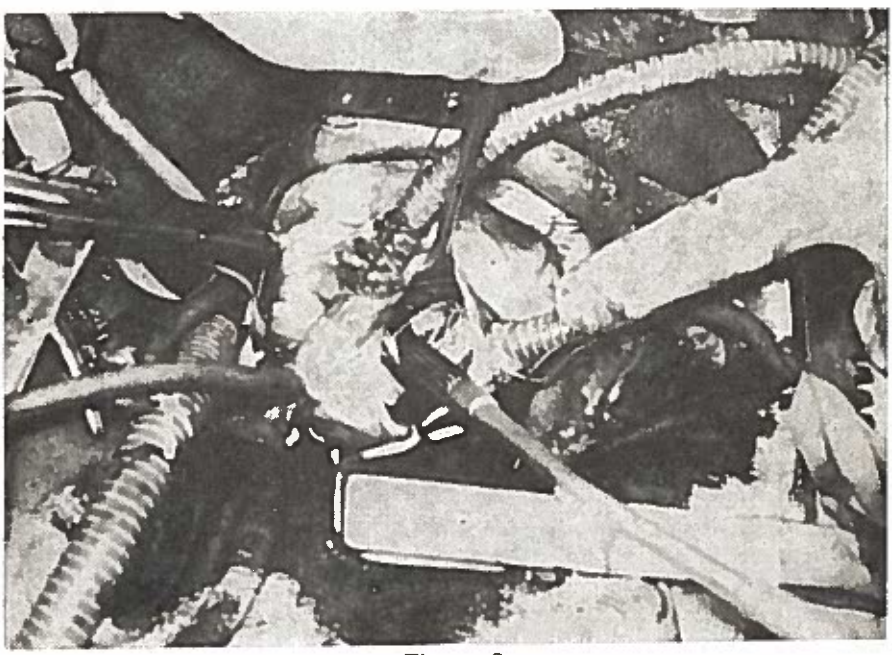

Figure 2

Discussion

Bullets that enter peripheral veins move by the venous flow and migrate to the heart and pulmonary arteries. The first case of a foreign body which entered the peripheral veins and migrated to the heart was published by Davis in 1836.[1] The first embolization of a bullet was

published by Simons in 1903.[2] And the first removal of a bullet from the heart was successfully accomplished by Grandgerard in 1916. It was a piece of shrapnel.[3] In 1962, Bozer and Hufnagel used a cardiopulmonary bypass and removed a bullet from the right heart cavity.[3]

In many of the previous cases surgeons have clamped the pulmonary artery to prevent bullet migration to the pulmonary arterial system. Total clamping of the pulmonary artery is not possible without performing a cardiopulmonary bypass or using hypothermia and inflow occlusion. It is always possible that the bullet may escape to the pulmonary artery system before bypass is performed. After opening the pericardial sac, we decided that partial clamping of the pulmonary artery would be a good precaution. In some cases[1, 3-5] surgeons have performed right ventriculotomy. We prefer the right atrial approach because it is less traumatic and more appropriate in reaching the ventricular cavity. Any foreign body that is detected in the heart cavity must be removed. If surgery is not performed some serious complications may occur, such as endocarditis, embolization, damage of the myocardium, etc.[3] An important procedure is to get an X-ray immediately before the opening of the heart in order to check the last known location of the bullet.

We find it most interesting to note how a 9 mm bullet can migrate into the small brachial vein. Literature also discloses bullet migration in the small, long saphenous vein.[3]

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Hacettepe Medical Journal
Volume 19 / No. 1 / January 1986 / pp. 35 - 38

Apical Hypertrophic Cardiomyopathy and Hypothyroidism

Çetin Erol, M.D.* / İsfendiyar Candan, M.D. / Derviş Oral, M.D.*** / Selahattin Koloğlu, M.D.******

Summary

A Turkish patient with coexistence of apical hypertrophic cardiomyopathy and hypothyroidism is presented. Hypothyroidism did not conceal the findings of apical hypertrophic cardiomyopathy and the coexistence of these two diseases was found to be unusual.

Key Words: Hypothyroidism, cardiomyopathy.

Introduction

Apical hypertrophic cardiomyopathy, which was recently described by Japanese investigators,[1] is a form of nonobstructive hypertrophic cardiomyopathy and is characterized by disproportionate hypertrophy of the left ventricular apical region associated with giant precordial negative T waves and high QRS voltage. "Ace of spades" configuration at end diastole on left ventriculograms is the other diagnostic feature. This cardiomyopathy has been described in Japanese,[1] Jewish,[2] American,[3,4] patients as well as in isolated cases in a South African,[5] a Korean female in the United States[6] and in five Asian males.[4] This is the first report of a Turkish patient with apical hypertrophic cardiomyopathy and also hypothyroidism. The coexistence of the two diseases is very unusual and interesting.

* Assistant Professor in Cardiology Department, Faculty of Medicine, University of Ankara, Ankara-Turkey.

** Professor in the same Department.

*** Associate Professor in the same Department.

**** Professor in Endocrinology Department.

Case Report

A 52-year-old man was referred to the Cardiology Department from the Departments of Neurosurgery and Endocrinology in order to evaluate his cardiac findings. He became aware of facial and peripheral edema and fatigue for the last 5 months. After his physical and laboratory examinations in these departments, primary hypothyroidism and a pituitary cystic adenoma secondary to hypothyroidism were diagnosed.

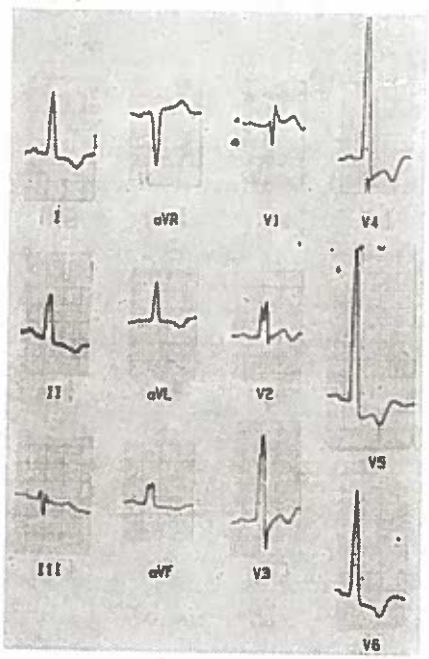

Figure 1
The patient's electrocardiogram showing deep negative T waves and high precordial voltage as well as intraventricular conduction defect.

He had no chest pain or any other cardiac symptoms. On physical examination he was obese and did not appear to be in respiratory distress. His blood pressure was 110/70 mm Hg and pulse was 60/min and regular. There were facial, periorbital and peripheral edema. His skin was dry and stiff. His thyroid gland was slightly enlarged. Chest and heart examination revealed nothing pathological. There was no hepatosplenomegaly. All the routine laboratory studies were normal except the increased serum total lipid (1400 mg/dl) and cholesterol (416 mg/dl). His serum T_3 and T_4 concentrations were low (0.22 ng/ml and 1.33 µg/dl consecutively) and TSH was high (57 µU/ml). The electrocardiogram showed sinus bradycardia, intraventricular conduction defect,

high precordial QRS voltages, deep negative T waves and the QTc value was 0.52 seconds (Figure 1). The chest X-ray showed cardiomegaly. Although it was diffucult to get clear pictures because of his obesity, 2-dimensional echocardiography demonstrated normal left ventricular dimensions, normal wall motions, very prominent apical concentric hypertorphy and minimal pericardial effusion (Figure 2). Coronary angiography showed 80 % obstruction in the proximal portion of the circumflex artery, but the distal part of it was normal. Left ventriculography revealed a "spade-like" configuration at end diastole, vigorous systolic contraction and normal wall motions (Figure 3). After completing all these procedures, he was put on Levothyroxine therapy, at one and a half tablet daily.

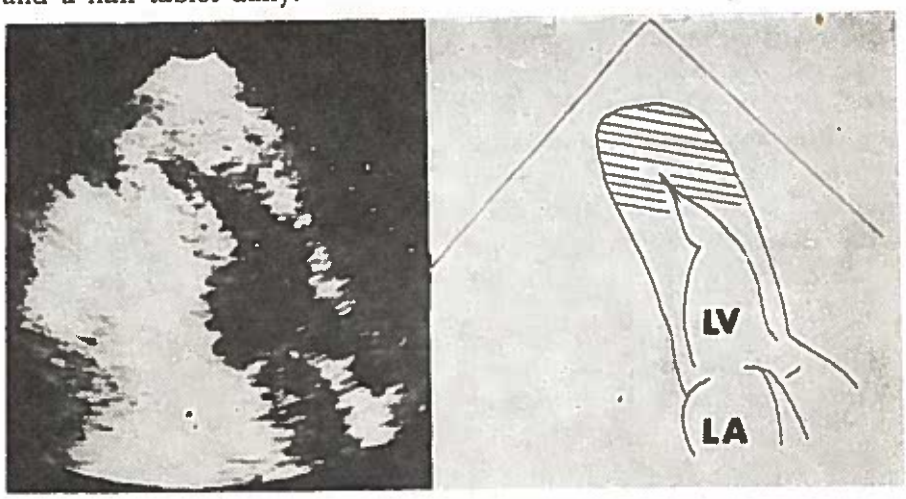

Figure 2
Two-dimensinoal echocardiogram (apical 2-chamber view) and its diagram. Note the marked apical concentric hypertrophy.

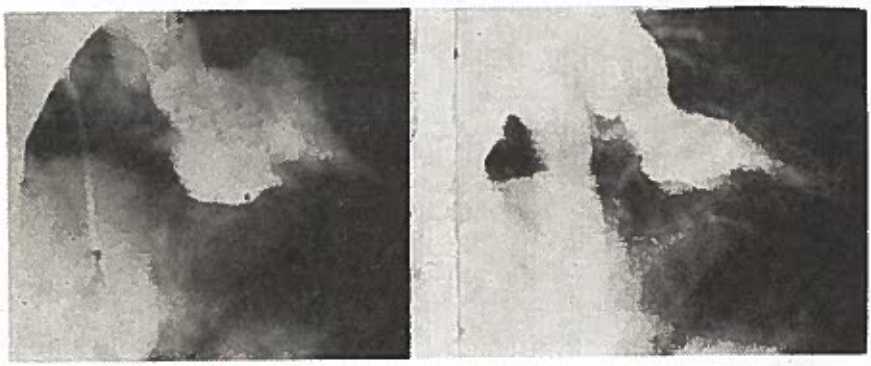

Figure 3
End-diastolic (left) and end-systolic (right) ventriculograms of the patient. The typical "spade-like" configuration is shown at end-diastole.

Discussion

Apical hypertrophic cardiomyopathy is a recently described entity and its world-wide distribution is still unknown.[1, 2, 4] About 3 % of Japanese patients undergoing left-sided cardiac catheterization for evaluation of suspected ischemic heart disease or cardiomyopathy were reported to have this entity.[1] Since then, only a few cases have been reported from other countries.[2-6] Our patient's findings were in agreement with the reported features of this syndrome.[1,2] His characteristic electrocardiographic findings and apical hypertrophy detected by 2-dimensional echocardiography, which are not usual in hypothyroidism, were suggestive of this entity. To confirm the presence of this entity, coronary angiography and left ventriculography were performed. The characteristic "spade-like" configuration at end diastole on ventriculogram was observed. Left anterior descending and right coronary arteries were normal. The significant obstruction in the circumflex artery did not cause any clinical manifestations or abnormal wall motions and this proved that coronary artery disease could coexist with apical hypertrophic cardiomyopathy as Yamagushi et al. mentioned in their study.[1] The interesting point was that the features of apical hypertrophic cardiomyopathy were not concealed by hypothyroidism.

After 3 months of therapy, the patient is in good health and his hypothyroid findings disappeared, but apical hypertrophy and its characteristics are still the same.

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hacettepe medical journal

A QUARTERLY PUBLICATION **VOLUME 19 / NO. 2 / APRIL 1986**

PUBLISHED BY HACETTEPE SCIENCE CENTER FOUNDATION

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Printed by
Hacettepe University Press
Printing Division

VOLUME 19 / NO. 2 / APRIL 1986

hacettepe medical journal

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Hacettepe Medical Journal
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Fetal Outcome in Cervical Cerclage*

Twenty Years' Experience

Ali Ayhan, M.D. / Kunter Yüce, M.D.*** / Bilal Memiş, M.D.******

Summary

During a 20 year period, 177 pregnancies were monitored in 155 patients with the diagnosis of an incompetent cervix.

Term birth rate was 16.8 % before surgical procedure and was 74.6 % after surgical intervention. Fetal wastage was increased in cases with bulged membranes beyond the cervix, cervix dilated more than 3 cm and/or gestational age greater than 26 weeks at the time of suture placement. No difference was noted with regard to clinical results between the Shirodkar and the McDonald procedures.

Complications included premature rupture of the membranes and chorioamnionitis in three patients.

Key Words: Cervical incompetency, Cervical Cerclage, Fetal Outcome.

Introduction

The incompetent uterine cervix is a well-established entity responsible for repeated fetal wastage, especially in the second trimester of pregnancy.[1, 2] Palmer and Lacomme[3] and Lash and Lash[4] originally described this condition and advised surgical correction in the non-pregnant state. Treatment with cervical cerclage during pregnancy was advocated by Shirodkar, McDonald and others.[2, 5, 6, 7]

The basic principle in most surgical procedures has been insertion of a non-absorbable material at the internal level so as to increase tissue resistance.

* The Department of Obstetrics and Gynecology, Faculty of Medicine, Hacettepe University, Ankara, Turkey.
** Associate Professor.
*** Assistant Professor.
**** Senior Resident.

The purpose of this study was to evaluate the fetal outcome after cervical cerclage.

Materials and Methods

177 pregnancies were managed from January 1964 to January 1985 in 155 patients in whom cervical incompetence had been diagnosed. The mean patient age was 29.5 at the time of suture placement (ranged from 20 to 36 years old).

A history of predisposing factors such as obstetric or surgical trauma to the cervix was elicited from 115 patients, of whom 18 had cervical tears during the previous delivery, 43 had a history of dilatation and currettage, and 13 gave a history of previous Manchester operation or cervical conization. Of the other 81 patients, 18 had corrected uterine anomaly concomittant with cervical incompetence, and 63 had a history of 2 or more spontaneous abortions.

All patients were admitted to the hospital for repeated spontaneous abortions during the late first and second trimesters of pregnancy. The diagnosis was established during the pregnancy or in the interval between pregnancies according to previously reported criteria.[2,7-9]

Surgical procedure time varied from 6 weeks to 28 weeks of gestation. The surgical techniques used and gestational ages are given in Table I. 21 patients underwent the Wurm procedure for advanced cervical dilatation (3 cm or more) and advanced gestational ages. All procedures were performed under general anesthesia.

TABLE I

SURGICAL PROCEDURES AND GESTATIONAL AGE AT THE TIME OF CERCLAGE PLACEMENT

Surgical Procedure	Gestational Age		
	18 and less	19 and more	Total
McDonald	106	20	126
Shirodkar	26	3	29
Wurm	1	21	22
Total	133	44	177

Steroid therapy was given pre-and postoperatively as to all patients previously described.[2]

Five patients were resutured for ineffective first suture in the same pregnancy. The removal of cerclage was performed after 37 weeks of pregnancy. Cerclage in 7 patients, who underwent cesarean section, were not removed for potential future pregnancies and served its purpose. Cesarean section rate was 13 % in this series.

Results

The overall term birth rate was 74.6 % after surgical procedures (Table II). This figure was 16.8 % before surgical intervention. The term delivery rate was 79.4 % for the McDonald procedure, 72.4 % for the Shirodkar and 50 % for the Wurm procedures (Table III). Term birth rate in patients who had advanced cervical dilatation (3 cm or more) and advanced gestational age (24 weeks or more) and cervical effaciement (50 % or more). The effect of steroid therapy on fetal outcome was reported previously.[2] Some complications such as premature rupture of the membranes, chorioamnionitis, abnormal vaginal bleeding and cervical deformity were seen in 7, 3, 5, and 13 patients recpectively.

TABLE II
FETAL OUTCOME BEFORE AND AFTER SURGICAL PROCEDURE

Fetal Outcome	Before Therapy		After Therapy	
	No	%	No	%
Term Delivery	94	15.0	132	74.6
Premature Delivery(29-37 weeks)	43	6.0	14	7.7
Immature Delivery (22-28 weeks)	162	24.0	12	7.0
Abortion (21 weeks and less)	371	55.0	19	10.7
Total	560	100.0	177	100.0

TABLE III
SURGICAL PROCEDURES AND FETAL OUTCOME

Fetal Outcome	Surgical Procedures			
	McDonald	Shirodkar	Wurm	Total
Term Births	100	21	11	132
Premature Births	7	3	4	14
Immature Births	6	2	4	12
Abortion	13	3	3	19
Total	126	29	22	177

Discussion

The reported incidence of fetal wastage caused by cervical incompetence varies between one in 125 and one in 1059 pregnancies.[1, 10, 11] This figure was one in 257 pregnancies in our series. This may reflect the stringent criteria for diagnosis.

The etiology of cervical incompetence continues to be somewhat unclear. Since the original suggestion by Lash and Lash (1950) that trauma was a major predisposing factor, other authors have also implicated obstetric and surgical damage to the cervix as a cause of cervical incompetence.[1, 12] In our study, such a history was elicited in 74 patients. On the other hand, 63 of the patients had only a history of repeated second trimester abortions at the time of diagnosis of cervical incompetence. This supports the concept that congenital weakness of the cervix may lead to incompetence.[10, 11, 13]

Incompetent cervix is diagnosed on the basis of the patients' past obstetrical history, the evaluation of the cervix with weekly examinations, and ultrasonic examination of the cervix during pregnancy.

Furthermore, diagnosis is made with the passage of an inflated Foley balloon or a no. 8 Hegar dilator through the cervical canal as well as hysterosalpingography during the non-pregnant state.[2, 12, 14, 15] The same criteria was used for diagnosis in our institution.

The term birth rate in our series varied from 50 % to 79.5 % based on the surgical procedure techniques (Table III). The overall survival rate ranged between 60 % and 92.5 % in the literature.[1, 2, 10, 12, 13, 16] This figure was 74.6 % in our series. Factors indicating a poor prognosis include: diagnosis later than 26 weeks, cervical dilatation greater than 3 cm, membranes bulging beyond the cervix at the time of suture placement, and vaginal complaints before the diagnosis. The term delivery rate in patients with poor prognosis was 40 % in this series.

The use of agents such as progesterone, ethyl alcohol, Mg SO_4, etc. in the intraoperative and postoperative period to prevent labor has been reported, but there is no controlled study indicating any beneficial effects.[10, 13, 16] Some beneficial effects have been reported by Ayhan et al.[2] In general, it has been reported that the cervical cerclage was removed at 36 and 38 weeks of gestation and vaginal delivery was allowed.[1, 2] However, if Cesarean section is done for obstetrical reasons, cervical suture might be retained in place for the subsequent births.

Despite the frequently implied simplicity of corrective surgical procedures, major complications such as rupture of the uterus, complete necrosis of the cervix, vesico-vaginal fistula, suture-line infections and abcesses, chorioamnionitis and sepsis with premature rupture of the membranes have been reported.[17-21]

Chorioamnionitis developed in 3 patients who were managed conservatively after rupture of the membranes before 34 weeks gestation.

Premature rupture of the membranes were seen in 7 patients who underwent removal of the cerclage to prevent infection, irrespective of the duration of gestation. Vaginal bleeding was observed in 5 patients, and cervical deformity developed in 13 patients.

We presently prefer the McDonald procedure because of its simple technique, minimal blood loss, and likelyhood of vaginal delivery after removal of the suture. In subsequent pregnancies, repeat cerclages are performed at about 12-14 weeks gestcation.

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Diagnosis of Tricuspid Regurgitation by Contrast Echocardiography

Seydi V. Aksüt, M.D.* / Aysel Oram, M.D. / Sırrı Kes, M.D.** / Şevket Uğurlu, M.D.*** / Erdem Oram, M.D.*****

Summary

Twenty-five subjects underwent M-mode and two-dimensional echocardiographic studies that included imaging of the inferior vena cava (IVC) in the course of upper extremity contrast injections. Group I consisted of 15 patients with clinically and surgically determined tricuspid regurgitation (TR). Group 2 consisted of 10 normal subjects. The IVC was imaged by two-dimensional echocardiography followed by M-mode in all subjects. The appearance of contrast in the inferior vena Cava simultaneously with "R" wave on ECG was considered as evidence of tricuspid regurgitation. Echocardiographic findings were correlated with clinical and surgical data.

All group I patients had positive echocardiographic results for tricuspid regurgitation while all group 2 patients had negative results suggesting that this technique may be specific for tricuspid regurgitation. At the same time, we measured the IVC dimension. The patients with TR had larger IVC dimensions than those without TR.

Key Words: Tricuspid Regurgitation (TR), Contrast Echocardiography, Inferior Vena Cava (IVC).

Introduction

Tricuspid regurgitation may be hemodynamically important and is relatively frequent in the presence of severe mitral valve disease, car-

Department of Cardiology, Faculty of Medicine, Hacettepe University, Ankara, Turkey.
* Fellow, Department of Cardiology.
** Associate Professor.
*** Professor.

diomyopathy or secondary pulmonary hypertension. It is still difficult to diagnose tricuspid regurgitation on the basis of clinical data. A. tall and broad V wave on the jugular venous pulse tracing is very helpful if present, but severe tricuspid regurgitation may also occur in association with relatively normal venous tracing.[1] In addition, broad V waves may be seen in patients with congestive heart failure in whom there is no other evidence of tricuspid regurgitation.[1] Right ventricular cineangiography is frequently inadequate with regard to tricuspid regurgitation, because of the presence of a cardiac catheter across the tricuspid valve which may itself induce a certain level of valvular incompetence. Thus, a technique for the detection of tricuspid regurgitation, which is more sensitive and specific than the existing methods, would be of value.

Bove[2,3] and Kremkau[4] have shown that the rapid injection of liquid into the vascular system causes development of tiny bubbles in the liquid, and that these microcavitations serve as excellent ultrasound targets. The utilization of microcavitations for "contrast echocardiography" has been described since 1968.[5] Echo targets produced by the rapid injection of small boluses of indocyanine green dye, saline, 5 % dextrose in water (DSW) or the patient's own blood have been utilized effectively for demonstrating cardiac anatomy, aortic and mitral regurgitation and intracardiac shunts.[6-10] Lieppe et. al. found in 1977 that contrast echocardiography was positive in all cases of clinical TR, whereas all normal subjects had negative contrast echocardiography. They pointed out that although they had no TR clinically, three of their cases showed positive contrast echocardiography, which was proven surgically and therefore, this technique was more sensitive than all other existing methods.[11] In 1981 Meltzer et. al.[12] found positive contrast echocardiography in all of their cases with clinical TR. In 2 of the 12 normal subjects, positive contrast echocardiography was determined as a false positive result. In these latter studies, an important statistical difference emerged in the IVC dimensions between the group with TR and the normal group. However, some overlapping was observed between the groups.

In the present study, our aim was to evaluate the role of contrast echocardiography and the IVC dimension for the detection of tricuspid regurgitation and to compare our results with those existing in literature. To achieve this, we applied 5 % dextrose in water by peripheral injection accompanied by two dimensional and M-mode echocardiography to determine TR. Echocardiographic findings were correlated with physical signs and surgical data.

Materials and Methods

Patients: Twenty-five patients underwent M-mode and two-dimensional echocardiography with peripheral contrast injections. Each patient was examined by a cardiologist, with particular attention to the jugular venous pulse, the presence or absence of a murmur consistent with TR, hepatic pulsations and peripheral edema. Patients were divided into two groups with respect to clinical assessment of the presence or absence of TR.

Group I included 15 patients with definite clinical diagnosis of TR, based on a prominent jugular systolic pulsation, a holosystolic murmur that increased with inspiration (Carvalho's sign) and pulsating liver on palpation. Eleven of these patients underwent cardiac surgery. 14 patients were in atrial fibrillation and one patient was in sinus rhythm. Tricuspid regurgitation was present in all eleven. Tricuspitoplasty or tricuspid valve replacement had been performed in all. Group 2 included 10 patients who were normal by history, physical examination, exercise test and M-mode and two-dimensional echocardiography.

Operative Diagnosis of Tricuspid Regurgitation: Intraoperative diagnosis of TR was confirmed if a thrill was present upon right atrial palpation and right ventricular systolic jet before cannulation for cardiopulmonary bypass.

Echocardiographic Methods: Patients were examined in the supine position with slightly flexed knees and hips to allow better relaxation of the abdominal musculature when the subcostal transducer position was used. The IVC was visualized in the sagittal plane by means of two-dimensional echocardiography in the course of the three to five contrast injections, with M-mode IVC imaging in the course of later injections. Two-dimensional contrast echocardiograms were also recorded from the left sternal border and apical transducer positions with the patient in the partial left lateral decubitus position.[2, 3] M-mode echocardiograms and two-dimensional echocardiograms were recorded with an Ultra Imager Honeywell Ultra 80 and Mechanical transducer with 3 MHz and stored on videotape of subsequent analysis. The ECG was displayed and recorded alongside the sector arc. Gain, reject, and damping settings on both instruments were adjusted to display the IVC cavity. Microbubbles, the source of contrast effect,[13] are strong reflectors and can usually be differentiated from noise by their characteristic motion patterns. Echocardiographic contrast was obtained by rapidly injecting 5-8 ml. of 5 % dextrose in water (DSW) into an upper extremity vein through a three-way stopcock and a # 19 or # 21 gauge butterfly needle.

Subcostal IVC imaging during contrast injection was performed in the course of deep inspiration and valsalva maneuver in each patient. Observations were made for the appearance of a cloud of echoes in the IVC and to demonstrate the appearance of microcavitations in the right heart chambers.

IVC dimensions were calculated at the maximal diameter which synchronized with the "R" wave on ECG. (Figure 1) Two groups were compared with respect to differences in IVC measurement: a definite TR group and a control (normal) group. The TR group included 15 patients with clinical and intraoperative diagnosis of TR. The group 2 patients included 10 normal subjects.

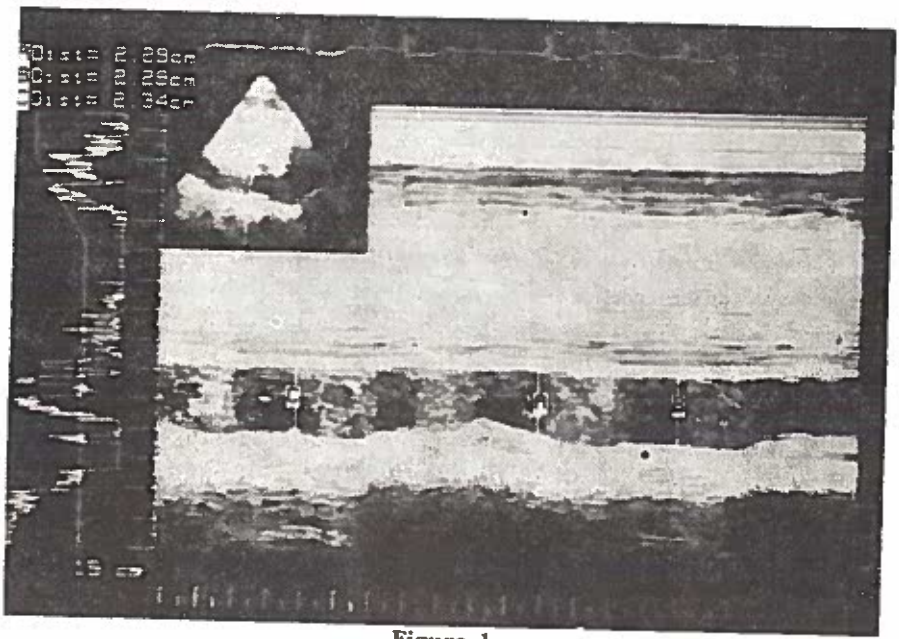

Figure 1
M-mode inferior vena cava (IVC) echocardiogram showing how measurements were made.

Results

IVC Size: The IVC was adequately visualized by both M-mode and two dimensional echocardiography in all patients. The patients with TR had larger IVC dimensions than those without TR (Table I). This was statistically significant for measurements made at the maximal dimension synchonized with "R" wave on ECG. The average dimension of IVC in patients with TR was 25,75 $\pm$ 5,39 mm. but 17,73 $\pm$ 1,85 mm in normal subjects. Thus IVC dimension can be used as a predictive test for TR'in individual patients.

TABLE I
INFERIOR VENA CAVA DIMENSIONS

Group	$\bar{x}$ (mm)	SD	P
Group 1 (TR)	25,75 n = 15	5,39	< 0,05
Group 2 (Normal)	17,38 n = 10	1,85	

TR = Tricuspid regurgitation, $\bar{x}$ = Mean Inferior Vena Cava dimension at maximal with "R" wave on ECG.
SD = Standard deviation.
n = Number of subjects with of sufficient quality to perform measurement.
p = p value of Mann – Whitney U test between the groups listed.

Patterns of IVC Contrast Appearance: No side-effects caused by contrast injections were noted. Contrast was detected in the IVC on M-mode and two-dimensional examinations in all patients in group I, but in none of the 10 normal subjects in group 2. Figure 2 is an example of the echo pattern in patients with TR. The appearance of contrast in middle and late systole is indicated by upward-slanting lines, because the contrast moves inferiorly and approaches the transducer; the contrast then reverses its direction and turns toward the heart during diastole, producing downward-sloping lines. This is the most common pattern seen in TR. The timing of the appearance of contrast in the IVC is simultaneous with "R" wave on ECG. All patients in group I with clinical TR had a "R" wave synchronous pattern of echocardiographic contrast appearance in the IVC (Figure 2). Eleven of the 15 patients had intraoperative right atrial thrills and right ventricular systolic jets and TR could be confirmed surgically. Seven of them underwent tricuspitoplasty and 4 underwent tricuspid valve replacement. None of the group 2 subjects had contrast in the IVC during deep inspiration.

Discussion

The diagnosis of tricuspid regurgitation is easy if it exists clinically. Further, examination is not necessary for the diagnosis of TR if the jugular "v" wave, positive Carvalho's sign, and pulsatile liver are observed. However, in adults, TR is frequently associated with diseases in the left side of the heart and pulmonary hypertension; and in most cases of TR, the patients suffer from atrial fibrillation.[14, 15] In atrial fibrillation, jugular venous pressure is not adequate for the diagnosis of TR. Moreover most patients with TR have systolic murmurs of aortic or mitral origin. Right ventricular cineangiography is not an ideal test, because it is invasive and the catheter may interfere with the normal valve structure causing false positive results.

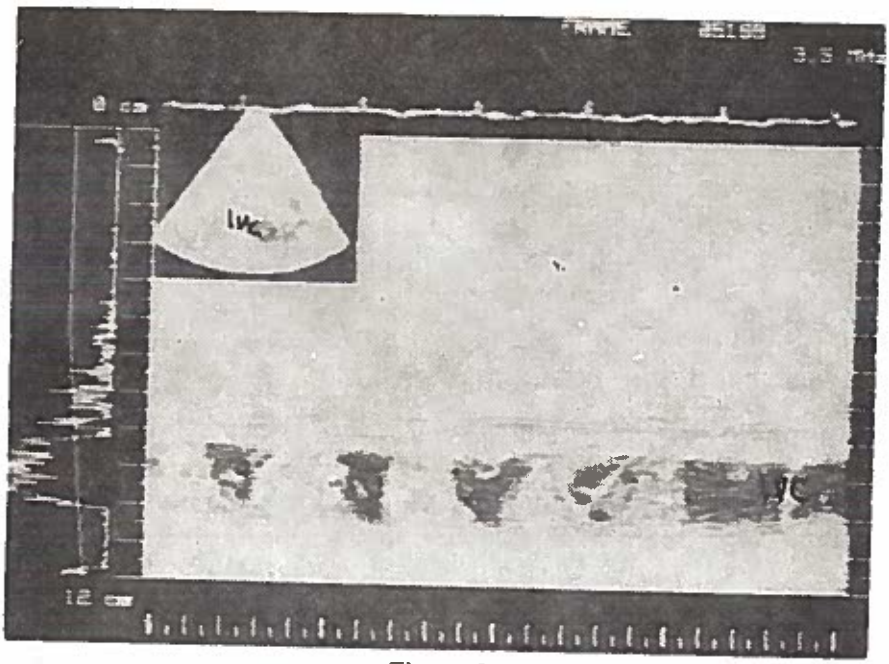

Figure 2
M-mode contrast inferior vena cava echocardiogram showing R-wave synchronous pattern typical for tricuspid regurgitation.

Therefore, a more definite method for diagnosis of TR is necessary. Unfortunately, there is no accepted "gold standard" today.[16,17] However, some recent studies have shown the benefits of contrast echocardiography. It has also been noted that contrast echocardiography is a useful and safe technique in the determination of cardiac anatomy, intracardiac shunts, aortic or mitral insufficiency.[6-10] In 1977 Lieppe et. al.,[11] and in 1981 Meltzer et.al.,[12] proved that contrast echocardiography is more sensitivite and specific for the diagnosis of TR. Howeover, they used M-mode and mostly two-dimensinal echocardiography and correlated it with right ventricular cineangiography. As is known, right ventricular cineangiography is not an ideal method, because the catheter may interfere with normal valve structure and lead to false results. Therefore it can not be the best standard technique for the assessment for contrast echocardiography.

