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Treatment of Acetaminophen Poisoning with Cimetidine in Mice*

Murat Yurdakök, M.D. / Melda Çağlar, M.D.*** / Kadriye Yurdakök, M.D.******

Summary

This study was undertaken to examine the possible protective effects of cimetidine administration on acetaminophen induced hepatic necrosis in mice. We have observed a striking protection against acetatminophen hepatotoxicity in cimetidine-treated mice. Cimetidine-treated animals had lower serum transaminases levels and they had less histological liver damage than those treated with acetaminophen alone.

Key Words: Acetminophen, Cimetidine, Poisoning, Mice.

Introduction

Poisoning with acetaminophen (paracetamol) has been shown to cause severe hepatic necrosis both in laboratory animals and in humans.[1] Toxicity is thought to be related to production of an intermediate that results from oxidation of acetaminophen by cytochrome P_{450} monooxygenases.[2-5] Cimetidine has been shown to be a potent inhibitor of cytochrome P_{450}-mediated drug metabolism both in laboratory animals and in humans after the usual therapeutic doses.[6-11] We have studied the effects of cimetidine against acetaminophen hepatotoxicity in mice and compared our findings with previous studies.

* From Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara-Turkey.

** Pediatrician, S.S.K. Ulus Hospital and Institute of Child Health, Hacettepe University, Ankara-Turkey.

*** Professor of Pediatrics and Pathologist, Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara-Turkey.

**** Resident in Pediatrics in the same department.

Materials and Methods

Male albino mice 6-8 weeks old and weighing 15-25 g were supplied by the Laboratory Animals Breeding Unit, Ministry of Health and Social Welfare for use in this study. The mice were divided into four equal groups of ten mice each as control, acetaminophen, cimetidine, and acetaminophen + cimetidine groups. Acetaminophen (Sigma Chemical Co.) was injected in a single dose of 500 mg/kg (25 ml/kg in corn oil) intraperitoneally in the second and fourth groups. Cimetidine (Ulkomet) was injected intraperitoneally in a single dose of 160 mg/kg in normal saline (25 ml/kg in 0.9 % NaCl) in the third and fourth groups. In the fourth group, cimetidine was given intraperitoneally approximately 45 minutes after the administration of acetaminophen. The dose of cimetidine chosen caused the most striking effect, with less than 5 % mortality.[12] The first group was separated as control and received no acetaminophen or cimetidine but did receive normal saline in the same amounts and in the same manner as the fourth group.

The mice were killed by cervical dislocation 60 minutes after the administration of cimetidine and/or acetaminophen under light ether anesthesia. Blood samples from the heart were taken for determination of serum aminotransferase activity. The livers of the mice were removed for examination under light microscopy.

Serum aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) were determined using Reitman and Frankel kits obtained from the Sigma Chemical Company.[13]

Coded histologic sections were examined under light microscopy by *two* blinded observers. The extent of necrosis was graded from 0 to 4 + as follows: histological normal sections were graded 0, minimal centrilobular necrosis 1 +, more extensive necrosis confined to centrilobular regions +2, necrosis extending from central cones to portal triads 3 +, and massive necrosis of most of the liver 4+.

Results were expressed as the mean ± SEM. Student's t test for serum aminotransferase activities and Kruskal-Wallis Analysis for the scores of hepatic necrosis were used to compare the groups.

Results

Serum aminotransferase levels are shown in Table I. In animals receiving acetaminophen only, there was a striking elevation ($p < 0.05$) of both serum aminotransferases with a mean of 840 ± 49 U for SGOT and 630 ± 10 U for SGPT. In animals treated with cimetidine, however the mean SGOT and SGPT levels were less elevated than in the group receiving acetaminophen alone ($p < 0.05$), but also higher than in the control and cimetidine (first and second) groups ($p < 0.05$).

Animals receiving acetaminophen showed evidence of marked hepatic necrosis when examined by light microscopy. The histologic index score was 3.2 ± 0.3; by comparison cimetidine-treated mice showed significantly less necrosis with a score of 1.1 ± 0.3 (Kruskal-Wallis: 78.44, $p < 0.05$, Table II).

TABLE I
SERUM TRANSAMINASES IN MICE TREATED WITH ACETAMINOPHEN, CIMETIDINE, AND ACETAMINOPHEN + CIMETIDINE

Group	SGOT (U)	SGPT (U)
Control (n: 10)	140 ± 7	125 ± 4
Cimetidine (n: 10)	164 ± 11	144 ± 13
Acetaminophen (n: 10)	840 ± 49	630 ± 10
Cimetidine + Acetaminophen (n: 10)	362 ± 58	337 ± 9

TABLE II
HISTOLOGICAL LIVER DAMAGE IN STUDY AND CONTROL GROUPS

Group	Histological liver damage index score
Control (n: 10)	0
Cimetidine (n: 10)	0.5 ± 0.1
Acetaminophen (n: 10)	3.2 ± 0.3
Cimetidine + Acetaminophen (n: 10)	1.1 ± 0.3

Discussion

The major pathway for elimination of acetaminophen is conjugation with glucronic and sulfuric acid.[14-16] With therapeutic doses of acetaminophen, only a small amount of the toxic metabolite, N-acetyl-p-benzoquinoneimine is formed by cytochrome P_{450}-mediated oxidation of acetaminophen, and this product is usually conjugated with glutathione thereby rendering the compound nontoxic.[17, 18] However after massive doses of acetaminophen, the formation of the toxic intermediate exceeds the ability of the liver and kidney to form glutathione conjugates, and binding to cellular macromolecules and subsequent necrosis result.[2-4]

Prevention of liver damage may be related to lowering the rate of metabolism of acetaminophen to the toxic compound, providing an alternative protector to glutathione or enhancing the supply of glutathione.[2,3] A number of thiocompounds, such as cysteamine, N-acetyl cysteine, methionine, dithiocarb and propylthiouracil, have been shown to decrease acetaminophen hepatotoxicity in humans and in laboratory animals.[19-26] But, except for methionine[21] and acetylcysteine[23,24] they are too toxic for humans.

Cimetidine is a potent inhibitor of the cytochrome P_{450}-mediated drug metabolism including acetaminophen.[7-9,11,27,28] So the mechanism of protection against acetaminophen hepatotoxicity by cimetidine is related to the ability of cimetidine to selectively inhibit cytochrome P_{450}-mediated conversion of acetaminophen to its toxic metabolite while allowing continued elimination of acetaminophen to proceed via its major pathways of glucronidation and sulfation. Our findings also support previous reports concerning the effectiveness of cimetidine against acetaminophen hepatotoxicity in laboratory animals.[27-29]

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T-Lymphocytes in Psoriasis*

Leyla Bozkaya, M.D. / Emin Kansu, M.D., FACP.*** / Fikret Kölemen, M.D.**** / Sevinç Akkaya, M.D.*****

Summary

Several investigations have suggested an immunologic mechanism in the pathogenesis of psoriasis. This study was undertaken to examine the E-Rosette Forming Cells (T-Lymphocytes) in patients with active psoriasis and compare the results with normal subjects. Twenty-five patients with psoriasis and fifteen normal control subjects were studied. Total Lymphocyte and Total E-Rosette forming cells were found to be significantly lower than control values. A numerical decrease in the relative and total T-Lymphocytes may contribute to the immunopathogenesis of psoriasis.

Key Words: Psoriasis, T-Lymphocytes, Cellular Immunology E-Rosettes, Lymphocytes.

Introduction

Several studies in recent years have suggested an immunologically mediated mechanism may be responsible in the etiopathogenesis of psoriasis.[1, 2, 3]

It is well-known that T-Lymphocytes play an important role in cellular immunity. There are conflicting reports regarding the T-lymphocyte numbers and T-cell subsets[4, 5] in psoriasis. The aim of this report has been to enumerate the total E-rosette forming cells, though this is not completely sufficient as an indicator of cell-mediated immunity, in patients with psoriasis.

* From Department of Dermatology and Internal Medicine-Hematology, Hacettepe University, Faculty of Medicine, Ankara-Turkey.
** Resident in Dermatology, same faculty.
*** Associate Professor of Hematology.
**** Associate Professor of Dermatology.
***** Professor of Dermatology, Head of Department of Dermatology.

Material and Methods

The patient population presented in this study was selected among the outpatients who were referred to the outpatients clinic of the Department of Dermatology. Subjects in our study included 25 randomly selected patients with active psoriasis and 15 normal control subjects. In the patients' group, 8 subjects were female, 17 were male, and all were adults with active disease. The mean age of the psoriatic patients was 35.6 years (range 17-62 yrs.). In the control group, there were 11 male and 4 female normal subjects. The mean age was 23.2 (range 19-36 yrs.) years. Blood samples were obtained from the patients prior to any type of therapy.

Lymphocyte Separation: Ten ml. of heparinized venous blood sample was obtained from patients and healthy control subjects. Lymphocytes were obtained by mixing one part peripheral blood with one part Hanks Balanced Salt Solution (HBSS), gently layering 20 ml. of this mixture over 5 ml. Ficoll-Hypaque and centrifuging at 320 g. for 35 minutes.[6] The lympocyte-rich mononuclear cell layer was removed by gentle aspiration with a Pasteur pipette and washed three times in HBSS. No granulocytes, red blood cells or platelets were observed in the cell preparation.

E-Rosette Assay: Washed lymphocytes were suspended in HBSS to a final concentration of $2x10^6$ cells/ml. Sheep erythrocytes (SRBC) were washed three times in HBSS before use and diluted to a final concentration of 0.5 % ($40x10^6$ SRBC/ml). 0.5 ml of the lymphocytes ($1x10^6$) was added to 0.5 ml. of the SRBC preparation and 0.1 ml. of heat-inactivated Fetal Calf serum was added to the cells. The mixture was incubated at 37 C° for 15 mins. and then centrifuged at 350 g for 10 mins at room temperature. Finally, the sample was put into 4 C° for 2 hours and spontaneous rosette forming cells were determined by counting a minimum of 200 lymphocytes.[7]

Statistical analysis was carried out in each group. Group comparisons for determination of significance were performed using Student's t-test method.

Results

Although there was no significant difference in the total white blood cells in the two groups, the total lymphocyte counts in the patients' group lower (1530.9 ± 94.9 / mm^3) than in the control group (1884.9 ± 91.6 /mm^3), ($P < 0.05$). The percentage of E-rosette forming cells obtained from active psoriatic patients was found to be significantly

lower (45.1 ± 1.3 %) than for normal control subjects (57.6 ± 2.2 %) ($P < 0.05$). Total rosette forming cells in psoriatic patients (685.2 ± 41.5 /mm^3) were also lower than normal subjects (1093.8 ± 81.6 /mm^3) ($P < 0.05$). The results are shown in Table I.

TABLE I
E-ROSETTE VALUES IN PATIENTS WITH PSORIASIS AND CONTROL SUBJECTS

		Total Lymphocytes (per mm^3)	E-Rosettes (%)	Total E-Rosettes (per mm^3)
Psoriatic Pattients	n: 25	1530.9 ± 94.9	45.1 ± 1.3	685.2 ± 41.5
Normals	n: 15	1884.9 ± 91.6	57.6 ± 2.2	1093.8 ± 81.6
	p values	< 0.05	< 0.05	< 0.05

Values are expressed as mean ± Standard Error.

Discussion

The capacity of human lymphocytes to bind sheep erythrocytes to form rosettes is accepted as a marker for the identification of thymic-derived lymphocytes. In our study, we observed a decrease in the number of E-rosette-forming cells (T-cells) in the patients with active psoriasis. Similar findings were reported previously by Glinski, et al. and Cormane, et al.[8, 9] In contrast, studies done by Levantine and Brostoff, and recently by Ligresti,et al.[1, 10] suggested that the total T-cell counts in psoriatic patients could be normal. Studies reported by Ligresti et al. demonstrated a significant decrease in the percentage of suppressor T-cells (T_S) and a significant elevation of helper -Tcells (T_H).[10] Sander et al and Gladman et al. studied a group of patients with psoriasis and demonstrated diminished suppressor cell activity.[11, 12]

Our results showed a significant decrease in the T-cell population which may cause substantial changes in the cell-mediated pathways of the immune response in psoriasis. Studies are in progress in our laboratory to identify the lymphocyte subsets by the monoclonal antibodies in psoriasis.

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Gallbladder Emptying in Response to Oral, Gastric and Duodenal Stimulation

(An Ultrasonographic Study)

Şafak Reka, M.D.* / Yücel Batur, M.D. / Özgül Özgüven, M.D.*** / Namık Kemal Menteş, M.D.*****

Summary

Gallbladder motor function was evaluated ultrasonographically in response to liquid test meal administered orally, intragastrically and intraduodenally, and to sham feeding in 19 healty men. The percentage of emptying and the rate of emptying were found to be greater after the oral meal than the gastric and duodenal meals. The rate of emptying was faster after the duodenal meal than the gastric meal, but the percentage of emptying was similar after the duodenal and gastric meals. Sham feeding also produced gallbladder emptying. These findings suggest that gallbladder contraction may be stimulated by preduodenal mechanisms.

Key Words: Cholecystokinin, Gallbladder, Ultrasonography.

Introduction

Gallbladder emptying is regulated by hormonal mediators released from the upper small bowel and the pancreas in response to luminal contents. Cholecystokinin is known to play an important role in stimulating gallbladder contraction. In addition several other mechanisms may be involved in the function of the gallbladder.[1-4] Real-time ultrasonography has made possible the safe, non-invasive and accurate visualization of the gallbladder, and the determination of its behavior in response to various physiologic stimuli. In the present study real-time ultrasonography was used for evaluating the effects of preduodenal stimulation in gallbladder motor function in 19 healthy men.

* Fellow in Gastroenterology, Aegean University Medical Center, İzmir-Turkey.
** Associate Professor in Gastroenterology, Aegean University Medical Center.
*** Professor in Gastroenterology, Aegean University Medical Center.

Materials and Methods

Nineteen men of average height and weight volunteered for this study. Ages ranged from 19 to 38 (mean age, 30 years). They had no history of any medication and /or any illness. All subjects were found to be normal on physical examination. Routine laboratory studies including complete blood count, fasting blood sugar, liver function tests and BUN were within normal limits, and upper gastrointestinal series and endoscopic examinations were found to be normal in all subjects. Ultrasound examination of the gallbladder excluded gallstones in all subjects.

Toschiba SAL-22 A Real-time Ultrasonography and 3.5 m Hz probe were used for the determination of the gallbladder size. The longest axis, and the greatest transverse and anteroposterior diameters of the gallbladder were measured. Gallbladder volume was calculated from the volume of a single cylinder,[5] ($V:\pi d^2h/4$), where h is equal to the longest axis and d is the average short axis [d: (Anteroposterior diameter + transverse diameter) /2].

The gallbladder size was determined in the morning on 4 consecutive days after overnight-fasting. Following this initial measurement the gallbladder size was measured again on the first day for a period of 60 minutes at 5 minute-intervals following sham feeding lasting 5-10 minutes and consisting of solid food stuffs. Post-prandial measurement was also carried out at 5 minute-intervals for 60 minutes after 450 cc of a standard liquid test meal[6] containing 420 k cal. (35 % as fat, 15 % as protein, and 50 % as carbohydrate) administered over 5 minutes orally, through a nasogastric tube and a duodenal tube passed through the nose and positioned in the second part of the duodenum with the aid of fluoroscopy on the second, third and fourth days, respectively.

Gallbladder function was expressed in terms of the rate of emptying and maximum percentage of emptying. The rate constant of the gallbladder emptying was calculated from In /linear regression of volume vs. time.[7] The percentage of emptying was equal to [1-(Residual gallbladder volume /fasting volume)] X100 %. The results were compared by Student's t-test.

Results

The percentage of emptying was significantly greater after the oral meal than after the gastric and duodenal meals ($p < 0.01$). But there was no difference between duodenal and gastric meals ($p > 0.05$). Sham feeding also produced gallbladder emptying. (Figure 1). The rate of emptying was faster after the oral meal than after the gastric and duodenal meals, and was smallest after sham feeding. But the rate of

emptying was faster after the duodenal meal than the gastric meal. (Figure 2). Maximum emptying occurred in 20 to 35 minutes and then the gallbladder began to refill in all subjects.

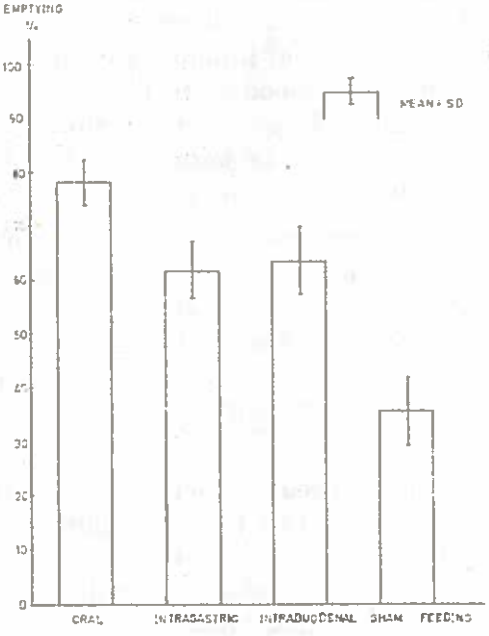

Figure 1

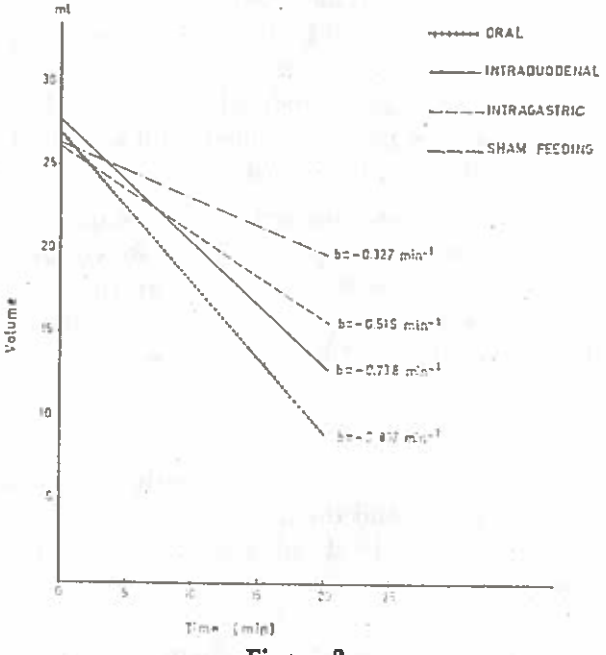

Figure 2

Discussion

Gallbladder emptying is stimulated when the gastric contents enter the duodenum; the gallbladder function is controlled by gastrointestinal hormones and the nervous system. However, gallbladder motor function has not been fully determined. Sham feeding is known to produce cholinergic stimulation and to stimulate the release of gut hormones. Gallbladder contraction occuring after sham feeding was reported.[8,9] Rock, et al. also showed that both cholinergic and hormonal mechanisms may be involved in the emptying responses of the gallbladder to meals and to sham feeding.[10] It was found that gallbladder emptying response to the oral test meal was more rapid than gastric emptying following this meal,[7,9,11] and it was suggested that the inital rapid phase of gallbladder emptying might be due to neurohumoral mechanisms and/or mechanisms other than duodenal stimulation. In addition Maton, et al. reported that both the timing and extent of the rise in plasma cholecystokinin values were insufficient to account for the postprandial gallbladder emptying rates observed.[12] So gallbladder emptying occurring after meals was not due to circulating cholecystokinin alone. Non-cholecystokinin peptides inducing gallbladder contraction have also been determined in human serum and it has been reported that the upper stomach may contain the highest concentration of these non-cholecystokinin substances.[4]

In the present study the percentage and the rate of gallbladder emptying were greater after a liquid oral meal than after gastric and duodenal meals. Sham feeding also stimulated the gallbladder contraction. The slower rate of emptying after the gastric meal than the duodenal meal might be due to slower gastric emptying. But, the percentage of emptying was similar after gastric and duodenal meals. These findings suggest that the gallbladder contraction may be influenced by the cephalic and oral part of the digestion. It would be more informative to determine the serum cholecystokinin values simultaneously. Similarly, in a cholesintigraphic study gallbladder emptying was found to be more rapid and complete after an oral than a duodenal meal.[9]

In conclusion it can be said that preduodenal mechanisms may affect the gallbladder motor function either by direct effects on the the gallbladder smooth muscle and/or by stimulating the release of hormonal mediators.

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The Prognostic Significance of Antinuclear Antibody Patterns in Scleroderma

Nazif Kürkçüoğlu, M.D.* / Nilgün Atakan, M.D.**

Summary

Antinuclear antibody patterns may have diagnostic and prognostic significance in scleroderma. The discrete speckled pattern is found frequently in those with a benign form of scleroderma characterized by acrosclerosis, Raynaud's phenomenon, sclerodactylia, and esophageal dysmotilitiy.

Key Words: The discrete speckled pattern, Benign subset of scleroderma.

Introduction

The association of nuclear immunofluorescent patterns and clinical characteristics with the prognosis of connective tissue diseases including systemic lupus erythematosus has been well established.[1-3] In previous studies the 'speckle'-inducing antinuclear antibodies were shown to be frequently observed in a benign subset of scleroderma patients characterized by acrosclerosis, Raynaud's phenomenon, calcinosis, sclerodactylia, and esophageal dysmotility. Thus it was stressed that the speckled pattern could be a marker for the prognosis of scleroderma.[4] We report herein the antinuclear antibody (ANA) patterns of 4 benign subsets of scleroderma, and the results are discussed.

Case Reports

Case 1: A 31 year-old woman had an 8-year history of Raynaud's phenomenon, sclerodactylia, masklike appearance of the face, beaklike nose. Family history was negative for similar lesions.

* Assistant Professor in Department of Dermatology, Hacettepe Medical School.
** Instructor in the same department.

Physical examination disclosed a thin woman with an expressionless face. The hands were clawlike. The skin of the hands was smooth, yellowish, firm and bound to the underlying structures. There were symptoms of Raynaud's phenomenon with blanching and intermittent arteriolar spasm. There was difficulty in opening the mouth and swallowing. The patient complained of heartburn and regurgitation of liquids.

Gastrointestinal tract series with barium revealed dilatation and decreased peristalsis in the esophagus. The immunoglobulin G level was 1900 mg/100 ml. The ANA test was positive in a titer of 1:40 with discrete speckled pattern. The skin biopsy disclosed the characteristic histopathologic features of scleroderma.

Case 2: A 25 year-old woman had a 5-year history of scleroderma with acrosclerosis, Raynaud's phenomenon, and dysphagia. Family history was negative for similar lesions.

On physical examination the skin overlying the hands and face was firm and taut. Sclerodactylia was observed. The fingers were immobile. Trophic ulcerations were present on the tips of the fingers. There was a progressive induration from the forearm and hand to the fingertips. The face was expressionless. The lips were thin and contracted. The nose was sharp and pinched.

Gastrointestinal tract series with barium revealed dilatation and decreased peristalsis in the esophagus. There was no abnormality in the stomach or small and large intestines. The ANA test was positive in a titer of 1:50. The pattern was discrete speckled type and skin biopsy was consistent with that of scleroderma.

Case 3: A 39 year-old man had a 10-year history of scleroderma on the acral prominences and the face. Family history was negative for similar lesions.

Physical examination revealed sclerodactylia, an expressionless face, beaked-shaped nose, microstomia. The skin overlying the hands, forearms and face was firm and taut. There was difficulty in swallowing. The patient complained of heartburn and regurgitation of liquids.

Esophageal dysmotility was observed. There was a slightly elevated erythrocyte sedimentation rate. The ANA test was positive in a titer of 1:40 with discrete speckled pattern. The skin biopsy was consistent with that of scleroderma.

Case 4: A 35 year-old woman had an 11-year history of acrosclerosis, Raynaud's phenomenon and dysphagia. Family history was negative for similar lesions.

On physical examination sclerodactylia, trophic ulcerations on the tips of the fingers, Raynaud's phenomenon, beaked-shaped nose, microstomia, and an expressionless face were observed. There was difficulty in swallowing and the patient complained of regurgitation o liquids.

Esophageal dysmotility was observed in gastrointestinal tract series with barium suggestive of scleroderma. The ANA test was positive in a titer of 1:40 with discrete speckled pattern. The skin biopsy was consistent with that of scleroderma.

In all of our patients the following laboratory tests were almost all normal or negative: Complete blood cell counts, hemoglobin, urinalysis, erythrocyte sedimentation rate, creatine phosphokinase, creatinine, blood urea nitrogen, creatinine clearance, serologic test for syphilis, rheumatoid factor, electrocardiogram, immunoglobulin levels, chest roentgenogram, and LE cell test. None of our patients had any evidence of pulmonary involvement either on clinical findings and chest X-rays, so no pulmonary function tests were performed.

Discussion

The detection of autoantibodies in scleroderma has been shown to be dependent on the substrate.[5,6] According to studies, using organ sections as substrate in immunofluorescent microscopy, antinuclear antibody test results can be classified on a morphological basis, and include:[7,8] (1) The discrete speckled pattern; (2) The thready, nucleolar pattern, and ANA negative test results; (3) The homogenous and small speckle-like thready pattern.

The use of tissue culture cells as substrate has revealed antibodies reacting with specific nuclear macromolecules that included antinucleolar, anticentromere, and anticentriole antibodies.[9,13] The anticentromere antibody (ACA) which reacted with the chromosomal centromeres (kinetochores), was shown to produce a discrete speckled pattern on organ sections.[10]

Kleinsmith et al,[8] reported that patients with the discrete speckled pattern, which may represent ACA, had a benign subset of scleroderma characterized by Raynaud's phenomenon, acrosclerosis, sclerodactylia, and esophageal involvement.

In our cases, all of the patients complained of vasomotor disturbances, suggestive of Raynaud's phenomenon, and of acrosclerosis. Esophageal dysmotility, suggestive of scleroderma, was documented by roentgenographic findings in all of our patients. None of our patients

had any evidence of renal, pulmonary, cardiac, or muscular involvement. The mean age at diagnosis was 26.5 years, and the mean duration of the disease was 8.5 years. The female-to-male ratio was three to one. These findings are consistent with those of previous studies which proclaim that the discrete speckled pattern of ANA (ACA, on tissue culture cells) is highly selective for a benign subset of scleroderma.[6, 9-12]

Kleinsmith et al,[8] reported that the thready ANA pattern was observed in patients with pulmonary involvement. On the other hand, diffuse skin involvement and Raynaud's phenomenon was found in those with nucleolar pattern. ANA negative test results had the most severe disease, including renal failure.[8] The ACAs were also observed in systemic lupus erythematosus,[14] diffuse scleroderma,[15] and primary biliary cirrhosis with scleroderma.[16] The antinucleolar antibodies were shown in morphea, CREST syndrome, and diffuse scleroderma.[9] The nonspecific ANA patterns, including homogeneous, granular, and mixed were noted in all forms of scleroderma and no clinical correlations were found.[9]

In this study, it has been demonstrated that the discrete speckled pattern, which may be ACA on tissue culture cells, is found in patients with scleroderma, characterized by Raynaud's phenomenon, acrosclerosis, sclerodactylia, and esophageal dysmotilitiy and that this finding usually reflected a good prognosis.

The importance of these antibodies and their relationship to disease pathogenesis should be elucidated by further studies.

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Co-Existent Coronary Artery Ectasia and Hypertrophic Cardiomyopathy

Baki Komsuoğlu, M.D.* / P.J. Lowry**

Summary

A 51-year-old man presenting with angina pectoris was found to have coronary artery ectasia and hypertrophic cardiomyopathy (HCM), a combination not previously reported.

Key Words: Coronary artery ectasia, hypertrophic cardiomyopathy, cardiac catheterization, echocardiography, myocardiol biopsy.

Introduction

Coronary artery ectasia is an irregular dilatation of the coronary vessels. It is most commonly atherosclerotic in origin[1] but has been reported in association with other diseases e.g. congenital heart disease,[2] Ehlers-Danlos syndrome,[3] polyarteritis nodosa.[4] We report a case of severe, diffuse coronary artery ectasia associated with hypertrophic cardiomyopathy (HCM), not previously documented.

Case Report

Mr. D.W., (Unit No: 074838, East Birmingham Hospital; Department of Cardiology) aged 51 years, was referred from another hospital with a 3 year history of exertional chest pain typical of angina pectoris. More recently he had begun to experience chest pain at rest. He had been admitted to hospital on two occasions with a history suggestive of myocardial infarction, but enzyme changes were not demonstrated although on two separate occasions, ECG's showed first degree heart block and infero-lateral T wave changes. In spite of antianginal therapy in the form of isosorbide dinitrate and β blockers, his symptoms had forced him

* Associate Professor Department of Cardiology, Karadeniz University Medical School, Trabzon-Turkey.
** East Birmingham Hospital, University of Birmingham, Bordesley Green, East Birmingham B9 5ST, England.

to reduce his activities and, ultimately, had resulted in loss of his job as an agricultural engineer. He has a past history of hypertension and migraine associated with depression in 1972, but treatment for his raised blood pressure was discontinued after a short time (3 consecutive blood pressure readings at clinics in 1972 were 180/125, 190/120, 140/110 mmHg. The third reading was taken after starting treatment). Diabetes mellitus was diagnosed in 1975 and this is well controlled by diet alone. He smoked 30 cigarettes a day until the beginning of 1980. There was no family history of heart disease.

On examination, he was a heavily built, slightly obese man (Ht. 1.70 m, Wt. 82.9 Kg) with a blood pressure of 140/90 mmHg. Pulse was 80/min and regular, and carotid upstroke felt normal. The heart size was not enlarged but there was a left ventricular heave. There were no abnormal sounds or murmurs. The rest of the physical examination was normal.

Chest x-ray and ECG, when seen by us, were normal. Echocardiogram (Figure 1) revealed an asymmetrically thickened septum (1.6 cm), small left ventricular cavity (end systole 2.2 cm) and appearances suggestive of systolic anterior motion of the mitral valve although there was no mid-systolic closure of the aortic valve. These findings suggested the

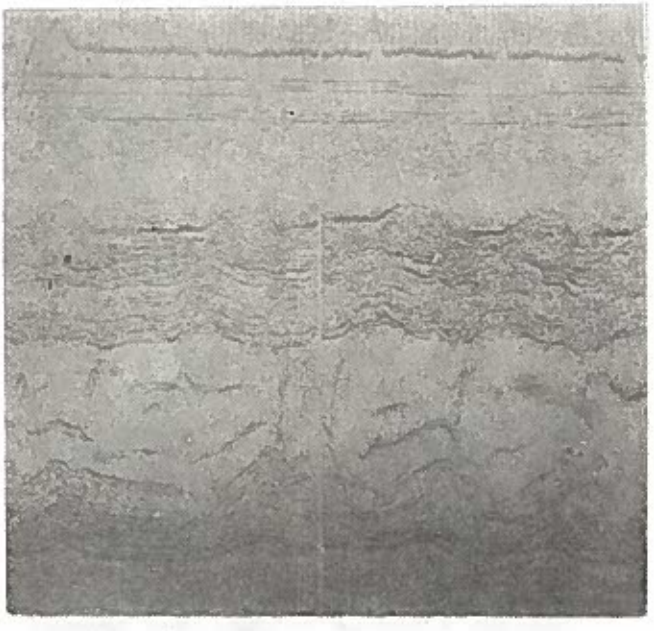

Figure 1
Echocardiogram demonstrating asymmetric hypertrophy and small left ventricular cavity.

diagnosis of HCM Fasting glucose was 6.7 mmol/l, fasting triglyceride 2.5 mmol/l (normal < 2.0 mmol/l), and fasting cholesterol 7.4 mmol/l (normal 2.3-3-8 mmol/l).

Cardiac catheterization revealed normal intracardiac pressures with no evidence of outflow tract obstruction at rest. Left ventricular angiogram demonstrated a vigorously contracting, thick-walled ventricle with almost complete obliteration of the cavity in systole. Ejection fraction calculated on systolic and diastolic volumes was 95 %. No left ventricular/aortic gradient could be demonstrated using amyl nitrate or Valsalva manoeuvre. Selective coronary angiograms showed grossly ectatic vessels (Figure 2). All vessels were affected diffusely, and segments between the dilated positions were narrowed and irregular. Retrograde filling of the left anterior descending artery was seen. Three left ventricular biopsies were taken using a King's bioptome. Under light microscopy, the myocardium appeared irregularly hypertrophied with fibres up to 25 μ in width, and an irregular arrangement of fibres was seen at one point. Nuclei showed some irregularity and minimal cytoplasmic degenerative change was seen. These changes were considered to be consistent with a diagnosis of hypertrophic cardiomyopathy.

Şekil 2
Coronary angiogram illustrating ectasia in right coronary artery.

Figure 3
Left ventricular biopsy. Irregular arrangement of mycordial fibrils, increase in mitocondria and electron-dense particles, (x17.000).

Discussion

Coronary artery ectasia is seen in about 1.4 % of coronary angiograms[1,5] The patients are usually suspected of having coronary artery disease on clinical grounds requiring further investigation. Markis et al.[1] suggested an increased incidence of hypertension, family history of coronary artery disease, abnormal ECG's, and past history of myoccardial infarction among these patients compared with non-ectatic coronary artery disease, but others[5] show an equal incidence of these factors in both groups. Antablian et al.[6] demonstrated higher serum triglycerides in the ectasia group but Swanton et al.[5] found the incidence to be the same as that in patients with nonectatic coronary artery disease.

Our patient presented with a history of angina pectoris and was investigated with a view to possible coronary artery surgery. He has a history of abnormal glucose tolerance and has an abnormal triglyceride level; he has a past history of hypertension, and has been a cigarette smoker. All these factors predispose to coronary artery disease but it is not known why a few people develop coronary artery ectasia while the majority do not.

The echocardiographic features of HCM were quite unexpected, but later confirmed on cineangiogram and myocardial biopsy. Patients with HCM usually have normal coronary arteries[7,8] and the symptom of angina is caused by mechanisms other than coronary artery disease.

There are now several reports of co-existent coronary artery disease and HCM in older people, i.e. in the age group where coronary artery disease[9, 10] is prevalent, but it does not follow that ischaemic heart disease either causes or predisposes to HCM Indeed, with a disease as common as IHDD, it is not surprising that at times it is found coincidentally with HCM.

Presumably, the combination adversely affects the prognosis. In isolated HCM, patients experience angina and have normal coronary arteries: ischaemia may be caused by impaired coronary blood flow in diastole (the time when the subendocardial region is perfused) because of impaired left ventricular relaxation.[11] Where the coronary arteries are grossly abnormal, the needs of the muscle must be jeopardized even further. Impaired left ventricular relaxation and reduced coronary blood flow may also predispose to abnormal ventricular rhythms and sudden death. Disease in the small vessels or intramural coronary arteries has also been postulated as a cause of myocardial infarction and life-threatening arrhythmias in patients with HCM and angiographically normal coronary arteries, a mechanism which would be compounded by the presence of abnormal coronary arteries.[12] This patient continues to be troubled by angina although he is on medical treatment (β blockers and nifedipine) and it is unlikely that surgery would be undertaken with such severe and diffuse coronary artery disease.

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Acute Abdomen Due to Mesenteric Cyst During Pregnancy

Ömer Aran, M.D.* / Sefa Önel, M.D. / Yılmaz Sanaç, M.D.*****

Summary

Mesenteric cysts are very unusual pathology. They are localized loculations of lymph, and are called lymphangiomata. Actually these cysts present as a slowly enlarging abdominal mass, but sometimes they may cause acute abdominal emergency.

A case of mesenteric cyst, presented with an acute abdomen during pregnancy, is reported. It is believed that, this is the first case of an acute abdomen during pregnancy, caused by twisting of an cystic intestinal loop, resulting in intestinal obstruction and infarction.

Key Words: Mesenteric Cysts, intestinal obstruction.

Introduction

In the experience of the general surgeon mesenteric cysts are a very unusual pathology. The incidence ranges from one in 30.000 to one in 250.000 hospital admissions.[1]

The first mesenteric cyst was reported as early as 1507 by the Florentine anatomist Benivieni,[2-5] but the first (unsuccessful) excision was reported by Tillaux[2] in 1880. Three cases of mesenteric cysts during pregnancy have been reported[4-6] previously. In the following case acute abdomen was caused by a twisted intestinal loop involved by the cystic dilatations, resulting in intestinal obstruction and infarction.

* Instructor in General Surgery, Hacettepe University School of Medicine, Ankara-Turkey.

** Resident in General Surgery, Hacettepe University School of Medicine.

*** Professor in General Surgery, Hacettepe University School of Medicine.

Case Report

The patient, an 18-year-old female, gravida I, para 0, was admitted on July 23, 1982, at 16 weeks gestation with a history of nausea, vomiting, abdominal distension and intermittent abdominal pain of 2 days duration. Her abdominal pain had first started suddenly, and was crampy in nature. She was not able to pass flatus nor defecate. Her past medical history was unremarkable. At physical examination the blood pressure was 100/80 mm Hg, pulse 118/min., respiration 20/min. and temperature 37°C.