In our study, we applied two-dimensional and M-mode echocardiography with 5 % dextrose in water peripheral injection and upon the appearance of contrast in the IVC, we diagnosed the case as TR. Contrary to previous studies, we correlated these with intraoperative findings (right atrial thrill and riht ventricular systolic jet).

Contrast positive echocardiography was observed in all 15 patients with clinically and surgically determined TR, who either had previously undergone mitral valve replacement or tricuspid valve replacement or suffered from pulmonary heypertension. In grup 2, all normal subjects had negative contrast echocardiography. These findings show that contrast echocardiography is specific for the diagnosis of TR. The results of lieppe and Meltzer also support our views. Eleven patients in group I received surgical examination which proved that they all had TR. Thus, our results which were obtained independently by means of contrast echocardiography, were further surgically confirmed.

Another important point in our study was the measurement of the IVC dimensions. Patients with TR had larger IVC dimensions than those without. This finding has statistical importance. The measurements were taken at the maximal IVC level with synchronized "R" wave on ECG. These measurements can be used as a non-invasive test to determine TR cases. Although Meltzer et al.,[12] found in 1981 that there was an important difference in IVC dimensions of TR versus normal cases and there was some overlap between them.

Despite its benefits, contrast echocardiography has certain limitations, some of which are partly related to the quality of the ultrasound. The method does not provide information about the quantity of TR. Sometimes the veins may not be large enough to give a good contrast. If no contrast is seen in the IVC, injections should be repeated in the apical and parasternal positions. Contrast echocardiography must not be considered negative until sufficient contrast is obtained in such situations. This procedure reduces the number of false negative results and improves the sensitivity of contrast echocardiography.

In our study, neither false positive nor false negative results were noted. This may be because of the selection of patients.

In conclusion, contrast echocardiography is a simple and safe noninvasive method of diagnosing TR. It can easily be applied on both inpatients and outpatients and may help to diagnose TR which is otherwise difficult to determine.

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Hacettepe Medical Journal
Volume 19 / No. 2 / April 1986 / pp. 53 - 59

Ultrasound Diagnosis of the Hydatid Liver

A Clinical Study of 34 Cases

Kayhan Özkan M.D.* / Naci Gürses M.D. / Ruhi Sungur M.D.*****

Summary

A clinical study of 34 cases with hydatid cysts using a real-time gray scale B-scanner was performed. All of these cases have been confirmed surgically as hydatid disease. The ultrasound characteristics of the hydatid cysts have been classified into three types; (1) Simple hydatid cyst (Type I), (2) Hydatid cyst with a split wall and multicystic pattern (Type II), (3) Hydatid cyst with heterogeneous echo pattern (Type III). Our conclusion is that ultrasound classification of the cysts increase diagnostic accuracy. However, if a hydatid cyst becomes secondarily infected these typical changes are lost and the ultrasound diagnosis may then become more difficult. Furthermore, periodic examinations should be performed by ultrasound after surgery.

Key Words: Ultrasonography, Hydatid Liver, Hydatid Cyst.

Introduction

Echinococcus granulosis is a tapeworm that infects man as intermediate host. It is fairly common in the large sheep-raising areas of Europe, the Mediterranean region, Middle East, Asia, South America and Australia.[1, 2, 3] Hydatid disease is seen quite frequently in Turkey. Many of the patients affected by the disease were born and have lived for many years in rural areas. The tapeworm has been known to affect any organ in the body, but liver seems to be the organ most commonly affected.[1, 2, 3] In those parts of the world where hydatid disease is endemic,

Departments of General Surgery, Radiology and Pediatric Surgery, Faculty of Medicine Ondokuz Mayıs University, Samsun, Turkey.
* Professor of General Surgery.
** Professor of Pediatric Surgery.
*** Resident in Radiology.

hydatid cysts comprise a large majority of liver masses presenting for evaluation. Since echographic examination has revolutionized the investigation of hydatid cysts of the liver, it should be considered as the first-choice diagnostic technique in the evalution of the cyst, including size, location, vascular relations in the liver and the number of the cyst.

In this paper, we present our experience with real-time gray-scale ultrasound evaluation in 34 surgically proven cases of hydatid disease.

Material and Methods

Ultrasound examination was performed with a real-time gray-scale B scanner, using probes of 4 MHz (PLB 308 M SAL-20 Toshiba). 34 patients with hydatid cysts were included in this study. The patients ages ranged from 6 to 73 years; 13 males and 21 females. All of these cases were confirmed surgically as having hydatid disease. Cysts were located within the right lobe of the liver in 30 cases. In contrast, cysts were found in the left lobe in four cases. In two cases, both lobes of the liver were affected. Multiple cysts were detected in eleven cases. Two patients were re-operated due to recurrence of the hydatid cysts.

Results

We have classified the ultrasound characteristics into three types on the basis of shape, echo pattern and appearance of germinative membrane.

Type I- Simple Hydatid Cyst: This type appears as an anechoic space with marked enhancement of back-wall echoes. It shows clearly defined outlines and it is round or spherical in shape. It walls often vary in thickness and double contour is seen in the majority of the cases. Apparently, the inner layer represents undisturbed germinative membrane and this should be systematically sought as a sign of uncomplicated, simple hydatid cyst (Figure 1). Fourteen of our 34 cases demonstrated this ultrasound pattern and when these cysts were aspirated during surgery, clear fluid was obtained.

Type II- Hydatid Cyst with a Split Wall and Multicystic Pattern: This type is composed of at least two groups. (a) Hydatid cyst with a split wall and (b) Hydatid cyst with multcystic appearance.

a) In this group, the split wall may be localized or it may become a "Collapsed Germinative Membrane" that is loose inside the cyst (Figure 2). This split wall and collapsed germinative membrane are characteristic of hydatid cysts and may be a result of a decrease in intracystic pressure, resulting in the detachment of the membrane.

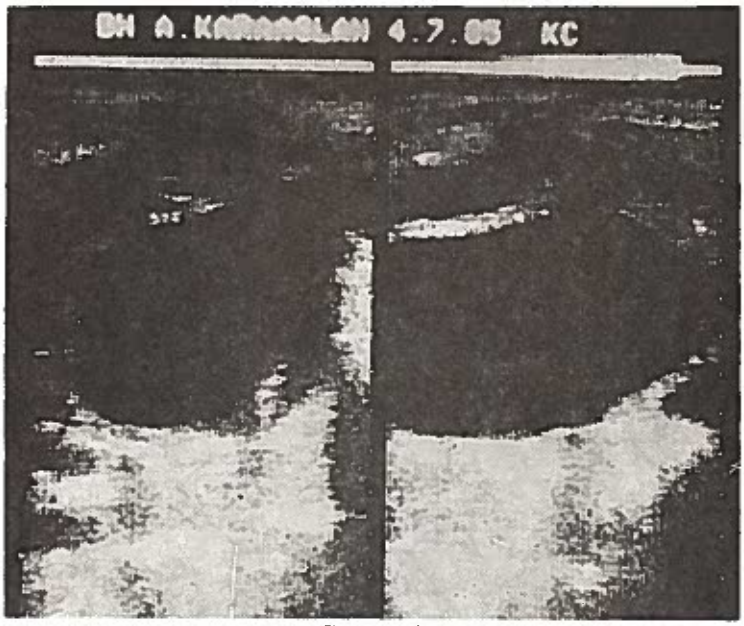

Figure 1
Simple hydatid cyst (Type I) with marked enhancement of back-wall echoes. Inner layer representing germinative membrane is clearly seen.

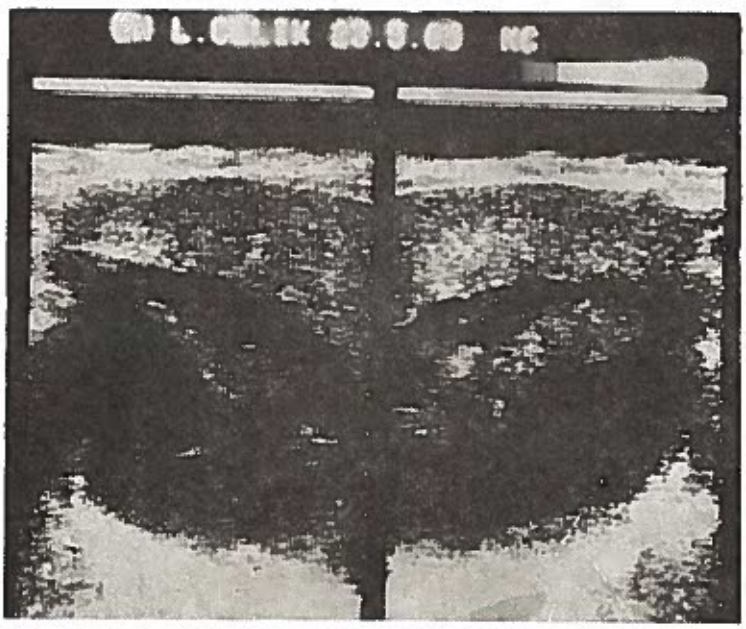

Figure 2
Hydatid cyst with a collopsed germinative membrane (Type II).

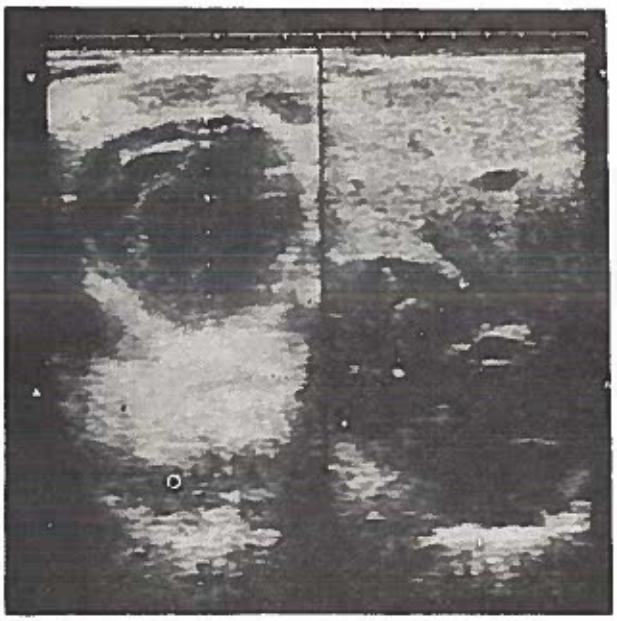

Figure 3
Hydatid cyst with multicystic appearance (Type II).

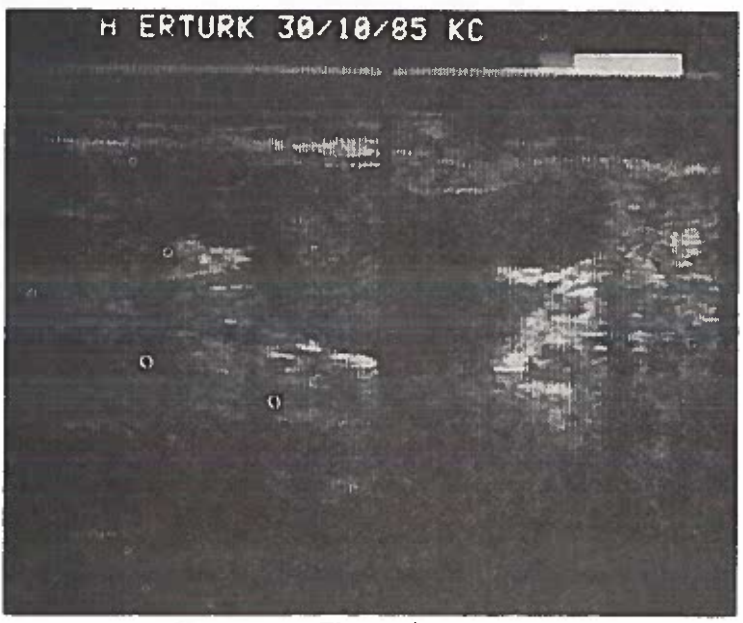

Figure 4
Hydatid cyst with hypo and hyperechoic pattern (Type III).

b) This group of cysts appear in a multicystic pattern. The most typical cases show a "Honeycomb" appearance representing daughter vesicles (Figure 3).

Twelve of our 34 cases demonstrated these ultrasound features and were confirmed by surgery.

Type III- Hydatid Cyst with Heterogeneous Echo Pattern: This type of cyst exhibits ill-defined borders with hypoechoic appearance or hyperechoic solid pattern or both (Figure 4). Small cystic areas may be seen in some of these cysts, representing daughter cysts. These patterns usually indicate infection of the hydatic cyst. Eight of our 34 cases were in this group and their diagnosis at surgery was infected hydatid cyst.

Discussion

There are no problems associated with diagnosing a simple hydatid cyst, provided it is solitary. Detection of a double layer surrounding the cyst is accepted as characteristic of hydatid disease. However, in multiple Type I cysts, particularly if a double layer is not demonstrated, differential diagnosis of the hydatid cyst and polycystic disease, based on ultrasound features, is not always easy. Although we did not have a case of a simple developmental cyst of the liver in our study, ultrasonic features of this cyst are quite similar to a simple hydatid cyst, Type I.[4-7]

Topographical localization is easier in the right lobe of the liver, because the upper pole of the right kidney, gallbladder and the diaphram are good anatomical landmarks. Hydatid cysts located in the left lobe of the liver present a diagnostic problem. Although we did not encounter any diagnostic difficulties in localizing the left lobe cyst, it is difficult to determine whether it is a part of the left lobe of the liver or a part of another organ of the left hypochondrium.

In Type II cysts, the presence of multicystic pattern in the cyst is quite helpful in diagnosing hydatid disease.[4, 8] It has been generally accepted that this appearance is due to the presence of daughter cysts within the hydatid cyst.[4, 9] In our series, the ultrasound examination of eight patients showed this pattern. At surgery, daughter cysts were removed from the primary cyst in seven cases. In one case, multiple small cysts, which are closely related to each other, were detected. We, therefore, share the same opinion with Niron et.al.,[8] that this pattern should be interpreted cautiously.

Demonstration of collapsed germinative membrane in the cyst indicates leakage of fluid from the cyst by one of many routes. Rupture

of the cyst into the biliary and portal system are well known complications of hydatid disease.[10, 11] Four cases in this group showed this appearance and biliary connections were detected at surgery.

The cysts in Type III exhibit ill-defined borders with hypo or hyperechoic pattern or both. It is visualized as a pseudotumor which is difficult to differentiate etiologically unless Type I cyst are seen elsewhere within the liver. Secondary infection of hydatid cysts should be suspected if type III cysts are diagnosed preoperatively. Various organisms which invade hydatid cyst via the blood or the biliary system, have been reported including salmonella and other pyogenic bacteria.[9] Secondary infection was suspected in our all cases of this type and it was confirmed by surgery.

Since calcification of hydatid cyst is a rim-like calcification which is seen at periphery of a cyst, generally no typical back-shadow secondary to calcifications can be seen. We were unable to detect any definite calcification of hydatid cyst on ultrasound, but in seven of our cases the existence of calcified hydatid cyst was reported by pathology.

Ultrasound examination is also helpful to diagnose hydatid cyst of the lung. Hydatid cysts which are located at the base of the right lung can easily be demonstrated during ultrasonic examination of the liver. Sometimes, both liver and lung hydatid cysts can be diagnosed at the same time as in one of our cases.

Periodic ultrasound examinations after surgery for hydatid disease should be performed to diagnose recurrence of cysts as early as possible. In addition, progressive healing of the cyst can be demonstrated after surgical drainage. If omentoplasty is performed as a surgical procedure, ultrasonic appearance of the omentoplasty appears to be quite similar to a solid tumor in the liver. Thus, great care should be taken to evaluate post-operative cases.

In this paper, we present our experience with ultrasonic appearances of hydatid cysts since they occur frequently in our region. We conclude that ultrasound classification of the cysts increase diagnostic accuracy. In addition, if a hydatid cyst in the abdomen is clinically suspected, ultrasound examination should be the first choice diagnostic method in the evaluation of liver masses, and periodic examinations should be performed by ultrasound after surgery.

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Hacettepe Medical Journal
Volume 19 / No. 2 / April 1986 / pp. 61 – 65

Androgen Receptors in Urological Tumours

Ziya Kırkalı, M.D.*

Summary

Hormonal treatment is a treatment modality in prostatic cancer and kidney tumours. Receptor studies have been developed in an attempt to identify hormone-dependent cancer and to predict hormonal responsiveness. Androgen receptors in urological tumours is currently being investigated by many medical centres. More accurate determination of androgen receptor content may help to better understand these tumours and may help to identify patients unsuitable for hormonal treatment.

Key Words: Androgen receptors, Prostatic cancer, Kidney tumours, Bladder tumours, Testicular tumours.

Introduction

It is well known that some types of human cancer are either induced or their growth is enhanced in the presence of various steroid hormones. In 1896, Beatson showed that one-third of pre-menopausal patients with advanced breast cancer underwent objective remission from their disease subsequent to oophorectomy.[1] Similarly, hormone dependence of prostatic carcinoma by Huggins and Hodges created a new era in urological oncology.[2] Today, 75 % of all patients with prostatic cancer show varying degrees and duration of subjective response to hormonal treatment.[3]

Hormones and Receptors

It is known that steroid hormones are bound to their specific receptors in the cytoplasm of target cells to achieve their desired physiological effects.[4, 5] These hormones enter the specific target organ cells by passive diffusion. Either the hormone itself or its metabolites are bound

Western Infirmary, Department of Urology, Glasgow, Scotland.
* Honorary Registrar. Present Address: Gülhane Military Medical Academy Ankara, Turkey.

to the free specific receptor protein, which is already in the cytoplasm, to form an activated hormone-receptor complex. This activated complex has increased affinity to the acceptor sites of the nuclear chromatin. This hormone-receptor-acceptor interaction results in the transcription of selected genes, which is either increased or decreased and the physiological response to the hormone is initiated by the formation of mRNA.

Despite the advances in techniques of more accurate estimation of the circulating steroid hormones, hormone-receptor interactions play the crucial role in the effect of these hormones on tissues. Therefore, determination of steroid hormone receptor content in tissue is thought to be the prime factor in showing the hormonal dependence of tissues, and is used as a prognostic factor in certain types of human cancer.[4-6] Today, measurement of oestrogen receptors is accepted as a reliable method for predicting response to therapy and for prognosis in breast cancer.[4, 7]

Various methods have been developed to estimate tissue androgen receptor (AR) contents. Nuclear and cytoplasmic AR can be detected separately by quantitative biochemical methods. Gel filtration, ammonium sulphate and potassium sulphate precipitation, ion-exchange chromotography, gel electrophoresis are some of the biochemical methods where different radioactive ligands may be used.[8] Histochemical detection of AR is also possible and claimed to be as accurate as more sophisticated biochemical methods.[9]

Prostatic Cancer

There has been a considerable receptor research in human prostate tissue in attempts to clarify the role of steroid hormones in the malignant transformation of this organ. AR have been detected in the cytosolic and nuclear fractions of normal, benign hyperplastic and carcinomatous prostatic tissues.[5, 6, 8, 10] Trachtenberg and Walsh found that there existed a correlation between the AR content and hormonal responsiveness; and measurement of nuclear AR may assist in identifying those patients (tissues) which are unlikely to obtain a prolonged response from hormonal therapy.[6] Ekman also showed that receptor positive prostatic cancer patients had more pronounced tumour regression after endocrine treatment.[10] De Vogt et. al. used cold agar gel electrophoresis and found no correlation between receptor content and response to treatment.[11]

There is still a debate about the advantages of different techniques and about the method of taking specimens. While it is claimed that electroresection may degrade and affect AR content in the tissues,[8, 10]

there is evidence that AR may still be found in tissues obtained by TUR[12] There are other problems in the methodology of AR measurement, such as the heterogeneity of the tissue, measurement of free receptors, and interference of AR with other steroid receptors, namely progesterone receptors.[4, 5] Recently Moffat et. al. introduced a new method to overcome interactions with other steroid hormone receptors.[12]

Estimation of epithelial growth factor, immunohistochemical detection of AR by monoclonal antibodies and improved techniques of receptor assays may also help understand better the natural behaviour of this disease and the effect of steroid hormones.

Kidney Tumours

Kidney tumours were induced in experimental animals by administration of oestrogens.[13] It is also claimed that oestrogens play a role in the formation of kidney tumours in humans.[14, 15] Steroid receptors were studied to understand the hormonal influence on kidney tissues; and oestrogen, progesterone and androgen receptors were determined.[16, 17] AR was found in normal kidney, and higher AR contents were found in renal cell carcinoma. It is suggested that treatment by medroxyprogesterone, even though it does not cause an anti-tumour effect, may increase survival in patients with positive receptors.[17, 18] Additional research in steroid hormone receptors in kidney tumours is necessary before a conclusion can be drawn on their hormonal dependence.

Bladder Tumours

Although relevance of hormones to normal development and malignant transformation of human bladder is unclear,[5] increased incidence of bladder tumours in males may suggest a hormonal basis.[19] Laor et. all found that bladder tumours had higher cytosolic AR than normamucosa.[19] Kırkalı et. al. studied AR in various transitional cell carcinoma and did not find any receptor positivity.[20]

Testicular Tumours

Testes are the major source of androgens in human body, but they have not been the subject of AR studies. This is partly because of the low incidence of these tumours, partly by the high cure rate achieved by chemotherapy. Nevertheless, AR was found both in cytoplasmic and nuclear fractions of normal and malignant testicular tissues with an unclear relationship to hormonal responsiveness.[21]

Conclusion

Urological organs may grow under the influence of steroid hormones. Furthermore, these hormones may play a direct role in uncontrolled malignant growth. New developments in a more accurate measurement of AR in urological cancer tissues will help in understanding this hormone-cell interaction and therefore assist in the prediction of patient response after hormonal manipulation.

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Volume 19 / No. 2 / April 1986 / pp. 67 – 91

New Approaches to Cancer Chemotherapy*

Wayne E. Criss, Ph.D / Nesrin Kartal Özer, Ph.D.*** / Özge Alper*****

All cells of the body begin from a single undifferentiated "fertilized" cell. Therefore, during the first few minutes of "new life", this cell(s) only undergoes cell division or cell proliferation. Differentiation of cells does not occur. Then, gradually, over the next few hours and days, rapid cell proliferation continues but cell differentiation also occurs. Several months later (e.g. 9 months) most cells in the new "person" have become differentiated, only a few cell types continue rapid proliferation. These alternating or opposing processes of cellular proliferation and cellular differentiation are extensively regulated by both extra and intracellular substances. Many of these *natural* regulatory substances have recently been identified; and their mechanisms of action are rapidly being elucidated.

In the child, as well as in the adult, over 90 % of the body's cells/tissues are considered to be differentiated and only very slowly proliferating. Less than 10% of the cells are undifferentiated and are rapidly proliferating. Yet, most of these latter cells retain the capacity to differentiate, if proper regulatory signals are present and are acknowledged. Today, it is currently being evaluated as to whether cancer cells, which at the extreme are undifferentiated-rapidly proliferating cells, arise in the body from dedifferentiation or from faulty differentiation (Figure 1). Dedifferentiation results when a series of events cause (or allow) a mature-differentiated cell to become a cancer cell. Faulty differentiation results when a series of events interfere with the normal processes of differentiation and the result is a cancer cell. In either situation, substantial research data is available to illustrate that many of the natural

* Department of Biochemistry and Institute of Oncology, Hacettepe University Medical School Ankara, Turkey.
** Professor of Biochemistry and Institute of Oncology.
*** Research Asistant in Biochemistry.

regulatory substances are present in cancer cells and/or are capable of controlling many cellular events involving both proliferation and differentiation in the cancer cells. Therefore, a new approach to the chemotherapy of cancers is now occurring. This new approach utilizes natural differentiation substances, anti-natural proliferation substances, and blockers of natural proliferation substances.[1-10]

Most current cancer chemotherapeutic drugs are very toxic. They are directed at selected enzymes and enzyme systems which are quantitatively in abundance in cancer cells. However, the same enzymes and enzyme systems also exist (albeit in less quantity) in other normal cells of the body. To date, no enzyme or substance has been identified or found to be exclusively in cancer cells. It is always present in some other types of body tissues; and it is usually in those normal body cells which are least differentiated and which are rapidly proliferating (e.g. intestinal mucosa, epidermis, myeloblasts, lymphoblasts, erythroblasts, etc.). In other words, malignant cancer cells are biochemically *and* histologically undifferentiated cells. They have the same range of enzymes and enzyme systems as *normal* undifferentiated cells of the body. Upon response to differentiation substances and/or diminished response to proliferation substances, undifferentiated normal cells become differentiated and stop proliferating. In a similar manner, many undifferentiated cancer cells can respond to differentiation substances and/or show decreased response to proliferation substances. Therefore, a new approach which utilizes these natural substances is highly justified in the laboratory and in the clinics.

Natural substances, or drugs related to the functioning of these natural substances, would be cytostatic in clinical action, as opposed to most current cancer drugs which are cytotoxic. They would inhibit or interfer with the proliferation positive signals and/or enhance differentiation positive signals, as opposed to the attempt to kill the cancer cells via cytotoxic mechanisms. In this way, it may be possible to "tame" or reverse the proliferative nature of malignant cancer cells by converting them to less proliferating-more differentiated cells, hence not or less dangerous to the body. In addition, if such events can be controlled by cytostatic drugs, cancer chemotherapy can be made much less debilitating to the cancer patient.

During the past few years, a wide variety of natural substances have been identified which are involved in the regulation of cell proliferation and/or cell differentiation. These substances include polyamines,[4-7] vitamin A,[8-10] steroid hormones,[11-14] polypeptide growth and differentiation factors,[15-18] prostaglandins,[19] viruses,[20] phorbol

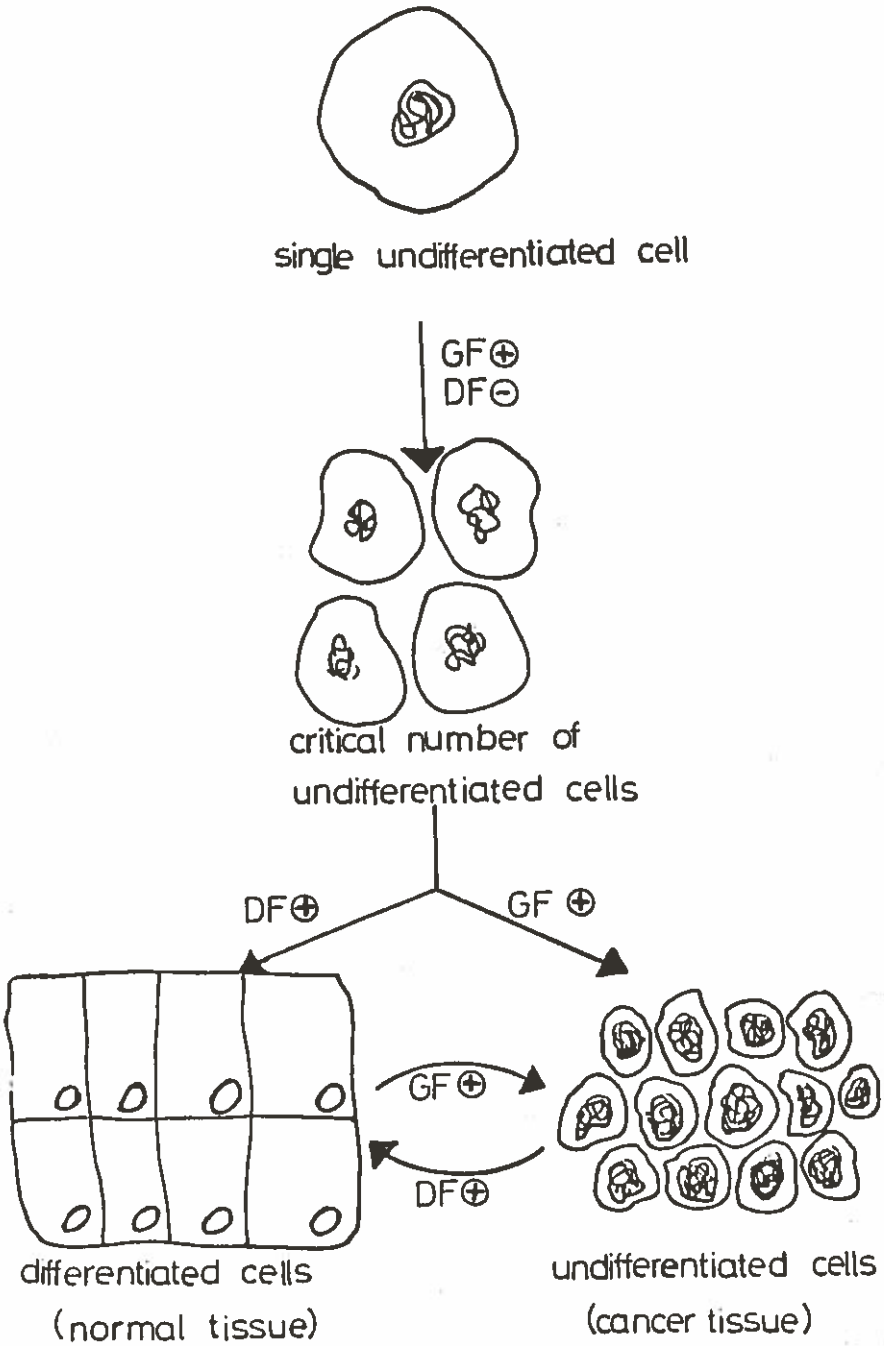

Figure 1
Proliferation Versus Differentiation.
GF : Growth Factors, DF : Differentiation Factors, ⊕ : Positive Response, ⊖ : No Response

esters,[21, 22] glycoprotein hormones,[23] cyclic nucleotides,[24] interferons,[25, 26] and interleukins.[27] This review will focus on polyamines and vitamin A modulation of cell proliferation/differentiation mechanisms (Figure 1), and it will suggest a possible new approach to cancer chemotherapy using these two systems.

Polyamines in Cellular Proliferation and Differentiation

Polyamines are small nitrogen containing substances which are found in all living cells and in all biological fluids. The major polyamines in human tissues and fluids are cadaverine, putrescine, spermidine, and spermine. They are synthesized by all body cells, and are also capable of being exported to other body cells via body fluids. Polyamines have been determined to play a key regulatory role in the proliferation and differentiation of all normal and cancer cells/tissues.[4-7]

One of the earliest changes, which takes place in a normal cell that is stimulated to grow, is a rapid increase in the intracellular concentrations of the polyamines. This is soon followed by an increase in the synthesis of DNA, RNA, and proteins; cell division then occurs.[6,7,28-33] Many studies show that the key enzymes which synthesize the polyamines and the polyamines increase during the early phase of natural growth stimulating signals upon selective target cells and tissues (e.g. estrogens,[11, 12] glucocorticoids,[13, 28] protein hormones,[28, 34-38] polypeptide growth factors,[17, 39, 40] tumor promoters,[22, 41] and various organics[42]).

The enzymes which synthesize the polyamines and the quantity of the polyamines are elevated in all cancer cells/tissues.[4, 5, 43-46] Cancer cells/tissues have increased capacity to synthesize polyamines and to release them into the surrounding fluids. This is true of neoplastic/cancer cells which have undergone morphological-biochemical modifications initiated by transforming viruses,[20, 46] chemical carcinogens,[47-51] or that occur spontaneously. Therefore, elevated levels of plasma and urinary polyamines and polyamine metabolites have been used to assist in the diagnosis and the monitoring of therapies in a wide variety of human cancers.[5, 6, 43-45, 52-54] Inhibiton of the synthesis of polyamines in cancer cells/tissues by selected means of polyamine deprivation (including drugs) inhibits cellular proliferation, causes numerous morphological aberrations, and initiatates cell death.[55-58] Therefore, the polyamines are directly involved in cancer cell growth.

Recently, in attempts to evaluate polyamine action, several investigators have utilized chemical carcinogens and tumor promoting agents in normal and cancer cells/tissues both *in vivo* and *in vitro*.[22, 51, 58-64]

Their findings can be summarized as follows. A wide variety of chemical carcinogens can stimulate increased levels of polyamines and the polyamine synthesizing enzymes prior to changes in cellular morphology. In addition, treatment with tumor promoting agents also causes increased levels of these growth regulators and their synthezing enzymes prior to morphological changes. These effects of the tumor promoting agents can be reduced or prevented by certain substances such as retinoids, prostaglandins, organic substances, and certain drugs which inhibit the activities of the enzymes that synthesize the polyamines.[7, 58, 65-73]

Metabolic Pathways of Polyamine Synthesis, Catabolism and Excretion

Polyamines are synthesized by all tissues of the body. They are synthesized from amino acids, and via urea cycle precursors. The amino acid, methionine, is attached to a nucleoside carrier molecule, adenosine-ribose to form S-adenosylmethionine. This molecule is converted to decarboxylated S-adenosylmethionine by one of the key regulatory enzymes, S-adenosylmethionine decarboxylase (SAM decarboxylase). Ornithine, produced via urea cycle, is decarboxylated to putrescine by the most highly regulated enzyme, ornithine decarboxylase (ODC). Spermine synthetase then adds the propylamine from decarboxylated S-adenosylmethionine to putrescine to make spermidine, and spermine synthetase adds another propylamine from decarboxylated S-adenosylmethionine to spermidine to make spermine (Figure 2). Spermidine and spermine are the two most potent polyamines in the body and ornithine decarboxylase is the rate limiting enzyme in the synthesis of the 3 polyamines: putrescine, spermidine, spermine.