Abdominal examination revealed distension of the adbomen with a fundal height just below the umblicus, compatible with 4 months' gestation with hyperactive intestinal sounds. There was generalized tenderness over the abdomen. There was no evidence of ascites. Pelvic examination revealed a gravid appearing cervix, which was soft and not dilated.

The hemoglobin was 13.20 gr %, hematocrit 36 %, and WBC 7600/mm^3 with a normal differential count. Urine analysis was unremarkable. X-ray examination of the abdomen revealed multiple air-fluid levels confirming intestinal obstruction. Chest X-ray was normal.

Figure 1
The resected segement of the small bowel with its cystic mesentery.

The patient was taken to the intensive care unit of general surgery and supportive therapy initiated. After 24 hours there was no change in her abdominal manifestations, so the day following admission a laparotomy was performed. The abdominal exploration revealed a multiloculated cystic dilatation of the small bowel mesentery involving about 125 cm of the intestine 250 cm distal to the ligament of Treitz. The cystic dilatations caused torsion of small bowel in a anticlockwise direction with a complete obstruction (Figure 1). There were some necrotic and stenotic areas in this small bowel segment. The involved segment of the small bowel was resected with the mesentery including cystic dilatations, and a primary end-to-end anostomosis was performed. The patient was discharged on the seventh postoperative day, after an uneventful recovery.

Histologically, there were regional necrosis and hemorrhagic areas in the small bowel, and the cyst wall was composed of fibrous tissue and in some areas there was lining of flattened epithelial cells.

Discussion

Mesenteric cysts are considered to be localized loculations of lymph, thus called "lymphangiomata", and because they do not arise from any organ in the abdomen they are named "mesenteric".

Many theories have been postulated concerninig the origin of mesenteric cysts. Most authors accepted the explanation of Beahrs, Judd, and Dockerty, who suggest that these cysts should be classified according to their basic histology in 4 groups.[7]

1- Embryonic and developmental,
2- Traumatic or acquired,
3- Neoplastic,
4- Infective and degenerative.

Most of these cysts reported were developmental in origin and arose from the continued growth of congenitally malformed and malpositioned lymphatic tissue.[2,7] Enteric, urogenital, lymphoid and dermoid cysts were also included in this group. The fluid in the cyst may be serous or mucinous.

The cyst wall composed of fibrous tissue and the cellular differentiation demonstrate the tissue derivation of the tumour. These cystic tumours usually present as a slowly enlarging abdominal mass producing few symptoms unless there has been an associated trauma. But sometimes they may cause acute abdominal emergency, such as localized compression or twisting of an intestinal loop causing acute intestinal

obstruction,[3,8] hemorrhage into a mesenteric cyst,[9] or rupture of the cyst,[3,8,10] with acute abdominal pain.

In all previously reported cases of mesenteric cysts during pregnancy, cysts presented themselves as a distinct mass, separate from the uterus. In our case the pregnancy was complicated by acute abdomen, caused by twisting of the multicystic intestinal loop resulting in intestinal obstruction and infarction.

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Abnormal Eye Movements in Amyotrophic Lateral Sclerosis

James A. Goodwin, M.D.*

Charcot Summarized the Clinical Symptomatology in ALS as Follows:

"Having described the necroscopic alterations proper to amyotrophic lateral sclerosis, it is important now to enliven the tableau by showing you the aggregate of symptoms which, during life, are associated with these lesions.

I ought to first say that the observations wich are going to serve as the foundation for my description are yet few in number, twenty at most. But it is proper to remark that such was the case at the time for progressive locomotor ataxia, and yet the clinical picture traced by Duchenne (de Boulogne) with the aid of a small number of facts almost twenty years ago has not become outdated. It subsists as is, even today in its essentials, without having undergone profound modifications. May the description I have just given of amyotrophic lateral sclerosis be of the same sort!

I will try to summarize in outline form the symptomatic characteristics of amyotrophic lateral sclerosis under what may be considered normal circumstances.

1. Paresis without anesthesia of the upper limbs, accompanied by rapid wasting of all the muscles and sometimes preceded by numbness and formication. Spastic rigidity comes about at a certain point involving the atrophic paralysed muscles causing permanent deformation by contracture.

2. The lower limbs are involved in their turn. There occurs first a rapidly evolving paresis without accompanying anesthesia which rapidly renders standing and walking impossible. To these symptoms are added

* Clinical Associate Professor, University of Chicago Ill, USA.

spastic rigidity, a tfirs intermittent, then permanent and complicated sometimes by tonic spinal fits. The muscles of the paralysed lower limbs undergo atrophy only late and never to the same degree as those of the upper limbs.

The bladder and rectum are little involved; there is no tendency to form bed sores.

3. A third period is constituted by aggravation of the preceding symptoms and by the appearance of bulbar symptoms.

These three phases succeed one another in a short space of time. Six months, a year after the start, and all the symptoms have accumulated and become very severe. Death arrives at the end of two or three years on the average by virtue of bulbar symptoms.

Such is the rule; but there is, certainly, the chapter on anomalies. These are small in number all the same and do not change anything essential in the tableau I have just outlined. Thus, the illness in certain cases starts in the lower limbs; in other cases it remains circumscribed at its beginning, be it in one arm or one leg; sometimes it remains limited for some time to one side of the body in a hemiplegic form. Finally, in two cases it stared with bulbar symptoms. But, these cases are, I repeat, only non-essential modifications. The ensemble of characteristic symptoms does not fail to be soon manifest.

The prognosis, at present, is most somber. There does not exist, to my knowledge, any case in which improvement has followed once the group of symptoms I have just described has become established. Is this a permanent standstill? Only the future will tell." Charcot, J. M.[1]

Most would agree that amyotrophic lateral sclerosis (ALS) should rightly be termed Charcot's disease. The above summary from his landmark thirteenth lesson provides a condensed embodiment of his careful observations carried out over many years prior to this remarkable exposition. Many subsequent authors have argued about the relation between the mixed upper and lower motor neuron degeneration known as ALS or Charcot's disease and the "purely" lower motor neuron disease variously known as progressive spinal muscular atrophy or the disease of Aran-Duchenne. Gowers[2] expressed the opinion that these two disorders were but different manifestations of the same disease and mentioned that he thought Charcot in error in his attempt to distinguish them as two separate diseases. Charcot's student, Brissaud (1895-who drew the well known ink picture of Charcot in black top hat and lab apron holding a brain) in his text "Lecons sur les Maladies Nerveuses" argued that

Charcot always made a point that his teachings were derived from concrete abservations and that the diseases ALS and Aran-Duchenne atrophy were *Nosologically* distinct. He made no comment on whether they were or were not distinct disease entities (especes morbides) since he felt that the data did not support such speculations. It seems that this fine point escaped many who later criticized Charcot on these issues.

Similar comment many be made concering the disorder that Duchenne (1861) dubbed "primary labio-glosso-laryngeal paralysis" also kown as progressive bulbar paralysis. In most cases it is a form of ALS but in certain cases the bulbar involvement is the presenting feature and may remain the dominant clinical manifestation. This suggests that *nosologic* distinction is not improper.

This brings us to the question of oculomotor involvement in ALS. Charcot in his lessons twelve and thirteen did not comment on the state of eye movements or on the pathologic examination of the ocular motor nuclei. He limited his comments in the section on bulbar involvement to the lower cranial nerves and the pathologic depopulation of their nuclei.

Gowers[3] in his section on ALS writes as follows: "I have once met with a remarkable reflex fixation of the eyeballs in a case of advanced progressive muscular atrophy. If the patient, looking to one side, was suddenly told to look at an object on the other side, his head was instantly turned toward the second object, while the eyes remained fixed on the first, by a movement corresponding to that of the head, but in the opposite direction, and then, after a few seconds, they were slowly moved toward the second object. The phenomenon continued to the end of the patient's life." He further comments in a footnote:

"As I pointed out in an account of this curious condition (Brain Vol. 1), it is interesting evidence of a normal reflex mechanism in the fixation of the eyes, which was, as it were, isolated by disease, which lessened voluntary control over it."

Apart from the fact that this is an early citation of a case of ALS with ocular motor involvement and that it was of a supranuclear variety, this comment shows that Gowers had a clear notion of the separation of "reflex palsy" as opposed to nuclear palsy even though the concept was not pursued further in this section of his book.

Later in his book Gowers[4] discussed chronic progressive external ophthalmoplegia. Most of the cases were in young people and a strong familial tendency was noted in many, such that a link with ALS was not apparent. Nonetheless, he included the following case in this section:

"In a case of Mr. Hutchinson's in which I examined the brain, the state of the nuclei of the ocular nerves was nearly the same as that of the gray matter of the spinal cord in progressive muscular atrophy."

This case had no clinical or pathologic evidence of lesions outside the nuclear oculomotor apparatus and Gowers wisely placed it in a section separate from his discussion of of ALS. Later, Wilson[6] was to discuss progressive external ophthalmoplegia in his section on ALS although he agreed with Gowers that most cases are quite distinct from motor neuron disease in that the disorder remains limited to the ocular motor system. Still, he acknowledged the existence of ocular motor palsy in ALS and cited the following case:

"A man of 49 had suffered for 10 months from dysarthria, nine months from weakness of legs, six from dysphagia, three from attacks of dyspnea and transient double vision. On examination the classical signs of bulbar palsy were in evidence, together with slight spasticity in the limbs and heightened reflexes; further, there was an all but complete ophthalmoplegia externa, pupil reactions being normal."

Wilson[5] also makes provocative observations concerning the supranuclear quality of ocular motor palsy in some instances:

"Following analogy, (with spinal and bulbar ALS) we should perhaps expect to find synchronous involvement of peripheral and supranuclear neurones. Very little attention has been paid to this matter; whether there be such a clinical entity as 'spastic' paralysis of eye muscles due to cortico-ocular lesions is not known.

I have seen a case of chronic progressive opnthalmoplegia in which the patient was unable voluntarily to look to either side; but if, with gaze fixed on an object in front, his head was slowly turned passively, his eyes could be kept on the subject and so come to occupy the lateral position which could not be otherwise attained. It has always seemed to me that this curious phenomenon might be evidence of (supranuclear) spastic ocular palsy."

Thus we see that one might not expect the literature even up to 1940 to reflect observations on subtle aspects of ocular motility disturbance such as the distinction between nuclear and supranuclear gaze palsies. It seems that knowledge of supranuclear gaze disorders was insular and undeveloped at best even though the concept and been thoroughly articulated by Parinaud in 1836.

In 1925 van Bogaert[7] wrote specifically about ocular and vestibular abnormalities in ALS. In this paper he described cases with dilated or

constricted fixed pupils, and others with vestibular symptoms (without spontaneous nystagmus). Yet, there was only one instance he could quote from his cases in which complete ophthalmoplegia accompanied ALS in a juvenile. A summary of the case follows (my translation):

"The illness began rapidly with weakness of the right leg associated with fever, and a diagnosis of infectious polyneuritis was entertained. The fever disappeared and two months later there was weakness, then flaccid paralysis of the right hand, arm and forearm with amyotrophy. Following this there was involvement of the left leg, left arm, speech, swallowing and movements of the face.

Neurologic exam revealed bilateral syndrome of Aran-Duchenne with marked amyotrophy of the legs, increased deep tendon reflexes and bilateral Babinski's signs.

There was typical bulbar palsy. The upper face was affected to the same degree as the lower face. There was conservation of the palatal and pharyngeal reflexes. Opening movements of the jaw were weak, especially on the left.

Global involvement of the neck muscles left the head freely swinging with no control.

Spontaneous flexion of the trunk was impossible and extension was very bad. There was considerable atrophy of the paravertebral muscles, the latissimus dorsi, the infra and supraspinati and the trapezei. There were abundant fibrillations (fasciculations).

Ocular Examination: One month before death bilateral palsy of the sixth cranial nerves appeared, producing a convergent strabismus. After six days, first on the right, then on the left, complete ophthalmoplegia with ptosis developed. The two pupils were dilated with abolition of all iris reflexes. The optic fundi were normal.

He died of his bulbar syndrome due to cardiac and respiratory arrest.

Autopsy: There was true lateral sclerosis with bulbar paralysis. Acute chromatolysis and proliferation of neuroglia were observed in the nuclei of the third and the sixth cranial nerves.

The anatomic demonstration of this case has value since it constitutes a response to the objection of Cassirer in that there was true lateral sclerosis having evolved with progressive ophthalmoplegia. Most previous cases involved descending forms in which ophthalmoplegia developed into bulbar paralysis which does not with certainty belong to the disease of Charcot."

I have included the complete description of this case since it is important to be sure that it is one of ALS. The main problem with cases on record prior to this one was that the syndromes were usually quite atypical in some regard casting doubt on the diagnosis of ALS. Even though this was a sixteen-year-old and the illness began with fever, the subsequent evolution and the pathologic demonstration seem most consistent with ALS.

It is of passing interest that one of the cases in the previous literature referred to by van Bogaert (Sauvineau cited by La Personne and Cantonnet in Neurolog. Ocul., 1923) was the poet Henri (Heinrich) Heine who developed complete ophthalmoplegia which evolved into a an "ophthalmo-bulbar" syndrome.

Walsh and Hoyt[8] describe a 44-year-old woman with severe bulbar and spinal ALS who developed nearly complete ophthalmoplegia with some sparing of downward gaze and adduction bilaterally. The pupils were normal. There were no responses to caloric stimulation, suggesting that the disorder was peripheral in type rather than supranuclear.

Harvey et al[9] supplied a similar case in a 57-year-old woman with fairly typical though severe ALS. There was ptosis and marked ophthalmoplegia which, like the case of Walsh and Hoyt, began with upgaze palsy and absent Bell's phenomenon. The pupils were normal. Autopsy revealed prominent cellular loss and degenerative changes along the axons of cranial nerves III and VI. The nuclear changes in the III complex were more pronounced in the caudal than the rostral parts. The IV nucleus was involved to a lesser degree.

The application of "modern methods" to the question of abnormal ocular motility in ALS has involved mainly electronic recording of the trajectory or dynamics of eye movements.

One of the first efforts along these lines in ALS was contributed by Steinmetz et al.[10] Using electro-oculography and AC coupling, these authors emphasized examination of vestibular abnormalities in their patients. They cited references to the effect that ALS may involve the vestibular system anatomically and that vestibular symptoms are occasionally encountered in these patients. The thrust of the study was to document the incidence of abnormal vestibular function as manifested by abnormal electro-nystagmography in ALS. They found some sort of abnormality in 94 % of 88 consecutive ALS patients tested. They analysed for 28 different abnormalities, most of which involved forms of nystagmus, both spontaneous and induced, along with forms of nystagmus, both spontaneous and induced, along with fixation behaviour, torsion

swing testing, and pursuit of moving targets (foveal pursiut). The use of terms such as "Type III tracking" and "aberrant optokinetic nystagmus" or "active random eye movements" without further description or qualification makes interpretation of their findings difficult for this author.

This was followed in 1981 by a publication by Jacobs, Bozian, Heffner and Barron[11] in which electro-oculography was used to study mainly slow pursuit movements; optokinetic nystagmus and saccades were described but not illustrated. They found low gain pursuit with frequent "catch up" saccades in 11 of 18 patients (61 %). This defect was symmetric in eight patients and predominated in one or the other horizontal direction in three. In five patients the defect was more prominent at slow pursuit velocities than at high, while in another six, pursuit was equally defective at all speeds. The incidence of abnormal pursuit was the same in all age groups tested making it unlikely to be simply a quasi-normal phenomenon of aging. All of the patients with abnormal pursiut had other brainstem findings on neurologic exam; four patients with normal pursuit also had brainstem signs. Three patients had depressed OKN (amp., freq., rhythmicity) in one horizontal direction. Two of these had, in addition, defective saccades (low vel., low amp.) in the same direction.

Post mortem exam of one patient with abnormal pursuit revealed degenerative changes and cell loss in the dorso-medial substantia nigra, and demyelination in the genu and posterior limb of the internal capsule. There was no cell loss in the cerebral cortex or basal ganglia; the state of the brainstem in this case was not commented upon. The authors believe that the patterns of eye movement abnormality they elicited were most consistent with a supranuclear lesion through the anatomy of this was not defined by their data.

We[12] studied ten patients with typical ALS using similar techniques. We used DC electro-oculography with paper stripchart recording of eye position and velocity. Slow pursuit was recorded at 24 degrees per second, and, if abnormal, at additional velocities. Saccades of 10, 20 and 40 degrees were also recorded.

Four out of the ten patients studied had abnormalities. This is roughly similar to the experience of Jacobs et al[11] All four with abnormalities had low gain pursuit with "catch up" saccades and two of these also had abnormal saccades. One of the patients with low gain pursuit demonstrated this only with rightward movements. Similar directional asymmetry was present in the cases reported by Jacobs et al[12] as mentioned above. Unidirectional defective pursuit cannot be attributed to

nonspecific factors such as fatigue or debility. This type of finding, therefore, strengthens the contention that the observed defects are truly related to the specific pathology of ALS.

One of our patients with abnormal saccades demonstrated progressive decremental velocity during trains of saccades. This same patient and three others had decremental ulnar nerve compound muscle action potentials on EMG. These decremental phenomena were not reversed by intravenous Tensilon. The other patient with abnormal saccades had uniform slowing of sacade velocity as compared with norms for the size of movement.

Our four patients with abnormal eye movements had severe bulbar disease and rapid evolution. Three of the four also had signs of pseudobulbar palsy. We undertook a limited discussion of the possible anatomic substrate of these findings but essentially left this an open question as the data did not support specific statements. We believe, however, as did Jacobs et all[11] that these pursuit and saccade abnormalities are the result of supranuclear dysfunction rather than neuronal attrition in the nuclei of the ocular motor cranial nerves.

Now I would like to pursue in more detail some thoughts on the anatomic substrate of abnormal supranuclear eye movement control in ALS.

First, let us consider the pathology of the disease to see at which loci one might possibly find lesions that could produce the observed abnormalities. Casual accounts refer to Charcot's disease as "motor neuron system disease" implying that the pathologic changes involve only the upper motor neurons in the precentral gyrus, their extension in the "pyramidal tracts" and the lower motor neurons in the anterior horns of the spinal central gray matter. Most pathologic studies of ALS, however, strongly support the notion that the degenerative changes are not limited to motor neurons as described above.

The most comprehensive account of the pathology of ALS remains that of Bertrand and van Bogaert.[13] The later large series (Lawyer and Netsky,[14] Brownell et al,[15] Castaigne et al[16] do not specify the findings at all levels of the cerebrum and brainstem in the same detail as the earlier study, and they add nothing essential to Bertrand and van Bogaert's description of the pathology. The 1925 study[13] will, therefore, form the basis for most of the following comment.

Many of the brains showed no gross change, although sometimes there was atrophy of the precentral gyrus, the paracentral lobule, and,

more to the point, the posterior parts of the first and second frontal convolutions which constitute part of Brodmann's area 8, "the frontal eye field".

Histologically more than half of the brains showed cytologic changes only anterior to the Rolandic fissure but in some cases the cellular loss either involved the whole brain or had its emphasis in the post central areas. The most intense cell loss involved the pyramidal cells of layer three and then, as the disease progressed, layer five. These changes occasionally extended throughout the frontal and temporal cortex. The lesions were often focal, appearing as punched out acellular areas involving several layers of the cortex. In other brains there was diffuse cellular dropout, the affected areas being poorly demarcated from surrounding areas. Such areas, the authors point out, may at first glance seem hypercellular because of astrocytic gliosis.

Ten brains were studied with respect to the intracortical myelinated fibers. In the precentral gyrus changes were most pronounced in the deep tangential plexus of fibers while in extra-Rolandic agranular cortex the middle fiber plexus was most abnormal and in the prefrontal area the superficial plexus in the molecular layer was hardest hit. In general the outer plexus was the most frequently involved, the middle plexus next most frequently, and the inner plexus the least often.

Special study of the centrum semiovale was carried out in six cases. The corpus callosum was involved as often as the motor pathways (about half of the cases). Of special interest was the occasional presence of degenerating fibers in the forceps major related to cell loss in the parieto-occipital region. These degenerating fibers were seen most often in the superior and middle horizontal layers at the splenium of the corpus callosum. Degeneration was also sometimes found along the occipito-temporal fasciculus. These changes fit nicely with the clinical concept that defective ocular pursuit arises from lesions involving parieto-occipital "opto-motor" pathways that descend through the pulvinar to brainstem centers. Variable degeneration was also observed in the region of the fronto-thalamic fasciculus which is a proper location for the frontal eye field outflow for control of saccades.

In the internal capsule degenerating fibers of the frontothalamic pathway could be further traced, although the changes were minor in degree and of questionable significance. At the genu of the internal capsule there were more definitely degenerating fibers coursing toward the cerebral peduncle, though their presence did not correlate with a clinically apparent bulbar syndrome. The most striking and constant cap-

sular lesion was a compact and well circumscribed bundle of degenerating fibers in the middle third where the cortico-spinal fibers are concentrated. Also at this level, degenerating horizontally oriented fibers linking the putamen and globus pallidus to the thalamus and various subthalamic nuclei could be traced. Using Marchi technique a more diffuse abnormality included the retrolenticular portion of the posterior limb where parieto-occipital "opto-motor" pathways are said to pass. There was also involvement of some horizontally oriented intrahemispheric association pathways.

At the level of the cerebral peduncle there was a triangular area of degeneration in the mid portion with base ventral and apex at the substantia nigra. The medial and lateral sectors of the peduncles were spared. This is of interest since the corticobulbar fibers are said to pass in the medial third of the peduncle.

It was specially noted that the third and fourth nerve nuclei are usually spared. Occasionally in juvenile cases acute chromatolysis is encountered in these nuclei associated with terminal ophthalmoplegia (see van Bogaert[7]). The midbrain reticular formation and superior cerebellar peduncle were always normal.

In the pons the normal-appearing tegmentum contrasted sharply with demyelination in the basis. This was sometimes diffuse, though in other cases more localized symmetric areas of demyelination were found on either side. Degenerated fibers could never be traced into any of the cranial nerve nuclei; because of this, the authors were tempted to postulate an intermediate neuron in the reticular formation. Using the Marchi method, degeneration of the fronto-pontine paths could be traced along with some degeneration in the medial peduncle (corticobulbar system) and in the lateral peduncle where occipito-pontine and parieto-pontine fascicles, among others, have been shown to pass.

The aberrant motor bundles (Dejerine) were involved as markedly as were the main pyramidal paths. This could be of considerable interest since there is some evidence that the supranuclear pathways serving volitional horizontal gaze pass in this contingent of fibers at the pontine level.[17]

In the medulla the pyramids were extensively degenerated as expected. In addition, however, there was an almost equal degree of degeneration in the lateral dorsal reticular formation. It seemed that all of the systems in the reticular formation at that level were involved. Nuclear involvement in the medulla included most prominently the twelfth but

also the pneumo-gastric motor portion and certain portions of the facial corresponding to the clinically greater involvement of the lower face than the upper.

Of special interest in terms of eye movements is the fact that the nucleus of Roller was affected as severely as was the main hypoglossal (XII) nucleus. Roller's nucleus is the ventral most of the three "perihypoglossal" nuclei which have strong connections to the pontine paramedian reticular formation, the sixth nerve nucleus and the cerebellum, all of which play pivotal roles in the regulation of eye movements. The main outflow from this group seems to be from the nucleus prepositus hypoglossi, but it is of interest that the other two periphypoglossal nuclei (n. of Roller, n. intercalatus of Staderini) constitute strong afferent contingents to the nucleus prepositus hypoglossi.[18, 19] It seems not too farfetched, therefore, to consider the possibility that lesions involving the nucleus of Roller might contribute to disordered eye movement control via its modulation of activity in the nucleus prepositus. Unfortunately, Bertrand and van Bogaert[13] do not comment on the appearance of the nucleus prepositus or the nucleus intercalatus at all. It would seem of extreme interest, therefore, to investigate this area prospectively in ALS pathological material.

There were also lesions involving the small-celled portions of the Deiters and Schwalbe vestibular nuclei. This is germane since vestibular symptoms are occasionally encountered[7] and subclinical vestibular abnormalities may be frequent in these patients, as was suggested by the electronystagmographic study of Steinmetz, Lebo and Norris.[10]

Space will not allow a complete discussion of the anatomic studies concerning the pathways that connect frontal and parieto-occipital eye fields with ocular motor and accessory ocular motor nuclei in the midbrain and pons. It is, however, instructive to consider the latest work on fronto-mesencephalic projections using tracer methods such as horseradish peroxidase.[20] These methods reveal corticofugal fibers that originate in the frontal eye field and traverse the anterior limb of the internal capsule before splitting into three branches. A dorsal, mainly ipsilateral bundle traverses the intralaminar portion of the thalamus and terminates in the pulvinar, medial dorsal thalamic nucleus, superior colliculus, periventricular gray and pretectum. The second bundle is the classically described "capsulo-peduncular" route coursing in the posterior limb of the internal capsule and medial cerebral peduncle enroute to terminations in the superior colliculus, periaqueductal gray, nucleus of Darkschewitsch, and contraletaral pontine paramedian reticular formation. An intermediate bundle probably derives from the other two

and travels bilateraly to the red nucleus, rostral interstitial nucleus of the MLF, and interstitial nucleus of Cajal.

A moment's reflection will reveal the striking fact that degenerating fiber systems in these same diencephalic and rostral brainstem regions were described by Bertrand and van Bogaert[13] as inconstant but recurrent lesions in ALS patients. This correlates nicely with the fact that supranuclear types of disordered saccades and pursuit have been demonstrated in roughly half of ALS patients studied with electro-oculography.[11, 12]

Information on Area 8 frontal connections is better documented than that concerning parieto-occipital outflow supposedly serving ocular pursuit. Given the available anatomic data, one cannot rule out the possibility that parieto-occipital influence on pursuit is channeled through the frontal outflow paths along with executive commands having to do with the metrics of saccades. This formulation is supported by a case of our own[21] in which a small thalamic hemorrhage caused contraversive hypometric saccades *and* ipsiversive low gain pursuit.

We plan to extend our studies by recording more patients with various clinical types of motor neuron disease and by scrutinizing the pathology in regions of particular interest as indicated by the above review. Specifically, it seems that one would want to make a special study of the following:

1. Quantitate assessment of neuronal dropout in the posterior parts of the first two frontal convolutions corresponding to Brodmann's area 8 or the "frontal eye field".

2. Search for degeneration products along the most recently described frontal eye field outflow pathways in the internal capsule and through the thalamus into the midbrain tectum and pontine tegmentum.[20]

3. Quantitative assessment of neuronal dropout in the lateral medullary reticular formation, and in the vestibular nuclei where Bertrand and van Bogaert[13] found degenerative changes.

4. I think there would be particular reward in study of the perihypoglossal nuclei, which have recently been shown to have special importance in modifying saccadic and pursuit eye movements, and which have been implicated in the pathology of ALS.[13] Though the observed changes were in the nucleus of Roller, it would be important to study the prepositus hypoglossi and the nucleus intercalatus of Staderini. The nuclei of Staderini and Roller provide strong input to nucleus prepositus, which in turn discharges prominently to the pontine paramedian reticular formation and abducens nucleus as well as to cerebellar structures important in the control of eye movements.

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Ultrasonographic Diagnosis of Hepatocellular Carcinoma and Metastatic Liver Tumor

Şafak Reka, M.D.* / Özgül Özgüven, M.D. / Yücel Batur, M.D.*** / Gül Yüce, M.D.**** / N. Kemal Menteş, M.D.****

Summary

Forty-two patients with histologically proven hepatocellular carcinoma and 60 patients with metastatic liver tumor were examined ultrasonographically. The ultrasound patterns of hepatocellular carcinoma and metastatic liver tumor were described and the differential diagnosis was discussed. Our findings showed that single and large tumoral lesions were more frequent with hepatocellular carcinoma, but multiple and small tumoral lesions with metastatic liver tumors located in the right lobe. When tumoral lesions were less than 5 cm. in diameter, irregular-shaped, hyperechoic and homogeneous internal echo patterns were frequent in cases of hepatocellular carcinoma, while round-shaped, hyperechoic and heterogenous internal echo patterns were frequent in those of metastatic liver tumor. When tumoral lesions were 5 cm. or more in diameter, although hyperechoic lesions were frequent in both hepatocellular carcinoma and metastatic liver tumor, the lesions frequently appeared to be round-shaped and heterogeneous in hepatocellular carcinoma and irregular-shaped and homogeneous in metastatic liver tumors.

Key Words: Hepatocellular Carcinoma, Liver Neoplasia, Ultrasonography.

Introduction

Ultrasonography is a valuable diagnostic method for the detection of the liver cancer.[1,2,3] However, hepatocellular carcinoma (HCC) and metastatic liver tumor (MLT) have no definite ultrasonographic

* Fellow in Gastroenterology Aegean University Medical Center İzmir-Turkey.
** Professor in Gastroenterology.
*** Associate Professor in Gastroenterology.
**** Associate Professor in Pathology.

image. Although hepatocellular carcinoma has poor prognosis, early detection may be important to increase the average survival with effective theraupetic methods. In this study the differences in ultrasonographic findings between the hepatocellular carcinoma and the metastatic liver tumor were investigated in 102 patients.

Material and Methods

Forty-two patients with HCC and 60 patients with MLT were studied at Aegean University Medical Center. There were 30 males and 12 females with HCC, 36 males and 24 females with MLT. Ages ranged from 38 to 66 in the HCC and from 19 to 78 in the MLT. Liver biopsies were obtained during laparoscopy and the diagnosis was established by pathological examinations in all patients. In lesions not visible on laparoscopy needle biopsy was obtained through insertion of the needle into the liver according to the ultrasonographic location of the lesion. Only those 102 cases yielding tumoral biopsy results on pathological examinations following laparoscopy were included in the study.

Real-time SAL-22 A ultrasonography was used to examine the liver. The ultrasonic characteristics were assessed according to location, number, and size of the tumoral lesions and the nature of their margins, and their internal echo patterns were compared with the echogenicity of the surrounding liver tissue. Ultrasonographic findings were classified into 3 groups on the basis of the location, number, and size of the lesions. The lesions less than 5 cm, or more in diameter were classified by the nature of the margins and internal echo patterns of the tumor sonograms.

Results

In HCC, single, large tumoral lesions, and in MLT, multiple, small lesions and right lobe location were frequent (Table I). In the presence of tumoral lesions less than 5 cm. in diameter, irregular-shaped, hypoechoic and homogeneous internal echo patterns (Figure 1) were frequently observed with HCC, and round-shaped, hyperechoic and heterogeneous internal echo patterns (Figure 2) with MLT (Table II). Tumoral lesions 5 cm. or more in diameter frequently exhibited round-shaped, hyperechoic and heterogeneous internal echo patterns (Figure 3) in cases of HCC, and irregular-shaped, hyperechoic and homogeneous internal echo patterns (Figure 4) in MLT (Table II).

Cystic changes in the tumoral lesions were visualized on sonography in 10 % of cases of HCC and 18 % of MLT. Hepatic cirrhosis was detected in 50 % of the patients with HCC. Gallstones were accidentally found ultrasonically in 12 % of the patients with HCC and 18 % of the patients with MLT.

TABLE I

TUMORAL LESIONS

Diagnosis	Location			Number		Size	
	Right Lobe	Left Lobe	Right and Left Lobe	Multiple	Single	Less than 5 cm.	5 cm. and more
HCC (42 patients)	16 (40 %)	15 (36 %)	11 (24 %)	18 (43 %)	24 (57 %)	13 (31 %)	29 (69 %)
MLT (60 patients)	40 (65 %)	5 (10 %)	15 (25 %)	43 (72 %)	17 (28 %)	42 (70 %)	18 (30 %)

TABLE II

TUMORAL LESIONS

Diagnosis	Number of Patients	Less than 5 cm.		5 cm. and more than 5 cm.	
HCC	42	5 (12 %)	8 (19 %)	26 (62 %)	3 (7 %)
MLT	60	25 (42 %)	17 (28 %)	15 (25 %)	3 (5 %)
		Hemogeneous	Heterogeneous	Homogeneous	Heterogeneous
HCC	42	9 (21 %)	4 (10 %)	2 (5 %)	27 (64 %)
MLT	60	12 (20 %)	30 (50 %)	12 (20 %)	6 (10 %)
		Round-shaped	Irregular-shaped	Round-shaped	Irregular-shaped
HCC	42	2 (5 %)	11 (26 %)	25 (60 %)	4 (9 %)
MLT	60	35 (58 %)	7 (12 %)	5 (8 %)	13 (22 %)

Figure 1
Hypoechoic and homogeneous internal echo patterns in a case of hepatocellular carcinoma.

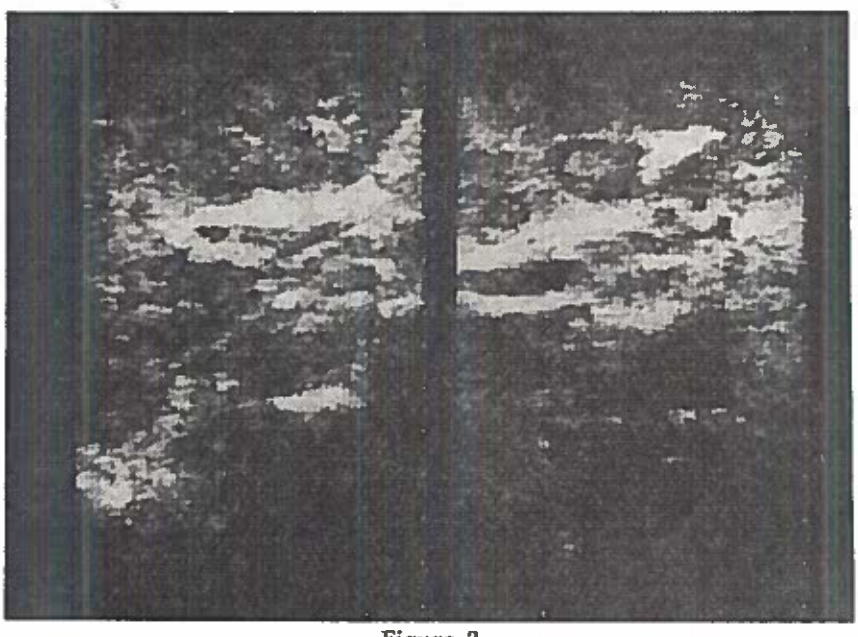

Figure 2
Hyperechoic and heterogeneous internal echo patterns in a case of metastatic liver tumor.

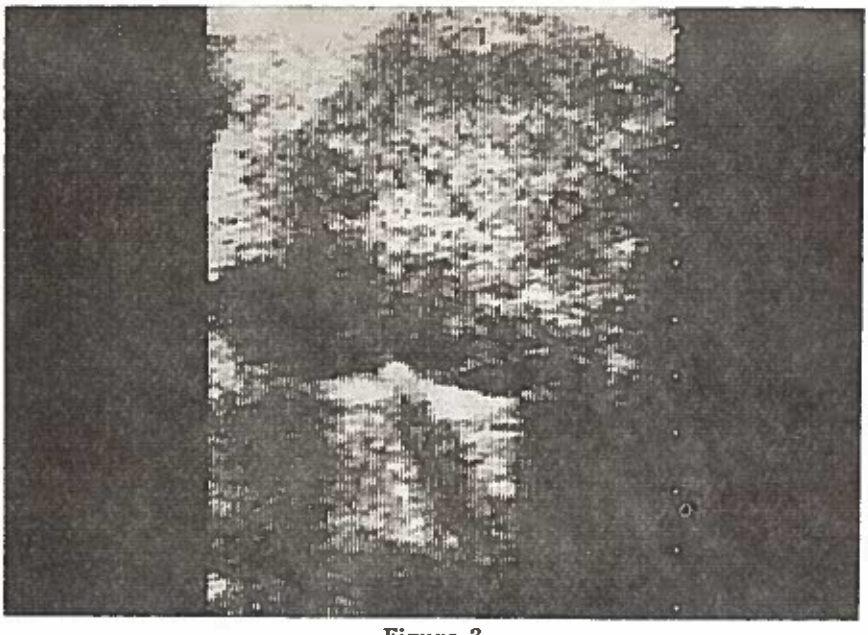

Figure 3
Hyperechoic and heterogeneous internal echo patterns in a case of hepatocellular carcinoma.

Figure 4
Hyperechoic and homogeneous internal echo patterns in a case of metastatic liver tumor.