Catabolism of polyamines occurs in liver peroxisomes. The enzyme, polyamine oxidase, oxidizes some of the spermine to spermidine to putrescine. These oxidations yield β-aminopropion-aldehyde, which is subsequently degraded to CO_2 and NH_4^+. Putrescine is also oxidized to CO_2 and NH_4^+ by other enzyme systems. However, the major portion of the polyamines are conjugated in the liver to from N^1-acetylspermidine and N^8-acetylspermidine by acetyl-transferases. These latter two substances are then excreted in the urine. Elevated levels of the N-acetylspermidines have been reported in cancer patients.[52-54, 74-76]

Molecular Mechanisms of Polyamine Actions

It currently is not understood as to how polyamines regulate components of cellular proliferation versus cellular differentiation. Certainly, polyamines are required for optimal growth of most cells. Rapidly growing cells have higher levels of ornithine decarboxylase and poly-

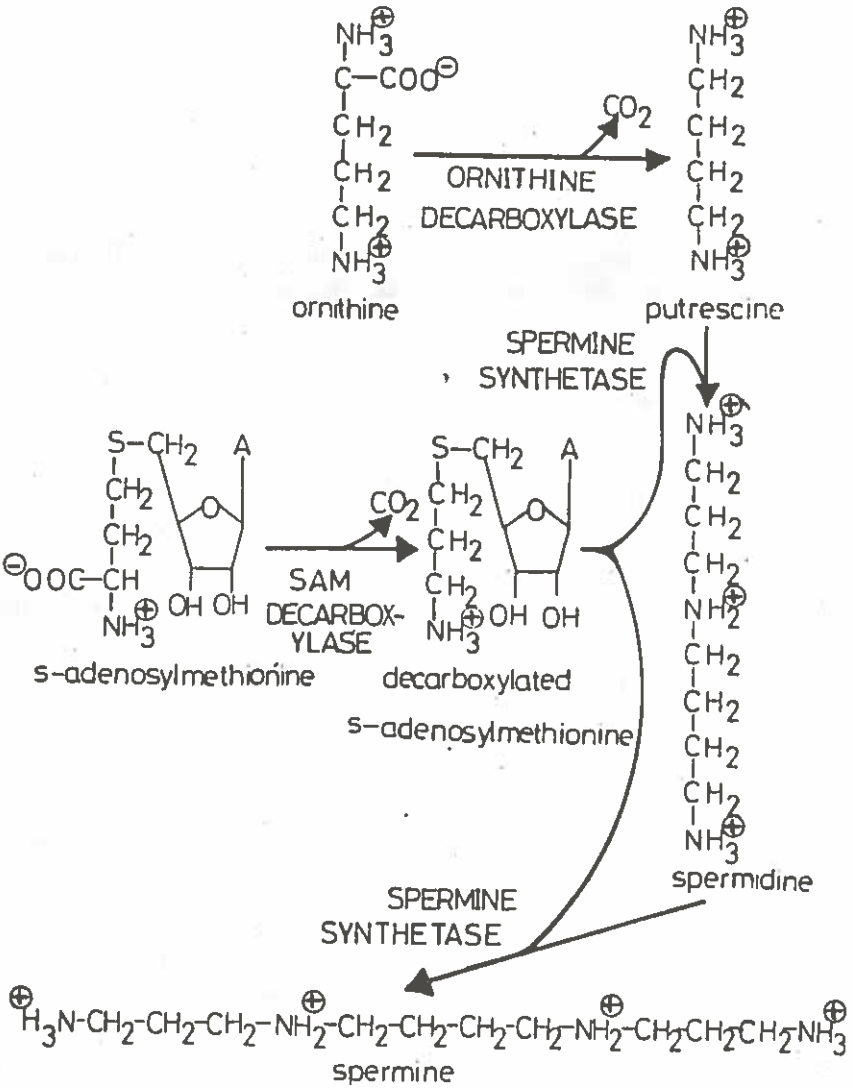

Figure 2
Metabolic Pathway of Polyamine Synthesis.

amines than slower growing or quiescent cells. And, when quiescent cells are stimulated to proliferate, ornithine decarboxylase activity and polyamines increase prior to an increase in DNA, RNA, or protein synthesis.[4-7] Which specific biochemical systems are affected? There are many!

Polyamines interact with and bind to individual DNA molecules. Such action apparently causes a compaction of the DNA molecule

and/or increased conversion from β-DNA to Z-DNA.[77, 78] Direct regulation of specific gene functioning by such interactions has not yet been established; however, it is assumed that such interactions cause the synthesis of new M-RNA and new protein molecules.

Increased polyamine levels and increased RNA synthesis are apparently tightly linked. This is particularly true for total cellular RNA and M-RNA.[79] Recently, data has been published which show that ornithine decarboxylase activity is converted to RNA polymerase activity by a polyamine responsive protein kinase.[80, 81] And, other studies show that polyamines bind to specific sites on the t-RNA molecule and appear to increase the stability of the anticodon loop.[82] This data is interpreted to mean that polyamines enhance transcription in cells.

Many papers have been published which establish relationships between polyamines and *in vitro/in vivo* protein biosynthesis. Data can be cited which show that polyamines facilitate ribosomal subunit associations,[83, 84] increase fidelity of M-RNA translation,[85] enhance the capacity of aminoacyl t-RNA to read stop codons,[86] and affect polypeptide chain initiation and/or elongation.[87] Hence, polyamines enhance translation in cells.

Recently several protein kinases have been identified in various cells and tissues which are dependent upon polyamines for maximal activities. Polyamine dependent protein kinases have been identified in most mammalian tissues and they have been purified and studied from hepatoma cytoplasm,[88-90] hepatoma nuclei,[91] epidermal tissue cytoplasm,[92] and from a slime mold.[80, 81] Collectively, these enzymes are independent of cyclic nucleotides, and phosphorylate such proteins as ornithine decarboxylase, casein, phosvitin, RNA polymerase I, microtubules, and several cellular proteins of unknown identitiy. Such phosphorylation apparently inhibits ornithine decarboxylase activity, increases RNA polymerase activity, and alters microtubule assembly rates.[6, 7, 88-92] Therefore, polyamines also enhance certain posttranslational systems in cells.

One additional mechanism of action of polyamines is in the formation of hypusine.[93, 94] Putrescine and/or spermidine is converted to hypusine which is incorporated into the eukaryotic protein synthesis initiation factor, eIF-4D. The physiological role of hypusine is unknown, but rapid growing normal and cancer cells have elevated levels of hypusine and increased protein synthesis.

Regulation of Polyamine Synthesis

The synthesis of polyamines is affected by several drugs, vitamin A, and certain intracellular metabolites. Most of these regulatory parameters

involve two of the key enzymes which synthesize the polyamines, ornithine decarboxylase and SAM decarboxylase.

Ornithine decarboxylase activity undergoes very rapid changes in *in situ* activity. This may be due to a group of complex regulatory controls involving M-RNA functioning, enzyme phosphorylation, anti-enzymes, anti-antienzymes, and/or transamidation.[80,87-91, 95-99] In addition a very specific "sucide" inhibitor, difluoromethylornithine (DFMO), irreversibly inhibits ornithine decarboxylase.[98] Numerous laboratories have used this latter inhibitor over the past few years to prevent *in vivo* polyamine synthesis in order to evaluate the role of polyamines in cell proliferation and/or cell differentiation processes, and to treat a variety of diseases.[99-122] Administration of DFMO to growing cells causes rapid depletion of intracellular polyamines and rapid inhibition of cell proliferation (Table I). DFMO administration to a variety of cell systems also results in either increased cell differentiation (Table I) or blocked cell differentiation (Table II and III). The DFMO induced modifications are rapidly overcome by administration of putrescine.

TABLE I
POLYAMINE SYNTHESIS INHIBITORS STIMULATE CELL DIFFERENTIATION

Beginning Cell Type	Ending Cell Type	Reference
Keratinoblasts	Keratinocytes	99
Erythroblasts	Erythrocytes	100
Teratocarcinoma cells	Differentiated cells	101
Neuroblastoma cells	Neuroblastocytes	102
Melanoma cells (S91)	Melanocytes	68,103
Melanoma cells (B16)	Melanocytes	55,104
Embryonal carcinoma cells	Germinal cells	101

TABLE II
POLYAMINE SYNTHESIS INHIBITORS BLOCK CELL DIFFERENTIATION

Cell Type	Differentiatin Stimulators	Reference
Erythroleukemia cells	Organic compounds	105
"preadipocytes"(3T3-L1)	Virus	106
Myeloblast cells (L6)	Insulin	107
Granulocyte progenitor cells	Colony stimulating factor	108
Promyelocytes	Colony stimulating factor	61,66,109,110
Promyelocyte cells	3'-5' cyclic AMP	61,66,115
Embryonic cells	(Natural progression)	111,112
Myeloblasts (CML)	Colony stimulating factor	22
Breast cancer cells	Estradiol	12
Melanoma cells	Melanocyte stimulating hormone	113

TABLE III
CELLS STIMULATED TO DIFFERENTIATE BY PHORBOL ESTERS*

Beginning Cell Type	Ending Cell Type	Reference
Myeloblasts (CML)	Macrophage like cells	22
Myeloblasts (AML)	Macrophage like cells	114
Leukemia cells (CLL)	Mature plasma cells	66,117
Promyelocytes	Macrophage like cells	61,109,116
Neuroblastoma cells**	Nerve like cells	118
Melanoma cells**	Melanocytes	119

* Not blocked by inhibitors of polyamine synthesis
** Not tested for polyamine involvement

A reasonably specific inhibitor of SAM decarboxylase, methylglyoxal bis-guanylhydrazone (MGBG), has also been extensively used to inhibit *in vivo* polyamine synthesis in a variety of cell systems (Table I). Administration of MGBG very rapidly depletes growing cells of spermidine and spermine, prevents cell proliferation, and initiates cell differentiation.

Polyamine synthesis inhibitors inhibit the proliferation and stimulate the differentiation of keratinoblasts, erythroblasts, teratocarcinoma cells, neuroblastoma cells, melanoma cells, and embryonal carcinoma cells (Table I). While these same inhibitors inhibit the proliferation and prevent the *induced* differentiation of erythroleukemia cells by organic compounds, preadipocytes by 3T3-virus, L6 myoblast cells by insulin, granulocyte progenitor cells by colony stimulating factor, promyelocytes by colony stimulating factor, and/or 3′ 5′ cyclic AMP, embryonic cells during natural progression, CML myeloblasts by colony stimulating factor, breast cancer cells by estradiol, and melanoma cells by melanocyte stimulating hormone (Table II). *Therefore, it is probable that polyamines are essential for cellular proliferation, and for the differentiation of those cells that require proliferation during one or more of their stages of differentiation.*

A variety of cell types are also stimulated to differentiate by tumor promoting agents such as the phorbol esters (Table III). Cells which have been reported to be directly effected by phorbol esters include CML myeloblasts → macrophage like cells, AML myeloblasts → macrophage like cells, CLL leukemia cells → mature plasma cells, promyelocytes → macrophage like cells, neuroblastoma cells → nerve like cells, and melanoma cells → melanocytes. In those cell systems which were tested with inhibitors of polyamine synthesis, no effect of the inhibitors was noted. Therefore, in comparing the phorbol ester stimulated differentiation of promyelocytes to macrophage like cells which is not effected by polyamine synthesis inhibitors[108] and the colony stimulating factor stimulated

differentiation of promyelocytes to granulated lymphocytes which is prevented by polyamine synthesis inhibitors,[110] one can say that *it is probable that multiple routes of differentiation are available to a "precursor" or mast type of undifferentiated cell.* Some of these "differentiation pathways" may require polyamines, some of them may not.

Polyamines in Cancer Therapy

A variety of antipolyamine approaches are currently being used in cancer therapy. These approaches include using combination chemotherapy: standard cancer drugs plus either an inhibitor of polyamine synthesis, an inhibitor of polyamine membrane transport, and/or a polyamine antimetabolite (Table IV).

TABLE IV
POLYAMINES IN COMBINATION CHEMOTHERAPY FOR CANCER

Cancer Type	Drug Combinations	Reference
L1210 leukemia	Arabinofuranosylcytosine (ara C) and DFMO	122
Gastrointestinal cancers	Mitomycin C, DFMO, MGBG	123
L1210 leukemia	Adriamycin, Vindesine, DFMO	124
Solid tumors	Adriamycin, Vindesine, DFMO	124
Renal adenocarcinoma	Interferon, DFMO	125
Colon adenocarcinoma	5-fluorouracil, DFMO	126
L1210 leukemia	Glyoxal bis (guanylhydrazone), DFMO	127,128,129
Brain tumors	Aziridinylbenzoquinone, DFMO	130
Prostate cancer	Glyoxal bis (guanylhydrazone), DFMO	129,131,132
L1210 leukemia	1,3 bis (2 chloroethyl)-1-nitrosourea (BCNU), DFMO	133
Renal adenocarcinoma	MGBG, DFMO	134
Brain glioma and gliosarcoma	1,3 bis (2 chloroethyl)-1-nitrosourea, DFMO	135,136
Brain tumor spheroids	1,3 bis (2 chloroethyl)-1-nitrosourea, DFMO	137
Renal adenocarcinoma	MGAG, MGBG	138
Mammary tumors	Antiestrogens, DFMO	139
Human adenocarcinomas*	1,3 bis(2 chloroethyl)-1-nitrosourea, DFMO	140
Brain tumor cells	cis-diamminedichloroplatinum II, DFMO	141
L1210 leukemia	4' (9-acridimylamins) methanesulfon-m-anisidide, DFMO	142
HeLa cells	Arabinosyl cytosine, DFMO	143
Brain tumor cells	1,3 bis (2 chloroethyl)-1-nitrosourea dicyclohexylamine sulfate	144
Several human cancer cell lines (5)	Interferon, DFMO	145
Chinese hamster V79 cells	(hyperthermia)	146

* Origin was stomach, colon, cervix, breast and lung

Initial approaches in cancer therapy, which utilized knowledge of polyamine action, focused on cell cycle specific cancer chemotherapeutic drugs and combinations of inhibitors of polyamine synthesis. Table IV documents enhanced therapeutic benefits obtained from this approach. The following cancers were most successfully treated: adenocarcinomas of the kidney, colon and prostate, breast carcinomas, and a variety of brain tumors. Phase I and II clinical trials using DFMO and either interferon or, 1, 3 bis (2 choleroethyl)-1-nitrosourea have been the most successful.

Additional polyamine antimetabolites are being tested in a variety of cancer patients (Table V). Both solid and blood cancers are currently being challenged with 14-16 different derivatives of spermidine/spermine. Some success is now being realized with certain of these antimetabolite derivations in child leukemias.

TABLE V

POLYAMINE ANTIMETABOLITES IN CANCER CHEMOTHERAPY

Cancer Type	Antimetabolite	Reference
L1210 leukemia	N^4-SPD, N^1-N^8SPD (11 derivatives)	147,148
Brain tumor cells	Dicyclohexylamine sulfate	144
Leukemia cells	Dicyclohexylammonium sulfate	149
Several human cancers	4'-(9-acridinylamino) methanesulfon-m-anisidide/DFMO	150,151
Human brain tumors	1-(2-chloroethyl)-3-trans-4-methyl cyclohexyl-1-nitrosourea, DFMO	152
Child leukemias	DFMO, MGBG	153
Lung carcinoma	DL-DFMO	154
Colon and lung carcinoma	MGBG	155
Several human cancers	DFMO, MGBG	156

During the treatment of cancers with DFMO, depletion of intracellular polyamines initiates a membrane bound polyamine transporter/importer system. This system transports plasma polyamines into the cancer cells to help maintain adequate polyamine levels for cancer cell growth. Therefore, during the past 5-6 years several studies have focused on the polyamine transporter system in cancer cells. Excellent therapeutic results can now be obtained by initial treatment with DFMO, to turn on the transporter system, followed up with a polyamine antimetabolite which is also readily taken up by this transporter system (Table VI). In this way, high concentrations of two antipolyamines can be selectively incorporated into cancer cells. Such approaches have been reasonably effective with prostate cancer and childhood leukemias.

TABLE VI
STUDIES ON CELLULAR UPTAKE OF POLYAMINES

Cancer Type	Metabolites	Reference
Prostate cancer	DFMO, MGBG	131
Prostate cancer	DFMO, putrescine, spermidine, diamines	157,158
Prostate cancer	DFMO, MGBG, 9-arabino-furanosyladenine	159
Child leukemias	DFMO, MGBG	153
L1210 leukemia cells	N^4-SPD, N^1-N^8SPD (11 derivatives) methylglyoxalbis (guanylhydrazone)	129,147,148,160,161
L1210 leukemia cells	Triamine homologues	162
Several human tumors	DFMO, MGBG	156
Tumor cells	MGBG, DFMO	163
Ehrlich ascites cells	DFMO, MGBG	161

Antipolyamine cancer therapy is accomplished with only minimal side effects. Short term use of DFMO is essentially free of all side effects. Utilization of DFMO with combinations of non-polyamine antimetabolite drugs causes very minor side effects. Continued use of DFMO for long periods causes hearing loss, reduced blood cells and platelets. However, these effects can be readily reversed by treatment of the patient with putrescine (Table VII). MGBG, however, is very toxic and causes numerous problems including: thrombocytopenia, leucopenia, dyspnea, hemolysis, jaundice, fever, nausea, diarrhea, and fatigue.

TABLE VII
TOXIC SIDE EFFECTS IN ANTIPOLYAMINE THERAPIES

Tumors	Drugs	Side Effects	Reference
Lymphoma, head-neck cancers	MGBG	Fatigue, vomiting, diarrhea	164
Several human cancers	DFMO	Hearing loss	156
Several human cancers	MGBG	Thrombocytopenia, leucopenia, dyspnea, hemolysis, jaundice, fever, nausea, diarrhea	156
Normal tissues	Prolonged DFMO	Reduced leukocytes, rbc's and platelletes	165

Vitamin A in Cell Proliferation and Differentiation

Vitamin A (Figure 3) is a fat soluble vitamin which is found in the form of β-carotene or retinol in green, red and orange vegetables and as retinol palmitate in meats, eggs and cheeses. It is readily digested with other fats and it is stored in the liver as retinol-palmitate. It is then trans-

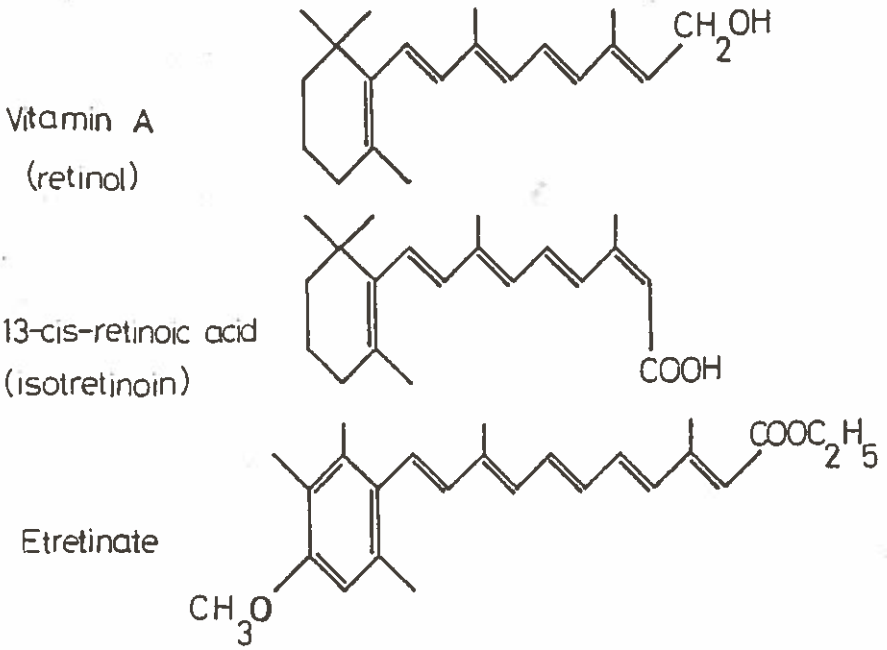

Figure 3
Structures of Vitamin A and Retinoids.

mitted from the liver to all cells/tissues of the body by a special blood carrier mechanism. This carrier is composed of retinol, retinol binding protein, transthyretin, and thyroxine. At the level of the tissue cell membrane the carrier complex associates with the membrane, retinol and thyroxine enter the body cell, while retinol binding protein and transthyretin remain outside. Retinol may then bind directly to an intracellular cytoplasmic receptor retinol binding protein. *Apparently*, the retinol-retinol binding protein then associate with various other intracellular proteins (including nuclear proteins) and initiates or maintains cellular events associated with processes of differentiation.[10] The molecular mechanism of action of retinol (Vitamin A) is simply not understood.

Administration of vitamin A to cells in culture stimulates cellular differentiation and inhibits cellular proliferation (Table VIII). Among the cells stimulated to differentiate by Vitamin A are promyelocytes and myeloblasts from patients with acute mylelocytic leukemia, chronic myelocytic leukemia, and acute promyleocytic leukemia, in addition, neuroblastoma and melanoma cells. In each of these above cell systems, *the vitamin A stimulated differentiation of these "cancer" cells is inhibited or blocked by polyamine antimetabolites. Thus there is a linkage between vitamin A and polyamine actions in cancer cells.*

TABLE VIII
CELLS STIMULATED TO DIFFERENTIATE BY RETINOIC ACID*

Beginning Cell Type	Ending Cell Type	Reference
Promyelocytes (APL)	Granulated neutrophils	166,167
Embryonic carcinoma cells	Germinal cells	111,112
Neuroblastoma cells	Nerve like cells	168
Melanoma cells	Melanocytes	169
Myeloblasts (CML)	Granulocytes	166,167
Myeloblasts (AML)	Granulocytes	166,167

* Blocked by inhibitors of polyamine synthesis

Vitamin A and Retinoids

Because of the ability of vitamin A to stimulate differentiation and /or inhibit proliferation of cells and tissues, a variety of vitamin A derivatives have recently been synthesized and tested for their potential to prevent cancer cell formation and /or cancer cell growth.[10, 170-173] The major biologically active derivatives of vitamin A are called retinoids. Two retinoids which have been found to be effective drugs are 13-cis retinoic acid (isotretinoin)and etretinate (Figure 3). Both of these are effective drugs in a variety of premalignant or early neoplastic cell states, in skin acne, and psoriasis.Both drugs are rapidly absorbed from the gut and are metabolized by the liver in about 24 hours. They are relatively non-toxic. Major side effects in patients are dryness of skin and mouth (mucous membranes), some changes in hair texture and skin fragility, and occasionally nasal cheilitis and blepharoconjunctivitis. In addition however, very negative teratogenic effects are observed in pregnant animals.

Molecular Mechanisms of Vitamin A

Intracellular actions of vitamin A are not understood. Recent scientific data shows a direct link of vitamin A function to polyamine synthesis.[174-179] Vitamin A as retinol, retinoic acid, or the retinoids cause a decrease in the activity of ornithine decarboxylase, the rate limiting enzyme in polyamine synthesis. Decrease in the activity of ornithine decarboxylase, may be due to a decrease in the production or translation of the messenger RNA for the enzyme, or direct modification of the enzyme via phosphorylation, or antienzyme action. In addition vitamin A may also function similar to the steroid hormones by controlling specific genomic functions (selected genes). These genomes, in turn, control the production of substances involved in cell differentiation such as ornithine decarboxylase. Hence, synthesis of polyamines which are involved with

cell proliferation/growth mechanisms may be inhibited by vitamin A. *Therefore, apparently vitamin A simultaneously turns off mechanisms which stimulate cell growth and turns on mechanisms which stimulate cell differentiation.*

Therapeutic Uses of Vitamin A/Retinoids

Vitamin A, in general, or specifically the derivatives of vitamin A called retinoids, are currently used in several clinical settings involving psoriasis, acne, and cancer.[10] Retinoids have been successfully used to prevent and treat a variety of premalignant and malignant skin lesions, and to treat several types of leukemias and lymphomas.[64, 69, 167, 180-184] In most cases, an increased differentiation of the lesion was observed. Clinical trials with several retinoids, especially isotretinoin and etretinate, are currently being carried out with a wide variety of cancer patients.

Combined Use of Biological Modifiers in Cancer Therapy

Polyamines and vitamin A derivatives (retinoids) are natural modifiers of cellular proliferation/differentiation. Polyamines are essential for proliferation of cancer cells. Retinoids stimulate cancer cell differentiation. The two systems have the enzyme, ornithine decarboxylase, in common. Therefore, any attempts to simultaneously inhibit synthesis or function of polyamines (e.g. ornithine decarboxylase) and enhance retinoid function should simultaneously slow cell proliferation and increase cell differentiation. Because several of the drugs which effect these two systems are available in relatively non-toxic forms, such treatment efforts would be much less debilitating to cancer patients than current treatment with available toxic drugs. Therefore, cancer physicians should consider using biological response modifier system mechanisms, such as polyamines and retinoids, in cancer therapy. They could be used separately, or in combination with currently established "killer" system mechanisms. Combinations of cytostatic drugs and cytotoxic drugs allow a new approach for cancer therapy.

Acknowledgements: The authors wish to thank Mrs Emine Tercan for her expert secretarial services.

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A QUARTERLY PUBLICATION **VOLUME 19 / NO. 3 / JULY 1986**

PUBLISHED BY HACETTEPE SCIENCE CENTER FOUNDATION

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Indexed by Excerpta Medica

Printed by
Hacettepe University Press
Printing Division

VOLUME 19 / NO. 3 / JULY 1986

hacettepe medical journal

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Volume 19 / No. 3 / July 1986 / pp. 93 - 100

Plasma Substance P Levels in Diabetic Neuropathy

N. Sema Akalın, M.D.* / F. E. Buchanon / G. Northrop, M.D.** / R. H. Glantz, M.D.** / W.G. Ryan, M.D.****

Summary

Plasma substance P (SP) levels and total glycosylated hemoglobin values were assessed in 20 insulin-dependent diabetic patients in conunction with evaluation of their peripheral, somatic and autonomic nerve function. Ten healthy volunteers acted as controls. Alhough there was no significant difference between the SP levels of diabetic patients (37.3 ± 14.1 pg/ml) and controls (38.8 ± 23.5 pg/ml), in the diabetic group, some of the somatic nerve tests correlated positively with SP (posterior tibial nerve conduction velocity, $p < 0.05$; peroneal nerve conduction velocity, $p < 0.05$; and median sensory potential amplitude, $p < 0.05$), whereas total glycosylated hemoglobin showed a significant correlation only with median motor nerve conduction velocity ($p < 0.05$). SP levels of patients with orthostatic hypotension were not different from those of the patients with normal blood pressure responses. Three patients with diabetic diarrhea had SP levels (47.7 ± 2.5 pg/ml) that were significantly higher than those of diabetics with normal bowel movements (35.5 ± 14.6 pg/ml). These findings suggest that SP may have a role in some of the manifestations of diabetic neuropathy.

Key Words: Substance P, diabetes, peripheral neuropathy, autonomic neuropathy.

Introduction

Diabetic neuropathy is a serious complication of diabetes mellitus. Autonomic neuropathy often accompanies peripheral neuropathy, but the two may occur independently.[1] Autonomic neuropathy poses seve-

* Section of Endocrinology, Department of Medicine Hacettepe University Ankara-Turkey.
** Section of Endocrinology, Department of Medicine and Department of Neurology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL.. U.S.A.

ral health hazards such as unawareness of hypoglycemia, postural hypotension, spontaneous cardiac arrest, painless myocardial infarction from cardiac neuropathy,[2] and together with peripheral neuropathy, is an important cause of morbidity and mortality in diabetic patients.

Substance P (SP) is an undecapeptide discovered in 1931 by von Euler and Gaddum.[3] It is found in endocrine cells of the gut mucosa,[4] and is distributed throughout the central and peripheral nervous system.[5] Elevated plasma levels of SP have been reported in patients with the carcinoid syndrome[6] and in a hereditary sensory neuropathy of the rat, neural tissue SP was found to be reduced.[7] Although patients with peripheral neuropathy of various etiologies and autonomic dysfunction have been reported to have significantly reduced cerebrospinal fluid SP concentrations[8], plasma levels of this peptide in neuropathies have not been determined.

The purpose of this study was to define the relationship between plasma levels of SP and diabetic neuropathy, and to determine whether altered concentrations of this peptide can be linked to the degree or kind of neuropathy.

Subjects and Methods

Subjects: Twenty stable insulin dependent diabetics were recruited. The mean age of the group was 34.1 years (range, 23 to 63). Of the 20 studied, 13 were female (65 %) and 7 were male (35 %). The mean period after the initial diagnosis of diabetes mellitus was 19 years (range, 6 to 32).

Ten healthy normal volunteers acted as control subjects.

Methods:

Clinical Evaluation: Informed consent was obtained and all subjects answered a standard questionnaire regarding neuropathy and were specifically asked about diabetic diarrhea, hypoglycemic unawareness, impotence, failure of ejaculation, postural hypotension, and numbness or tingling in limbs. They had detailed physical examinations, including a neurologic examination which recorded muscle weakness or wasting, signs of sensory loss, i.e. hypoaesthesia or anesthesia, loss of vibration and proprioception, and diminished or absent deep tendon reflexes.

Analytic Methods: After an overnignt fast with the subject supine for 15 minutes, blood was drawn at 8:00 AM for glycosylated hemoglobin and substance P determinations. Total glycosylated hemoglobin was measured by an electrophoretic method:[9] the range for normal subjects

in this laboratory was 5.5 – 8.5 %. Substance P was measured by radioimmunoassay (Substance P RIA kit, Immuno Nuclear Corporation, Stillwater, Minnesota).

Autonomic Nerve Tests: Four simple cardiovascular autonomic reflex tests were performed on each subject. The heart rate changes during the Valsalva maneuver (Valsalva ratio), deep breathing (max-min heart rate), and on standing from the supine position (30:15 ratio) reflect parasympathetic damage, while the blood pressure response to standing detects sympathetic damage. These tests have been described in detail previously.[10-12]

Peripheral Somatic Nerve Tests: All diabetic subjects had nerve conduction studies performed by the same observer with a TECA-TE 4 electromyograph. Motor nerve conduction velocity (MNCV) was measured in the median nerve (elbow-wrist), posterior tibial nerve (popliteal fossa-medial malleous), and peroneal nerve (knee-ankle). Sensory nerve conduction velocity (SNCV) and sensory potential amplitude (SPA) were recorded orthodromically in the terminal segment of the median nerve and antidromically in the proximal segment of the sural nerve.

Statistical Analysis: Comparisons of the means between two groups were based on Student's t test. Pearson's correlation coefficient was used to evaluate the association between pairs of variables. Multiple regression analysis was used to relate levels of substance P to the other independent variables.[13]

Results

Substance P Plasma Levels: Mean $\pm$ SD of substance P levels were 38.8 $\pm$ 23.5 pg/ml for controls and 37.3 $\pm$ 14.1 pg/ml for diabetic patients. The difference between the two groups was not statistically significant. According to the results of electrophysiologic studies, 7 patients did not have neuropathy, 6 had borderline neuropathy, and 7 had significant neuropathy, with mean $\pm$ SD substance P levels of 38 $\pm$ 15.6, 37.8 $\pm$ 6.5, and 36.1 $\pm$ 18.8 pg/ml, respectively. The differences between the three groups were not significant.

Clinical Features: Symptoms of somatic and autonomic neuropathy are summarized in Table I. Three patients (15 %) described diarrhea that could not be attributed to any cause other than diabetes. These patients with diabetic diarrhea had SP levels that were significantly higher than those of diabetics with normal bowel movements (Table I). Of the 20 diabetic patients questioned, 45 % could not recognize symptoms of hypoglycemia, and 45 % had numbness in their feet or hands.

TABLE I

DISTRIBUTION OF DIABETIC PATIENTS ACCORDING TO SYMPTOMS AND THEIR SUPSTANCE P (MEAN ± SD) LEVELS)

	Diabetic Diarrhea		Hypoglycemic Unawareness		Paresthesia-Hypoesthesia		Impotance-Hypotension	
Symptom	Number of Patients	SP pg/ml (Mean ± SD)	Number of Patients	SP pg/ml (Mean ± SD)	Number of Patients	SP pg/ml (Mean ± SD)	Number of Patients	SP* pg/ml (Mean ± SD)
Negative	17	35.5 ± 14.6	11	35.2 ± 16.5	11	40.8 ± 11.5	6	37.5 ± 9.3
Positive	3	47.7 ± 2.5	9	39.9 ± 11	9	33 ± 16.5	1	0
P Value	–	$p < 0.005$	–	NS†	–	NS		–

* Because there was only 1 patient with impotance and hypotension p value was not calculated.