Discussion

Various ultrasonographic findings have been described in the ultrasonographic literature. Conn[4] reported that HCC lesions appeared echofree in a hyperechoic cirrhotic liver. Dubbins[5] reported 62 % rounded, well-defined, 54 % echofree, 37 % echoic and 19 % mixed lesions with frequently right lobe location in HCC and stated that these findings were more valuable in the patients with hepatic cirrhosis. But, Boultbee[6] described large, 57 % single, 90 % irregular-shaped, 67 % highly echogenic and 27 % mixed lesions with frequently left lobe location in HCC. In the present study single, large, round-shaped and heterogeneous lesions were frequent in HCC. Tanaka, et al.[7] showed a close relation between echo patterns and histologic findings in HCC and classified 6 lesions corresponding to a solid tumor as "hypoechoic", 14 lesions corresponding to a tumor with partial necrosis as "mixed lesion" and 3 lesions corresponding to a tumor with fatty metamorphosis or marked sinusoidal dilatation as "hyperechoic lesion". Green[8] in an ultrasonographic evaluation of the patients with hepatic tumors tried to correlate the ultrasonographic patterns with the degree of vascularity but could not find an association, and showed 32 % to be echogenic, 23 % to be hypoechoic and 35% to be mixed lesions in MLT. Metastases from colonic or urogenital tumors associated with echodense lesions were also reported.[9] However, no correlation between the echo patterns of MLT and the cell type of the primary tumor was found.[10-13] In the present study small lesions frequently exhibited hyperechoic and heterogeneous internal echo patterns in MLT, but large lesions frequently exhibited homoegeneous internal echo patterns. Similar results were reported by Takeuchi.[14]

In HCC the incidence of hepatic cirrhosis was found to be 50 % in the present study. It was 46 %, 41 % and 70 % in other studies.[5, 6, 14] Cystic changes were reported to be 10 % in MLT.[14] whereas in the present study cystic changes were found in 18 % of cases of MLT and 10 % of those of HCC.

In conclusion it can be said that ultrasonographic findings may be helpful for the differential diagnosis of HCC and MLT. However, the definitive ultrasonic criteria remain unestablished.

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TABLE I

ANALYSIS OF CLINICAL AND PATHOLOGICAL FINDINGS

Case	Age (yrs)	Sex	Site of Origin	Size (cm)	Signs	Previous diagnosis	Treatment	Pathology	Follow-up
1	40	M	External auditory canal.	0,5	Mass occluding external meatus.	Papilloma	Excision	Ceruminous adenoma.	Unavailable.
2	45	F	Upper Part of the right mastoid	3	Growing mass since 1 year. After excision, it recurred in the last 6 months.	Cystic tumor.	Excision.	Ceruminous adenoma.	Recurrence 6 months after excision (the size of an orange).
3	20	F	Posterior side of the left ear (Mastoid region).	2	Slow growing tumoral mass, for 8 years.	Tumor	Total Excision	Adenoid cystic carcinoma.	No recurrence in a follow-up of one year.
4	24	-	Left external auditory canal.	1,5	-	Malignant tumor.	Excision	Pleomorphic adenoma.	Unavailable.
5	40	F	Left external auditory canal.	1	Mass	Polyp	Excision	Adenoid cystic carcinoma.	No evidence of tumor in 8 months.

Contineu TABLE I

Case	Age (yrs)	Sex	Site of origin	Size (cm)	Signs	Previous diagnosis	Treatment	Pathology	Follow-up
6	21	M	Right external auditory canal.	1,5	A mobile, soft tumoral mass covered by the skin.	Polyp	Excision	Ceruminous adenoma.	No evidence of tumor in two years.
7	73	M	Right external auditory canal and epidermoid carcinoma of the auricle.	0,5	A growing tumor since 1 year; and an epidermoid carcinoma of the auricle.	Papilloma of the external meatus and carcinoma of the auricle.	Excision of the adenoma with tumoral part of the auricle.	Ceruminous adenoma and epidermoid carcinoma of the auricle.	Unavailable.
8	33	M	Mastoid region	–	Growing mass for two years.	–	Excision and radiotherapy.	Ceruminous adenocarcinoma.	Dead. Due to cranial tumor invasion.
9	50	M	Exsternal auditory meatus.	2	Tumoral mass in external meatus.	Polyp	Excision and radiotherapy.	Ceruminous adenocarcinoma.	Recurrence and living with tumor, 2 years.
10	51	F	External auditory meatus.	1,5x2	Growing tumoral mass for 6 months.	Cystic tumor.	Total excision.	Eccrine spiradenoma.	No recurrence in a follow-up of 6 months.

Pathologic Features

The histologic features of ceruminous adenoma consisted usually of well-defined glandular structures beneath an intact epidermis. Many of the cells closely resembled the normal ceruminous epithelium. As a whole, the tumor was embedded in a collagenous stroma, while in some areas, mucoid change was present. Two distinct cell layers were present, and those cells on the luminal side had abundant acidophilic cytoplasm with focal apical secretions by "decapitation" (Figures 1, 2). There were also rare glands composed of cells with foamy cytoplasms. Occasionally, the epithelium tended to form intraluminal papillary formations. In some areas and particularly in the deeper part of infiltration, the tumor was composed of closely-packed epithelial cells with small irregular glands or cleft-like formations. The nuclei showed some variation in size and in intensity of staining. Many cells contained PAS-positive diastase-resistant cytoplasmic granules. There was no evidence of invasion of neighboring structures.

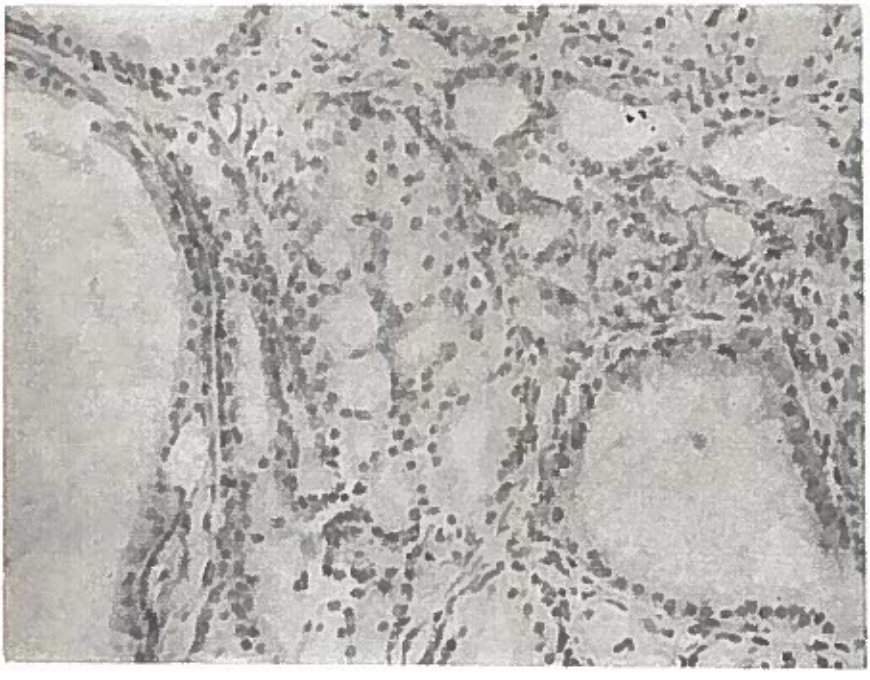

Figure 1

Case 6. Ceruminous adenoma consisting of well defined glandular structures. The cells on the luminal side has acidophilic cytoplasm with focal apical secretions by "decapitation". (Hem. Eosin, X 150).

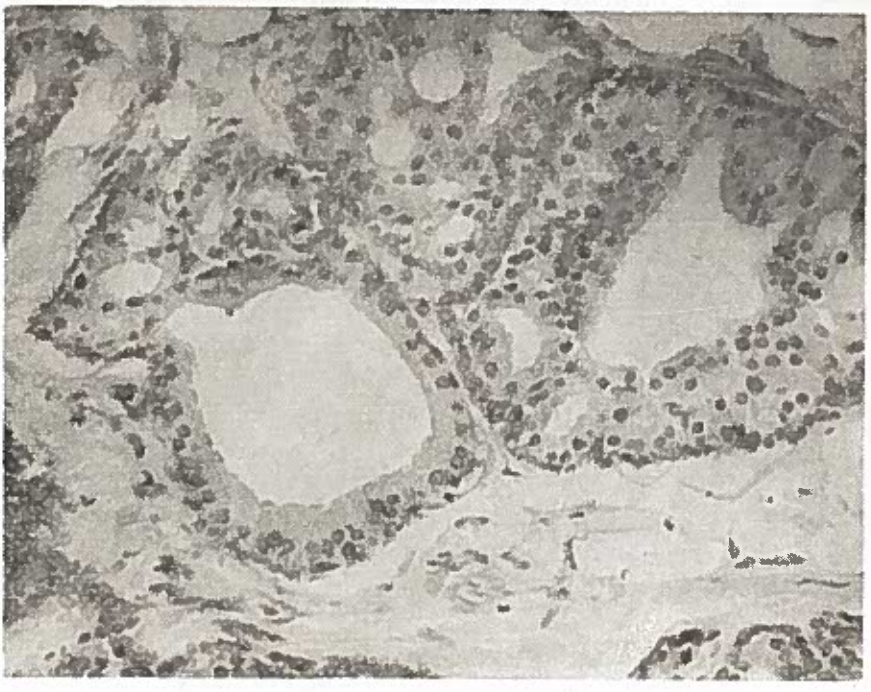

Figure 2
Case 7. Ceruminous adenoma. (Hem. Eosin, X 200).

The case of pleomorphic adenoma (case 4) was clearly recognizable by its epithelial tissue being intermingled with mucoid, myxoid, or chondroid stromal tissues. The epithelial cells, which were generally eosinophilic and polygonal in shape in some areas formed ducts and sheets of myoepithelial cells (Figure 3).

The case of eccrine spiradenoma (case 10) consisted of a mixture of small cells with round uniform nuclei and slightly larger cells with paler nuclei. Some glandular structures were also present (Figure 4).

The cases of ceruminous adenocarcinomas showed both moderate and low differentiated areas consisting of irregular glandular structures. Cytoplasmic acidophilia and in some glands apical secretion reminiscent of apocrine differentiation were noted (Figures 5, 6). The glands were generally lined by two-layered eosinophilic epithelium and, in many areas, by multiple layers of epithelial cells whose nuclei were moderatly pleomorphic. Scattered mitotic figures were seen. And finally, the histologic features of adenoid cystic carcinoma were similar to those seen in salivary glands elsewhere in the body (Figure 7).

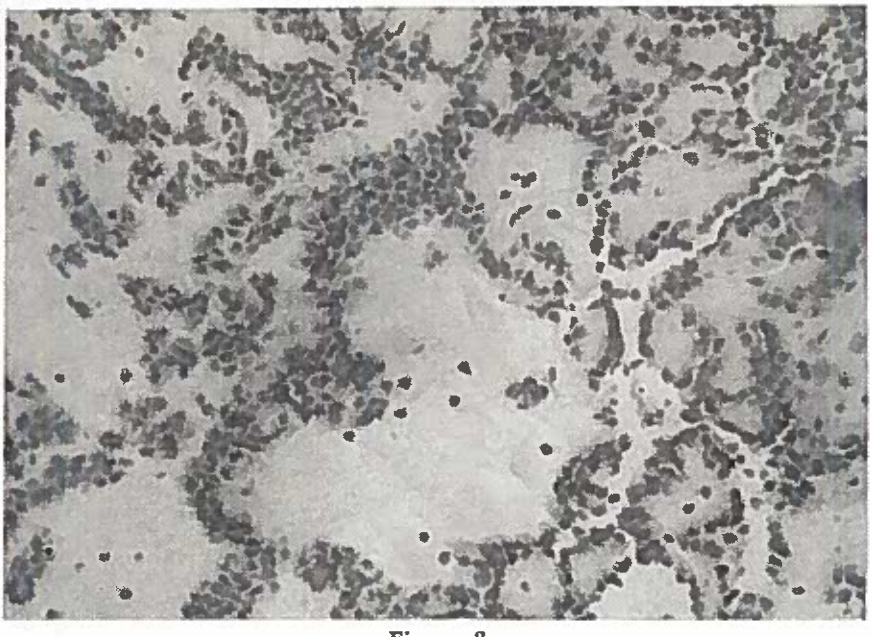

Figure 3

Case 4. Pleomorphic adenoma. Strands and sheets of epithelial cells with ducts merging into hyaline and myxoid background. (Hem. Eosin, X 200).

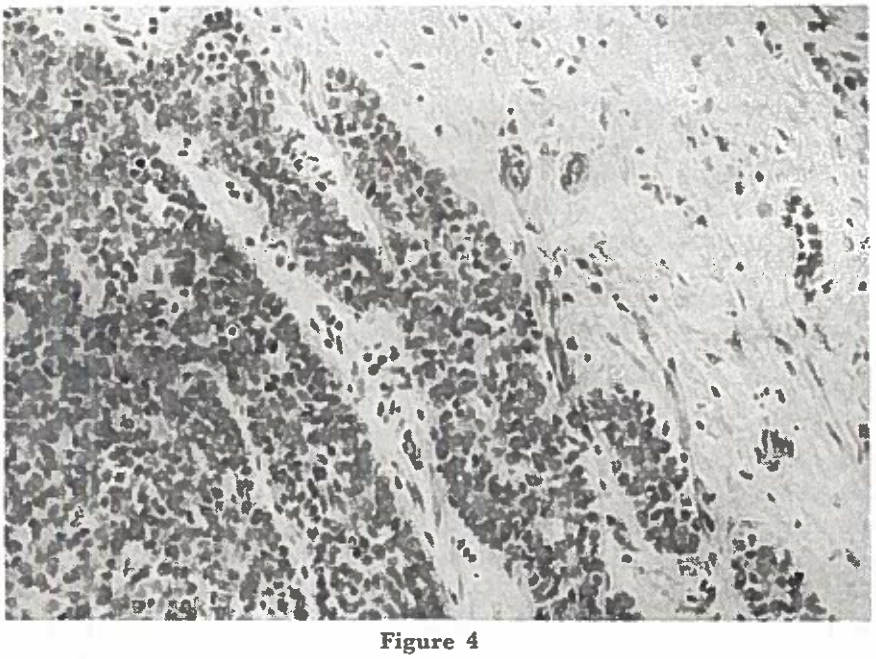

Figure 4

Case 10. Eccrine spiradenoma, consisting of a mixture of small and slightly larger cells with paler nuclei. Some glandular structures are also present. (Hem. Eosin, X 200).

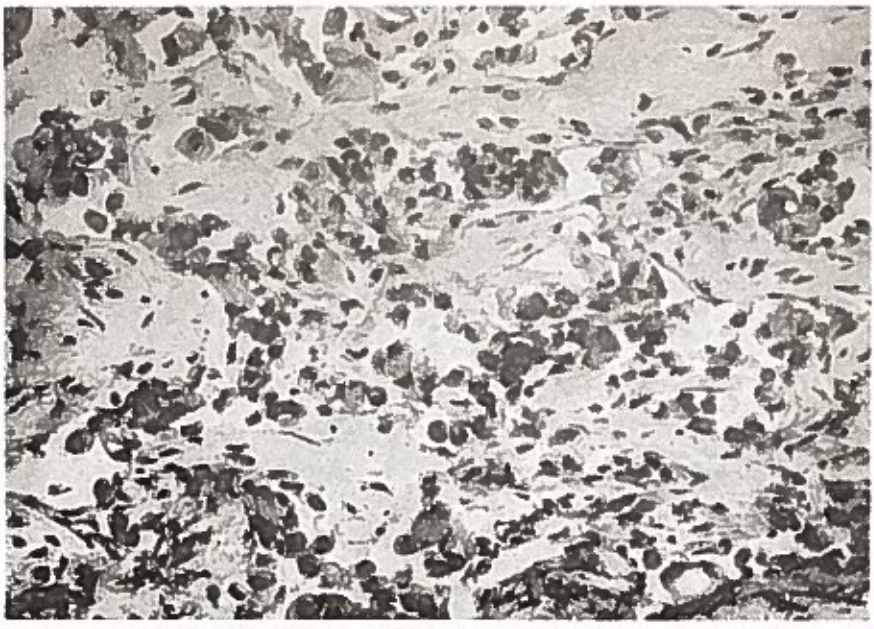

Figure 5
Case 8. Ceruminous adenocarcinoma. Irregular glandular structures showing cytoplasmic acidophilia and atypical nuclei. (Hem. Eosin, X 350).

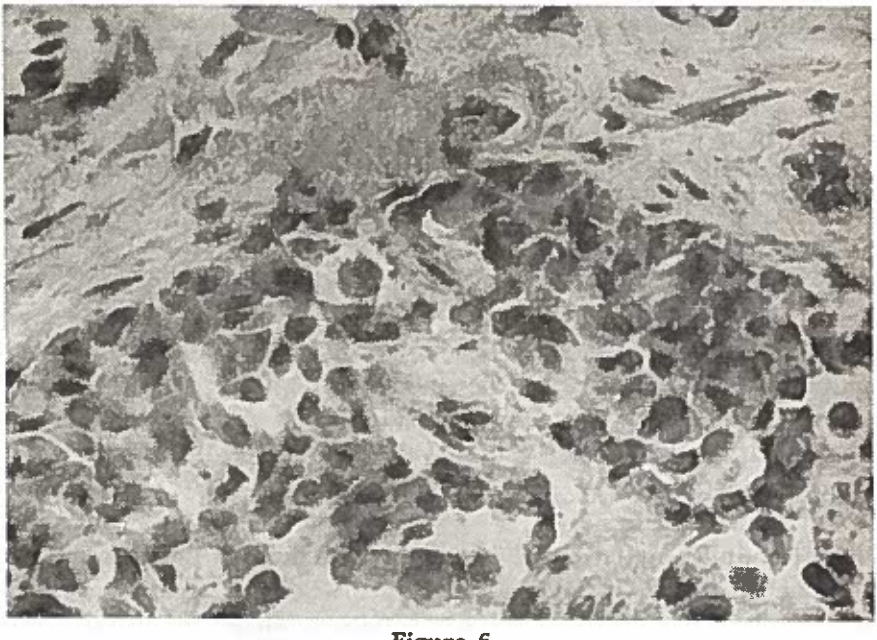

Figure 6
Case 9. Ceruminous adenocarcinoma. Irregular glandular structures lined by multiple layers of atypical epithelial cells. (Hem. Eosin, X 500).

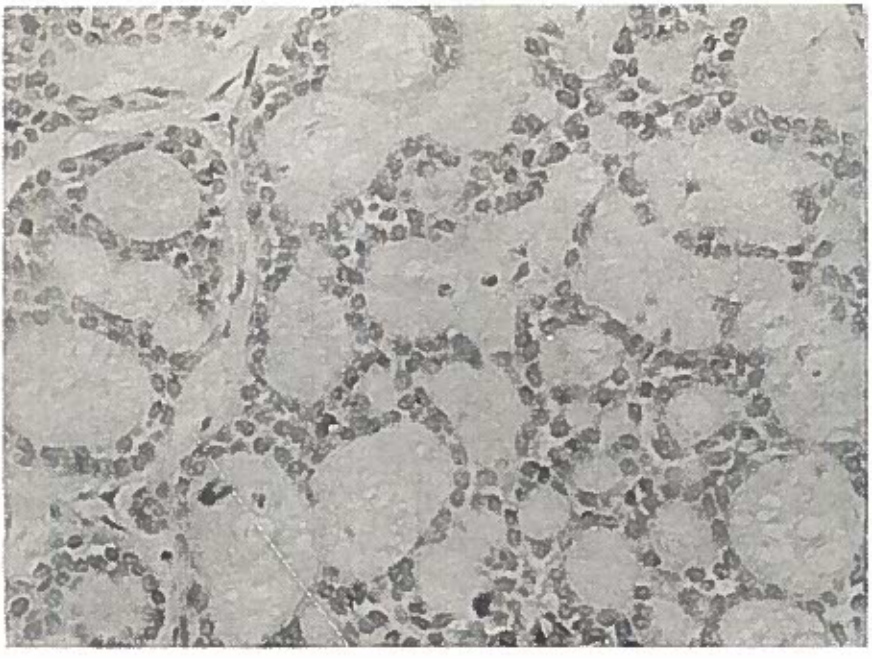

Figure 7
Case 5. Adenoid cystic carcinoma with characteristic cribriform pattern. (Hem. Eosin, X 350).

Discussion

The auditory canal contains both sebaceous and ceruminous glands and it is generally admitted that ceruminous glands are modified sweat glands. The tumors in this area have therefore features of cutaneous apocrine tumors, while others appear more eccrine, and some of them most closely resemble salivary gland tumors.

There is confusion in the literature concerning the nomenclature of these tumors. Those favoring the generic term "ceruminoma" refer to the fact that the tumors arising from this area are derived from the modified apocrine glands of the auditory canal (ceruminous glands) and appear to have a distinctive clinical aspect because of their unique anatomical location. Those who call these tumors hidradenoma, cylindroma, myoepithelioma, mixed tumors, or clear-cell carcinoma feel that neoplasms arising from this region are by and large analogous to other well-differentiated sweat gland tumors cocuring in other parts of the body.[9-12] The few reported histochemical studies of tumors of ceruminous gland origin have given variable results. In ultrastructural studies of "ceruminous tumor" some had findings consistent with an eccrine origin[8] while another[5] showed a ceruminous gland origin. But, whether or not

the external auditory canal is one of the few places devoid of integuments of eccrine sweat glands, the source of these tumors may be either an ectopic salivary gland tissue in the ear-mastoid region or the differentiation of the tumor to an eccrine structure.

The case of eccrine spiradenoma described in this study (tenth case of the series) is, to our knowledge, a unique case arising from the external auditory canal. This case with the other varieties, such as pleomorphic adenoma and adenoid cystic carcinoma are identical to the sweat and salivary gland equivalents. This strongly suggests that these tumors could be histologically classified with varieties of tumor occuring in the sweat glands elsewhere. Such a classification may offer a more accurate description of the pathologic process, in terms of its histological pattern.

The site of origin in three cases of the present series (cases 2, 3 and 8) were the mastoid. Ceruminous adenoma (case 2) and ceruminous adenocarcinoma (case 8) arising from this area showed certain histologic features reminiscent of ceruminous gland tumors. These possibly originated from the apocrine modified glands in the mastoid system.

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Colonic Atresias in Newborn Children

Mehmet Ali Altın, M.D.* / Nebil Büyükpamukçu, M.D / Akgün Hiçsönmez, M.D.****

Summary

Congenital colonic atresia is a rare cause of intestinal obstruction in newborns, causing less than 10 % of all intestinal atresias and stenoses.

Eight cases were treated surgically at Hacettepe University Pediatric Surgery Department between 1964-1984. Two cases were treated with resection and primary end to end anastomosis and six cases with initial colostomy which were closed about one year later. We believe performing a colostomy decreases the early mortality.

Key Words: Atresia, Colon.

Introduction

Congenital colonic atresia is a rare cause of intestinal obstruction in the newborn.[1] It accounts for less than % 10 of all intestinal atresias and stenoses.[2] It may be diagnosed when abdominal distention, constipation, and fecal vomiting occur after several feedings. Delay in diagnosis leads to higher mortality.[3]

Between 1964 and 1984, 8 colonic atresias were diagnosed at the Hacettepe University Department of Pediatric Surgery. Our aim in this article is to discuss the results and the management of colonic atresias.

Material and Method

Eight newborns were operated on between 1964 and 1984 in our clinic. Multiple atresias of the small intestines and colon were not included. The findings on physical examination are shown in Table I, along with clinical courses.

* Instructor, Department of Pediatric Surgery, Hacettepe University Medical School, Ankara-Turkey.
** Professor, Department of Pediatric Surgery, Hacettepe University, Medical School.

TABLE I

THE CLINICAL FINDINGS AND COURSES OF OUR CASES

Case	Age/Sex	Symptome	Site of Atresia	Type of Operation	Outcome
C.B.	2d./F	Int. Obst.	Asc. Colon	Colostomy	Doing with colostomy
E.O.	4d./M	Int. Obst.	Tr. Colon	Resection-colo-colostomy	Anastomotic leak. Died of sepsis
H.K.	3d./M	Int. Obst.	Tr. Colon	Colostomy	Colostomy colored
Ö.H.	3d./M	Int. Obst.	Desc. Colon	End to side anastomosis	Anastomotic leak, died of sepsis
H.Y.	4d./F	Int. Obst.	Asc. Colon	Colostomy	Colostomy closed
A.B.	4d./M	Int. Obst.	Asc. Colon	Colostomy	Colostomy closed
C.Y.	6d./F	Int. Obst.	Tr. Colon	Colostomy	Doing with colostomy
Z.K.	6d./M	Int. Obst.	Desc. Colon	Colostomy	Colonic fistula, died of sepsis

Five cases were male and 3 were female. They were admitted to the hospital at their 2nd to 6th days and the diagnosis of colonic atresia was made by physical examination and laboratory findings. Three of the cases were explored without a barium enema. Almost all of the newborns were admitted with abdominal distention, fecal vomiting and constipation. The upright abdominal X-Ray revealed gas-fluid levels suggesting mechanical obstruction (Figure 1). Barium enema was performed on the patients who had signs of intestinal obstruction and the atretic segment was demonstrated with an unused segment distally (Figure 2). The cases were followed with I. V. fluid replacement and nasogastric decompression. In all of the cases, I. V. penicillin G 250000u/kg and Gentamycin 5 mg/kg were used. After the patients were stabilised, an abdominal exploration was performed with a transverse right upper quadrant incision. Colonic atresias were classified as proximal and distal in relation to the splenic flexure. As shown in table I, two of the patients had colonic atresias distal to the splenic flexure, and the others proximal to the splenic flexure. None of the patients had perforation of the bowel. Only one of our cases showed a type III colonic atresia; all of the other cases were of type I. During the operation, the proximal and distal colonic segments and the small intestines was explored for multiple atre-

Figure 1
Upright X-Ray film of a neonate with an isolated colonic atresia.

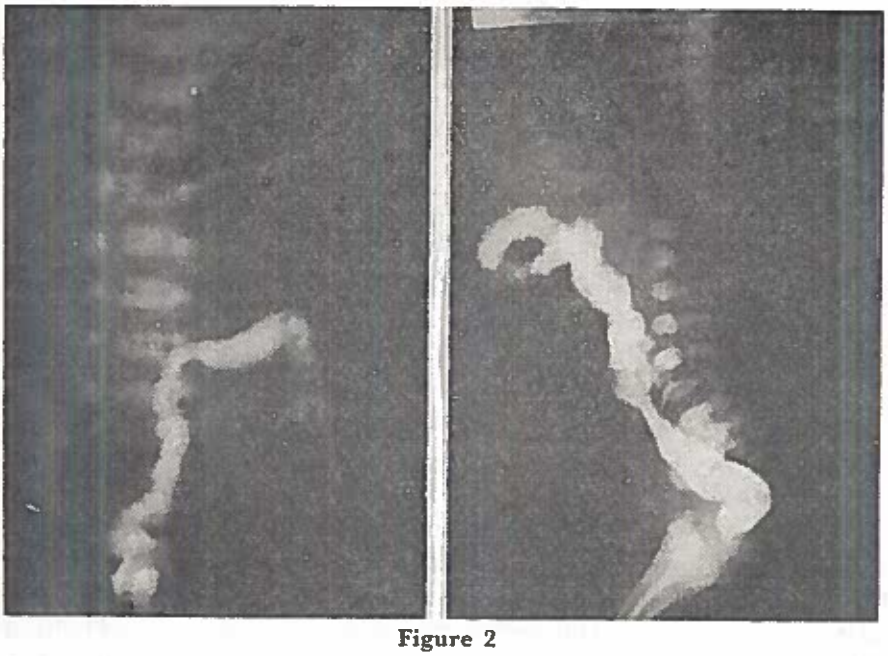

Figure 2
Barium enema examination of the same neonate.

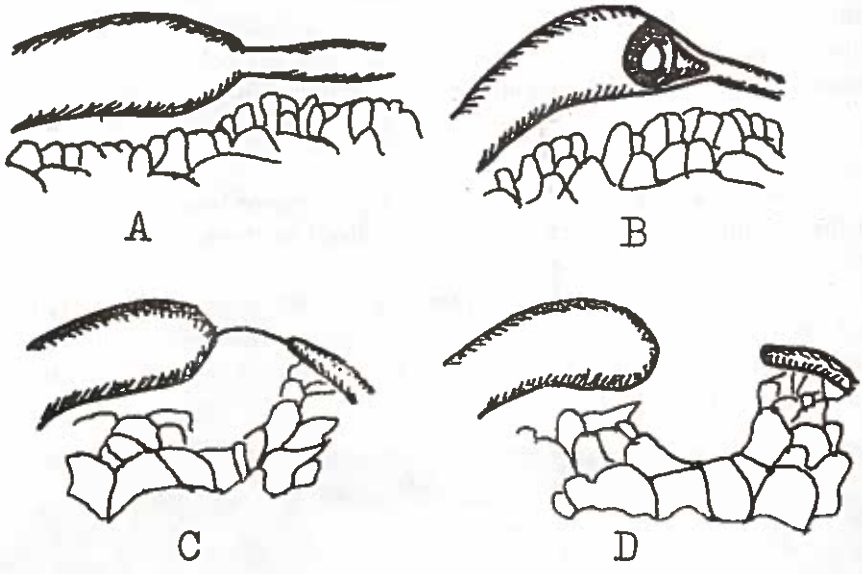

Figure 3
Types of colonic atresia according to Louw's classification (A) Colonic stenosis (B) Atresia type I (C) Atresia type II (D) Atresia type III.

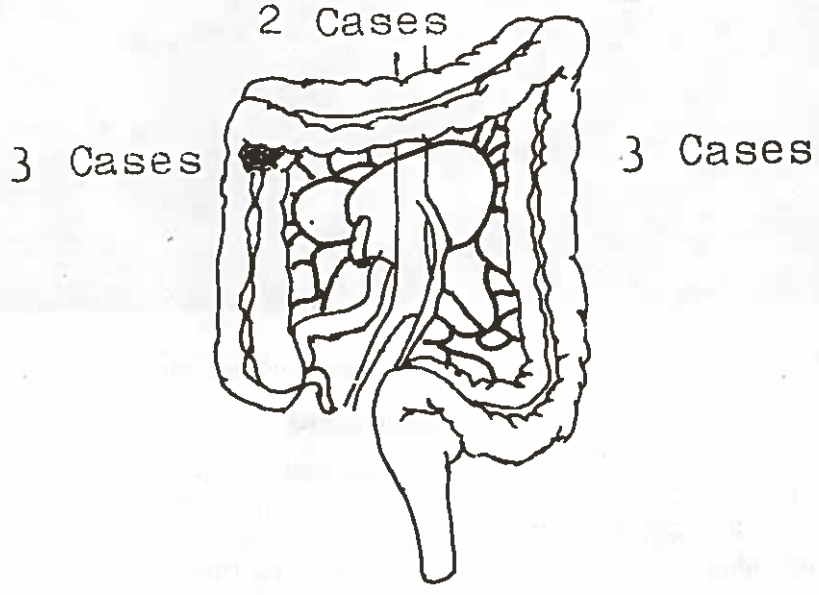

Figure 4
The sites of atretic segments in our cases relative to the splenic flexure.

sias. After resection of the dilated segment of the proximal colon, proximal and distal colonic segments were exteriorised as a double-barrel colostomy, in seven cases. The cases with type III colonic atresia was treated by end-to-end anastomosis of the colon (Figure 3, 4).

Results

As summarised in Table I, the atretic segment was found proximal to the splenic flexure in six patients and distal to the splenic flexure in two patients. In one of the cases with distal type colonic atresia anastomosis was performed, and the other expired because of colonic fistula and sepsis. Colostomy was performed in all of the cases with atresia proximal to the splenic flexure, and the colostomy was closed almost one year later. (Figure 5).

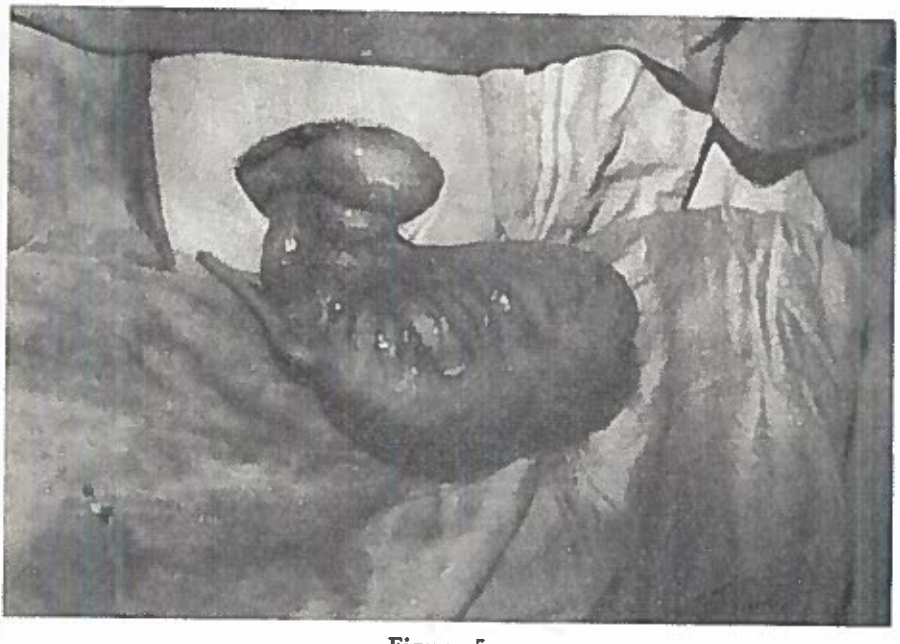

Figure 5
The operative view of our first case (This patient is still well after colostomy).

Discussion

Congenital colonic atresia is a rare anomaly of the gastrointestinal tract. It is seen in 1/15000-1/200000 of births.[4] It was first reported by Birningan in 1673. In 1922, Gaub reported his cases of atresia of the sigmoid colon treated by sigmoid colostomy.[5] In 1947, Pott treated a case of transverse colonic atresia by end-to-end anastomosis.[6] Recent developments in reanimation and hyperalimentation, better knowledge

of fluid and electrolyte balance, rapidly enlarging newborn surgical units and other factors have led to a better prognosis. The literature has over 85 cases of living colonic atresias.[7]

As in other types of intestinal atresias, the etiology of colonic atresia is unknown. Banard and Louw's is the most widely accepted theory based on experimental studies. According to this theory the normal intestinal development is disturbed by some sort of intrauterine volvulus, invagination vascular sclerosis and thrombosis.[7] Experimentally, one or more mesenteric vessels, when ligated may lead to intestinal atresia. Abrams had performed a similar study on sheep;[8] Chiba, Jabulai, and Davis also claimed that the vascular theory is valid.[9] Chiba claimed that when newborns have necrotising enterocolitis, they are candidates for colonic atresia.[10]

Colonic atresia is associated with congenital anomalies less often than other atresias. Jejunal and ileal atresias, gastroschisis, and congenital heart diseases are the most frequent associates of colonic atresia.[4] It can be generally classified in three groups: Type I, a diaphragm is present intraluminally; type II, the ends of the colon are atretic and the mesentery is intact; type III, the two ends of the colon are atretic and the mesentery is interrupted. Seven of our cases were of type I, and only one was of type III.

Congenital colonic atresia is diagnosed with the signs of intestinal obstruction. Upright abdominal X-ray films show gas-fluid levels. Barium enema is the least traumatic and the most rewarding diagnostic procedure. A differential diagnosis of meconium plug, congenital aganglionic megacolon, and the colonic atresia can be made with barium enema (Figure 2). Barium enema was performed in five of our cases and was diagnostic in patients.

There is a delay in the diagnosis of colonic atresias when compared to atresias of the upper gastrointestinal tract. Generally this delay is about 2-6 days.[3] The mortality rate is over 90 % if this delay is more than 6 days. Two of our cases were 6 days old whereas the rest were 4 days or less. One of the cases who was 6 days old died of sepsis. The rapid deterioration of the patient, with a competent ileocecal valve giving rise to huge dilatation of the proximal colon which in turn causes dehydration, perforation and sepsis, is the leading cause of increased mortality.

Colonic atresia should be managed urgently. Preoperatively the newborn must have normal serum electrolytes and fluid balance.

An upper right quadrant transverse abdominal incision was preferred as it is recommended by others.[1] The small intestines must also be

explored. When the segment with the atresia is found the distal portion must certainly be examined for another atretic portion by means of saline injection.

The surgical approach to the patient with colonic atresia varies with the site of the pathology, dilatation of the proximal colonic segment, and the general condition of the patient. If atresia is proximal to the splenic flexure, resection of the dilated segment and primary end-to-end anastomosis is the treatment of choice.[11] Randall performed seven primary anastomosis in his series of nineteen cases, all of which were proximal to the splenic flexure, with one complication.[5] In the cases with atresias distal to splenic flexure, proximal colostomy with a resection and closure of the colostomy 8-12 months later should be preferred. Complications such as anastomotic strictures, stricture of the colostomy, and pelvic peritonitis with a mortality rate of 10.5 % is reported. Eraklis reported 33.3 % mortality with the same approach.[12] Eraklis, Pellerin and Bienaime suggested colostomy also in colonic atresias proximal to the splenic flexure.[12]

In our series, six of the cases were proximal and two were distal to the splenic flexure. We managed six of our cases with initial colostomy and closure almost one year later. We recommend that a colostomy be performed, especially if the proximal colonic segment is dilated. Two of our cases who had resection and end-to-end anastomosis died in the early postoperative period, because of anastomotic leak and sepsis. One of the cases with colostomy died also of sepsis. Our mortality rate is 37.5 %.