† NS is not significant

Patients with these symptoms did not have SP levels that were statistically different from those without symptoms. Of the seven male diabetics, only one described impotence and postural hypotension and his SP level was undetectable.

Glycemic Control: Mean $\pm$ SD total glycosylated hemoglobin was 11.4 $\pm$ 2.8 %. The correlation between SP and total glycosylated hemoglobin was not significant.

Autonomic Nerve Function Tests: According to previously presented criteria,[10-12] 35 % of the diabetics had normal cardiovascular reflex tests. The means of the Valsalva ratio and 30:15 ratio were significantly higher in controls than in diabetics, but controls and diabetic patients did not show significant differences in max-min heart rates and blood pressure responses to standing. In order to determine if any relationships existed between each of the 4 cardiovascular reflex tests and the remaining three, their cross relationships were evaluated. Significant correlations were found for blood pressure response to standing with max-min heart rate ($p < 0.001$) and Valsalva ratio ($p < 0.05$); max-min heart rate with 30:15 ($p < 0.01$), and Valsalva ratio ($p < 0.005$); and 30:15 ratio with Valsalva ratio ($p < 0.01$). This demonstrates a clear relationship among the various cardiovascular reflex tests.

There was a significant negative correlation between SP and the 30:15 ratio ($r = -0.31$, $p < 0.05$). No correlations were found between the other cardiovascular reflex tests and SP. It is of interest to note that all four cardiovascular reflex tests were abnormal in only one diabetic patient, and this patient had an undetectable substance P level.

Peripheral Somatic Nerve Tests: There was a clear interrelationship between the various tests of peripheral somatic nerve function, in keeping with the known uniform involvement of the peripheral nerves in diabetic polyneuropathy (data not shown). There was a significant positive correlation between SP levels and posterior tibial MNCV ($p < 0.05$), peroneal MNCV ($p < 0.05$), and median SPA ($p < 0.05$). The other peripheral somatic nerve tests did not correlate with SP levels (Table II). It is again important to note that the patient who had a very severe neuropathy according to nerve conduction studies had an undetectable SP level.

Multiple regression analysis revealed that the variables of insulin dose, abnormal sural SNCV, median SPA, vibration sense and abnormal bowel movements can be used to explain 87 % of the variability in substance P.

TABLO II
CORRELATION OF INDIVIDUAL PERIPHERAL SOMATIC NERVE TESTS WITH SP AND TOTAL GLYCOSYLATED HEMOGLOBIN

	SP		Total Glycosylated Hemoglobin	
Peripheral Nerve Test	Correlation Coefficient	Significance	Correlation Coefficient	Significance
Median MNCV	0.01	NS	– 0.44	$p < 0.05$
Posterior Tibial MNCV	0.42	$p < 0.05$	– 0.3	NS
Peroneal MNCV	0.47	$p < 0.05$	– 0.22	NS
Median SNCV	– 0.24	NS	– 0.23	NS
Sural SNCV	0.20	NS	– 0.17	NS
Median SPA	0.38	$p < 0.05$	– 0.13	NS
Sural SPA	0.09	NS	– 0.11	NS

NS is not significant

Discussion

Substance P has been observed in the brain, spinal cord, spinal and trigeminal ganglia, nerve fibers surrounding sweat glands, and unmyelinated fibers that constitute free nerve endings in the skin. It is preferentially present in primary sensory neurons.[5] Recently, SP was found to be reduced in the spinal cord of the mf rat that has a hereditary sensory neuropathy.[7] It was also reported to be significantly reduced in the cerebrospinal fluid of 9 patients with both demyelinating and axonal types of peripheral neuropathy, but there was an overlap of SP levels between controls and patients with neuropathy.[8] In our study, although there is no significant difference between plasma SP levels of controls and diabetic patients or between SP levels of patients with various degrees of diabetic neuropathy, we have shown that there is a significant positive correlation between plasma SP levels and three of the six peripheral somatic nerve tests. Since MNCV measurements reflect predominantly Schwann cell damage,[14] and can also be related to axonal dysfunction[15] and sensory potential amplitude is proportional to the number of intact large myelinated conducting fibers,[16] our findings indicate that plasma SP levels change in demyelinating and axonal neuropathy of diabetes mellitus. It is important to note that several studies have reported a correlation between increasing glycosylated hemoglobin concentrations and slowing in nerve conduction velocities.[17,18] In this study, the number of peripheral somatic nerve tests that significantly correlated with plasma SP levels was more than those that correlated with total glycosylated hemoglobin levels. This finding may suggest that plasma SP is a better predictor of diabetic neuropathy than blood glucose control.

Some SP-positive nerve fibers traverse autonomic ganglia,[19] and by virtue of this localization, may have a role in autonomic reflexes. Indeed, cerebrospinal fluid SP-like immunoreactivity is found to be reduced in patients with orthostatic hypotension due to Shy-Drager syndrome.[8] In our study we were not able to show a significant correlation between plasma SP levels and orthostatic blood pressure changes. This may be due to the small number of diabetic patients in our group with orthostatic hypotension or to the different nature of the two diseases.

There was a significant negative correlation between plasma SP levels and the immediate heart rate response to standing (30:15 ratio). Since this test reflects vagal damage when the value is less than 1.03, our findings imply that plasma SP levels tend to increase when the 30:15 ratio indicates vagal neuropathy. It is very difficult to speculate on the cause of this SP increase in relation to the decrease in the 30:15 ratio.

Substance P is widely distributed in the intestine in large quantities. It stimulates the tone and rhythm of the isolated intestine.[3] Holzer found additional evidence that SP enhances the phasic longitudinal contractions of the isolated rabbit ileum by a direct action on the smooth muscle cells.[20] Plasma SP levels are elevated in patients with the carcinoid syndrome. On the other hand, SP levels are extremely low in the aganglionic segments of Hirschprung's disease.[6] To our knowledge, ours is the first study that documents elevated levels of plasma SP in patients with diabetic diarrhea. Although the sample size was small, this significant elevation may point to the role that SP plays as a mediator of increased intestinal motility in diabetic diarrhea.

In summary, we have studied plasma SP levels in diabetic neuropathy, and found that although there was no significant difference between diabetics and healthy controls, decreases in plasma SP levels significantly correlated with the slowing of nerve conduction in some nerves. There was no relationship between orthostatic hypotension and plasma SP levels, contrary to what has been reported for substance P cerebrospinal fluid levels. Yet one of the patients with severe orthostatic hypotension had an undetectable plasma SP level. On the other hand, plasma SP was significantly increased in a small group of patients with diabetic diarrhea.

Acknowledgements

The authors are grateful to Marija Norusis,Ph.D. for statistical analysis, and Ms. K.L. Williams for excellent secretarial help.

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Hacettepe Medical Journal
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Vaginal Cancer After Hysterectomy for Benign Disease and Cervical in Situ Carcinoma (CIN III)

Ali Ayhan, M.D.* / Kunter Yüce, M.D. / Sakıp Pekin, M.D.*** / Ayşe Ayhan, M.D.**** / Emek Özen, M.D.***** / Bilal Memiş, M.D.******

Summary

Of the 11 patients who were treated for primary malignant tumor of the vagina, five had undergone total hysterectomy for benign disease (3 cases) and for CIN III (2 cases). Vaginal bleeding was the most common presenting symptom although there was one patient who was entirely asymptomatic. Of these patients, one had stage 0 (VaIN III), three had stage I disease and one had stage II disease. Pap smears were positive in 4 of the 5 patients tested, with a sensitivity rate of 80 %. The findings of this study indicate that patients who have a hysterectomy for benign disease and for CIN III should continue to have Pap smears taken from the vaginal apex and walls with regular intervals.

Key Words: Vaginal cancer, Vaginal in situ carcinoma, Cervical in situ carcinoma, Vaginal intraepithelial neoplasia (VaIN I, II and III).

Introduction

Primary carcinoma of the vagina is rare and constitutes only 1-2 % of all gynecological malignancies.[1] Vaginal intraepithelial neoplasia

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology and Pathology, Faculty of Medicine, Hacettepe University, Ankara-Turkey.
* Associate Professor of Obstetrics and Gynecology
** Assistant Professor of Obstetrics and Gynecology.
*** Professor of Obstetrics and Gynecology.
**** Assistant Professor of Pathology.
***** Professor of Pathology.
****** Senior Resident, Department of Obstetrics and Gynecology.

(VaIN I, II, III) have been reported more frequently in recent studies.[2] It is demonstrated that vaginal cancer can occur after hysterectomy for benign disease and cervical intraepithelial neoplasia (CIN I, II, III), including in situ carcinoma.[3,4,5] It is thought that biological behavior of vaginal carcinoma is similar to that of cervical carcinoma. Rutledge,[6] using serial biopsies of vagina noted that in several patients with lesser degrees of cellular atypia the condition progressed to carcinoma *in situ* and then to invasive carcinoma. Once carcinoma of the vagina becomes invasive, the 5-year survival rate is generally poor.

Cytologic smears (as a screening test), iodine staining of the vagina, and colposcopic examination are important diagnostic tools for the detection and localization of vaginal neoplasms after hysterectomy for benign disease and CIN III.[2,3,5,7]

One aim of this study was to evaluate the patients with primary vaginal malignancies which developed after hysterectomy for benign disease and CIN III. The other aim of this study was to stress the importance of vaginal cytology, iodine staining and colposcopic examination in hysterectomised patients.

Material and Method

During January 1964-January 1968 eleven patients with primary malignant vaginal tumor were seen and treated at the Division of Gynecologic Oncology. The clinical records, follow-up sheets and pathology slides on all patients were reviewed. This study includes only five patients with primary vaginal cancer that developed after hysterectomy for benign disease (3 cases) and for cervical carcinoma *in situ* (2 cases). Prior to 1981, the diagnosis of vaginal carcinoma was made by punch biopsy or surgical excision of Schiller positive vaginal mucosa in patients with abnormal Pap smear or a clinically suspicious lesion. Since 1982, cases have ben diagnosed with colposcopically directed biopsy in our institution. The diagnosis in one patient was established by colposcopically directed biopsy, and by punch-excisional biopsy in four patients. After tissue diagnosis, one patient with VaIN III was subjected to the total vaginectomy and vaginoplasty. Three patients with stage I disease had undergone pelvic-paraaortic lymph node dissection plus total vaginectomy and vaginoplasty. One of these three patients had received additional external radiation for pelvic lymphatic metastasis. The remaining one patient who had stage II disease was subjected to internal and external radiation. The follow-up duration varied from six months to 12 years, the median being 8 years.

Results

The median age at the time of diagnosis of vaginal carcinoma was 43 years, patient age ranged from 34 to 52 years. Vaginal bleeding was the most common symptom. Of the five patients, 3 had vaginal bleeding, one had vaginal bleeding and mass, and one did not have any symptoms. Eighty percent (4 cases) of our patients had an abnormal Pap smear. Of these patients, 4 had invasive squamous cell carcinoma and one had VaIN III. Correlation between initial lesion and vaginal cancer which developed after hysterectomy is given in Table I.

TABLE I

CORRELATION BETWEEN INITIAL LESION AND VAGİNAL CANCER

Present vaginal neoplasia	Initial genital tract lesions		Interval between initial procedure and present lesion	Total
	CIN III	Myoma		
VaIN III	–	1	10 year later	1
Invasive vag. carc.	2	2	5 and 7 years (CIN III) 10 and 12 years (myoma)	4
Total	2	3		5

Of these 5 patients, 3 had stage I disease, one had stage II disease and the remaining one had stage 0 (VaIN III) according to FIGO.

There was no recurrence and mortality during the follow-up. After the surgical procedure, vaginal obstruction in one patient with VaIN III appeared and leg edema in one patient, who had invasive vaginal cancer and who received post-operative external radiation for pelvic lymph node metastasis, occurred.

Discussion

Carcinoma of the vagina, especially *in situ*, has been reported more frequently in the recent literature.[1] Studies have shown that patients with both premalignant and malignant cervical disease have an increased risk of developing vaginal neoplasia.[3,4] In this study two (40 %) of the patients with vaginal cancer had previously undergone hysterectomy for CIN III. Recently, some other studies indicate that vaginal cancer can also occur in patients who had previously undergone hysterectomy for benign disease.[5] It has been reported that 29.8-48 % of all patients with vaginal cancer had prior hysterectomy for benign disease.[5, 8, 9] This figure, in this study, was 27.3 % of all patients with malignant vaginal tumor and 42.8 % of all patients with vaginal squamous cell carcinoma. The present study and others in the literature demonstrate that vaginal cancer can develop during a prolonged follow-up after hysterectomy for benign uterine disease and CIN III.[2-5, 8, 9]

The Pap test is the best method to screen patients who previously had hysterectomy for benign disease and CIN III. Some studies confirm the sensitivity of the Pap test in vaginal carcinoma, giving sensitivity rates of approximately 80 %.[10, 11] Abnormal Pap tests were found in 80 % of the patients in the present series. The major benefit of the Pap tests is its ability to detect neoplasia in early stages, which then, are more successfully treated. In some recent studies, including this one, colposcopy was found to be a valuable tool in identifying abnormal vaginal lesions and the location as a reperesentative site for biopsy in patients with abnormal Pap tests. Therefore, the role of colposcopy in the evaluation of abnormal vaginal smear is very important.[12] Colposcopically directed biopsy must be done on suspected areas by using either Kevorkian or Ependerfer punch biopsy. Iodine staining of the vagina in patients with abnormal vaginal smears is another diagnostic tool for identifying and locating a representative point for biopsy.

It is generally recommended that patients have Pap test of the vagina every three years, if they underwent hysterectomy for benign disease, and annually if treated for cervical intraepithelial neoplasia (CIN III).

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Hacettepe Medical Journal
Volume 19 / No. 3 / July 1986 / pp. 105 – 115

Diagnosis of Tricuspid Regurgitation by Pulsed-Doppler and Two-Dimensional Echocardiography

Seydi V. Aksüt, M.D.* / Sırrı Kes, M.D. / Aysel Oram, M.D.** / Şevket Uğurlu, M.D.*** / Erdem Oram, M.D.*****

Summary

In 34 subjects we analyzed non-invasively tricuspid regurgitation by means of ultrasonic pulsed Doppler and two-dimensional and M-mode echocardiography. Group I consisted of 17 patients with clinical tricuspid regurgitation. Group 2 consisted of 7 patients without definite clinical signs of TR but with conditions known to be frequently associated with TR (e.g. mitral valve disease, pulmonary hypertention). Group 3 consisted of 10 normal subjects. Our study covered 32 of the 34 patients. Two cases were excluded in our study due to poor ultrasound. 17 of them underwent surgery. In 17 of the 22 patients which in the group that were suffering from heart diseases, pansystolic abnormal Doppler signals were detected in the right atrial cavity and were interpreted as tricuspid insufficiency. Two-dimensional echocardiograms in parasternal four-chamber view demonstrated that the region in which the abnormal Doppler signals were detected was spindle-shaped and extended from the tricuspid orifice towards the right atrial posterior wall parallel to the interatrial septum.

Department of Cardiology Faculty of Medicine, Hacettepe University, Ankara, Turkey.

* Fellow of Cardiology
** Associate Professor of Cardiology.
*** Professor of Cardiology.

The severity of regurgitation was graded on a four-point scale, based on the distance covered by the abnormal signals from the tricuspid orifice towards the posterior wall of right atrium. Our results correlated with surgical data. The results obtained by the two methods agreed with each other in 16 cases but differed in one case. We concluded that noninvasive grading of TR by ultrasonic pulsed-Doppler and two-dimensional and M-mode echocardiography was a safe and sensitive method. We also measured inferior vena cava dimensions. Patients with TR had larger IVC dimensions than those without TR.

Key Words: Tricuspid Regurgitation (TR), Pulsed-Doppler Echocardiography, Two-Dimensional Echocardiography, Inferior Vena Cava (IVC).

Introduction

Although tricuspid valve regurgitation can sometimes be due to an organic disease of the tricusipd valve, it is generally a functional disorder and it is found in association with the rheumatic disease of other valves.[1-4] or in association with congenital heart diseases.[5]

Although tricuspid regurgitation is functional, it can affect the hemodynamic state of the patient adversely.[6, 7] Thus methods for assessing the severity of TR are needed. Angiocardiography has been useful in assessing insufficiency of other valves, but the procedure itself has been reported to cause TR in dogs.[8] Also it is an invasive technique and carries some risks. Attempts have been made to assess the degree of regurgitation by contrast echocardiography,[9-11] but this method necessitates the injection of contrast material and does not give information about the degree of regurgitation.

Pulsed-Doppler echocardiography is a new non-invasive technique that allows qualitative assessment of blood flow patterns within intracardiac chambers and thus may be useful in detecting the presence of valve insufficiency or stenosis as well as a variety of congenital heart defects.[12-16]

Materials and Methods

Thirty-four patients underwent M-Mode, two-dimensional and pulsed-Doppler echocardiography. Each patient was examined by a cardiologist, with particular attention to the jugular venous pulse, the presence or absence of a murmur consistent with TR, hepatic pulsations and peripheral edema. Patients were divided into three groups with respect to the clinical assessment of the presence or likelihood of TR.

Group I included 17 patients with definite clincal diagnosis of TR, based on a prominent jugular systolic pulsation, a murmur that increased

with inspiration (Carvalho's sign) and pulsating liver on palpation. The Doppler study was inadequate in two patients because the penetration of the sound through the chest wall was poor. These two cases were, therefore, excluded. The remaining 15 patients aged 22-52 (average 38.66 ± 8.59), were the subjects of the study. 14 patients were in atrial fibrillation and one patient was in sinus rhythm. Eleven of these 15 patients underwent cardiac surgery. Tricuspid regurgitation was present in all eleven. Three of these 15 patients had right ventricular angiograms. Group II included 7 patients who did not have clinical TR but had cardiac disorders frequently associated with TR such as rheumatic mitral stenosis, pulmonary hypertension and mitral valve replacement. Patients were of 18-48 years of age (average 33.14 ± 10.57) 4 patients were in sinus rhythm and 3 patients were in atrial fibrillation. Five of these 7 patients had right ventricular angiograms and 6 underwent cardiac surgery. 5 out of 6 had no TR but one had. Doppler echocardiography was also negative in the same cases which underwent surgery and one out of 6 was positive at 2 cm who had minimal TR in surgery. Group III. included 10 patients who were normal by history, physical examination, exercise test and M-mode and Two-dimensional echocardiography. The patients were of 24-47 years of age (average 32.5 ± 5.5 years).

Operative Diagnosis of Tricuspid Regurgitation: Intra operative diagnosis of TR was confirmed if a trill was present upon right atrial palpitation and right ventricular systolic Jet before cannulation for cardiopulmonary bypass. Although, this is the most accurate method of assessing of the tricuspid competence according to Breyer et al,[33] we couldn't find any detailed literature about the sensitivity and the specificity of this method.

Echocardiographic Methods: Patients were studied in the supine position with slightly flexed knees and hips to allow better relaxation of the abdominal musculature when the subcostal transducer position was used. The inferior vena cava was visualized in the sagittal plane by Two-dimensional and M-mode echocardiography. Two-dimensional and M-mode echocardiograms were recorded by means of an ultra Imager Honeywell Ultra 80 and mechanical transducer with 3 MHz. The ECG was displayed and recorded alongside the sector arc.

Pulsed Doppler echocardiograms were performed utilizing a commercially available Echo Doppler Unit (Ultra Imager Honeywell Ultra 80 with a 90°-angle mechanical sector scanner). This equipment provides Doppler analysis of the Ultrasound frequencies reflected at a variable distance from the transducer, which can be selected in any of

the lines of the 90° sector in a sample volume of approximately 2x2x4 mm. The result of the Doppler analysis is expressed by means of a time interval histogram analogic net and signal intensity, all of which are recorded with the M-mode echocardiogram obtained by the ultrasound beam on hard-copy paper at a speed of 50 mm/sec and on a videotape recorder together with the stereo acoustical signal. The time-interval histogram is displayed as a series of dots, the distance from each dot to the zero line represents a Doppler frequency shift proportional to the velocity of blood flow and to the cosine of the angle formed between the direction of flow and the ultrasonic beam.[26] Using the parasternal and apical approaches we first located the image of the tricuspid valve. For this aim the 3.0 megahertz transducer was placed along the left sternal border in a manner similar to that used for standard M-mode echocardiography and directed medially to record the tricuspid valve. The sample volume was then placed in the right atrium slightly posterior to the systolic motion of the tricuspid valve echo and anterior to the artial septum. After the instrument gain was set to an optimal signal to noise ratio, systolic turbulence was sougnt by moving the sample volume within the right atrium while carefully listening to turbulent sounds from the speakers. The diagnosis of TR repended on the objective interpretation of the time interval histogram for the presence of systolic turbulence in the right atrium.

Results

IVC Size: The inferior vena cava (IVC) was adequately visualized by both M-mode and two-dimensional echocardiography in all patients. The patients with TR had larger IVC dimensions than those without TR (Table I). This was statistically significant for measurements made at the maximal dimension during the "V" wave (Figure 1). The average dimension of IVC in patients with TR was 25.75 $\pm$ 5.39 mm but 16.93 $\pm$ 5.26 in patients who did not have clinical TR but had cardiac disorders frequently associated with TR such as pulmonary hypertension and mitral valve stenosis, and 17.73 $\pm$ 1.85 mm in normal subjects. There were statistically significant differences in IVC dimensions between group I and group II. There were no differences between groups II and III. Thus IVC dimensions can be used as a predictive test for TR in indiviudual patients.

Pulsed Doppler Velocity Studies :

Normal subjects: This group consisted of 10 normal subjects and abnormal pansystolic Doppler signs within the right atrium were recorded in none of them.

TABLE I

INFERIOR VENA CAVA DIMENSIONS

	$\bar{x}$ (mm)	SD	n	P
Group I (TR)	25.75	5.39	15	< 0.05
Group II	16.93	5.26	7	
Group I	25.75	5.39	15	< 0.05
Group III (Normal)	17.38	1.85	10	
Group II	16.93	5.26	7	> 0.05
Group III	17.38	1.85	10	

$\bar{x}$: Mean inferior vena cava dimension at maximal "V" wave

SD : Standard deviation

n : Number of subjects with of sufficient quality to perform measurement

TR : Tricuspid regurgitation

P : P value of Mann-Whitney U test between the groups listed

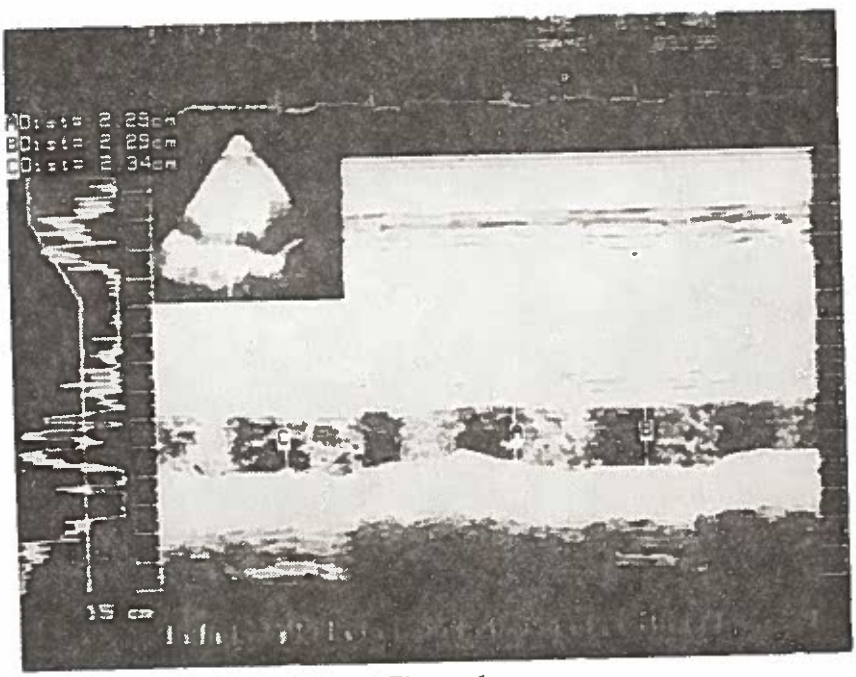

Figure 1

IVC dimensions were calculated the maximal diameter during the "V" wave.

Patients suffering from heart diseases.

In 22 of the 24 cases which were suffering from heart diseases, Doppler echocardiography was performed adequately. Two cases were excluded in our study due to poor ultrasound. In 17 of the 22 patients abnormal pansystolic Doppler signs were recorded within the right atrium adjacent to the tricuspid valve in the course of systole. The abnormal Doppler signs continued until the reopening of the tricuspid valve and mainly consisted of ultrasound waves waay from tricuspid valve. The fact that these signs appeared in wide-band velocity spectrum indicated turbulent blood flow. The signs were of spindle-shape and extended from the tricuspid valve towards the right atrium and parallel to interatrial septum (Figure 2). These signs were interpreted as tricuspid insufficiency due to the following conditions:

1- Tricuspid regurgitation was found in all cases with abnormal pansystolic Doppler signs.

2- The time of appearence was pansystolic.

3- The blood flow was away from the tricuspid valve.

4- The region where the signs appeared extended from the right atrium to the tricuspid valve. In cases with surgically proved minimal TR abnormal Doppler signs lasted for a shorter period of time.

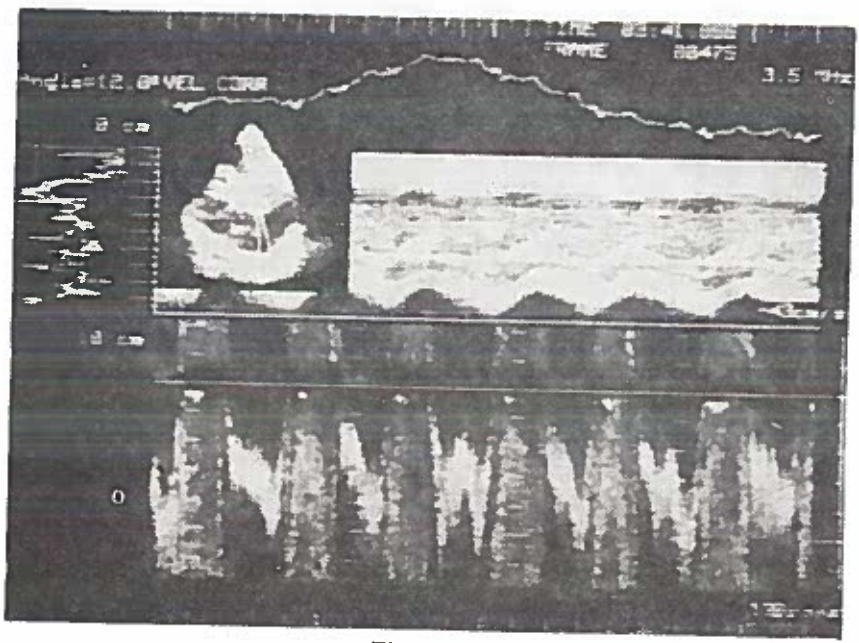

Figure 2
Pulsed-Doppler echocardiographic recording of tricuspid regurgitation (TR).

The severity of TR was assessed according to the distance covered by the regurgitation flow sign. The maximal distance covered by the regurgitation flow from the tricuspid valve was measured in parasternal 4- Chamber and apical 4- Chamber positions. The severity of TR was classified by means of a 4- point scale and on the basis of this distance (Figure 3).

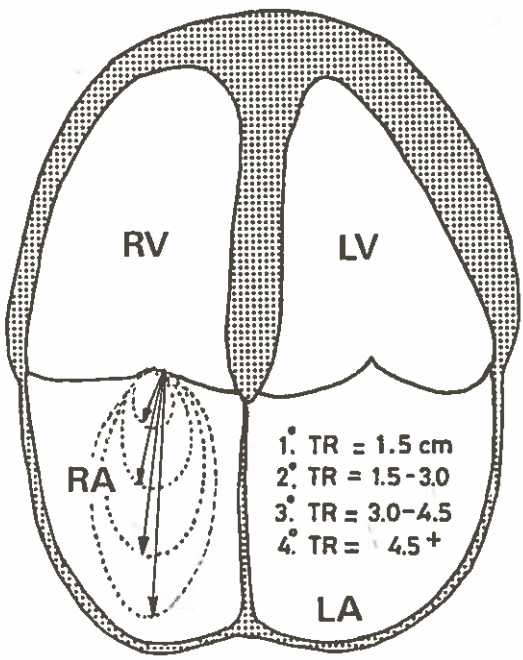

Figure 3
Grading the severity of tricuspid regurgitation on a four-point scale by the Doppler technique. Grading based on the maximal distance from the tricuspid orifice reached by the regurgitant flow.

1 + = less than 1.5 cm, 2 + = 1.5-3 cm.
3 + = 3-4.5 cm. 4 + = more than 4.5 cm.

According to this classification abnormal pansystolic Doppler signs were positive in 4 cases of group I (with clinical definite TR) at 4 cm, in 3 cases at 3 cm. in 1 case at 2 cm and in 6 cases at over 4.5 cm. Eleven cases in this group underwent surgery. One out of 11 patients had minimal TR whereas in 10 of them severe TR was found. Tricuspid annuloplasty was performed in 6 cases and tricuspid valve replacement in 4.

In 5 out 7 cases of Group II (without clinical TR), pulsed-Doppler echocardiography was negative. In 2 out of 7, however it was positive at

1 cm and 2 cm respectively. 6 cases underwent surgery. In one of these which Doppler echocardiography was positive at 2 cm, minimal TR was surgically proved and in the rest (5 cases) on TR was observed. None of the cases in Group III (normal subjects) had abnormal Doppler signs.

Discussion

When tricuspid regurgitation is definite, clinical diagnosis is easy enough. The presence of obvious jugular venous wave, positive Carvalho's sign, and pulsatile liver makes further examination unnecessary. However in adults TR frequently coexists with other valve lesions (mitral valve diseases and pulmonary hypertension and most cases of TR have atrial fibrillation.[7, 17] In the presence of atrial fibrillation jugular venous pulse is less helpfull for diagnosis. Furthermore, in many patients with TR, systolic murmur originating from the mitral or aortic valve can occur. It is therefore useful to have a definite method for the diagnosis of TR. Right ventricular angiography is not an ideal test because it is an invasive method and the catheter may itself produce TR by upsetting the mechanical structure of the tricuspid valve. Thus although dye dilution,[18] intracardiac phonocardiography,[19] and angiography,[30] provide useful information, they have not solved all of the problems of diagnosis.[18] Unfortunately, there is yet no gold-standart for the diagnosis of TR.[31] Various attempts have been made with contrast echocardiography[9-11] but these only provided nonspecific diagnostic information lacking in sensitivity and have given no information relating to the severity of TR.[9, 22]Moreover, this method necessitates the use of contrast injections.

Much work has been devoted to the value of Doppler ultrasound in the diagnosis of TR.[23-26] Continue-wave Doppler was originally used for the diagnosis of TR. However except in cases of severe TR this method has a low level of sensivity.[23, 24]

It is possible to diagnose TR by means of pulsed Doppler ultrasound at a certain sample volume and by studying the blood flow. Diagnosis is ascertained by the measurement of systolic turbulance of the blood within the right atrium.[26] The primary advantage of this method is that it provides information directly from the lesioned area ccmbined either by one,[25-29] or two-dimensional echocardiography.

In most of these studies the place of the Doppler sample volume has been determined by means of M-mode or two-dimensional echocardiography. It is rather difficult to determine abnormal Doppler signs within the right atrium by M-mode echocardiography. Moreover, all information obtained by means of pulsed-Doppler echocardiography was compared with right ventricular angiography. As is known, right ventricular

angiography is not an ideal test, because the catheter itself may produce tricuspid regurgitation.[8, 21] Therefore, in our study we used both M-mode and two-dimensional echocardiography to determine the place of the sample volume. Tricuspid regurgitation was thus analyzed utilizing pulsed-Doppler technique combined with M-mode and two-Dimensional echocardiography. This method enabled us to determine the place and distribution of the Doppler sign within the right atrium with more certainty and to confirm that the abnormal Doppler sign was related to the tricuspid orifice. We correlated our results with intraoperative findings. Intraoperative right atrial palpation may sometimes be inadequate and due to the disturbance caused by palpitation a trill may appear and may give false positive results.[10] However, despite its disadvantage this is the most reliable method.[33]

Group I and II consisted of 22 cases, 15 of whom had clinical TR. 7 cases had no clinical TR but suffered from other cardiac lesions (mitral valve diseases or pulmonary hypertension). We observed in our study that this technique (pulsed Doppler echocardiography) is specific, because we found positive abnormal Doppler signs in all group I (cilinical TR) cases but normal signs in all members of group III (normal subjects). It is rather difficult to determine the sensitivity of this technique but no standard exits for comparison. However the fact that abnormal ponsystolic Doppler sings were found in two out of the 7 cases without clinical TR and also that minimal TR was surgically diagnosed in one of them (at the intraoperative stage) indicates that the technique is quite sensitive. We also found that our results agreed with those of other literature.[26, 30, 31]

The fact that TR was found in 11 patients in group I during their surgical examination shows that our results, which were independently obtained, are supported by surgical findings.