Our mortality rate is significantly higher than the rates reported in the literature. Resection and primary end-to-end anastomosis was the most important factor increasing this rate. The mortality rate was much less when colostomy was performed as the initial procedure. We believe performing a colostomy initially and closing it about 12 months later decreases the mortality rate significantly.

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M-Mode Echocardiography in the Diagnosis of Left Atrial Myxoma

Ferhan Özmen, M.D.* / Seydi V. Aksüt, M.D. / Aydın Karamehmetoğlu, M.D.*** / Erdem Oram, M.D.******

Summary

A 33-year-old woman patient with signs of rheumatic heart disease (mitral regurgitation), was found to have left atrial myxoma at echocardiography. The myxoma was surgically removed. Our purpose here is to present a case which was followed-up as mitral regurgitation for years with an overlooked myxoma and give a summary of related literature and of other cases simulating myxoma.

Key Words: Myxoma, Left atrium, Echocardiography.

Introduction

Primary cardiac tumours are very rare. Myxoma is the most common of these. 90-95 percent of myxomas originate in the atrium.[1-4] The occurrence of myxoma in the left atrium is three times as high as in the right. Rarely, Myxoma can be multicentric or solitary in the other cardiac chambers.

Other cases which simulate myxoma opon echocardiography are: mitral valve prolapsus, flail mitral valve, calcific mitral stenosis, left atrial thrombus, myocarditis, cor triatriatum, collagen tissue diseases and idiopathic paroxismal atrial fibrilation.

Through M-mode echocardiography we diagnosed a case of myxoma which had been followed up as mitral regurgitation for years. Our diagnosis was confirmed angiographycally and surgically.

* Associate Professor in Hacettepe University Medical Faculty, Department of Cardiology, Ankara-Turkey.
** Fellow in Same Faculty, Department of Cardiology.
*** Professor in Same Faculty, Department of Cardiology.
**** Professor, the Chief of Internal Medicine in Same Faculty.

Case Report

A 33-year-old woman, married and with three children, on December 11, 1983 was referred to the Hacettepe University Hospital because of palpitation, malaise, and pain in both legs. Previous history: She was found to have had rheumatic heart disease, mitral regurgitation, and bilateral femoral embolectomy four years previously and right hemiparesis and aphasia two years previously (thought to represent an embolic stroke). She also complained of exertional dyspnea and palpitation.

On physical examination the pulse rate was 88/min regular blood pressure 110/80 mm Hg and respiration 18/min., regular. There was no venous distention. The lungs were normal at oscultation. There was a grade 2-3/6 apical holosystolic murmur radiating to the left axilla. The liver and spleen were non-palpable. Peripheral edema was not observed. 50-60 % power loss was detected in her right upper extremity, 40-50 % in the distal left lower extremity, and 30-40 % in the proximal extremity.

Laboratory data revealed Hb 12.3 g/dl, Hct 40 percent, leucocyte 9600/mm^3 ESR 105-84 mm/h, ASO 4 Todd U; Latex and CRP were negative. Urine analysis was normal. Resting ECG showed sinus bradicardia and left ventricular hypertrophy and strain (Figure 1). The chest X-ray was normal (Figure 2).

On M-Mode echocardiogram, the EF slope of the anterior mitral leaflet was normal. There was an "echo-free" area in early diastole; multiple dense echoes were seen behind the anterior mitral leaflet during diastole and the posterior leaflet appeared normal in diastole. No intra-atrial echoes were seen in systole (Figure 3, 4).

Right cardiac catheterisation and pulmonary angiogram-Hemodynamic results are shown in Table I. Contrast material was injected into the pulmonary artery and the filling of the left atrium and left ventricle was observed. A radioopaque mass that moved between the left atrium and left ventricle was seen during the systole and diastole. The patient was sent to surgery with diagnosis of left atrial myxoma.

At surgery: A solid, pink gray mass measuring 4.5x4.5 cm in diameter and attached to the interatreal septum with a peduncle was seen the left atrium. The mass was removed and the interatrial septum closed with a teflon patch 2x5 cm. in diameter. At microscopic examination the

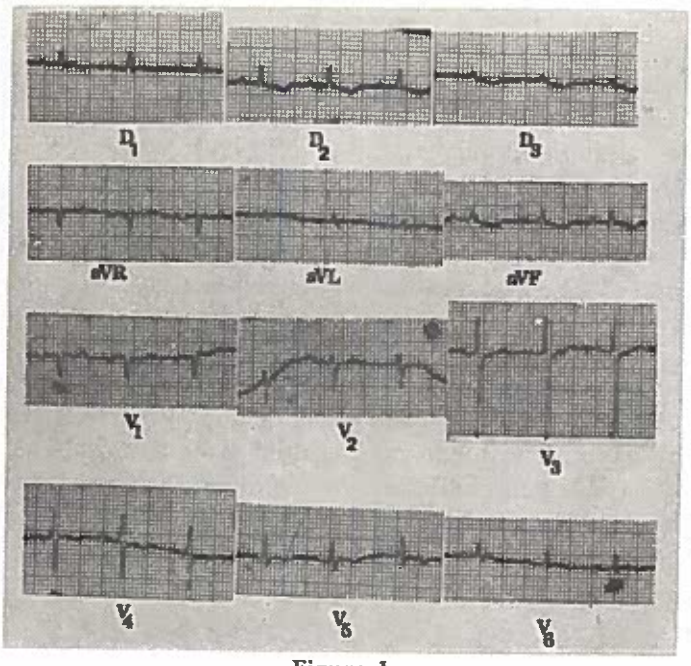

Figure 1
The electrocardiogram demonstration left ventricular hypertrophy and strain.

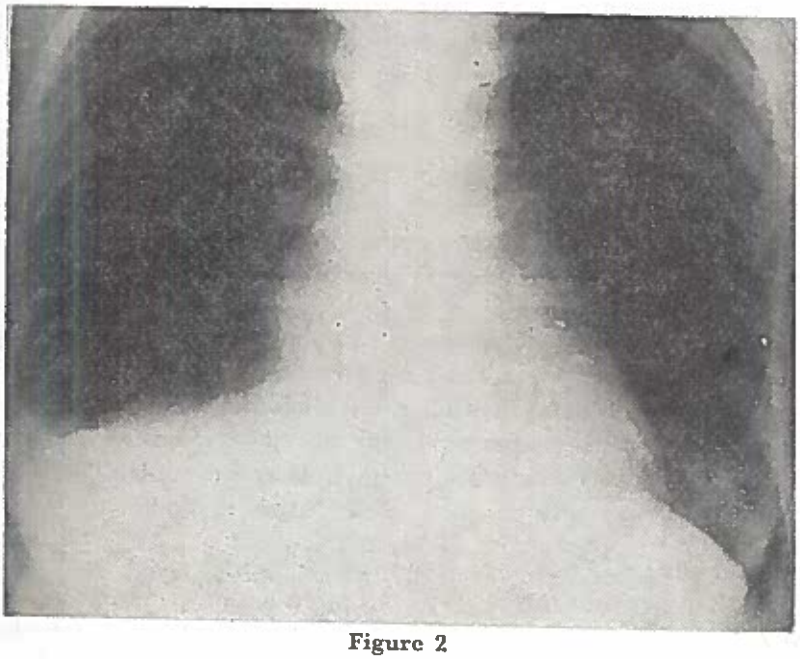

Figure 2
Telecardiography.

pink gray mass was 4.5x4.5 cm in diameter and myxoid in appearence and was compatible with myxoma.

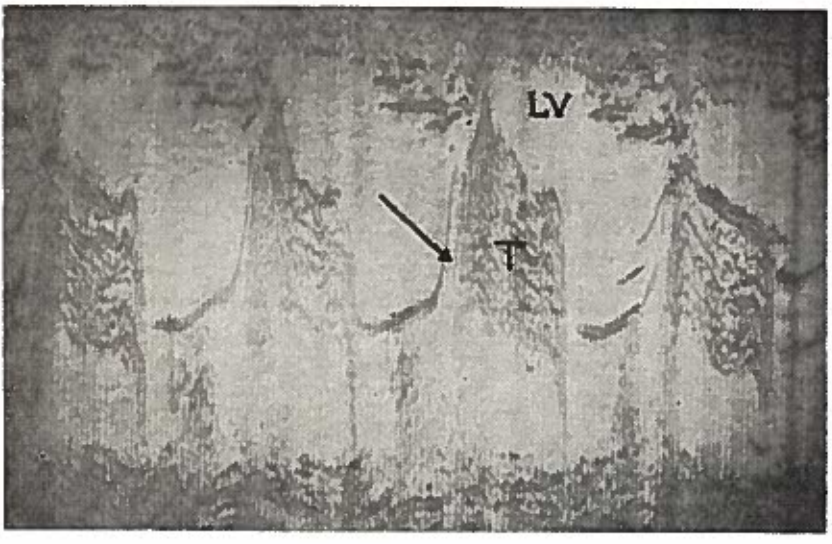

Figure 3
Left atrial myxoma is illustrated on this echocardiogram (T). The black arrow points to an "echo-free" space behind the mitral leaflet which represents the time delay from the onset of diastole when the mitral valves first open to the moment the myxoma protrudes into the left ventricular inflow tract (LV, left ventricle).

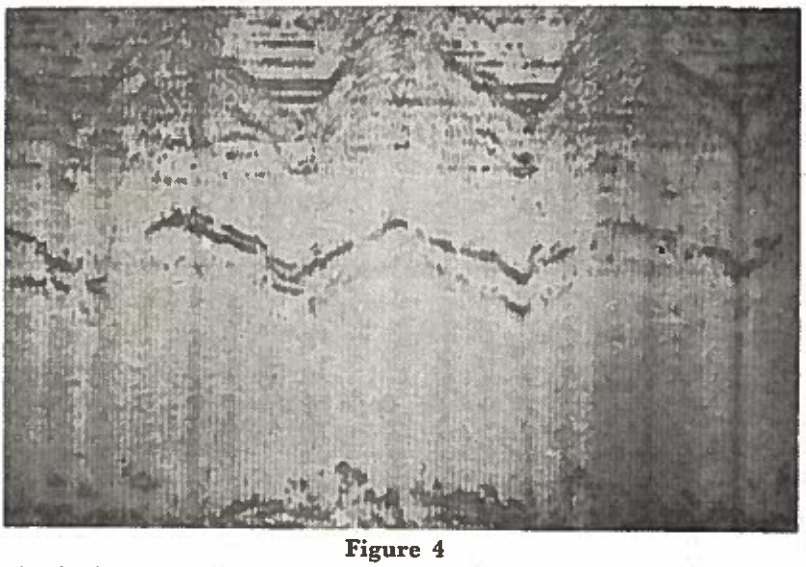

Figure 4
At the level of the aortic root, tumor mass is not seen in left atrium.

TABLE I
HEMODYNAMIC RESULTS

Regions	Pressures (mm Hg) Systolic/diastolic	Average
PC		14
PA	36/19	27
RV	36/7	
RA		7

Discussion

Approximately half of all primary cardiac tumors are myxomas and about 75 percent of these are located in the left atrium.[5,6] The clinical symptoms and signs of left atrial myxomas consist of such non-specific signs as fever, malaise, weight loss, anemia; systemic embolus, and mechanical obstruction of cardiac functions.

Systemic embolisation is seen in approximately 40-50 % of cases.[7-10] Organs most commonly affected by embolus are the brain, kidneys, and extremity arteries. In 40-50 % of central nervous emboli, the cause is left atrial myxoma. In cases of peripheral emboli, the origin of embolus is usually not investigated. After peripheral embolectomy, the thrombus must be studied pathologically for diagnosis of myxoma. As a matter of fact, our case, had a the history of two emboli one of which was peripheral and the other central. If there is an embolic history in a case of cardiac murmurs and sinus rhythm, myxoma must be considered primarily. Echocardiography, which is a non-invasive and easily applicable method, has a great value in definite diagnosis of myxoma. Accurate diagnosis of myxoma is possible with the echocardiographic method without angiography.[11] Today, in many clinics most cases are operated on after echocardiographic diagnosis only.[12] So we can say that the echocardiographic method is the most important in the diagosis of myxoma. Since the left atrial tumors mostly have stalks, they pass from the mitral valve to the left ventricle in diastole and fall back on the left atrium in systole and they appear behind the anterior mitral leaflet.[13] Therefore in echocardiography dense echoes appear behind the anterior mitral leaflet in diastole and they disappear in systole. The decrease of the EF slope of the anterior mitral leaflet is due to the opening of leaflets by the tumor. The presence of an "echo-free" area between the anterior mitral leaflet and tumor mass in early diastole is pathognomonic in the diagnosis of myxoma.[14] Typically, in echocardiography of the left atrium, dense echoes are seen within the left atrium in systole and disappear in diastole.[15-17]

The chance of diagnosis is high with M-Mode echocardiography in myxomas. However, false positive and false negative results have been reported in a few cases.[18-21] The main causes of these are; (1) The acoustic impedence characteristic of the mass lesion may not differ sufficiently from those of blood or endocardium, (2) The intracardiac mass may be located in a position inaccessible to current techniques of echocardiographic study,[22-24] (3) If gain is too high the atrial and ventricular structures give various echocardiographic images which may be misdiagnosed as myxoma. Various cardiac diseases give echocardiographic images simulating myxoma, for example, mitral valve prolapsus, infective endocarditis, calcific mitral stenosis, flail mitral valve, left atrial thrombus, myocarditis, cor triatriatum, collagen tissue diseases and idiopathic paroxismal atrial fibrillation. To prevent false positive or negative results in echocardiogrophy; (1) the anterior mitral leaflet and posterior mitral leaflet must be recorded together, (2) the left ventricle and the left atrium must be examined and, (3) the echo-free area must be examined. Echocardiographic diagnosis of myxoma is also possible with the presence of dense echoes behind the anterior mitral leaflet with cyclic appearance of dense echoes within the left atrium. However, it is reported that small myxomas without peduncle may not be seen in echocardiography. In our case, although the myxoma originating from interatrial septum was large we could not obtain an echo image within the left atrium. Such a case has not been reported in the literature. This may be due to the high degree of vascularity seen in some tumors. Also homogeneous echoes in a case with clear-cut border were not seen, probably because of the large amount of vascularity.[25]

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Dyskeratosis Congenita in a 21-Year-Old Man

Nazif Kürkçüoğlu, M.D.* / Suzi Serezli, M.D. / Nilgün Atakan, M.D.** / Fikret Kölemen, M.D.*****

Summary

Dyskeratosis congenita is a rare genodermatosis with systemic manifestations. This disease is characterized by a triad of clinical findings: reticulated pigmentation of the skin, nail dystrophy and leukoplakia of the mucous membranes.[1-3]

In this paper a case of dyskeratosis congenita is presented.

Key Words: Dyskeratosis Congenita, leukoplakia.

Introduction

Dyskeratosis congenita is a genodermatosis characterized by reticulated pigmentation, nail dystrophy and leukoplakia. About 75 cases have been reported to date.[4] Patients with this disorder may have, in addition, pancytopenia and malignant neoplasms which frequently constitute a common cause of death.[3]

Case Report

A 21-year-old young man was referred to us for evaluation of hyperpigmentation of the skin, nail dystrophy and leukokeratosis of tongue and buccal mucosa which had been present since early childhood.

The family history was negative for similar lesions.

On physical examination the patient was a poorly developed and malnourished young male; body length, 158 cm, body weight, 40 kg, sparse growth of hair, leukokeratosis of tongue and buccal mucosa (Figure 1).

* Assistant Professor in Department of Dermatology, Hacettepe Medical School, Ankara-Turkey.
** Resident in the same department.
*** Associate Professor in the same department.

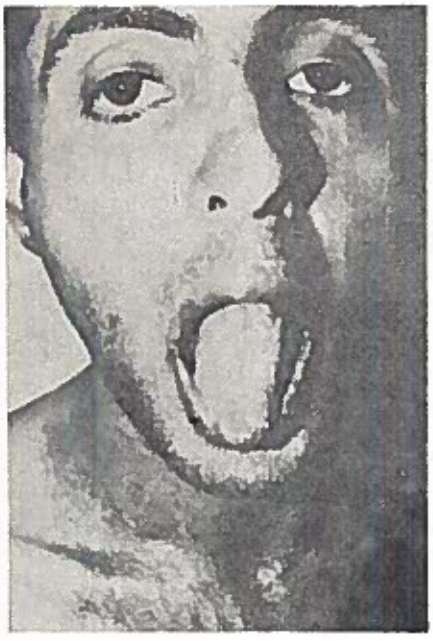

Figure 1

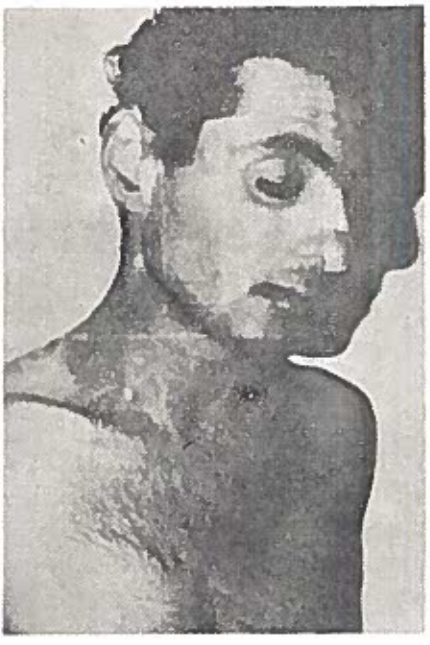

Figure 2

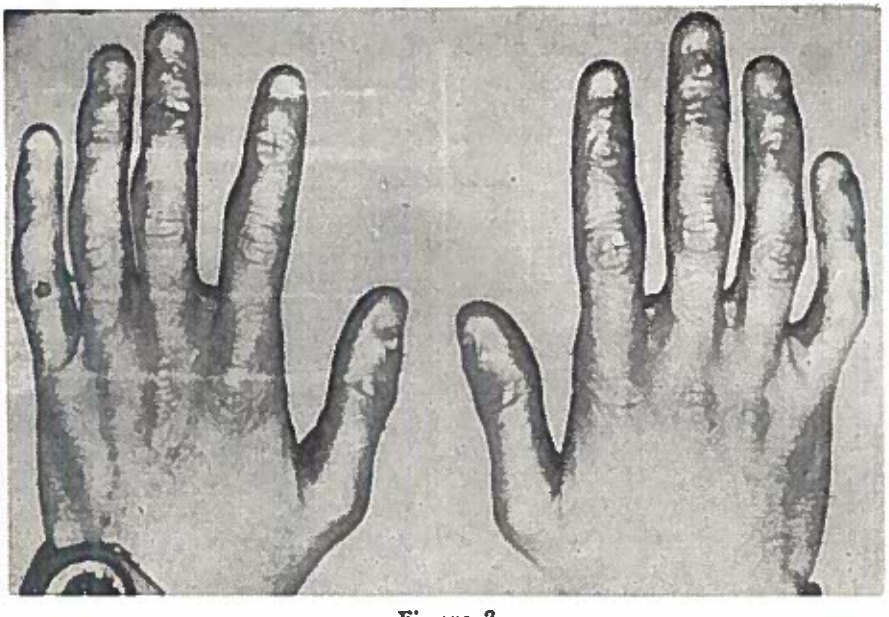

Figure 3

Ophtalmologic examination revealed bilateral blepharoconjunctivitis, and occlusion of both lacrimal ducts. The skin of his face, neck, trunk, and limbs showed reticulated darkish hyperpigmentation enclosing normal skin islands (Figure 2). Tips of all fingers and toes were tapered with dystrophic changes of all nails (Figure 3). His palms showed desquamation, loss of finger prints, and hyperhidrosis.