Another important point in our study is the measurement of inferior vena cava (IVC) dimensions (Table I). IVC dimensions in cases with clinical TR were larger than those without. This had statistical significance. The measurement were taken at maximal IVC level synchronized by ECG. No difference was found between cases without clinical TR and normal subjects. Thus those measurements can be helpful as a predictive test of the diagnosis of TR. Meltzer's findings in 1981 support our views but in his studies there was some overlapping between the groups.[10] We had instances of overlapping in 3 cases only.

Although pulsed-Doppler echocardiography has a high level of sensitivity it also suffers from some limitations. For instance Doppler signs cannot be obtained in patients with wide-chest walls. Other factors

that prevent definite quantification of TR are the selection of the sample volume in annulus, uncertainty of the angle between the ultrasound and blood flow and change in tricuspid annulus size with the cardiac cycle.[32] Despite its limitations, we observed in our study that it is a useful non-invasive method in the assessment of TR.

In conclusion, pulsed Doppler echocardiography is a simple and safe non-invasive method. It can be easily and efficiently applied on both in-and out-patients.

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Hacettepe Medical Journal
Volume 19 / No. 3 / July 1986 / pp. 117 - 122

Primary Malignant Tumors of the Vagina

Histologic type, therapy, prognosis and complications

Ali Ayhan, M.D.* / Kunter Yüce, M.D. / Sakıp Pekin, M.D.*** / Timur Gürgan, M.D.** / Ayşe Ayhan, M.D.**** / Emek Özen, M.D.*****

Summary

Eleven patients with primary malignant tumor of the vagina, treated at the Division of Gynecologic Oncology were presented. Of these patients, 6 had squamous cell carcinoma, one had VaIN III, one had melanoma and three had sarcoma. Five patients with squamous cell carcinoma had undergone hysterectomy for benign disease (3) and for CIN III (2) prior to the diagnosis of vaginal cancer.

One patient with stage IV squamous cell carcinoma, one patient with melanoma and one patient with leiomyosarcoma expired during the follow-up.

Postoperative complications such as vaginal obstruction and leg edema developed in two patients. The prognosis, stages, treatment of choice and survival are discussed.

Key Words: Primary vaginal cancer, Vaginal in situ carcinoma, Sarcoma botryoides, Leiomyosarcoma, Vaginal bleedings.

Introduction

Primary malignant tumors of the vagina are rare and vary from 0.5 % to 2 % of all gynecological malignancies.[1] The majority of cases

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology and Pathology, Faculty of Medicine, Hacettepe University, Ankara, Turkey.
* Associate Professor of Obstetrics and Gynecology.
** Assistant Professor of Obstetrics and Gynecology.
*** Professor of Obstetrics and Gynecology.
**** Assistant Professor of Pathology.
***** Professor of Pathology.

are squamous cell carcinoma, clear cell carcinoma, adenocarcinoma sarcoma and melanoma. Endodermal sinus tumors are rarely seen in this region of the genital tract.[2, 3] Reported survivals vary widely with treatment, consisting of combinations of internal and external radiotherapy, surgery and chemotherapy.[4, 5]

The purpose of this study was to evaluate patients with primary vaginal tumor treated in our institution and to review the current literature.

Materials and Methods

Eleven patients with primary malignant tumor of the vagina treated at the Division of Gynecologic Oncology from January 1964 to January 1986 were reviewed. Data were obtained from patients' charts, tumor registery records and pathology reports. In this study, primary vaginal malignant tumor was defined as a primary tumor arising in the vaginal wall, without involvement of the cervix, vulva or urethra, and without evidence that the tumor was metastatic from another site.[6] The patients' average age was 41.6 years (ranging from 6 to 68). Of these patients, 6 had vaginal bleeding, 3 had vaginal bleeding and mass, one had vaginal discharge and urinary disturbance, and one was symptom-free. Three of these eleven patients had undergone hysterectomy for benign disease, 10,11 and 12 years respectively, (before the diagnosis of vaginal cancer) and two for CIN III, 5 and 7 years respectively, before the diagnosis of vaginal cancer. Pap smears were positive in 7 of the 9 patients tested, and two patients did not have cytologic examination. The diagnosis of primary vaginal malignancies was made by punch biopsy of Schiller-positive vaginal mucosa in 6 patients with abnormal Pap smears, by surgical excision in 4 patients with clinically suspicious lesions, and by colposcopically-directed biopsy in one patient with abnormal smear. All patients' specimens were studied and reviewed by one of the team's pathologists. After tissue diagnosis was made, seven patients with squamous cell carcinoma were subjected to clinical staging procedure described by FIGO. Three of the remaining patients had sarcoma and one had melanoma. Of the 7 patients with squamous cell carcinoma, 4 had stage I disease, one had VaIN III, one had stage II, and one had stage IV disease (Table I).

Four patients in this group recieved only radiation therapy (two patients with stage I, one with stage II and one stage IV). The remaining three patients who had had hysterectomy for benign disease (2) and CIN III (1) were treated by surgical procedures such as pelvic-paraaortic lymphadenectomy, total vaginectomy and vaginoplasty in two patients

and total vaginectomy-vaginoplasty in one patient with VaIN III pathology. Additional external radiation was given to one patient subjected to lymphadenectomy for pelvic lymph node metastasis.

Bulky resection was performed in three patients with sarcoma and in one patients with melanoma who had additional posterior exenteration. Chemotherapeutic treatment was as follows: VAC (Vincristine, Actinomycin, Chlorambucil) in one patient with leiomyosarcoma and in one patient with sarcoma botryoides, VAD (Vincristine, Adrioblastine, DTIC) in one patient with rhabdomyosarcoma and external-internal radiation in one patient with melanoma. Follow-up was conducted on 9 of the 11 patients. One of the two patients without follow-up had stage II b squamous cell carcinoma and the other had rhabdomyosarcoma.

Results

Of the 11 patients, 6 had squamous cell carcinoma, one had VaIN III the other had melanoma and three sarcoma. The sarcomas were rhabdomyosarcoma (1), leiomyosarcoma (1) and sarcoma botryoides (1). Incidence of tumors in the upper third, lower third and mid third regions of the vagina were 56 % (6), 36 % (4) and 8 % (1), respectively.

One patient with stage IV squamous cell carcinoma died on the seventh day of radiation therapy, the remaining 5 cases of squamous cell carcinoma had no problems during follow-up. Correlations between stages, therapy and prognosis in patients with squamous cell carcinoma are given in Table I. Patients with other primary malignant tumors of the vagina died during the follow-up. Relationships between histologic types, therapy and prognosis in patients with other vaginal malignancies are shown in Table II.

TABLE I
STAGE, THERAPY AND PROGNOSIS

Patients	Stage	Therapy	Prognosis
1	I	S	Normal findings in the third year
2	I	S + R	Normal findings (except leg edema) in the 7th year
3	0	S	Normal findings (except vaginal obliteration) in the fourth year
4	I	R (int + ex)	Normal findings in the fifth year
5	I	R (int + ex)	Normal findings in the fifth year
6	II b	R	No follow-up
7	IV	R	Exitus on the seventh day of therapy

S: Surgery R: Radiation S+R: Surgery + radiation

TABLE II
HISTOLOGIC TYPE, THERAPY AND PROGNOSIS

Patients	Histologic type	Therapy	Prognosis
1	Rhabdomyosarcoma	VAD	No follow-up
2	Leiomyosarcoma	S + VAC	Exitus in the third year
3	Sarcoma botryoides	S + VAC	Normal findings in the third year
4	Melanoma	S + R	Exitus in the first year

As shown in Table I, vaginal obstruction in one patient and bilateral leg edema in another developed after therapy.

Discussion

Squamous cell carcinoma is the most frequent histologic type; the incidence ranges from 93 to 97 % in some series.[7-9] The incidence of squamous cell carcinoma in our study is found to be 64 % (Table I-II). Several authors have suggested that the upper vagina is the most common site of vaginal cancer.[10, 11] The results of this study have demonstrated that the tumors in five patients (56 %) was in the upper third of the vagina.

TABLE III
MODALITIES OF TREATMENT OF THE MALIGNANT TUMOR OF THE VAGINA AND THEIR APPLICATIONS

Modality	Application
Radiotherapy	Preferred for all stages (except for inaccessible secondary spread)
Surgery	
Wertheim's hysterectomy, lymphadenectomy, vaginectomy	Tumor at upper vagina
Radical vulvectomy, lymphadenectomy, vaginectomy	Tumor at lower vagina
Exenteration	Tumor invading the bladder or rectum (tumor has not reached the pelvic wall or has not spread beyond the pelvis)
As indicated above	For irradiation failures (local recurrence)
Combined radiotherapy and surgery	In selected cases not suitable for other treatment
Chemotherapy	Minor role - mainly in advanced stage

Treatment was instituted in each case according to the stage, histologic type, size and location of the tumor, the patient's age and overall medical status and vaginal function.[1] Radiation therapy is a preferred treatment in this type of cancer because of the excellent results obtained by modern radiotherapy.[4, 12, 13] This therapy consists of either external beam radiotherapy or interstitial-intracavitary treatments.[14]

Selected patients were treated by a variety of surgical procedures including radical vulvectomy, vaginectomy, ingiunal lyphadenectomy (tumor at the lower part of the vagina), radical hysterectomy and lymph node dissection (pelvic and paraaortic) (tumor at the upper part of the vagina) and pelvic exenteration (tumor invading the bladder or rectum).[1, 6] The types of therapy are listed in Table III.

In this study, of the 7 patients with squamous cell carcinoma, 2 had primary surgery, one had surgery and radiation, and 4 had primary radiation. The patients with sarcoma were subjected to debulking procedure and chemotherapy.

It has been reported that the 5 year relapse-free survival for primary carcinoma was 88 % for stage I,44 % for stage II, 35 % for stage III and 0 % for stage IV.[15]

In the treatment of patients with rhabdomyosarcoma, little emphasis is currently being placed on radical pelvic surgery, i.e., pelvic exenteration, as the basic treatment for early carcinoma[1, 6]. More effective results are obtained when complete surgical resection is performed and radiation therapy is utilized first to control the disease in situ then chemotherapy for distant metastases.[16, 17, 18]Varying patterns of treatment were carried out on patients with leiomyosarcoma of the vagina. In the past, wide local excision provided a few cures, but radical pelvic surgery gave the greatest number of cures. Radiation therapy was notoriously poor for leiomyosarcoma of the vagina. Chemotherapy, including vincristine-dactinomycin-cyclophosphamide, doxorubicin and imidazole carboxamide have shown promising results in patients at advanced stage of the disease.[19]

Improvement in the survival of patients with primary malignant tumors of the vagina is dependent on early diagnosis, histologic type, stage, size, the types of therapy and close follow-up.

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Hacettepe Medical Journal
Volume 19 / No. 3 / July 1986 / pp. 123 – 127

A Rare Variant of Cor Triatriatum Dexter

Aydın Aytaç, M.D.,F.A.C.S.,F.A.C.C.* / Argun Saylam, M.D. / Arman Bilgiç, M.D.*** / Atıf Akçevin, M.D.**** / Tahsin Tuncalı, M.D.*****

Summary

A rare variant of cor triatriatum dexter, diagnosed preoperatively as "the abnormal drainage of the inferior vena cava into the left atrium", is presented. The right atrium was completely divided into two chambers by an intact aberrant fibromuscular septum. The anterior compartement contained the superior vena cava orifice, tricuspid valve and the coronary sinus opening. The inferior vena cava drained into the posterior chamber which communicated with the left atrium by a secundum atrial septal defect. The patient was subjected to a successful surgical correction, where the aberrant septum was resected, the atrial septal defect was closed with a pericardial patch, and the right atrial cavity was enlarged by a triangular pericardial autograft sutured on the atriotomy incision.

Key Words: Triatrial Heart.

Introduction

"Cor triatriatum" means a triatrial heart, mainly consisting of two forms as "sinister (subdivided left atrium)" and "dexter (subdivided right atrium)", the first one being the common type.[1] Aberrant septation of the involved atrium by an accessory web is the main pathology in both types. "Cor triatriatum dexter" is an uncommon anomaly, developed embryologically by the persistence of the right valve of the

Departments of Thoracic and Cardiovascular Surgery and Pediatric Cardiology Faculty of Medicine, Hacettepe University, Ankara, Turkey.
* Professor of Thoracic and Cardiovascular Surgery.
** Associate Professor of Thoracic and Cardiovascular Surgery (deceased).
*** Professor of Pediatric Cardiology.
**** Resident in Thoracic and Cardiovascular Surgery.

sinus venosus. Sixteen such cases were reported prior to 1976 (quoted by Gerlis and Anderson)[2] and a few more from that date on, mostly being necropsy findings. A limited number of these cases were subjected to surgical correction.[3-5]

A rare variant of cor triatriatum dexter, simulating the hemodynamics of "the abnormal drainage of the inferior vena cava into the left atrium" is the subject of this paper.

Case Report

N.Y., A 17 year-old girl was referred to our hospital due to cyanosis since birth, with palpitation and shortness of breath on exertion in the past few years. Cyanosis increased during exercise. Physical examination displayed mild cyanosis at rest and clubbing of the fingers. Blood pressure was 130/80 mmHg. Pulse rate was 84/min and regular. No heart murmur was auscultated. Systematic examination was non-contributory. ECG and chest X-rays showed normal findings.

Catheterization was performed for diagnosis. A no. 7 NIH catheter was inserted via the femoral vein and was passed into the inferior vena cava, entering into the left atrium and the left ventricle. The right atrium could not be entered by this catheter. Angiograms taken by this route showed filling of the left atrium and the left ventricle, but not the right atrium. Another catheter of the same size was passed through the basilic vein, which entered the right atrium, the right ventricle and the pulmonary artery, which were opacified during angiocardiography via the catheter. The catheter inserted through the basilic vein could not be pushed into the inferior vena cava. It was unfortunate that the angiograms observed on the scope could not be permanently documented owing to the mechanical failure of the angiography machine during that time. Catheterization data were as follows:

	Pressure (mmHg.)	O_2 Saturation (%)
Left atrium	10 (mean)	78
Left ventricle	95/0-5	–
Pulmonary veins	–	98
Right atrium	2 (mean)	–
Right ventricle	25/10	–
Pulmonary artery	25/12	–

Preoperative diagnosis was "the abnormal drainage of the inferior vena cava into the left atrium".

The patient was subjected to open heart surgery. Pericardium was prepared after sternal split for atrial reconstruction. The right atrium was small in size. Digital exploration via the right atrial appendix revealed no atrial septal defect. When the finger was inserted into the superior vena cava orifice, it did not enter into the inferior vena cava. The superior vena cava was cannulated through the appendix. Since the cannulation of the inferior vena cava was not possible through the right atrium, extracardiac cannulation was performed just above the diaphragm; a right-angle venous cannula was inserted into the inferior vena cava by a purse-string suture on its wall. The patient was cooled down to 28°C

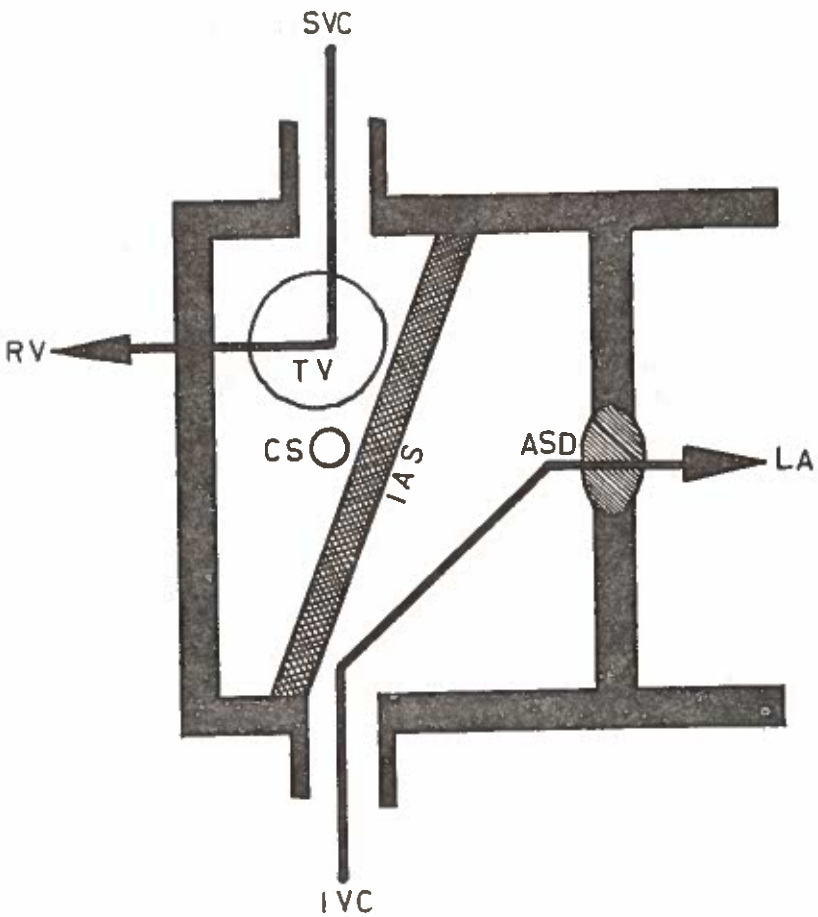

Figure 1

Schematic representation of the operative findings (Right atrium-Lateral view). SVC: Superior vena cava, IVC: Inferior vena cava, TV: Tricuspid valve, CS: Coronary sinus, IAS: Intact aberrant right atrial septum, ASD: Atrial septal defect (secundum) RV: Right ventricle, LA: Left atrium.

by extracorporeal circulation and cold cardioplegic solution perfused via the aortic root after aortic cross-clamping. The right atrium was opened. Opening of the superior vena cava, coronary sinus and the tricuspid valve, (normal in structure) were seen in this chamber which contained an intact fibromuscular septum. This septum was incised and it was observed that there was another right atrial chamber behind this septum, receiving the drainage of the inferior vena cava. The latter chamber communicated with the left atrium by a secundum atrial septal defect of 3x4 cm. in size. Thus, the operative pathology turned out to be a "cor triatriatum dexter associated with atrial septal defect" simulating the hemodynamics of the inferior vena cava drainage into the left atrium (Figure 1). The aberrant right atrial septum was incised and the atrial septal defect was repaired with the pericardial patch. The right atrial wall was also closed by a triangular pericardial autograft to enlarge the right atrial cavity.

The postoperative course of the patient was uneventful and the cyanosis disappeared.

Discussion

Embryologic development of the venous valves of the right atrium were reviewed in detail by Yater in 1929[6] and the term "cor triatriatum dexter" was first used by German pathologists early in this century.[7] It is agreed that the persistence of the embryonic right valve of the sinus venosus creates an aberrant septation of the right atrium in this anomaly.[7] Varying degrees of the right atrial septation take place when the right valve of the sinus venosus fails to regrees.[7]

This malformation may be associated with other congenital anomalies such as hypoplastic small tricuspid valve, tricuspid atresia, imperforate Ebstein's anomaly, hypoplastic right ventricle, pulmonary atresia, atrial septal defect and ventricular septal defect.[2-4, 7, 8] A patient with cor triatriatum dexter is usually asymptomatic unless associated anomalies of the tricuspid valve exist[2, 3, 8] the inferior vena cava is obstructed,[9] or arrhythmias occur.[5, 8] A right-to-left shunt at atrial level via an interatrial communication (patent foramen ovale, atrial septal defect) can lead to cyanosis.[3, 4, 8] Aberrant septation of the right atrium is incomplete in most of the reported cases or fenestrations of accessory septum are present in some.[2-5, 7-9] Therefore, the intact complete aberrant septation in our case is an interesting variation of this pathology.

The exact pathologic features are difficult to demonstrate preoperatively despite repeated catheterizations and angiocardiograms,[3, 4]

as was observed in our patient. Hence, it should be borne in mind that such a malformation can be encountered as a surprising finding during surgery at the atrial level.

Successful surgical corrections have been reported only in a limited number of cases.[3, 4, 5] Incomplete right atrial webs were resected in all, and associated atrial septal defect and/or ventricular septal defect was closed.[3-5]

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Hacettepe Medical Journal
Volume 19 / No. 3 / July 1986 / pp. 129 – 132

Splenogonadal Fusion

Atila Tatlışen, M.D.* / İsmet Nane, M.D.* / Ümit Bayol, M.D.**

Summary

A case of splenogonadal fusion is presented and the literature related to this rare anomaly is reviewed.

Key Words: Ectopic spleen, splenogonadal fusion.

Introduction

Splenogonadal fusion is a rare anomaly, with 87 cases reported in the literature.[1] To our knowledge this is the first case in the Turkish literature.

Case Report

A 6 -year-old boy was admitted to our Service of Urology for the evaluation of a left scrotal mass. The parents reported history of growth in the left testicle for about four years. On examination a 3x2x2 cm, firm and nontender mass that was attached to the upper pole of the left testicle was palpated. This did not transmit light. The remainder of the examination was normal.

On September 13, 1985, under general anesthesis the left testiscle was explored. Firmly attached to the upper pole of this testicle and to the head of the epididymis was a reniform, smooth, brownish-red mass within the tunica vaginalis. The mass with a rubbery consistency had a prominent vascular pedicle, mixed with the spermatic vessels (Figure 1). A coiled fibrous cord measuring 5,5 cm in length, 0,2 cm in diameter found in the cavity of the tunica vaginalis come out of the upper pole of the mass. On this cord, two nodules with a 0,5 cm diameter resembling the main mass in color and consistency was present with intervals of 0,5 cm. During surgery, the nature of the mass was unknown and because of the nonavailability of a frozen sectionex amination, the mass was removed via orchiectomy.

* Specialist in Urology of the S.S.K. Hospital, Manisa, Turkey.
** Associate Professor of Pathology of the Tepecik S.S.K. Hospital, İzmir, Turkey.

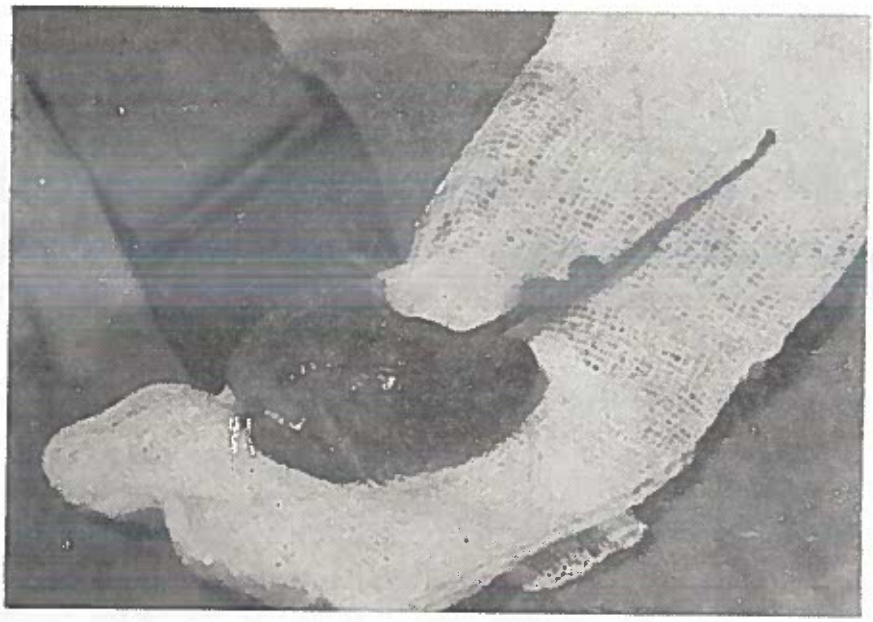

Figure 1
Mass attached to the upper pole of left testicle and to he head of the epididymis.

Histological examination showed normal splenic tissue separated from the testicle and the head of epididymis with a fibrous capsule (Figure 2). The nodules on the fibrous cord were also composed of splenic tissue.

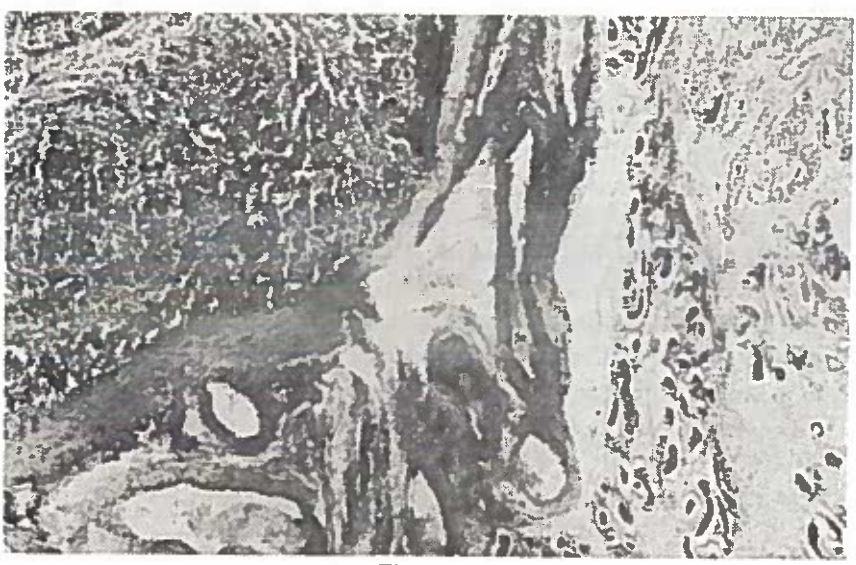

Figure 2
Photomicrography of ectopic spleen. Hematoxylin and eosin Staining x 44.

Discussion

The first detailed description of such a case was published by Pommer in 1889, but the anomaly had been mentioned earlier by Bostroem in 1883.[2] In 1908, Allbutt and Rolleston described an ectopic scrotal spleen connected via a retroperitoneal cord to the abdominal spleen and in 1913 Sneath reported the first case in American literature. These cases were discovered at autopsy. In 1917, Heitzman first discovered a scrotal spleen intraoperatively and traced the complete intraperitoneal splenic connecting cord to the spleen.[3]

In 1956, Putschar and Manion classified splenogonadal fusion into continuous and discontinuous types. In the continuous type, the main spleen is connected by a cord of splenic and fibrous tissue to the gonadal-mesonephric structures, and in the discontinuous type, discrete masses of splenic tissue are found fused to these same structures.[2]

While the cause of splenogonadal fusion is uncertain, study of this malformation in its embryologic aspects indicates that it has its origin between the fifth and eighth weeks of embryonic life.[2] The splenic anlage forms in the dorsal mesogastrium when the embryo is 8 to 10 mm in length, at about the fifth week. The anlage consists of multiple small masses which eventually fuse into one organ. This splenic anlage is in close relationship with the mesonephros and gonadal anlage until involution of the mesonephros and descent of the gonad begins in the eighth week at 20 mm length. The limb buds and Meckel's cartilage (anlage of the mandible) also begin to differantiate at 6-7 weeks of gestational life. It is easy to assume that an injury during this period would produce splenogonadal fusion because of the close proximity of the two anlagen. The same explanation is useful for the commonly associated anomalies because these structures also form during this period.[4]

There have been 48 continuous types and 39 discontinuous types, excluding our case, of splenogonadal fusion reported. Only 2 cases involving the right testicle have been reported. About two third of the cases were in children or teenagers .Splenogonadal fusion involving the left ovary has been reported in 7 female subjects, including 5 discovered at neonatal autopsy.[1]

Of the patients with continuous splenogonadal fusion, 37 percent have one or more associated severe anomalies. By contrast, only one of the 38 reported cases of discontinuous splenogonadal fusion has been associated with peromelus and micrognathia. No theories have been advanced to resolve the dramatic difference in the incidence of anomalies in the continuous and discontinuous types of splenogonadal fusion.[1]

The ectopic splenic tissue rarely causes symptoms. Patients usually are explored for an undescended testicle, inguinal hernia or a scrotal mass. Splenogonadal fusion was suspected because of the combination of limb abnormalities and a left undescended testicle. Other presentations of splenogonadal fusion include acute scrotal pain associated with malaria, exercise, mumps, leukemia and mononucleosis.[1,5] Only one case was diagnosed correctly preoperatively by a ^{99m}technetium sulfur colloid scan that revealed the ectopic scrotal spleen.[6] In the correctly diagnosed cases, extirpation of the ectopic tissue would have been sufficient. A normal intra-abdominal spleen has been invariably confirmed in cases further evaluated by some methods.[7]

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Hacettepe Medical Journal
Volume 19 / No. 3 / July 1986 / pp. 133 - 140

The Etiopathogenesis of Osteoarthritis

Öner Gedikoğlu, M.D.*

Summary

Osteoarthritis, which is one of the topics of orthopaedic surgery was revised in regard to its etiopatogenesis.

In the literature between 1963-1985, possible trigger mechanisms inducing articular cartilage breakdown, stages, natural course of the disease, biochemical and histological changes occurring in the articular cartilage and synovial membrane were reviewed.

Key Words: Osteoarthritis, Etiopathogenesis.

Introduction

Osteoarthritis is a degenerative joint disease that results from progressive loss of certain elements in the intercellular matrix of the articular cartilage, especially of the proteoglycans.[1,2] Proteoglycan loss starts at the superficial layers of the cartilage and gradually progresses to the deep layers.

In osteoarthritis, a series of histopathological and biochemical changes are observed in the articular cartilage. These changes[1,3-8] and a staging based on their progression are summarized below (Table I):

Initial Stage

At the beginning of the disease, surface irregularities of the cartilage and loss of substance in the superficial tissues develop. These superficial changes have been identified as the "Initial lesion". For example, initial lesions in the hip joint usually starts around the fovea capitis femoris and the corresponding areas of the acetabulum. When the proteoglycan con-

Department of Orthopaedic Surgery, Faculty of Medicine, Uludağ University, Bursa, Turkey.
* Professor of Orthopaedic Surgery.

TABLE I

HISTOPATHOLOGIC AND BIOCHEMICAL CHANGES IN OSTEOARTHROTIC CARTILAGE

Stages	Histopathologic Changes	Biochemical, Metabolic Changes		
		Proteoglycan Content	Collagen Content	Chondrocyte metabolism (Proteoglycan, DNA synthesis)
Initial	1. Loss of superficial cartilage layer (Initial lesion) 2. Chondrocyte proliferation 3. Decrease in metachromatic staining 4. Violation of the "tidemark"	(Decrease (–)	Normal	Increase (+)
Intermediate	1. Progressive vertical cleft formation 2. Extension of the vertical clefts to the calcified zone (Fibrillation) 3. Large numbers of chondrocytes in clumps or clones in the matrix between the clefts	Decrease (– –)	Normal	Increase (+ + +)
Terminal	1. Partially and completely loss of cartilage leaving denuded sclerotic and eburnated bone 2. Subchondral cyst formation, development of osteophytes	Decrease(– – –)	Normal	Marked decrease Loss of metabolic activity

centration in these areas are measured by uronic acid and hexosamine assay, they are found to be less than normal.[4,6] Histologically, this loss in proteoglycan is demonstrated by a reduction in metachromatic staining of the intercellular matrix. The appearence of the initial stage triggers the repair mechanism of the tissue, and metabolic activity by the chondrocytes is stimulated. For example, there is an increase in DNA synthesis, and the rate and number of mitotic divisions among the chondrocytes are also increased.[6] In addition, proteoglycan synthesis is increased as demonstrated by ^{3}H-glucosamine and $^{35}SO_4$ studies.[4,7-9] In the initial stage, penetration of the Tidermark by capillaries from underlying bone tissue is considered to be a typical finding of osteoarthritis. The capillaries from subchondral bone pass through this line to induce calcification and new bone formation in cartilage.[10] It has been argued that this change is responsible for osteophyte formation.[11]

Intermediate Stage

As the disease advances, superficial cartilage loss progresses to a vertical cleft extending into the calcification level at the meeting point of cartilage and bone (Fibrillation). There is a proportional increase in the metabolic activity of the chondrocytes[6,12] and these cells arrange themselves in groups between the clefts. It has been stated that this grouping of chondrocytes is the most important histological finding in osteoarthritis and that it serves to distinguish this disease from cartilage degeneration due to aging.[6]

Terminal Stage

In the last stages of osteoarthritis, the metabolic activity of the cells decreases gradually and closes. As the tissue loses its ability for repair, destruction accelerates and the classical findings of osteoarthritis become manifest. The most prominent of these findings are: complete loss of cartilage in some areas of the joint, sclerosis of subchondral bone, cyst formation, narrowing of the joint space, and development of osteophytes.

In the course of the disease, interestingly, there is no quantitative change in the collagen content despite loss of proteoglycans and progressive changes in the cells.[13] Studies with labelled hydroxyproline,[7,14] for example, show that the amount of collagen in the cartilage remains within normal limits during the course of the disease. Some qualitative alterations at the moleculer level have been demonstrated in the collagen fibrils.[15-18] Ultrastructural evidence suggests that there is an increase in fiber diameter.[15] Studies with specific fluorescent antibodies[16] demonstrated type I collagen in cartilage in the advanced stages of

the disease. Using gel electrophoresis, Fukae[17] could only detect type II collagen and interpreted his result as not a change in collagen type. Lippiello,[19] on the other hand, showed that the hydroxylysine/hydroxyproline ratios in the osteoarthrotic cartilage were unchanged and claimed that no major shifting occured in collegen type. A more recent study by Adam,[18] using immunofluorescense methods, has shown the presence of type III collagen in addition to types I and II in osteoarthrotic cartilage.

In the course of osteoarthritis, a series of changes develop in the synovial membrane. From the standpoint of pathological anatomy, the most prominent of these changes is the varying degree of inflammation and hyperplasia in the membrane.[2, 20-22] When the hyperplastic membrane is observed histologically, islands of lymphocytes, hypertrophy of the villi, and in cases where primary osteoarthritis is progressing fast, even pseudopannus formation on cartilage are found.[3] That these changes in the synovial membrane accompany the early stage of osteoarthritis when the initial lesion is occuring is an interesting finding in the pathogenesis of osteoarthritis.[23]

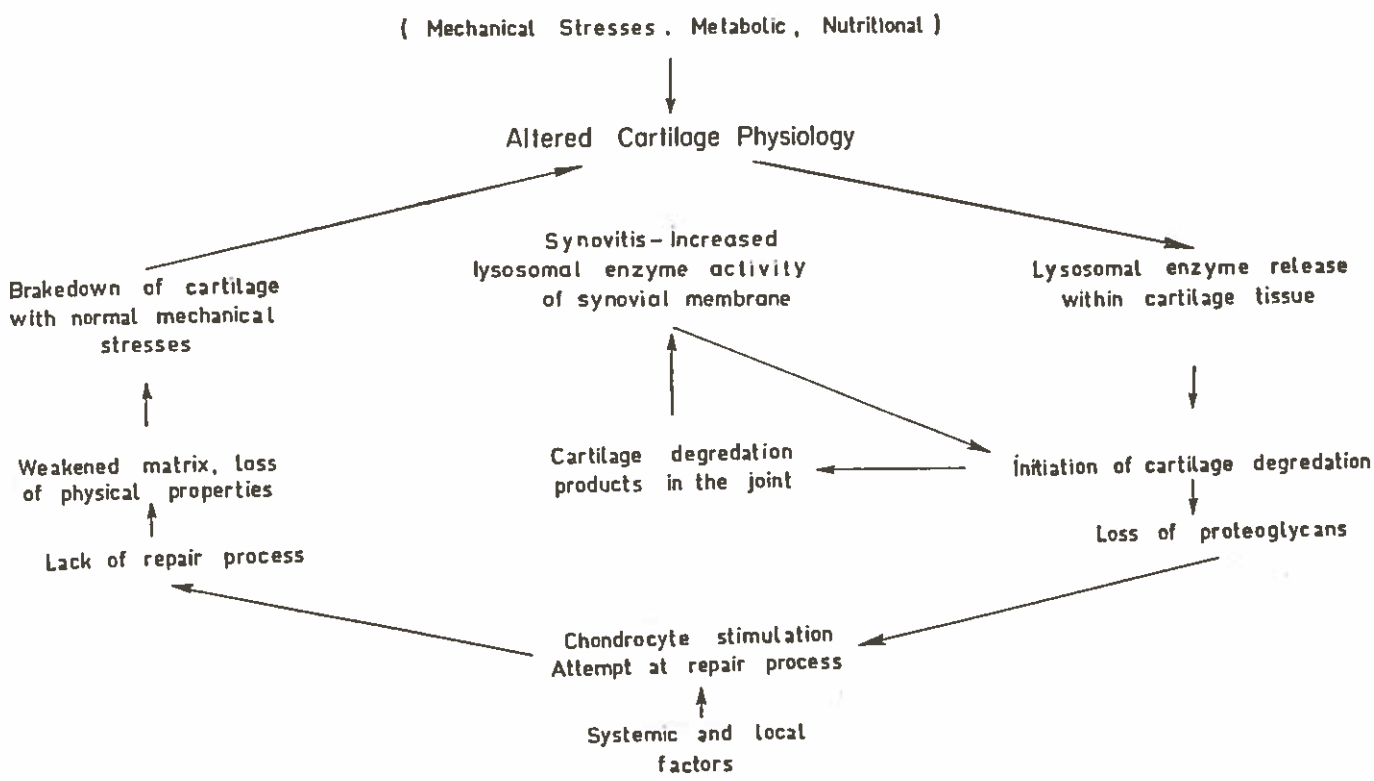
Pathogenesis of Osteoarthritis

In the normal joint there exists a balance between the formation and breakdown of intercellular cartilage matrix as in other connective tissues of the body. This metabolic activity is most prominent in the proteoglycans[5] When this balance is lost and breakdown predominate, there is a reduction in intercellular matrix, especially in the proteoglycans. With the loss of its supporting structure, the tissue has reduced resistance to mechanical stresses.

The exact role of aging in the pathogenesis of osteoarthritis has long been subject to debate. The work of Byers et al[24] on postmortem specimens has shed new light on this controversy. According to their findings, the cartilage changes observed in aging appear to be different from osteoarthritis and aging does not seem to have an important role in the pathogenesis of this disease.[2, 24] For example, the cartilage clefts seen in aging develop in nonweight bearing peripheral areas of the joint, do not progress into subchondral bone, and there are no areas of complete tissue loss. By contrast, in osteoarthritis, vertical clefts are found in the weight-bearing areas of the cartilage, (where cartilage is subject to maximum mechanical stress) do progress into the subchondral areas, and there are areas of complete tissue loss.

In the course of investigating both physiologic and osteoarthritic articular cartilage breakdown, it has been determined that enzymes,

TABLE II


VARIOUS UNKNOWN FACTORS
(Mechanical Stresses , Metabolic , Nutritional)
Altered Cartilage Physiology
Brakedown of cartilage with normal mechanical stresses
Synovitis – increased lysosomal enzyme activity of synovial membrane
Lysosomal enzyme release within cartilage tissue
Weakened matrix, loss of physical properties
Cartilage degredation products in the joint
Initiation of cartilage degredation
Loss of proteoglycans
Lack of repair process
Chondrocyte stimulation Attempt at repair process
Systemic and local factors

and especially lysosomal enzymes are the single most important factor in the loss of proteoglycans[2, 25-33]

What is the origin of these enzymes that cause articular cartilage destruction through reducing the proteoglycans in osteoarthritis? Enzyme studies have shown that their origin could be the cartilage itself or the synovial membrane. Increased levels of Cathepsin D, Cathepsin B_1, acid phosphatase, and alkaline phosphatase in the articular cartilage, and increased Cathepsin D, alkaline phosphatase, acid phosphatase and β glucuronidase in the synovial tissue have been cited as evidence for the presence of these enzymes from both sources.[2, 20, 25, 26, 34-36]

The pattern of histochemical changes during the course of osteoarthritis and the role played by certain enzyme systems in cartilage destruction have thus been demonstrated, leading to a better understanding of the pathogenesis of the disease. However, the initiating factors leading to imbalance in the cartilage metabolism are not clearly understood.[1, 2, 26, 37] The pathogenetics of osteoarthritis and various factors implicated are summarized in Table II.

The pathology starts when various unknown mechanical and metabolic factors act on the cartilage. Mechanical trauma has attracted attention as being an initiating factor, but its exact role is unclear. According to a certain hypothesis, local mechanical injury in the joint ruptures the chondrocytes' lysosomal membranes leading to release of proteolytic enzymes.[38] The synovial membrane has been implicated as another source for the proteolytic enzymes that breakdown the cartilage (Bollet,[14] Gedikoğlu,[20] and Glynn[39]).

With the start of intercellular matrix breakdown in tissue, changes occur in matrix composition, the most prominent of these being a reduction in the amount of proteoglycans. This breakdown activates the repair mechanism of the tissue. Various systemic and local factors such as Connective Tissue Activating Peptide, somatomedine and growth hormone have been implicated in the stimulation of chontrocytes.[3, 40] As the pathology advances, the reparative ability of the tissue decreases. In the end, the physical strength of the tissue is lost and normal mechanical loads on the joint lead to tissue breakdown resulting in a vicious cycle of cartilage destruction.

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hacettepe medical journal

A QUARTERLY PUBLICATION **VOLUME 19 / NO. 4 / OCTOBER 1986**

PUBLISHED BY HACETTEPE SCIENCE CENTER FOUNDATION

SUBSCRIPTION RATES

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HACETTEPE-ANKARA

Indexed by Excerpta Medica

Printed by
Hacettepe University Press
Printing Division

VOLUME 19 / NO. 4 / OCTOBER 1986

hacettepe medical journal

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Hacettepe Medical Journal
Volume 19 / No. 4 / October 1986 / pp. 141 - 149

Synthetic Salmon Calcitonin Therapy in Osteogenesis Imperfecta*

Öner Gedikoğlu, M.D. / Yahya Laleli, M.D.*** / Ufuk Aydınlı, M.D.******

Summary

In order to evaluate the therapeutic effects of calcitonin in osteogenesis imperfecta, 5 patients were treated with synthetic salmon calcitonin with a dose of 4 MRC units/kg and followed up for one year.

It was found that there was no alteration in the serum calcium, phosphorus, somatomedine-C, growth hormone and parathyroid hormone levels in contrast to the rise in serum calcitonin levels. Serum alkaline phosphatase and bone alkaline phosphatase enzymes were found to be significantly elevated after therapy. Urinary calcium and phosphorus excretion was slightly increased in four patients.

Based on these labaratory findings and a marked improvement in the physical activities of the patients, it was concluded that calcitonin has a beneficial therapeutic value in osteogenesis imperfecta.

Key Words: Osteogenesis imperfecta-Calcitonin therapy

Introduction

Osteogenesis imperfecta is a connective tissue disorder which primarily affect the skeleton and is characterized by bone fragility and

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* This study was undertaken at the Ondokuzmayıs University School of Medicine, Samsun and at the Düzen Laboratory, Ankara, Turkey.

** Professor of Orthopaedic Surgery, Uludağ University, Bursa, Turkey.

*** Professor of Biochemistry and Nuclear Medicine, Düzen Laboratory, Ankara, Turkey.

**** Former resident in Orthopaedic Surgery, Ondokuzmayıs University, Samsun, Turkey.

frequent fractures that may result in severe skeletal deformities. Although its pathogenesis has not been fully understood, inadequate periosteal accumulation of bone during growth, faulty collagen chemistry and structure, insufficient bone matrix formation, increased bone turnover most likely due to defective osteoblastic activity are claimed to be the main defects of the disease.[1]

Therapeutic measures such as sodium fluoride, anabolic steroids and ascorbic acid have been shown to be ineffective in the treatment.[2, 3] Recently, based on the favorable therapeutic effects on Paget's disease and osteoporosis[1, 4] some studies[3, 5-7, 8] have indicated that calcitonin may be useful in the treatment of osteogenesis imperfecta.

In this study, we have undertaken to clarify the value of calcitonin therapy in osteogenesis imperfecta by evaluating the response to synthetic salmon calcitonin, administered to 5 patients with osteogenesis imperfecta who were followed up for one year.

Materials and Methods

This study was undertaken at the orthopaedic surgery department of Ondokuzmayıs University School of Medicine in Samsun and at the Düzen Laboratory in Ankara.

We treated 5 patients, ages 3, 3.5, 4, 5 and 24 years with synthetic salmon calcitonin for one year.

Clinical diagnosis was based on the major criteria[9] of this disease such as radiologic findings and a history of multiple fractures. On admission to the study each patient was hospitalized for 5 weeks.

In order to assess the clinical and laboratory response to therapy, studies given below were undertaken before and after therapy:

1- Functional activity level of the patient (the ability of the patient to sit up, stand and walk).

2- Fasting serum calcium, phosphorus, alkaline phosphatase, heat resistant alkaline phosphatase (indicator of bone originated alkaline phosphatase), calcitonin, growth hormone, somatomedine-C and parathyroid hormone levels 48 hr. after the injection of salmon calcitonin. Calcitonin and parathyroid hormone levels were determined by radioimmunoassey (RIA) from IRE, Belgium. Somatomedine-C level was measured by RIA from Nichols Int. Diag., California, USA. Total and heat resistant alkaline phosphatase levels were measured by Beckman Astra 8 bioche-

mical analyzer. The phosphorus level was determined by direct phosphomolybdate reaction without deproteinisation.

3- 24 hr. urine calcium and phosporus levels 48 hr. after the injection of salmon calcitonin.

Patients were put on a diet contaning 1000 mg calcium, 1200 mg phosphorus and low hydroxyproline during the treatment period.

The treatment regimen started one week after the initiation of diet and consisted of intramusculer injection of synthetic salmon calcitonin three days a week and the dose (1 MRC units/kg every week) was increased to 4 MRC units/kg at the end of the fourth week. Prior to the initiation of calcitonin administration, patients were tested for sensitivity to calcitonin by intradermal skin tests.

During the treatment period, all laboratory studies were repeated every week in the first month and at varying intervals later on.

Laboratory values obtained before and after therapy were compared by the Wilcoxon signed rank test.

Results

All the patients tolerated the therapeutic regimen of thrice weekly injections of synthetic salmon calcitonin (4 MRC units/kg) and no side effects were detected.

All the patients showed marked improvement in their physical activities by the third month of therapy. Four children who were not able to walk, started walking at the end of a year. The 24 year old bedridden patient was able to sit up after six months of therapy.

Serum calcium, phosphorus, parathyroid hormone, growth hormone and somatomedine-C levels were within normal range in all patients before and after therapy. Serum calcitonin levels were found to be elevated during therapy in varying degrees except for one patient and this elevation was not statistically significant ($p > 0.05$) (Figure 1). Urinary calcium excretion was slightly increased in three and phosphorus in four patients after therapy.

Serum alkaline phosphatase enzyme activity was increased in all patients after therapy and this increase was statistically significant ($p < 0.05$) (Figure 2). Percentage of heat resistant alkaline phosphatase was decreased in four patients and this decrease was statistically significant ($p < 0.05$) (Figure 3).

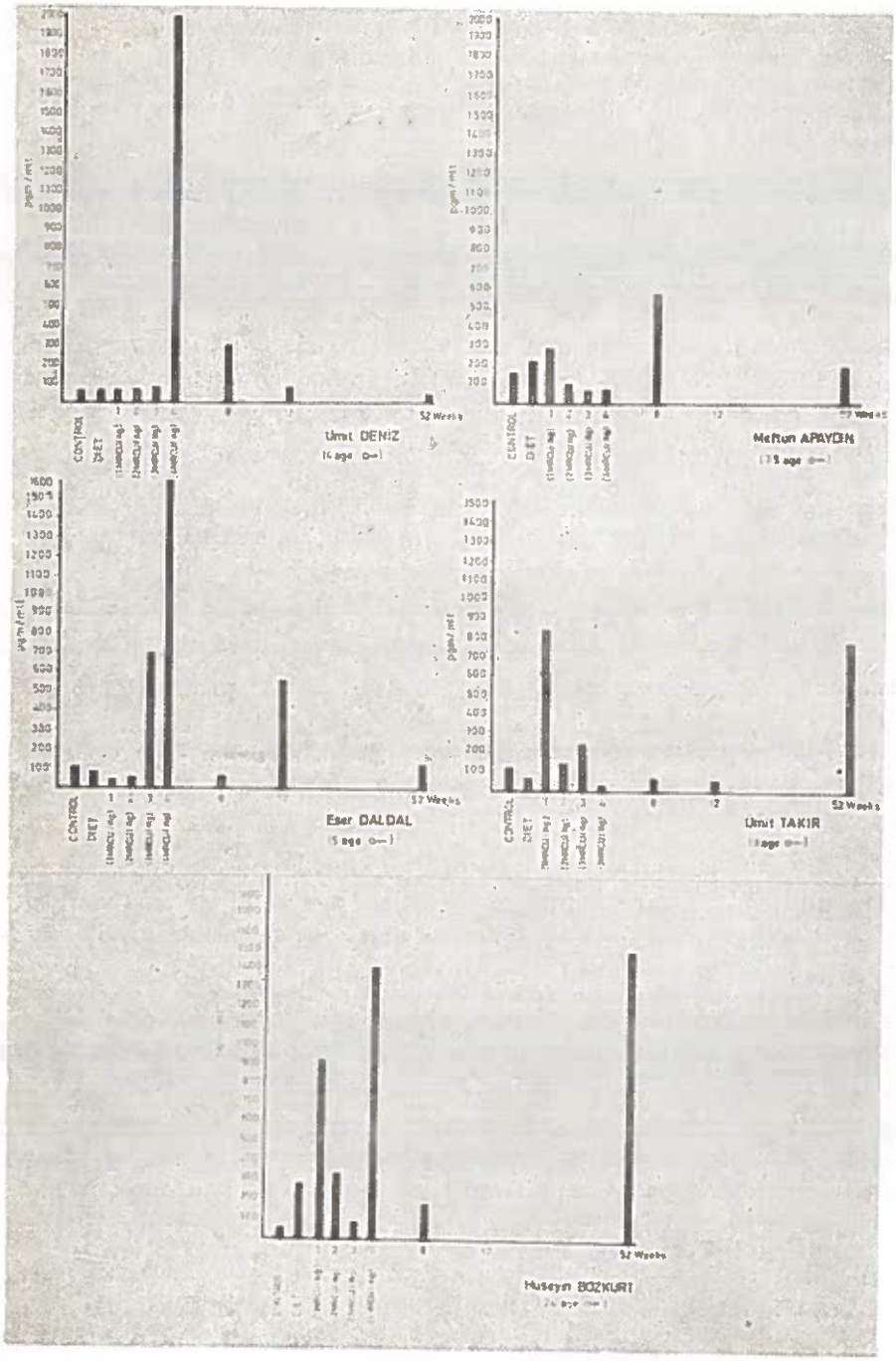

Figure 1
Serum calcitonin levels (N-30-90 pgm/mlt)

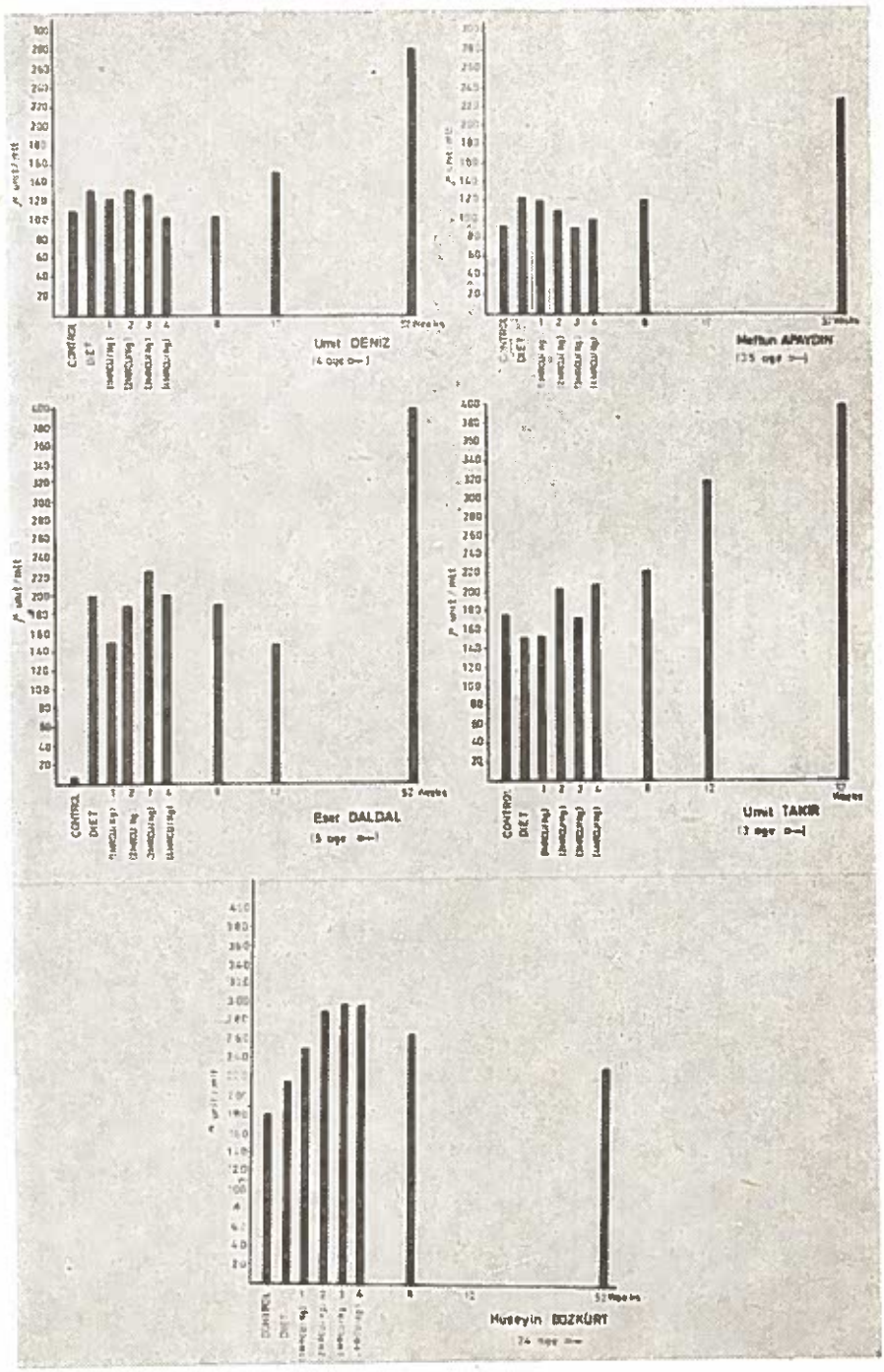

Figure 2
Serum alkaline phosphatase levels (N-38.0-138.0 μ unit/mlt)

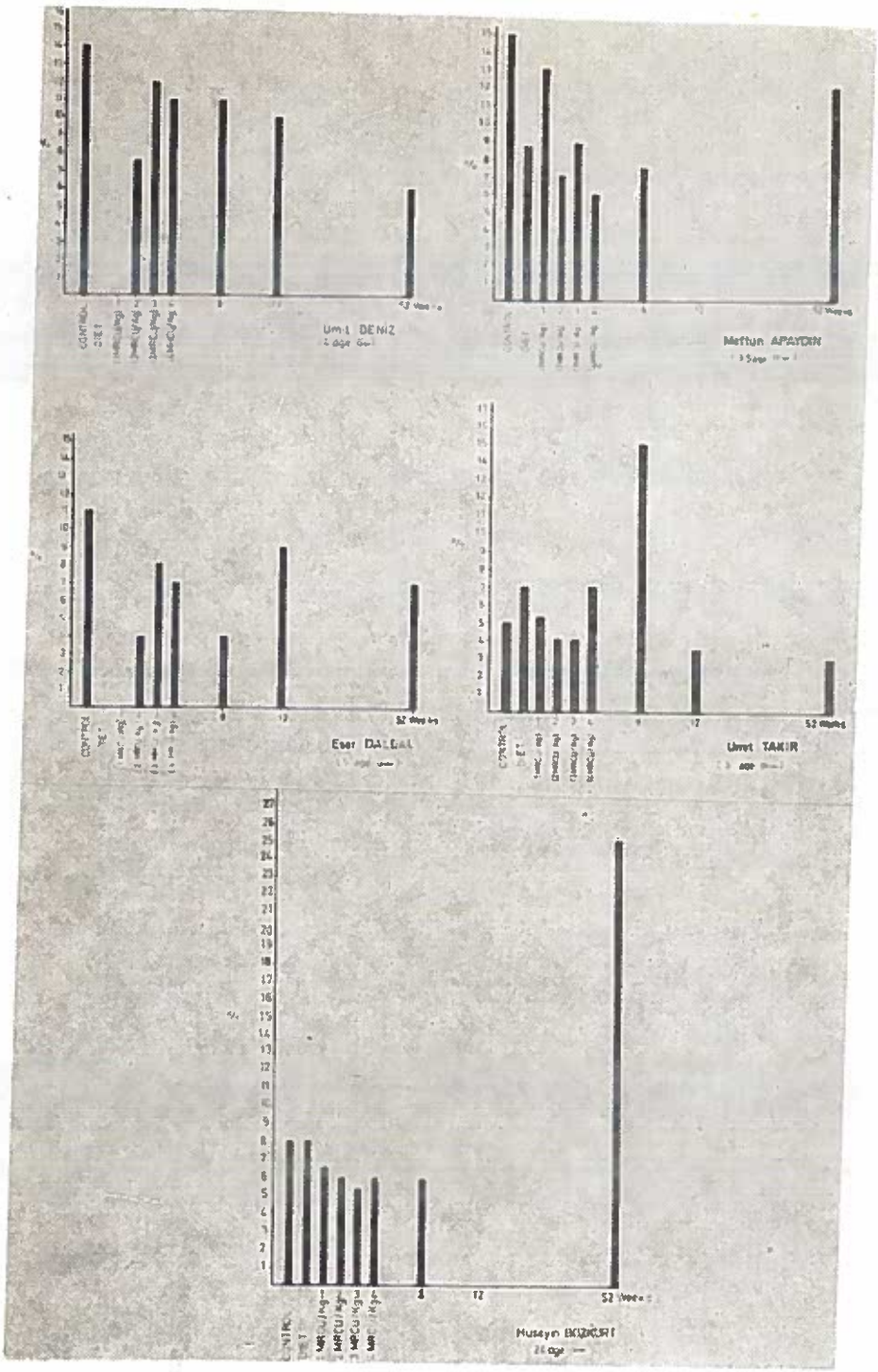

Figure 3
Percentage of heat resistant alkaline phosphatase (N- % 20-30)

Discussion

Although the pathogenesis of osteogenesis imperfecta has not been completely determined, it appears that bone fragility and osteoporosis result from defective bone matrix formation as shown by tetracycline labelling studies.[10] In order to reduce the increased bone turnover, calcitonin has been tried and found to be promising in the treatment of the disease.[2, 3, 5-8, 11-13] This study was undertaken to verify the value of calcitonin in the treatment of osteogenesis imperfecta which is claimed to be promising. In our study, salmon calcitonin was preferred as it has been shown to be more potent and longer lasting than human or porcine types.[14]

The finding of serum calcium, phosphorus and parathyroid hormone levels within normal range in all our patients before and during therapy is in agreement with August,[2] Castells,[5-7] Lanes,[8] Nishi[3] and Rosenberg[12] who found similiar results in their studies.

In contrast to the finding of Nishi,[3] varying degrees of elevated serum calcitonin levels were determined in our study (Figure 1). For example, Nishi,[3] in his study comprising only one patient, found normal serum calcitonin levels during the treatment period. Elevation of serum calcitonin level found in this study was attributed to a rebound like action occuring between endogen human and synthetic salmon calcitonins. In our opinion, further studies are required to clarify this action and possible cross reactions between these two types of calcitonin.

A slight increase in urinary calcium and phosphorus in some patients were attributed to increased calcitonin levels.

In contrast to other studies,[2, 6, 7] the most outstanding finding obtained from this study was the significant elevation of serum alkaline phosphatase enzyme activity in all patients after therapy (Figure 2). For example, August[2] and Castells[6 7] did not detect increased levels of this enzyme during treatment period. The most valuable finding emerging from this study is the significant decrease in the percentage of heat resistant alkaline phosphatase enzyme which reflects an increase in bone alkaline phosphatase enzyme activity (Figure 3). After heating, the activity of bone alkaline phosphatase is reduced (more) than liver alkaline phosphatase and the decrease in the percentage of the enzyme indicates an increased activity of bone alkaline phosphatase.[15] We were not able to compare this finding with other studies as the heat resistant alkaline phosphatase enzyme was not determined in previous studies. In our opinion, increased serum alkaline phosphatase enzyme activity together with an increase in its bone fraction after calcitonin

therapy strongly indicates an increased osteoblastic activity and verify the beneficial therapeutic effect of salmon calcitonin on the treatment of osteogenesis imperfecta.

Based on our findings we conclude that:

1- Calcitonin has a beneficial therapeutic value in osteogenesis imperfecta in regard to the patients' physical activities.

2- Calcitonin therapy results in the elevation of both bone and serum alkaline phosphatase enzyme levels which indicate an increased osteoblastic activity.

3- Serum and especially bone alkaline phosphatase enzyme activity levels give valuable information about the response to the treatment without necessitating sophisticated techniques.

Note: The authors are grateful to Sandoz Ltd. for providing synthetic salmon calcitonins utilized in this study and to Dr. Osman Saka from the Biostatistics Department, University of Hacettepe for this generous help in carrying out the statistical work.

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Hacettepe Medical Journal
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Methylprednisolone Pulse Therapy in Rheumatoid Arthritis

Servet Arıoğul, M.D.* / Ahmet Oktay, M.D.* / Ali Oto, M.D.* / Tümay Sözen, M.D.* / Şahika Şahin **

Summary

Eleven patients with active rheumatoid arthritis refractory to conventional therapy such as rest, physiotherapy, theurapeutic doses of non-steroidal anti-inflammatory agents, intraarticular steroid injections or penicillamine were given a course of methylprednisolone intravenously. In each course an infusion of 1 gm of methylprednisolone was administered on 3 consecutive days. The therapeutic response was evaluated in six of the patients because of drop-outs. After seven days there was marked improvement in the clinical parameters, namely in tender joint count, morning stiffness and grip strength in addition to a marked decrease in the erythrocyte sedimentation rate ($p < 0.05$). However, this favourable response was not apparent at the fourth and eight weeks following the first one. It is concluded that high-dose methylprednisolone pulses may only be used as a temporary mode of therapy inducing a short-term remission in selected patients.

Key Words: Rheumatoid arthritis, Methylprednisolone, Pulsed methylprednisolone.

Introduction

High-dose intravenous methylprednisolone pulse therapy has recently been tried in various immune-mediated disorders such as renal allograft rejection,[1, 2] lupus nephritis[3, 4] non-renal lupus[5-7], rapidly progressive glomerulonephritis[8], minimal change neprotic syndrome,[9]

Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey.

* Associate Professor.

** Resident.

multiple sclerosis[10], ankylosing spondylitis,[11] polyarteritis nodosa,[12] aplastic anemia[13] and rheumatoid arthritis.[14-17] Moreover, its effect on chronic idiopathic thrombocytopenic purpurae has been studied by our group very recently.[18] Although some encouraging results have been found in most of the studies mentioned above, it is difficult to reach a consensus. Favourable results particularly in rheumatoid arthritis do not seem to be supportive enough to recommend this therapy, widely. At this point we tried to elucidate the effectiveness of methylprednisolone pulse therapy in our cases with rheumatoid arthritis resistant to conventional modes of treatment.

Patients and Methods

Eleven patients (7 women, 4 men) with definite or classical rheumatoid arthritis according to the American Rheumatism Association criteria[19] were included in the study. At the time of admission all patients showed disease activity despite conventional therapy, namely rest, physiotherapy, therapeutic doses of non-steroidal anti-inflammatory agents, intra-articular steroid injection or penicillamine. Patients continued to take their drugs throughout the study. No patients were included in the study who had been on oral steroids during the previous 60 days or who had received intra-articular steroid injections during the previous 30 days. Further, patients who were on non-steroid immunosuppressive agents were excluded. All patients had been receiving therapeutic doses of non-steroidal anti-inflummatory agents for at least 30 days at the beginning of the study. These agents were continued during the study.

One gram methylprednisolone Succinate (Prednol-L^{R}) in 250 ml of 5 % dexstrose in water was given intravenously over two hours and repeated over two successive days (3gr totally for three days). Close clinical and cardiac monitoring was carried out during the intravenous methylprednisolone treatment period for 72 hours. Patients were evaluated at the first, fourth and and eighth week of pulse therapy for drug efficacy using the following criteria: 1. Tender joint count, 2. Walking time assessed by recording the length of time in seconds (it was required of the patient to walk 15 m), 3. Morning stiffness assessed by the avarage duration in minutes over the previous 3 days, 4. Grip strength was assessed by a standard folded, taped sphygmomanometer cuff inflated to 20 mm Hg. The cuff was grasped and squeezed by each hand in three separate attempts and the maximum sustained value for each hand was recorded, 5. Proximal interphalangeal joint swelling, assesed by sizing the joints (two) in millimeters.

Additionally erytrocyte sedimentation rate was measured and latex fixation test for rheumatoid factor was performed in each control visit.

Serum electrolytes, serum amylase and complete blood count were measured during control visits for drug toxicity. Cardiac arrythmias, visual disturbances, spinal pain and tenderness, amenorrhea, cushingoid appearance were also checked for clinical toxicity.

Statistical analysis was done by the department of Biostatistics according to Wilcoxon's signed-rank test. Since there is a marked difference between the values of observation, median value was used for statistical evaluation.

Results

Four of the 11 patients failed to come to the second and third control visits. One patient was discarded from the study because of the necessity to commence oral steroids. Therefore, we could only document the results obtained from six patients. No clinical and laboratory evidence for corticosteroid toxicity was encountered in any of the cases.

The effect of pulse methylprednisolone therapy upon the clinical parameters of tender joint, walking time and morning stiffness is shown in Table I. The effect of pulse therapy upon grip strength, proximal interphalangeal joint swelling and sedimentation rate is shown in Table II. Median values for the parameters are shown in Table III.

TABLE I

THE EFFECT OF PULSE METHYLPREDNISOLONE THERAPY UPON TENDER JOINT COUNT, WALKING TIME AND MORNING STIFFNESS

	Patient No	Pre-treatment	Follow-up visits (weeks) 1	4	8
Tender Joint count	1	12	0	0	6
	2	20	3	12	11
	3	6	0	5	–
	4	5	0	17	10
	5	10	1	3	–
	6	8	3	2	–
Walking time (sec)	1	19	17	15	20
	2	0	120	0	0
	3	10	15	15	–
	4	20	15	15	15
	5	37	20	18	18
	6	0	0	62	60
Morning stiffness (min)	1	90	0	60	60
	2	60	60	120	120
	3	180	0	0	–
	4	180	0	360	360
	5	75	50	10	–
	6	480	300	0	–

TABLE II

THE EFFECT OF PULSE METHYLPREDNISOLONE THERAPY UPON GRIP STRENGTH, PROXIMAL INTERPHALANGEAL JOINT SWELLING AND SEDIMENTATION RATE

	Patient No	Pre-treatment	Follow-up visits (weeks) 1	4	8
Grip strength (mmHg)	1	8	30	55	30
	2	0	25	10	20
	3	37.5	80	75	–
	4	40	90	40	32
	5	60	70	70	–
	6	40	40	40	–
Proximal interphalangeal joint swelling (mm)	1	59	61	61	61
	2	66	64	61	62
	3	60	57	58	–
	4	64	65	65	65
	5	67	68	69	–
	6	64	64	66	–
Sedimentation rate (mm/h)	1	27	18	35	
	2	55	12	30	
	3	103	40	30	
	4	18	15	30	50
	5	56	45	50	
	6	82	75	–	–

TABLE III

MEDIAN VALUES AND STATISTICAL SIGNIFICANCE OF THE RESULTS

	Pre-treatment	Weeks 1	4	8
Tender joint clunt	9	0,5	4	–
		$p < 0.05$	N.S.*	–
Walking time	19	16	15	–
		N.S.	N.S.	
Morning stiffess	135	25	35	–
		$p < 0.05$	N.S.	
Grip strength	38.7	55	47.5	
		$p < 0.05$	N.S.	–
Proximal interphalangeal joint swelling	64	63.5	63	–
		N.S.	N.S.	
Sedimentation	55.5	34	30	–
		$p < 0.05$	N.S.*	

NS* : non-significant.

1. Tender Joint Count: Number of tender joints were significantly decreased at the first control ($P < 0.05$). No significant change was obtained thereafter.

2. Walking Time: Alterations were not found to be significant.

3. Morning Stiffness: Striking amelioration in this parameter was found at the first control ($P < 0.05$). No significant change was observed on other control visits.

4. Grip Strength: A significant improvement was observed in this parameter at the first control ($P < 0.05$). There was change during the other control visits.

5. Proximal Interphalangeal Joint Swelling: No significant alteration was obtained in this parameter.

6. Erytrocyte Sedimentation Rate: Erytrocyte sedimentation rate was found to be significantly decreased during the first week controls ($P < 0.05$). However, the measurement obtained in the other controls did not reveal any significant changes compared to initial values.

Rheumatoid factor was persistently positive in all cases.

Discussion

Several groups have reported promising results with intravenous methylprednisolone therapy in active rheumatoid arthritis recently.[14-17] The early and prominent response in the clinical variables and the laboratory measurements was a striking point common to all these studies. More importantly improvement was sustained for a considerable time rendering this therapy quite attractive.

In one study clinical remission lasted a mean of 10 weeks and erythrocyte sedimentation rate remained within normal limits for a mean of 7 weeks. Moreover, three patients had clinical remissions lasting more than 42 weeks.[15] Another group reported significant improvement in all clinical variables measured which lasted for at least 6 weeks.[16] A recent report described uncontrolled clinical observations in patients with rheumatic disease with a single dose of 320 mg of intramuscular methylprednisolone acetate. The favorable therapeutic response that had been obtained in several patients with rheumatoid arthritis led the author to suggest that intermediate-dose intramuscular therapy may offer several advantages over higher-dose intravenous pulse therapy.[20]

In this study we have demonstrated the beneficial effects of intravenous methylprednisolone pulses on some of the studied clinical and serologic parameters (namely tender joint count, morning stiffness,

grip strength and erythrocyte sedimentation rate) ($p < 0.05$). It was noted that the favorable response peaked within the first week of the treatment. Although some improvements were noted during later visits they were not statistically significant. The reason for the shorter duration of remission seen in our patients when compared to other series was not apparent.

This early and striking short-term improvement may be advantageous in some patients since penicillamine, antimalarials, parenteral gold, azothioprine and cytotoxic drugs require a considerable period of time (usually months) to become effective.[21] Additionally, although this point has not been proven yet, it might be possible to keep the patient in remission more easily and with smaller doses of second-line drugs after the induction of intravenous methylprednisolone pulses.

Although large intravenous boluses of methylprednisolone were initially thought to be relatively free of significant side effects, this concept has changed during the last few years and various complications related to this mode of therapy have been described.[22] We have not seen any serious toxicity in this group of patients. Nevertheless, we had observed a case with acute non-infectious peritonitis due to pulse methylprednisolone therapy previously.[23] Therefore, this therapy should not be considered as a completely benign treatment and physicians ought to be cautious for possible serious side effects. Close cardiac monitoring of patient during the early treatment period and slow infusion rate have been recommended to reduce complications.[21]

The benefit of high doses of corticosteroids is unknown. Although suppression of a humoral or cellular immune mechanism is a superficially attractive hypothesis, it is not in accordance with observations which indicate a very early effect.[24, 25] It is more likely that these high doses of methylprednisolone improve the signs and symptoms of rheumatoid arthritis by direct anti-inflammatory effects impending the access of neutrophils and macrophages to the inflammatory site.

In conclusion, it seems to be acceptable to use the pulse methylprednisolone therapy in some patients with rheumatoid arthritis refractory to conventional treatment. The main usage may be in managing acute flare-ups while simultaneously a more effective long-term conventional therapy is started. The temporary but early striking effect and lack of abundant toxicity may favour its use in selected patients for whom rapid remission is critical.

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Volume 19 / No. 4 / October 1986 / pp. 159 – 164

The Length of the Human Umbilical Cord and its Relationship with Fetal and Maternal Variables

Kunter Yüce, M.D.* / Ali Ayhan, M.D. / Aysel Yüce, M.D.*****

Summary

The cord length of 276 infants delivered at term was measured. The mean cord length was 61.217 cm. and the relationship between the cord length and some fetal and maternal variables was investigated. There were significant correlations between cord length and fetal and placental weight and the number of coilings of the cord around the neck of the fetus. There was no positive correlation between Apgar score and the encirclement of the cord and true knots in this study.

Key Words: Human umbilical cord, Placental weight, Fetal weight, Circumvolution of the cord.

Introduction

There are few studies of human umbilical cord length in the literature.[1,2] Yet these studies are very important because the vessels contained within the cord are essential parts of the fetal circulatory system.

The length of the human umbilical cord varies considerably but the most common length is 50-60 cm. Most authors agree that a cord of more than 35.5 cm. in length is necessary for normal delivery.[1-4] Others have reported a shorter average length[1] and in some studies, positive correlations between the cord length and some fetal and maternal variables were shown.[1,2,5]

The Department of Obstetrics and Gynecology, Faculty of Medicine, Hacettepe University, Ankara, Turkey.
* Assistant Professor of Obstetrics and Gynecology.
** Associate Professor of Obstetrics and Gynecology.
*** Pediatrician.

This study was designed to investigate the average umbilical cord length of Turkish infants delivered at term and relate it to some fetal and maternal variables. In this way we attempted to find whether there was any correlation between cord length and the various findings.

Materials and Methods

The cord lengths of 276 infants delivered by spontaneous vaginal delivery at 37-42 weeks' gestation at the Department of Obstetrics and Gynecology of Hacettepe Medical School Hospital were determined. The cords were measured with a steel ruler immediately after delivery. Cutting the cord about 10 cm. from the umbilicus is a routine practice in our hospital. Therefore, the lengths of the placental and fetal cord pieces were measured separately and then two were summed. All placentas were obtained immediately after delivery. The membranes were trimmed off the placental edge and cords were cut off close to the placentas with a pair of scissors and all blood clots were removed. The large vessels on the fetal surface were drained and the placentas were blotted free of blood. The placentas were then weighed. The infants were weighed within 10 minutes of delivery and their crown-heel lengths were measured with a steel ruler.

Details about the mother and child, such as parity, age, gestational week, fetal sex, fetal weight and length, placental weight, Apgar score, the number of coilings of the cord around the neck of the fetus and true knots in the cord were recorded.

Results

The mean cord length was 61.217 $\pm$ 13.785 cm. (range 21.3-121.9 cm.) (Figure 1).

The mean crown-heel length of Turkish infants was 50.768 $\pm$ 4.845 cm. and the mean fetal weight was 3.349 $\pm$ 266.35 g. Data of the fetal cord length and the other fetal and maternal variables are shown in Table I.

Statistical correlates between the cord length and the fetal and maternal values that were studied are shown in Table II. Significant correlations were found between the cord length and the fetal as well as placental weights and between the cord length and the number of coils of the cord around the neck of fetuses. There were no significant correlations between the cord length and the other variables studied (Table II).

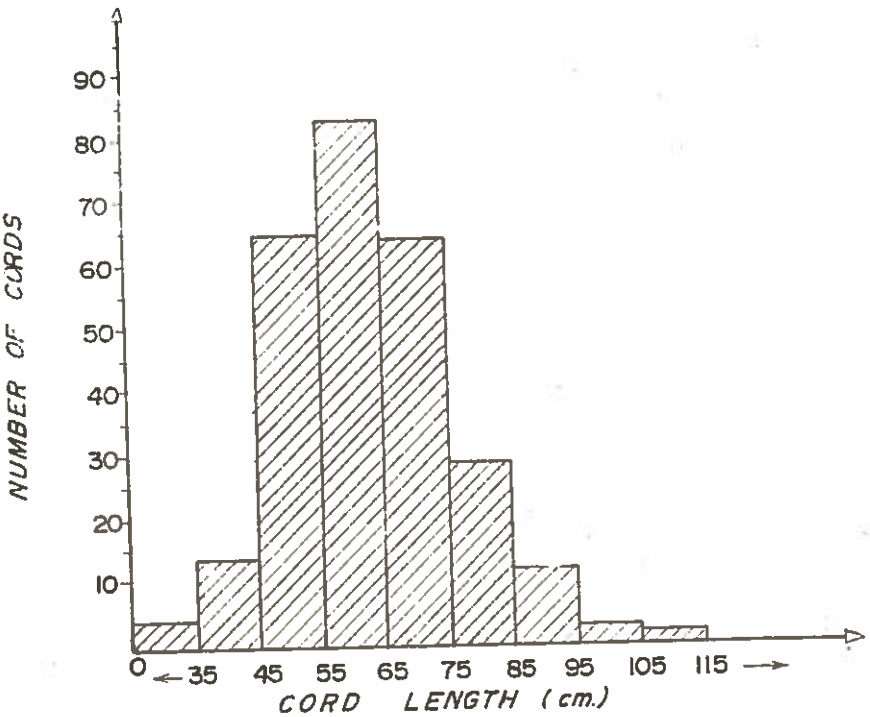

Figure 1
Distribution of umbilical cord length.

TABLE I

STATISTICAL DETAILS OF CORD LENGTH AND SOME RELATED FETAL AND MATERNAL VARIABLES

	Mean	S.D.
Age (years)	22.706	4.947
Parity	2.134	0.660
Gestational week	39.681	1.185
Fetal weight (g.)	3349.14	266.35
Placental Weight (g.)	626.236	126.442
Crown-heel length (cm.)	50.768	4.845
Cord length (cm.)	61.217	13.785

The cord was found to be coiled around the body in 34.7 % of the cases (96 cases). The findings were: cord normal in 180 cases, cord around neck once in 78 cases, cord around neck twice in 15 cases and cord around neck three times in 3 cases. There was also a positive correlation between the cord length and the number of coils ($p < 0.05$). When cord length increases the possibility of encirclement of the cord also

TABLE II
STATISTICAL CORRELATES BETWEEN CORD LENGTH AND SOME FETAL AND MATERNAL VARIABLES

Variables			
Maternal age	$x^2 = 5.83$	$p > 0.05$	NS
Parity	$x^2 = 8.15$	$p > 0.05$	NS
Gestational week	$x^2 = 9.92$	$p > 0.05$	NS
Fetal weight	$x^2 = 7.319$	$p < 0.05$	S
Apgar score	$p = 0.165$	$p > 0.05$	NS
Placental weight	$x^2 = 17.29$	$p < 0.05$	S
Crown-heel length	$x^2 = 8.1339$	$p > 0.05$	NS
Circumvolution of the cord	$x^2 = 40.81$	$p < 0.05$	S
Fetal sex	$x^1 = 6.539$	$p > 0.05$	NS

increases. We determined true knots in the cord in 4 cases. In one of them the cord length was 50 cm., and the other cord lengths were above 65 cm. (67.73 and 92 cm.) We found no significant correlation between the cord length and the possibility of true knots ($p > 0.05$).

There were 3 stillbirths in this series (1.08 %). Apgar scores of 10 cases (3.6 %) were below 6[3] (including stillbirths). The cord lengths were below 64 cm. in 8 of them, and in 2 of them above 65 cm. However, we found no statistically significant correlation between the cord length and Apgar scores ($p > 0.05$). Of the 10 cases which had 6 and below Apgar scores, coiling of the umbilical cord around the neck was found in only 2 cases, and no true knots were present in these cases. We found no positive correlation between Apgar score and the encirclement of the cord and true knots.

47.4 % of the infants were male and 52.5 % were female, and there was no significant difference in cord length between these sex groups ($p > 0.05$).

Discussion

Our findings show a wide range of umbilical cord lengths for Turkish infants delivered at term. The cord length varied between 21.3 and 121.9 cm. with a mean of 61.217 ± 13.785 cm. This mean length is similar to findings reported by authors in other countries[1, 2, 5] showing that there is no racial difference.

Spontaneous delivery of normal children occurred with cords at all lengths. Thus, if normal gestation and parturition can occur with any cord length from 21.3 to 121.9 cm., why is the cord usually more than 55-60 cm. There are many theories concerning this point. In most mam-

mals the umbilical cord is reasonably well adapted to the immediate postnatal requirements of the mother and child. While the length of the cord varies widely and is unimportant for gestation and parturition, there may be an advantage immediately after the birth the child if the cord is long. Some argue that the length of the human cord is important in order to allow the mother to pick up her helpless newborn child and carry it away from danger without exerting harmful traction on the placenta.[2] Further, it is stated that a cord of more than 46 cm. will allow the child to be placed on the breast with the placenta in utero and the reflex stimulation of suckling may promote an easy and bloodless third stage in birthing.

Of the fetal and maternal factors studied, fetal weight and placental weight were found to correlate with cord length. The other findings were not correlated. It is well known that in normal preterm and term infants there is a direct relation between birth weight and weight of the placenta. Placental weight and cord diameter are significantly smaller in the intrauterine growth-retarded infants compared to those in the normal preterm and term infants.[6-10] As the umbilical cord is also an essential part of the fetal-maternal circulatory system, it is natural that the same relation exists between the cord length and fetal and placental weight.

Many authors have observed that there is no significant growth in cord length after 28 weeks of gestation.[1, 2] Also there is general agreement that the weight of the placenta does not increase appreciably after the thirty-sixth week of gestation.[9] The content of desoxyribonucleic acid (DNA) in normal placentas does not increase beyond the thirty-sixth week. After this time the placental cells cease to multiply and any further increase in placental weight is the result of cell enlargement and growth of fibrous tissue. Therefore, birth weight and placental weight are not as well correlated after 36 weeks. We reached the same conclusion for cord length. After the 36th week of gestation there is no significant correlation between the cord length and gestational week.

The cord was found to be coiled round part of the body in 34.7 % of the cases. The mean cord length seemed to increase according to whether the position of the cord was normal or around the neck of the fetus. There was a positive correlation between the cord length and the number of coils ($p < 0.05$). We determined true knots in the cord in 4 cases, and we found no significant correlation between the cord length and the possibility of true knots.

The coiling of the umbilical cord around the neck of the fetus causes decreased fetoplacental circulation. In the majority of the cases it was

possible to correlate the oxygen values in the umbilical vessels with the clinical state of the newborn (evaluation according to Apgar)[3, 4, 11, 12] However, we did not investigate this in our study. We did not determine any positive correlation between Apgar score and the encirclement of the cord and true knots. In fact, the question of whether the development of metabolic acidosis in some cases of umbilical cord encirclement is only a consequence of coiling or whether placental dysfunction plays a decisive or a secondary role still remains to be answered.[4]

Finally, it has been stated that variable cord lengths may be due to the fact that umbilical blood vessels grow in one dimension only, independent of contiguous structures. The factors responsible for this fetal vascular growth need further study because they may be linked first with Hoboken's valves or endothelial cushions in the umbilical arteries or secondly, with intravascular pressure in the umbilical arteries.[1]

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Volume 19 / No. 4 / October 1986 / pp. 165 – 170

Radical Vulvectomy For Squamous Cell Carcinoma of the Vulva

Mortality, Recurrence and Complications

Ali Ayhan, M.D.* / Kunter Yüce, M.D. / Sakıp Pekin, M.D.*** / Ayşe Ayhan, M.D.**** / Emek Özen, M.D.***** / Bilal Memiş, M.D.******

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology and Pathology, Hacettepe University, School of Medicine, Ankara-Turkey.

* Associate Professor of Obstetrics and Gynecology.
** Assistant Professor of Obstetrics and Gynecology.
*** Professor of Obstetrics and Gynecology.
**** Assistant Professor of Pathology.
***** Professor of Pathology.
****** Senior Resident of Obstetrics and Gynecology.

Summary

Twenty-one patients with squamous cell carcinoma of the vulva who were subjected to radical vulvectomy and inguinal-pelvic lymphadenectomy were studied. The overall mortality rate was 24 %. Operative and tumor related mortality was 9.5 % and 14.2 % respectively. Recurrence were seen in 5 patients. The most common complications were wound infection and breakdown. Related literature is reviewed.

Key Words: Vulvar carcinoma, Radical vulvectomy, Lymphadenectomy, Mortality rate.

Introduction

Squamous cell carcinoma is the most common malignant tumor of the vulva, comprising over 90 % of all vulvar malignancies and accounting for 4 % of all genital malignancies in women.[1] The frequency of this disease increases with age, and it is most common in women over the age of 75, in whom its incidence is 19.9 per 100.000 women.[2] The

standard primary therapy is radical vulvectomy and inguinal lymphadenectomy, irrespective of the size of the vulvar lesion or the presence or the lack of disease in inguinal lymph nodes and additional deep pelvic lymphadenectomy in selected patients. The prognosis for this carcinoma is directly related to the size-stage of tumor, the area of lesion, grade, depth of invasion, lymph node metastasis at the time of diagnosis and treatment are undertaken.[3] In stage I-II disease, the corrected 5-year survival rate should approach 90 %. The operative mortality varies from 1 % to 20 % in the literature.[4] Recurrence may be local or distant and over 80 % will occur in the first 2 years after therapy.[4]

The purpose of this study is to evaluate the mortality, recurrence and complications in patients who were subjected to radical vulvectomy, inguinal and pelvic lymphadenectomy for squamous cell carcinoma of the vulva.

Materials and Methods

Twenty-one patients with squamous cell carcinoma of the vulva treated at the Division of Gynecologic Oncology from 1964 to 1986 were reviewed. Data were obtained from patients' clinical records, pathology reports and follow-up records. The age of these 21 patients ranged from 32 to 83 years with a mean of 56.7 $\pm$ 13.2 anda median of 56 years. Five patients had hypertension and another four patients had diabetes mellitus. Although 90.5 % (14) of the patients had one or more pregnancies, 0.5 % (2) did not have any pregnancies. Of the 21 patients, 9 had ulcus, 7 had ulcus-mass, 4 had only vulvar mass and one had discoloration. Lesions were seen on the clitoris in 5 patients, on the labia in 14 patients, and in the fourchette and in the perineum in two patients. The final diagnosis was made by the histologic examination of specimens obtained from each patient. Of the 21 patients 9 had stage I disease, 11 had stage II and one had stage III disease according to FIGO and TNM (Table II). All patients were subjected to radical vulvectomy, bilateral superficial and deep inguinal lymphadenectomy. After removing the Cloquet node in every patient, it was sent for freezing. Additional pelvic lymphadenectomy was performed in 12 patients who had central involvement (7) and who had a positive Cloquet (5).

In addition, radiation therapy was given to patients with inguinal or pelvic node metastase and with grade 2 or more.

Pathological review of the slides of the original biopsies and the operative specimens was performed; particular note of the depth of stromal invasion, grade, lymphatic and vascular channel involvement

and lymph node metastasis was made. Lymph node metastasis was found in 9 of 21 patients. The correlation between lymph node metas tasis and localisation of tumor is shown in Table I. As shown in Table I, 5 patients with tumor of the clitoris had inguinal, one had inguinal and pelvic lymph node and only one did not have any lymph node metastasis.

TABLE I
LYMPH NODE METASTASES AND LOCALIZATION OF THE TUMOR

Localization	Lymph node metastasis Present	Absent	Total
Clitoris	4*	1	5
Labia, fourchette-perine	5	11	16
Total	9	12	21

* One patient had concomitantly pelvic node metastasis

The follow-up time varied from 3 to 17 years.

Results

The overall mortality rate was found to be 24 %. Of the five patients who died, two (9.5 %) were lost due to postoperative complications and three (14.3 %) had tumor related deaths (Table II). One of two patients who died postoperatively was lost due to the pulmonary emboli on the 14th day of surgical procedure and the other one because of wound infection-sepsis on the 24th day of surgical intervention.

The interval between initial procedure and at the time of death in three patients with tumor related deaths was 2.5, 4 and 5.5 years, respectively. The correlation between the stage and patients death is given in Table II.

TABLE II
STAGE AND MORTALITY RATE

Stage	Not tumor-related deaths (due to the postop. comp.)	Tumor-related deaths	Total patients
I	1*	1	9
II	1**	1	11
III	–	1	1
Total	2	3	21

* One patient died from pulmonary embolus on the 14th day of surgical procedure
** One patient died from sepsis, on the 24th day of initial surgery

The mortality rate was 33.4 % in patients (3/9) with lymph node metastasis and was 16.7 % in patients (2/12) without lymph node metastasis (Table III).

TABLE III
LYMPH NODE METASTASIS AND DEATHS

Lymph node metastasis	Deaths	Total	%
(+)	2 (3)	8 (9)	25
(−)	1 (2)	11 (12)	9
Total	3 (5)	19 (21)	15.8

( ) including all deaths and patients

Recurrence was observed in 5 patients after surgical intervention (Table IV). Of these 5 patients 3 died, as noted above.

TABLE IV
RECURRENCES SEEN IN FIVE PATIENTS

Recurrence	Stage	Lymph node metastasis	Interval between initial surgery and recurrence	Therapy	Results
Local vulva	I	−	13 years	S	Normal in 3rd year
Local vulva	II	+	2 years	S	Normal in 3rd year
Diffuse	II	+	5 years	R + Che	Exitus in 6th month
Diffuse	I	+	1.5 years	Che	Exitus in 1st year
Diffuse	III	−	1.5 years	R	Exitus in 1st year

S: Surgery R: Radiation Che: Chemotherapy (as Bleomycin)

Some complications such as wound infection-breakdown in 10 patients, lymphocyst in 3 patients, leg edema in two patients, tromboph-lebitis in 3 patients, sexual dysfunction in another three patients and severe scars in one patient occurred after initial surgical procedure.

Discussion

Squamous cell carcinoma is the most common malignant tumor of the vulva, comprising over 90 % of all vulvar malignancies.[1] In the present series, this figure was 82.0 % of all patients with vulvar malignancies.

Radical vulvectomy with inguinal lymphadenectomy should be the standard surgical procedure if the primary tumor and regional metastases are operable.[5] Pelvic lymph node dissection was recommended in patients with metastases to the Cloquet and central tumor (clitoris, comissura posterior).[6] In this study, 12 patients were subjected to ra-

dical vulvectomy with bilateral inguinal and pelvic lymph node dissection and the remaining 9 had radical vulvectomy and bilateral groin dissection. Pelvic lymph node dissection was routinely performed in our patients with positive Cloquet and central tumor. Although pelvic metastases occur after inguinal metastasis, it may be seen without inguinal node metastases. The overall risk of pelvic node metastases is between 8.5 % and 16 % in patients with positive inguinal node.[1-4] In our series positive pelvic lymph node was seen in one patient who had inguinal node metastases.

The prognosis of squamous cell carcinoma of the vulva is directly related to the extent of disease, stage, clinical and pathologic status of the inguinal nodes, depth of invasion, vascular invasion, the area of the tumor and treatment are undertaken.[3,5,6] Hacker et al, reported a 5-year survival rate of 98 % in stage I disease and 90 % in stage II[7]. Regardless of the stage, if negative lymphatic nodes were present, there was a 96 % survival rate. This dropped to 66 % if positive nodes were present.[4,8] The mortality rates were 33.3 % for patients with positive lymph node and 16.7 % for patients without positive lymph node in our series.

Operative mortality varies from 1 % to 25 % in the literature; at radical vulvectomy it is 1-3 % and at radical vulvectomy and groin lymphadenectomy it is 5-10 % and at pelvic exenteration it is 6-25 %.[4,5,9] Operative mortality, in this series, was 9.5 %.

High rates of wound breakdown, local infection-sepsis, pelvic relaxation, lymphedema, decreasing of sexual satisfaction have accompanied radical vulvectomy, groin and pelvic node dissection.[10] Wound infection and dehiscence have been reported with an incidence that varies from 20 to nearly 60 %.[11] This figure, in this study, was 42.8 %. Removing less amount of skin and decreasing the undermining of the skin flaps have reduced the incidence of wound breakdown. Suction drainage has also added to decreased morbidity. Careful debidement and vigorous care to keep the wounds clean and dry will result in almost adequate healing.

Lymphedema of the lower extremities is another major problem, especially in patients who have had both inguinal and deep pelvic node dissection. In the study reported by Podratz, Symmonds and Taylor varying degrees of lymphedema of the lower extremities occurred in 69 % of their patients.[12] Lymphedema of lower extremities was seen in three patients in the present study. The incidence of this debilitating long-term complication can be reduced by routine use of custom-made

elastic support hose during the postoperative period while collateral pathways of lymph drainage are being developed.

The development of a lymphocyst in the groin area is an infrequent occurrence and it usually resolves spontaneously. Occasionally, intermittent aseptic aspiration of the fluid and infection of tetracyclin facilities resolution of these collections. Lymphocyst developed in three patients and resolved spontaneously in our series.

Symptoms related to stress incontinence and the development of a cystocele or rectocele are sometimes reported by these patients.

Removal of significant vulvar tissue, particularly the clitoris, can result in decreased sexual satisfaction.

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Volume 19 / No. 4 / October 1986 / pp. 171 – 175

Unusual Karyotype-46XY, t(15q,22q)-in Primary Thrombocythemia Terminating in the Megakaryocytic Leukemia

Meral Beksaç, M.D.* / Lennart Iselius, M.D. / Åke Öst, M.D.,Ph.D.*** / Bengt Lagerlöf, M.D.*** / Peter Reizenstein, M.D.***

Summary

A case of Primary Thrombocythemia is presented. Initial hematological examination showed a platelet count of $2700x10^9/l$ and a WBC of $4.8x10^9/l$. 52 % of peripheral blood cells were blasts and 51.5 and 68.5 % of the bone marrow were blasts and promyelocytes/promonocytes respectively. Chromosomal analysis revealed 46XY,t(15q,22q). At autopsy megakaryocytic leukemia infiltrating the bone marrow and the white pulpa of spleen was detected. Chromosomal abnormalities of primary thrombocythemia and megakaryocytic leukemia are reviewed.

Key Words : Karyotype, Primary thrombocythemia, Megakaryocytic leukemia.

Introduction

Primary thrombocythemia (PT) is a rare myeloproliferative disorder characterized by proliferation of hematopoietic tissues predominantly megakaryocytes and resulting in marked thrombocytosis. Some of the clinical and laboratory features of Chronic Myelogenous Leukemia and

Departments of Medicine, Clinical Genetics and Pathology, Karolinska Institute and Hospital, S-104 01 Stockholm, Sweden.
* Division of Hematology, Department of Medicine.
** Department of Clinical Genetics.
*** Department of Pathology.

Polycythemia Vera such as leucocytosis and splenomegaly may also be present. In order to distinguish PT from these disorders, a platelet count in excess of $10^9/l$, marrow megakaryocyte hyperplasia, a normal red cell mass and absence of Philadelphia chromosome are helpful. Various karyotypes have been described in PT, but the dominant finding is a normal karyotype.[9, 12] PT can also evolve into acute leukemia. In this report we describe a thrombocythemia patient with a translocation between chromosomes 15 and 22 who developed a megakaryocytic leukemia.

Case Report

A 47 year old male with gingival hyperplasia showed thrombocytosis $2700x10^9/l$, hemoglobin 94 g/l and WBC $4.8x10^9/l$.52 % of the white cells. In the peripheral blood smear were megakaryocyte or monocyte like blast cells which did not carry any antigens against the monoclonal antibodies Leu MI, OK IaI, OKT3, or J5. Plasma lysozyme was 8.6 and 5.1 mg/l(Normal: 5-15) and urine lysozyme was <1.0 mg/l(Normal: <20 mg/l). The bone marrow had a cellularity of 90 %. The number of blasts and promyelocytes/promonocytes were 103/200 and 137/200, respectively. There was an abundance of megakaryocytes, each with one small pycnotic nucleus. There were no Auer rods, or any sign of myelofibrosis. Peroxidase and esterase stains were negative, and sodium floride inhibition was positive. These data suggested a megakaryocyte leukemia. Despite treatment with rubidomycin, cytosine arabinoside, vincristine and low dose heparin, and after he became febrile, treatment with gentamycine, carbenicillin, trimethoprim-sulfamethexasole and cephalosporin there appeared melena, Pseudomonas septicemia and an axillary abscess after which the patient died on the 14th day. Adequate transfusions of erythrocytes, platelet concentrates and freshly frozen plasma were given according to vital signs and blood counts.

A bone marrow specimen was taken at the time of diagnosis. G banding consistently showed a translocation between the long arms of the chromosomes 15 and 22. In contrast, cultured fibroblasts had a normal male karyotype.

At autopsy, bone marrow was highly cellular and full of megakaryoblasts and megakaryocytes. Similar infiltration was observed in the reduced splenic white pulpa.

Discussion

Both Primary Thrombocythemia (PT) and Megakaryocytic Leukemia (M7) are rare disorders. Marked peripheral thrombocytosis and an abundance of mature megakaryocytes in the bone marrow were findings in favour of PT. The proliferation of poorly differentiated megakaryoblasts in the peripheral blood, bone marrow and spleen suggested progression to M7. To our knowledge our finding of t(15q,22q) has not been reported in either PT or M7. Various karyotypes have been described in PT which are summarized in Table I. The initial findings of Zaccaria which suggested a constant 21q- deletion was later found to be nonspecific.[5] As the number of studied patients increased, normal karyotype appeared as the dominant finding.[9, 12] Third International Workshop on Chromosomes in Leukemia have concluded that only 5.3 % PT patients showed definite chromosomal abnormalites.[9]

TABLE I
CHROMOSOMAL ABNORMALITIES OBSERVED IN PRIMARY THROMBOCYTHEMIA

Chromosome changes	Reference
Normal karyotype	4, 9, 12
t(9, 22)	4, 6, 7, 13, 14, 15
Complex t(9, 22, X)	11
21q-	5
Extra chromosomes (9,8 or10)	1, 4
Aneuploidy (groups B, C, D)	3
Dicentric chromosome, acentric fragment	2
Partial trisomy (2q+)	9
Pseudodiploidy	9

TABLE II
CHROMOSOMAL ABNORMALITIES OBSERVED IN MEGAKARYOCYTIC LEUKEMIA

Chromosome Changes	Reference
Various abnormalities of 21	10, 19, 20
t(9, 22)	8, 16, 18
Trisomy 9 (and t(1, 9) + t(12, 13))	8
t(12, 13)	16
Trisomy 8, Trisomy 2, abnormalities of 1	20
t(11, 22)	20
Hypodiploidy	17

Cytogenetic abnormalities of chromosome 21 have been associated with M7 as well as with PT.[10, 19, 20] There are other abnormalities observed in M7 cases (Table II). At present no specific karyotype for M7 has been defined. Our patient carrying the features of both PT, initially and M7 later, had a crromosomal abnormality which has not been defined in any of the diseases. Obviously, further cases have to be studied before any conclusions can be drawn regarding the correlation between specific chromosome aberrations and M7.

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Hacettepe Medical Journal
Volume 19 / No. 4 / October 1986 / pp. 177 – 184

Pelvic Actinomycosis with and without the Presence of Intrauterine Device

Kutay Biberoğlu, M.D.* / Tekin Durukan, M.D.* / Emek Özen, M.D. / Mehmet Erk, M.D.*****

Summary

Three cases with pelvic actinomycosis are presented. Besides the fact that actinomycotic involvement of the pelvic viscera is a rare occurrence, the inflammatory process was unilateral and isolated in all three cases. In the first patient the source of the infection was thought to be the bowel whereas in the second one, it was suggested the intrauterine device may have played a part in the pathogenesis of the disease. In the last case, we found no clue as to what the predisposition could have been in the development of the disease.

Key Words: Pelvic actinomycosis, intra-uterine device, unilateral pelvic abscess.

Introduction

Actinomyces Israelii is an anaerobic gram positive filamentous bacterium which is a common saprophyte of the oropharynx and the intestinal tract. Under normal circumstances, it cannot penetrate intact anatomical barriers, therefore requires tissue injury like bowel surgery or ruptured appendix or the presence of a foreign body like intrauterine device (IUD), for the development of pelvic actinomycosis.

Until the first cases of pelvic actinomycosis associated with intrauterine device were reported,[1,2] direct extension from the gastrointes-

Departments of Obstetrics and Gynecology and Pathology, Hacettepe University, School of Medicine, Ankara - Turkey.

* Associate Professor of Obstetrics and Gynecology.
** Professor of Pathology.
*** Instructor of Obstetrics and Gynecology.

with oral tetracycline and intramuscular penicillin procaine for an additional 10 days. When she was seen 6 weeks post-operatively at the out-patient GYN clinic, she did not have any complaints and physical findings were normal. In December 1983, she presented to have her undesired 8 weeks pregnancy terminated.

Case 3: A 39 year old, married woman, gravida 6, para 2, abortus 4, was seen at the out-patient GYN clinic in June 1985. Her main complaints were meno-metrorrhagia for the last two months and lower abdominal pain on her right side. She had had 4 terminations of unwanted pregnancies in the past with no postabortive complications. Her vital signs were all normal. The pelvic examination findings were as follows the vagina was relaxed and the cervix was multiparous There was a right sided adnexal mass of 10 cms. in size, fixed in the pelvis with undefined borders and a slightly enlarged, myomatous uterus in bimanual examination. Pre-operative laboratory tests were normal.

She underwent laparotomy on June 27, 1985 .The uterus and left adnexal area were free of any pathology. An isolated inflammatory mass of 7 cms by 8 cms. in dimension involving the right tube and ovary was detected. The appendix was long and erectile, therefore an appendectomy was also performed besides hysterectomy and bilateral salphingo-oopherectomy. Post-operative antibiotic regimen included penicillin G aqueous, gentamycin and chloramphenicol for 10 days. Her post-operative course was uneventful and she was discharged in good condition.

Pathology: Histologic examination of the removed ovaries revealed multiple microabscesses, some of them containing colonies of Actinomyces. Sulfur granules were also seen. Gram stain demonstrated that these granules were composed of delicate branching beaded gram-positive filaments, as well as many pleomorphic coccobacillary forms. The presence of these organisms was further confirmed by PAS stain. There was endosalphingitis of non-specific type in the removed tube specimens. Light microscopic exam of the endometrium and the myometrium in the hysterectomy specimens revealed no peculiar pathology.

Discussion

The route of infection in genital actinomycosis is still little understood. Actinomyces Israelii is not a normal inhabitant of the female genital tract of healthy women.[4] Such a source of infection is quite probable if there is prior involvement of the appendix or caecum, particularly if adnexal disease is present on the right side. In addition to the direct spread from the bowel, the entrance may well be by direct extension

from the exterior of the patient's bowel across the perineum to the vagina and the rest of the genital tract. The presence of an intrauterine device may provide the site of entry by acting as a wick with its string and by eroding the endometrium. A combination of chronic tissue injury, a foreign body and the vaginal anaerobic flora creates a favorable environment for the growth of actinomycetes.[6] A copper "IUD" might produce an even more favorable medium because of the reducing power of metal.[14] The precise role of an "IUD" in facilitating infection is conjectural. Reports in the literature citing the occurrence of genital actinomycosis in "IUD" users arouse the suspicion that "IUD" somehow predisposes the upper genital tract to this infection.

It is also possible that the tube and ovary may be infected by hematogenous spread from the infected teeth and gingiva[1] since some of the species of the actinomycotic organisms have been considered normal inhabitants of the carious teeth.[13] The source of actinomycotic infection in this report may have been the ileocecal region in the first case since the patient had had an appendectomy in the past (although not very likely since the infected ovary was the left one and strangely enough the right tube was intact) and the genital tract associated with uterine perforation and "IUD" in the second patient. In the third case, no predisposing factor as a potential source could be detected.

The length of "IUD" use at the time of diagnosis of pelvic actinomycosis ranged from 15 months[14] to 25[1] in the literature. In our case, the time interval was only 7 months. More important than the duration was the occurrence of unrecognised uterine perforation during termination of her pregnancy 3 months prior to the diagnosis of actinomycotic ovarian abscess at laparotomy.

The organism which grows as a facultative anaerobe is difficult to culture and in most of the cases in the previous reports including ours, the diagnosis has been based on the finding of typical granules consisting of Gram positive branching bacilli in tissue sections.[8, 13-16] Since recognition of the disease has never been made pre-operatively by the clinician, the pathologist must have a high index of suspicion especially when the adnexal inflammatory process is unilateral.[8] This interesting feature of finding unilateral tuboovarian abscess with the "IUD" has led some authors to suggest that this association may represent a "definite clinical entity". Actually, like ours', most of the previously reported cases of actinomycotic tuboovarian abscess were unilateral. There was no evidence that the infection had spread beyond the genital tract in any of the patients reported.[8] Actinomycosis of the urinary bladder

was reported in an "IUD" user in whom the lesion in the bladder was thought to be a malignant neoplasm.[17]

A retrospective study by cervico-vaginal smears showed a prevalence (19.7 %) of actinomycetes-like organisms among "IUD" users whereas no positive smears were obtained in non-IUD users.[11] Since it is possible that Actinomyces may be confused with other morphologically similar anaerobic organisms, accurate identification of actinomycosis in the uterine environment in the presence of "IUD" by cervico-vaginal smears is very difficult.[7, 11] The demonstration of actinomycotic involvement of the endometrium by culture or histology has never been made yet.[1] The rarity of reported cases of tuboovarian actinomycosis as a complication of "IUD" usage seems to favor the suggestion that some other unknown factor(s) play a role in the development of clinical pelvic infection. It is also possible that in some cases of adnexal inflammation, the diagnosis of the disease is being missed by the pathologist if she does not carefully search many sections of the tissue looking for sulfur granule.

Penicillin appears to be the drug of choice in the treatment of actinomycosis. Surgical extirpation of infected tissue in combination with penicillin offers the best therapeutic results.[1, 6, 11-13, 15, 16, 18] For positive cervico-vaginal smears, therapy has included "IUD" removal, antibiotic treatment or a combination of both.[11] The operative management of the second patient in the present report represents a deviation from "established" gynecologic practice. The reasons for removing just the involved ovary and the adjacent fallopian tube, leaving the rest of the pelvic organs intact were, her desire for future fertility, the patient's young age and the normal appearance of the opposite adnexal structures.

There are few reports in the literature where similar conservative surgical approaches were performed successfully.[5, 14] In the above cited report[14], the patient conceived and carried a full term pregnancy following conservative surgical treatment of a unilateral actinomycotic tubo-ovarian abscess. We believe that these patients on whom conservative surgery is performed should be observed for some time before cure is assured since recurrences have been reported in such cases.[12]

Most recently Persson from Sweden reported a very interesting and innovating study[19] on Actinomyces-like organisms (ALOs) detected in Papanicolaou-stained cervico-vaginal smears. Of 367 asymptomatic women examined, 20 (5 %) were found to harbour the organism. When women without IUDs were compared with women with current IUD use for three years, six years and for more than six years, no statistically significant differences in colonization frequencies were found. Persson

also performed a longitudinal study where 15 healthy women were examined three times a week for two consecutive menstrual periods. Five women were IUD users, five used oral contraceptives and five used no contraception. All women examined harboured A. Israelii, the colonization frequency varying between 7-74 % of sampling occasions. From this study it is concluded that A. Israelii occurs as a part of the normal genital flora and that IUD use per se does not increase colonization frequency. The identification of A. Israelii in the genital tract does not predict disease.

In summary, the possibility of actinomycosis should be considered whenever a patient who carries an IUD or mentions having had a bowel injury in the past, develops evidence of pelvic inflammation especially if the adnexal involvement is unilateral. The pathologist should search carefully for sulfur granules, particularly when a granulomatous process is seen histologically. In young patients where future fertility is of concern, a more conservative surgical treatment may be considered.

There is no agreement on dosage and duration of antibiotic therapy. It has been suggested that penicillin therapy should continue for at least 60 days.[1] Most of the authors, however conceded that the beneficial response of penicillin is only temporary and recommended surgery as the best therapy. In the clinical management of the 3 cases presented, the mainstay of therapy was the surgical extirpation of the involved pelvic organ combined with antibiotics for shorter than the recommended period of time. Whether administration of long term antibiotic regimen is really essential or not, needs to be further studied in larger series.

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Hacettepe Medical Journal
Volume 19 / No. 4 / October 1986 / pp. 185 – 189

Simultaneous Tubal and Intra-Uterine Pregnancy Following Hyperstimulation Syndrome with Combined Clomiphene and Gonadotropin Therapy

Kutay Biberoğlu, M.D.*

Summary

A case of combined tubal and intrauterine pregnancy is presented. The difficulties in diagnosis and proper management of this rare entity are discussed.

Key Words: Combined pregnancy, infertility, ovulation induction, hyperstimulation syndrome, human menopausal gonadotrophin.

Introduction

In rare instances tubal pregnancy may be complicated by a coexisting intrauterine gestation, a condition designated as combined pregnancy. This obstetric rarity can be encountered more often in patients undergoing ovulation induction therapy. Since it can have serious and fatal consequences, physicians dealing with infertility problems should be aware of this possibility.

This report presents a case of a typical combined pregnancy.

Case Report

A 25-year-old woman was first examined at the Infertility -Reproductive Endocrinology Clinic for oligo-amenorrhea and primary infer-

* Associate Professor, Department of Obstetrics and Gynecology Faculty of Medicine, Hacettepe University, Ankara, Turkey.

tility in March 1983. Gynecologic history revealed abnormal menstural cycles which occurred every 60 to 90 days. Initial infertility evaluation showed normal semen analysis and bilateral tubal patency with a normal shaped uterine cavity on the hysterosalphingogram. Hormonal workup was compatible with an ovulation indicating no specific endocrine abnormality except that the serum luteinizing hormone level was increased four-fold with low serum follicle stimulating hormone values. She was not obese and had no clinical feature of hirsutism. Peripheral androgen levels were all within normal limits. Clomiphene (Clomid-Merrell) was started at a dose of 50 mg./day between days 5 through 9 with Human Chorionic Conadotropin (H. C. G.) injection on day 14 of the cycle. When she failed to respond to Clomiphene, as indicated by no ovulation during 6 months of treatment with increasing amounts of Clomiphene (up to 200 mg./day for 5 days), Human Menopausal Gonadotropin (H. M. G.) was added to the ovulation induction regimen.

Ovarian follicular ultrasonography and estrogen monitoring was begun when cervical mucus revealed the effect of estrogen stimulation. Clomiphene was given, 50 mg/day from 3 rd through 7 th days followed by HMG (Humegon-Organon) injections of 2 ampoules/day (75 units of FSH&LH in each) between 8 th and 15 th days (total of 16 ampoules administered) of the treatment cycle. Two dominant follicles on each ovary (26x22 mms. and 24x20 mms.) were detected ultrasonographically on the 15 th day of the treatment cycle.

The patient received 10000 units of HCG intramuscularly on day 16, when the serum estradiol concentration reached 1300 pg/ml. Her basal body temperature rose from 36.4 °C to 36.9 °C the next day after HCG administration and stayed elevated on the BBT chart. Despite the biphasic ovulatory BBT curve, the ultrasonography showed further increase in the diameters of both the dominant follicles on each ovary (28x26 mms. right and 36 x 30 mms. left).

No further treatment was given to induce ovulation for fear of creating hyperstimulation. Periodic pelvic examinations indicated mild ovarian hyperstimulation during the following week and she was adviced to rest at home taking her daily body weight and to report in case severe abdominal pain took place. On Jan. 27, 1985 (16 days following HCG administration) she was admitted, complaining of abdominal distention and pain accompanied by nausea.

Severe hyperstimulation was diagnosed based on bilateral ovarian enlargement filling the whole pelvic cavity, minimal ascites, pleural

effusion and vulvar edema. On jan. 28, serum progesteron, estradiol and B-HCG levels were as follows P: 50 ng/ml., E_2: 1300 pg/ml., B-HCG 7.20 ng/ml (N: less than 0.75 ng/ml.). During her stay in the hospital, the vital signs and serial blood hematocrit and electrolytes remained stable. The B-HCG levels continued to rise thereafter, and was found to be 25 ng/ml (a three-fold increase in 8 days) on Feb.6, 1985. A week later (Feb. 13 th.) B-HCG level stopped increasing at a level of 25.7 ng/ml. Pelvic ultrasonography on Feb. 27, revealed an intrauterine gestational sac with a single fetus of 7.5 weeks with no cardiac activity, accompanied by bilateral ovarian enlargement of 113 x 62 ms and 99 x 94 mms in dimensions respectively. On the same day, urine pregnancy test (Neo-Planotest Duoclon) was positive. The patient was informed that the fetus was no longer alive but based on the positive urine pregnancy test, she refused to have a dilatation and currettage. Her pleural effusion, ascites and vulvar edema dissappeared and she felt more comfortable. She was discharged upon her request and her repeat urine pregnancy tests remained positive on March 1,4,7 and 15, 1985. On March 15, her repeat ultrasonic examination confirmed the diagnosis of an intrauterine missed abortion and hyperstimulated ovaries. She eventually agreed to have a curettage based on the second pelvic ultrasound report and a negative urine pregnancy test. On March 18, 1985, a dilatation and vacuum curettage was performed under general anesthesia. The analysis of the tissue obtained was compatible with the diagnosis of a missed abortion. Examination under general anesthesia revealed bilateral ovarian cysts of 6 cms. in diameter on each side. Approximately 6 hours following the procedure the resident in charge informed that the blood pressure was declining with a rapid pulse rate. The abdomen was tender with signs of rebound. Undetected uterine perforation was suspected and she was immediately taken to the operating room and a laparotomy was performed. Free blood measuring a liter and a half was seen in the peritoneal cavity with a ruptured right tubal ampullary pregnancy. A conservative tubal surgery was not feasible due to the extreme tubal damage therefore a right partial salpingectomy was performed. Both ovaries were enlarged which is compatible with hyperstimulation. The patient made an uneventful recovery and was discharged on the 6 th postoperative day. Microscopic examination confirmed the diagnosis of intrauterine and tubal pregnancies.

She developed regular menstrual cycles following combined pregnancy and conceived spontaneously, 4 months later. She has delivered a healthy baby boy at the time of this writing.

Discussion

The incidence of combined pregnancy is 1/15000 to 1/30000 births with the intrauterine fetus surviving in one of 3 cases.[1] Berger reported two cases of simultaneous intrauterine and tubal pregnancy following induction of ovulation with clomiphene therapy in one and gonadotropin treatment in the other.[2]

In this rare and specific type of complication, medical literature indicates that tubal pregnancy may terminate early and intrauterine pregnancy may be lost at the same time, or tubal pregnancy may terminate early and intrauterine pregnancy may remain intact. As in the presented case, the uterine pregnancy may be lost first and the tubal one may rupture later.

Most of the authors believe that the spontaneous abortion rate is increased in pregnancies that follow clomiphene and/or gonadotropin therapy. Faulty ovum formation, multiple pregnancy and corpus luteum inadequacy (in the case of clomiphene therapy) are possible consequences of ovulation induction that could increase the abortion rate. Ovulation induction causing maturation of multiple follicles, results in the secretion of estradiol and other sex steroids above physiologic levels. Mc Bain et al., suggested that an unexpectedly high rate of ectopic pregnancy after conceptions following gonadotropin-induced ovulation was due to this high rate of estrogen production affecting oviductal motility.[3] Schenker et al., reported that as many as 1 % of pregnancies that follow gonadotropin treatment might be complicated by an unusual problem with the occurrence of intrauterine and extrauterine pregnancies simultaneously.[4]

A laparoscopy should have been done along with curettage as an auxiliary diagnostic procedure on the case presented, but it was not considered because multiple ultrasonic examinations and pelvic examination under anesthesia revealed bilateral adnexal masses compatible with hyperstimulated ovaries. Re-evaluating the presented case retrospectively, several clues such as the occurrence of two dominant follicles on each ovary and positive pregnancy tests lasting long after ultrasonic diagnosis of intrauterine fetal death should have led us to consider the possibility of a combined intrauterine and tubal pregnancies.

This possibility creates an obligation for the clinician to differentiate between concurrent intrauterine and extrauterine pregnancy rather than ovarian hyperstimulation syndrome when investigating adnexal enlargements after gonadotropin-induced ovulation.

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Hacettepe Medical Journal
Volume 19 / No. 4 / October 1986 / pp. 191 – 194

Bone Involvement in a Patient with Acne Fulminans

Nazif Kürkçüoğlu, M.D.* / Fikret Kölemen, M.D.* / Tülin Akan, M.D.* / Sevinç Akkaya, M.D.**

Summary

Acne fulminans which runs an acute course is characterized by ulcerated skin lesions with systemic manifestations. Musculoskeletal system involvement is seen in more than half of the cases. Review of the English literature revealed 40 such cases. To the best of our knowledge, acne fulminans associated with bone lesions has not been reported in Turkey. Such a case is presented here.

Key Words: Acne Fulminans, Bone Involvement

Introduction

Acne fulminans is an acute form of acne and has a predilection for young men aged between 13 to 22 years.[1] Besides painful and scarring cutaneous lesions, systemic manifestations such as fever, fatigue and musculoskeletal pain are usually present. Leukocytosis, elevated erythrocyte sedimentation rate (ESR), hematuria, and radiological or scintigraphic abnormalities suggestive of musculoskeletal system pathology are among the laboratory findings.

Case Report

A 19 year-old man was admitted to the hospital for evaluation of painful skin lesions on his face. He had had mild acne for the last two years and several treatments including tetracycline hydrochloride had been employed with only a temporary beneficial effect. Five days before admission he experienced an intense musculoskeletal pain most notably on the presternal region.

Department of Dermatology, Faculty of Medicine, Hacettepe University, Ankara, Turkey.
* Associate Professor.
** Professor.

Physical examination disclosed painful, inflammed pustules and ulcerated nodules on the face (Figure 1). On palpation there was deep pain at the sternal region. Other positive findings included fever, weakness and weight loss.

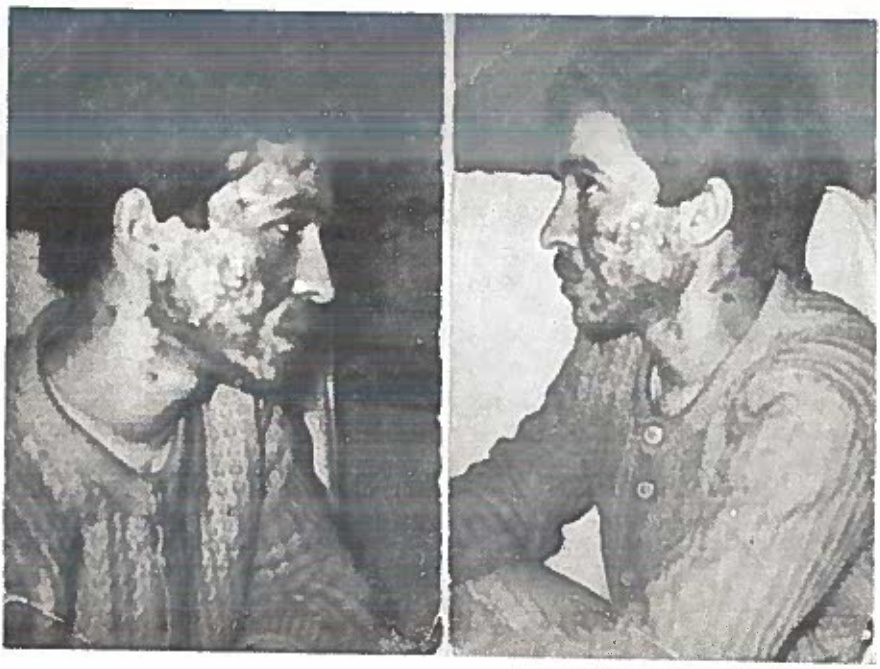

Figure 1
Painful inflammed pustules and ulcerated nodules on the face.

Laboratory studies revealed the following values: hemoglobin, 12.0 g/dL; white blood cell count, 15.000/cu mm with 73 % neutrophils, 20 % lymphocytes, 6 % monocytes, and 1 % eosinophils; hematocrite, 42 %; ESR, 62 mm/hr. Staphylococcus epidermidis was isolated from the pustules on the face.

The following laboratory findings were all normal or negative: serologic test for syphilis, urinalysis, platelet count, blood urea nitrogen, leucocyte function tests, fasting glucose level, lactic dehydrogenase, alkaline phospatase, serum albumin and total protein levels, uric acid, creatinine, immunoglobulin levels, antinuclear antibody titer, rheumatoid factor, complement components C_3 and C_4 levels. Blood cultures were negative. Roentgenograpic examination of the bones were normal.

Serial technetium Tc 99m scans disclosed increased uptake at corpus and manubrium sterni (Figure 2). Bone biopsy could not be performed due to the patient's disapproval.

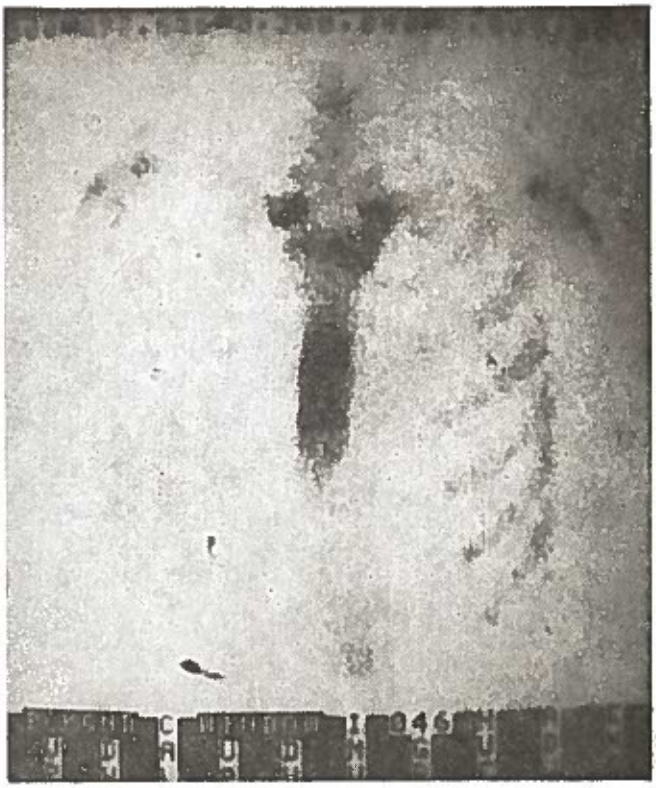

Figure 2
Technetium Tc 99m scan showing increased uptake (darker area) in sternum.

Oral prednisolone (50 mg/day) was started. The musculoskeletal pain disappeared within a few days while skin lesions showed a favourable response.

Discussion

Acne fulminans is characterized by the sudden appearance of painful inflammatory ulcerated skin lesions that show spontaneous remission with scar formation. The lesions favour young men between 13 to 22 years of age. At least 40 cases have been reported to date.[2] To the best of our knowledge such a case has not been reported in Turkey.

Skin lesions are usually accompanied by systemic manifestations that include fever, anemia, leukocytosis, elevated ESR and weight loss. Musculoskeletal system involvement is seen in more than half of the cases, and is characterized by bone pain (especially involving trochanters, spine and thoracic cage), myalgia, peripheral arthritis (asymmetrical, non-erosive, and self-limiting).[3]

As in our case, patients often complain of anterior chest pain. This is presumably secondary to rib and sternum involvement.[3] In some patients osteolytic bone lesions are observed by roentgenograms and/or scintigrams. In our case, bone scans showed marked uptake of the isotope while the roentgenograms were all normal.

The etiology of the musculoskeletal system involvement in acne fulminans is not fully understood.[2] One of the theories that has been advanced to explain the pathophysiology of the bone lesions is the possibility of Propionibacterium acnes septicemia originating from the pustular lesions.[7] However, in some cases blood cultures were negative and no clinical response could be achieved with antibiotic treatment.[2] In our case blood cultures were all negative.

Among other theories, the presence of an autoimmune disease,[4] an abnormality in leukocyte functions,[2] hypersensitivity reaction to a bacterial antigen,[2] or Arthus or Schwartzman phenomenon[2] could be mentioned. In our case there was no abnormality in leukocyte functions. A low C_3 level and hypergammaglobulinemia, suggestive of an autoimmune disease, was not observed, but we could not perform a direct immunofluorescent microscopic examination.

At present, a hypersensitivity reaction to a bacterial antigen in the skin and to a similar antigen in the bone seems to be a possible explanation for the pathophysiology of the disease.[2]

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Hacettepe Medical Journal
Volume 19 / No. 4 / October 1986 / pp. 195 – 200

Maternal Deprivation

Aysen Özkan, M.D.*

Summary

It is essential for mental health that the infant and young child should experience a warm, intimate and continuous relationship with its mother or permanent mother substitute where both find satisfaction and joy. If the child does not have this relationship the situation is referred to as "maternal deprivation". A review of the literature in the field of mother-child relationship shows the complexity of the maternal deprivation concept. Even the concept itself is not clearly defined. In addition to maternal deprivation per se, maternal separation, multiple mothering and distortions in maternal care are usually dealt with under the same heading. Although there is general agreement on the immediate and short term effects of maternal deprivation, there is much contraversy over its long term effects.

Key Words: Maternal deprivation, Hospitalism, Anaclitic depression.

Maternal Deprivation

Studies dealing mainly with maternal deprivation include studies of deprivation of sensory, affective or social stimulation. Most data come from studies on infants and young children who have gone through institutional care at some point in their medical histories.[1] Some of the findings are also supported by animal studies, mainly studies on infant rats and rhesus monkeys.[2,3] There is consistency in the general findings in that infants subjected to prolonged residence in very poor institutional environments show deficiencies and disturbances. Such children's development may be affected physically, intellectually, emotionally and socially. In these studies, all children under seven years of age seemed to be vulnerable and some of the immediate effects were clearly seen within the first few weeks of life. Spitz claims to have found gross developmental retardation and personality distortion as a result of ma-

Department of Psychiatry, Faculty of Medicine, Ondokuz Mayıs University. Samsun, Turkey.
* Associate Professor of Psychiatry.

ternal deprivation occuring in the first year and the clinical picture thus described has been named "hospitalism".[4]

Infants under six months of age who have been in an institution for some time present a well defined picture. The outstanding features are listnessness, emaciation and pallor, relative immobility, quietness, unresponsivness to stimuli, failure to gain weight properly despite ingestion of diets (which in the home are entirely adequate), frequent stools, poor sleep, and appearence of sadness, proneness to febrile episodes and absence of sucking habits.[5] This clinical picture has been described by Spitz and Wolf who named it "anaclitic depression".[6]

In confirmation of earlier work, Spitz and Wolf's results show that most of the retardation in development takes place during the first six months, especially between three to six months. Other studies show however, that not all aspects of development are equally affected. The least affected are neuromuscular development, including walking, other locomotor activities and manual dexterity. The most affected aspect is speech, the ability to express being more hampered than the ability to understand. Midway in retardation between motor development and speech come social responses and adaptability. Although the early literature suggested that severe intellectual retardation and personality disturbances were the inevitable outcome of early institutional care, recent research has found considerable variation in the level of retardation and degree of disturbance in children in different institutional settings. It seems likely that the absence of a mother figure is associated with a number of direct variables operating in such settings. These include the amount, the quality and the variety of sensory and perceptual stimulation provided directly or mediated by the care taker, the extent of opportunities for acquiring and practising skills, the quality of affectionate interchange with substitute mothers, age of the child and the duration of institutional care.

Findings on the direct effects of improverished environments on infants and young children are more clear cut than the longterm effects. The long term effects of maternal deprivation appear to be: a) developing only superficial relationships, b) a lack of care for people or inability to make true friends, c) inaccessibility, d) no emotional response to stimulation, e) deceit and evasion, f) stealing, and g) lack of concentration in school.

Multiple Mothering

A number of mother figures simultaneously provide care for the child with varying degrees of responsibility and differentiation of func-

tions. Multiple mothering is not always associated with severe deprivations or traumatic discontinuities in care. The presence of more than one mother figure may be associated with more varied stimulation in the context of individualized care. Margaret Mead[7] suggested that children who are brought up in cultures in which the childcare functions are shared by a number of mother figures are better equipped to tolerate separation and often develop more complex personality characteristics as a consequence of having more varied figures to identify with. It seems clear that the effects of multiple mothering depend on specific patterns of interaction between child and mother.

The situation of working mothers involves both recurrent and very brief separations, and the maternal care which is provided by several or even many mother figures. In the past it has been claimed that the children of working mothers are particularly likely to become delinquent or develop some form of psychiatric disorder. There is abundant evidence from numerous studies that this is not the case.[8]

Maternal Separation

Maternal separation involves a break in the continuity of a relationship with a mother figure after a meaningful relationship has been established. Although maternal separation frequently preceeds deprivation of maternal care, deprivation experiences are not an inevitable consequence of separation.

Maternal separation occurs under a wide range of circumstances such as: 1) Temporary single brief separation followed by reunion with parents. This may be caused by parents going on a trip, operative procedures or short term hospitalization of the child for acute illness. 2) Repeated short term separation with reunion. This could be caused by illness of mother and hospitalizations. 3) Single long term separation with reunion. Hospitalization of long duration, severe family crisis and national catastrophies are examples of this type of separation. 4) Repeated long term separation with reunion. This category includes children who have been placed in foster homes or institutions during family crisis. 5) Single permanent separation. This could be caused by a parents death, desertion, incompetence or cruelty of parents which result in permanent foster home residence or adoption. 6) Repeated separations without reunion. These include change of foster homes and shifts in institutions following a permanent separation from parents. Among the above listed separations, the last two lead to maternal deprivation more frequently.

A break in the continuity or relationship with the mother figure is a disturbing experience for infants and young children as evidenced

by their behavior at the time and immediately following the separation.[9-11] Bowlby described the characteristic sequence of responses to separation as phases of protest, despair and detachment.[12] At first, with tears and anger, the child demands his mother back, and hopes he will succeed in getting her back. This phase of protest may last several days. Later, he becomes quieter but it is clear that he still yearns for her return; by then, his hopes have faded and he is in the phase of despair. Often these two phases alternate; hope turns to despair and despair to renewed hope. Eventually, however, a greater change occurs. He seems to forget his mother so that when she comes for him he remains uninterested in her and may seem even not to recognize her. This is the phase of detachment. The child's behavior upon returning home depends on the phase reached during the period of separation. Usually for a while he is unresponsive and undemanding. The degree and the duration of this period depends on the length of separation. Then there is a storm of feeling, intense clinging and whenever his mother leaves him he shows acute anxiety and rage. After the child has been back with his mother a few hours or a few days, the detached behavior is replaced not only by all the old attachment but by attachment of heightened intensity. From this it is clear that during detachment, the ties binding him to his mother have not quietly faded, as is suggested by Anna Freud,[11] nor has there been a simple forgetting. On the contrary, the data strongly suggest that during the phase of detachment the responses that bind the child to his mother and lead him to strive to recover her are subject to a defensive process. In some way they are removed from consciousness, but remain latent and are ready to become active again and even reach a high intensity when circumstances change. If the child has been away for a period of more than six months or when separations have been repeated, so that he has reached an advanced stage of detachment, there is danger that he may remain detached and never recover his affection for his parents.[13]

Since Freud[14] first presented the idea that hysteria and melancholia are manifestations of pathological mourning which follow the loss of or separation from the loved one, there has been a number of studies trying to trace the childhood roots of depressive illness and of personalities prone to develop it.[15] In a significant number of studies, loss of one or other parent in childhood was held responsible as cause of or a precipitant of psychiatric illness including psychoneurosis, schizophrenia and delinquency.[16-21] There are also authors who, although acknowledging the importance of childhood experiences, have been unable to show that separation or deprivation lead to mentally ill

health. [22-26] Some investigators have gone so far as to try and establish a relationship between maternal deprivation and physical illnesses such as hypoglycemia, hypotonia and altered immune responses.[27-29]

Distortions in Maternal Care

Frequently included in the concept of maternal deprivation are the deviations in the mother child relationship, characterized by rejection, hostility and ambivalence. These deviations are primarily in the quality of affectional relationship. Authors who have studied personality disorders tend to support the idea that it is not the maternal separation or deprivation per se but rather distortions in maternal care and family disharmony that is more important in developing such disturbances.[24]

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SUBJECT INDEX

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