The following laboratory tests were all normal: Complete blood cell count with differential cell counts, total platelet count, liver function tests, fasting glucose level, urinalysis, gastrointestinal tract series with barium, intravenous pyelogram, rectal examination and rectal biopsy.

Skin biopsy revealed epidermal keratinization, perivascular mononuclear cell infiltration in the upper dermis and melanin in dermal melanophages.

Discussion

On the basis of our clinical findings, this case can be diagnosed as dyskeratosis congenita.

Dyskeratosis congenita is a rare genodermatosis characterized by reticulated pigmentation of the skin, nail dystrophy and leukokeratosis of mucosal surfaces. About 75 cases have been reported to date.

Most of the cases have been in males. The mode of inheritance is sex-linked recessive. Pedigrees with autosomal dominant inheritance have also been described.[1-3] Structural abrormalities of the chromosomes have not been reported.[3]

The diagnosis is not established until the ages of 5 and 13 when there is loss of the nail plate. Cutaneous changes follow the onset of the nail changes and include a fine reticulated hyperpigmentation that surrounds hypopigmented and atrophic patches of uninvolved skin, telengiectasia of the trunk, alopecia, redness and atrophy of the face, palmoplantar hyperkeratosis and hyperhidrosis, pronounced loss of skin markings, transparent and shiny appearance on the dorsal aspects of the hands and feet.[1-3]

Mucosal lesions on the oral, vaginal, urethral and anal epithelium present as small blisters, erosions, mucosal thickening and subsequent leukoplakia, carcinoma of the tongue, nasopharynx, buccal mucosa, esophagus and rectum have been reported.[5] Atresia of the lacrimal ducts, excessive lacrimation, chronic blepharitis, conjunctivitis and ectropion may also be seen. The teeth may become defective and peridontitis may occur.[5]

In some patients severe anemia with leukopenia, splenomegaly, hypoplastic bone marrow and hemorrhagic diatheses resembling Fanconi's aplastic anemia have been reported.[1]

Other associated conditions are; squamous cell carcinoma (tongue, oral, esophagus, nasopharynx, cervix, skin), mucinous carcinoma (rectum), adenocarcinoma (rectum), and cutaneous amyloidosis.[1,4]

In the autosomal dominant form of dyskeratosis congenita a defect in cell-mediated immunity has been reported.[1]

Since this condition is hereditary, genetic counseling may be advised. Pancytopenia or malignant neoplasms constitute a common cause of death in these patients.[3]

There is no specific treatment. Dilatation for esophageal stenosis, fulguration, curettage and surgical excision of leukokeratosis of the mucosal lesions may be helpful.

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Pericardial Coelemic Cyst*

İlhan Paşaoğlu, M.D. / Öztekin Oto, M.D.*** / Ahmet Hatipoğlu, M.D.**** / İlhan Günay, M.D.****

Summary

In this paper we have reported a case of pericardial coelemic cyst which has been surgically removed.

Key Words: Pericardial cyst, mediastinal mass, mediastinal cyst.

Introduction

Pericardial cysts are relatively uncommon lesions. They characteristically occupy the right cardiophrenic angle and are usually diagnosed in adolescents or in adult life.[1] Communication of the cyst with the pericardial cavity has been rarely reported.[1,2] This report represents a case of pericardial cyst which communicated with the pericardial cavity and was successfully excised.

Case Report

D. G., an 18-year-old girl admitted to our outpatient clinics with the complaint of "coughing" for 2 weeks. Investigations were carried out with the suspected diagnosis of upper respiratory tract infection. Postero-anterior (PA) chest x-ray revealed an anterior mediastinal mass at the right cardiophrenic angle. Apart from the complaint of coughing for two weeks, the patient was completely asymptomatic. On physical examination no abnormal sign was detected.

Laboratory investigations including complete blood count, urine analysis, blood electrolytes, blood sugar, nasopharyngeal swab and sputum cultures were all normal. Right lateral and repeated PA chest x-rays showed a round opacity 5 cm. in diameter at the right cardiophrenic sinus (Figures 1, 2). Also examination of chest tomography confirmed

* From the Department of Thoracic and Cardiovascular Surgery Hacettepe University Faculty of Medicine. Ankara-Turkey.
** Assistant Professor, in the Department of Thoracic and Cardiovascular Surgery.
*** Resident, in the Department of Thoracic and Cardiovascular Surgery.
**** Lecturer, in the Department of Thoracic and Cardiovascular Surgery.

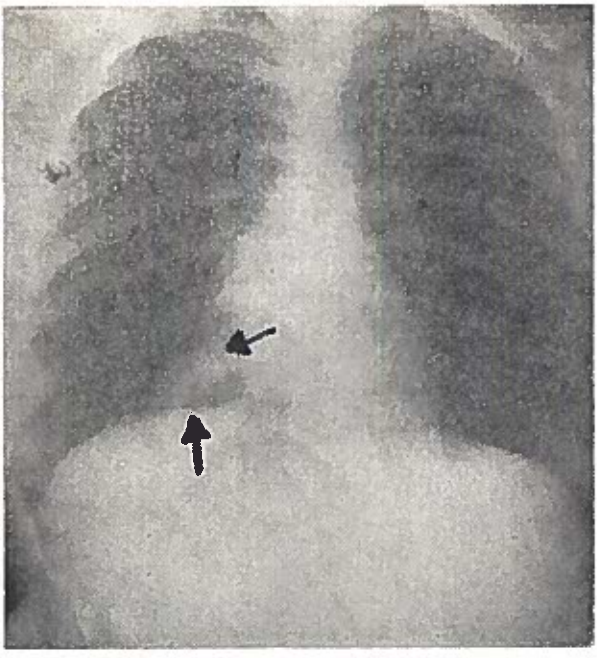

Figure 1
Preoperative PA chest X-Ray.

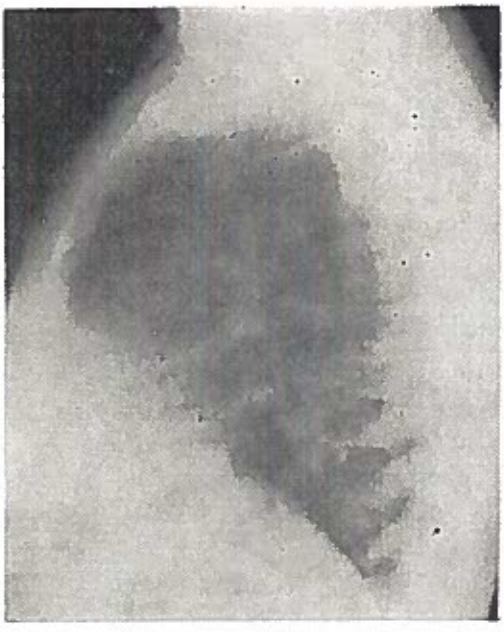

Figure 2
Preoperative right lateral chest X-Ray.

a round, cyst-like mass at the right cardiophrenic angle which was remarkably visualised at the sixth centimeter (Figure 3). Esophagogastroduodenography with barium and colon graphy showed no sign of intrathoracic herniation of abdominal organs while Casoni and Weinberg tests were also normal.

The patient underwent operation for this anterior mediastinal mass with limited "right anterolateral thoracotomy" from the sixth intercostal space.

A multiloculated, thin-walled cyst full of "spring-water" like fluid and five to six cms. in diameter was observed at the anterior portion of the cardiophrenic angle and two centimeters above the phrenic nerve. The cyst was connected to the pericardial space through an opening which was four mm. in diameter. No pleural adhesion or sign of inflammation in the lung tissue existed.

The cyst was excised completely by sharp and blunt dissection. The involved portion of the pericardium, about 3 cm^2, was also removed. After haemostatic control the pericardial window was closed with simple interrupted silk sutures and the chest was closed in a routine manner, inserting a right basal chest drainage tube.

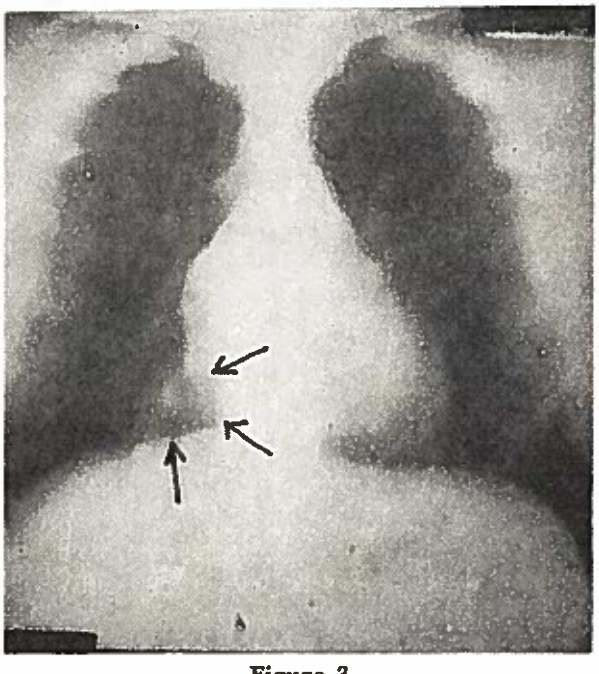

Figure 3
PA chest tomography at sixth cm.

Pathological examination confirmed the diagnosis of pericardial cyst consisting of a single layer of cubical and partially flattened cells which were covered by collagen fibers.

The patient did very well post-operatively and no complication appeared. Post-operative PA and right lateral chest x-rays were normal (Figure 4). She was discharged on the eighth post-operative day in excellent condition.

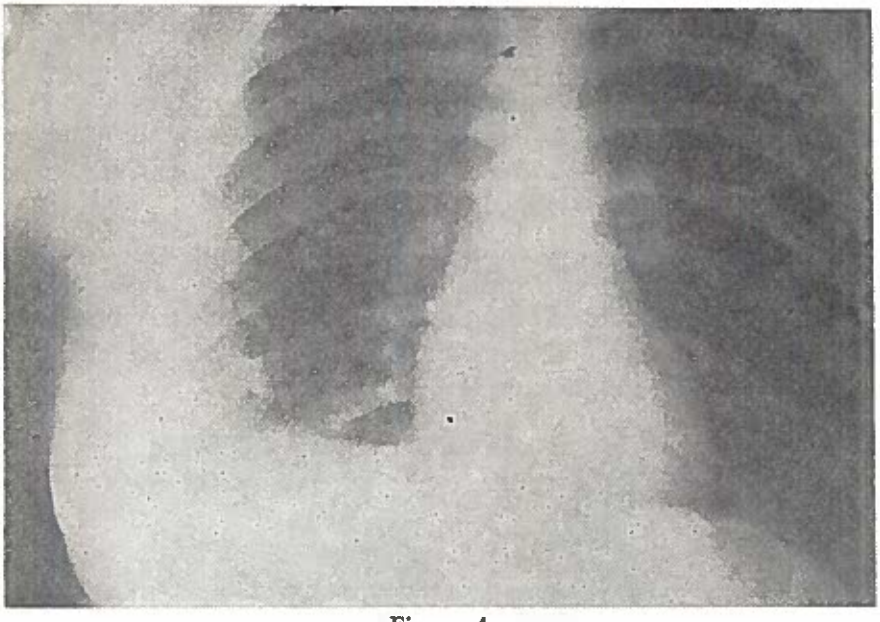

Figure 4
Postoperative PA chest X-Ray.

Discussion

Pericardial cysts are relatively uncommon compared with other mediastinal masses and are usually asymptomatic.[2,3] Collectively, all the congenital mediastinal cysts constitute approximately twenty percent of primary mediastinal lesions and have an equal incidence in children and adults.[4,5] Only one fifth to one fourth of these cysts have been reported as primarly pericardial origin.[5,6]

They may be located anywhere in the pericardium but seventy percent are located at the right cardiophrenic angle.[7] They may be unilocular or multilocular and may vary in size. The wall of the cyst usually consists of collagen fibers that are lined by a single layer of flattened mesothelial cells.[3]

Embryologically they are thought to originate either from a failure of fusion of the primitive pericardial lacunae or from abnormal folds in the embryonic pleura.[1,2]

Despite their pericardial origin they are rarely found communicating with the pericardial space directly. In our case, communication between the cyst and pericardial space was enough to permit the pericardial fluid to pass freely.

It has been recommended that congenital cysts should be excised even the asymptomatic ones because of their tendency to become infected or enlarged. They should be differentiated from mediastinal masses that may be malignant.[4,8,9] Although differential diagnosis of the cyst could be done from Morgagni hernia and hydatid cyst by means of preoperative laboratory tests, in our case it was not possible to diagnose the pericardial cyst with certainty. Therefore, surgical removal was carried out as recommended by several authors to rule out other lesions and to avoid the possible complications of a potentially hazardous mediastinal cyst.

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   A. (1) An informative summary for not more than 200 words must be included and should appear at the beginning of the paper (2) Key Words, (3) Introduction, (4) Materials and Methods, (5) Results, (6) Discussion and (7) References.

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      1. Steward JH, Castaldi PA. Uremic bleeding: a reversible platelet defect corrected by dialysis. QJ Med. 1967; 36: 409-23.

2. Bearn AG. Wilson's Disease. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. The metabolic basic of inherited disease. New York: McGraw-Hill, 1972: 1033-50.

7. Tables should be as few as possible and should include only essential data. Tables should be typed in double spacing on separate sheets and provide a legend for each. Diagrams or illustrations should be drawn with black Indian ink on white paper and should be given Roman numerals. Each illustration should be accompanied by a legend clearly describing it: all legends should be grouped and type-written (double spaced) on a separate sheet of paper.
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Idiopathic Hepatosplenomegaly

A Study of 37 Cases

Şafak Reka, M.D.* / Şükran Karacadağ, M.D.**

Summary

Thirty-seven patients with idiopathic hepatosplenomegaly were studied at Hacettepe University Medical Center. All patients underwent haemetologic studies, liver function tests and special studies including liver biopsy and endoscopy. In addition, splenoportographies were performed on 12 out of 37 patients. All of these studies were found to be normal. Patients were followed from 2 to 10 years. Repeated studies remained normal and no organic diseases developed in any of these thirty-seven patients.

Key Words: Idiopathic splenomegaly, hepatosplenomegaly, splenomegaly, liver biopsy.

Introduction

The diagnosis of idiopathic hepatosplenomegaly can only be made after the exclusion of other disease states which may present with hepatosplenomegaly. It is rare, and remains a diagnostic and therapeutic dilemma. In this study we investigated 37 patients with idiopathic hepatosplenomegaly.

Materials and Methods

Thirty-seven patients were studied at the Hacettepe University Medical Center between 1970 and 1982. There were 16 males and 21 females. Their ages ranged from 21 to 55 years and the mean age was 36. Patients applied to the hospital with nonspecific abdominal complaints, and they were not aware of the enlargement of the liver and spleen until

* Fellow, the Depertment of Gastroenterology, Hacettepe University Medical Center, Ankara - Turkey.
** Professor the Depertment of Gastroenterology, Hacettepe University Medical Center.

the present examination. They had no history of other diseases which could have caused the enlargement of the liver and the spleen. Physical examinations revealed no abnormal findings other than enlarged liver and spleen.

Table I is the list of the studies performed on all patients for the exclusion of other diseases which could have caused hepatosplenomegaly such as haematologic, neoplastic, myeloproliferative, infiltrative, parasitic, collagen, vascular, infectious, chronic liver diseases and portal hypertension.

These patients were followed from 2 to 10 years. Laboratory studies were repeated during each examination on all patients. Second liver biopsies were performed on 12 out of 37 patients.

TABLE I

LABORATORY TESTS AND SPECIAL STUDIES

Routine Laboratory Tests	**Special Studies**
Complete blood count	ANA
BUN and creatinine	Group agglutinations
Glucose tolerans test	Cold agglutinations
Liver function tests	Malaria blood tests
HB_sAg, HB_sAb.	Heterophile antibody titers
Special Studies	Bone-marrow aspiration.
Hbg electrophoresis	Chest x-ray and upper gastrointestinal series
Eritrocyte sickling test	Esophagoscopy
Coombs test	Scanning (Tc^{99m}) of the liver and spleen
Latex fixation	Liver biopsy
Protein electrophoresis	Splenoportography and intrasplenic pressure
Immune electrophoresis	(only in 12 patients).
LE cell.	

Results

Physical examinations revealed enlargement of the liver and spleen 2 cm. to 8 cm. below the costal margin. The physical findings were confirmed by scanning the liver and spleen and showed normal distribution of activity. None of these patients had symptoms of chronic liver disease and/or portal hypertension. Laboratory studies were found to be within normal limits on all patients. Endoscopic examination revealed no esophageal varices and the liver biopsies were all found to be normal. Splenoportographies showed normal portal tree. Intrasplenic pressures were measured from 11 to 15.5 cm. of water.

All patients were followed at regular intervals from 2 to 10 years, an average period of 3.5 years. The patients' general conditions were good and they were able to perform their regular work. Physical examination showed that the size of the liver and spleen was unchanged. Laboratory studies also remained within normal limits. Second liver biopsies were performed on only 12 patients. Four were performed after 3 years, 2 were performed after 4 years, 2 were performed after 5 years, 1 was performed after 6 years, 2 were performed after 7 years and 1 was performed after 8 years. No changes were seen in second liver biopsies.

Discussion

Hepatosplenomegaly may be the first manifestation of various diseases, and all efforts should be made to eliminate the diseases which may cause the enlargement of the liver and the spleen. To the best of our knowledge, this is the only detailed study of idiopathic hepatosplenomegaly with a large number of patients. The previous reports were on non-tropical idiopathic splenomegaly.[1, 2, 3] This is described in patients with splenomegaly and pancytopenia. Hepatomegaly may also be present in some of these patients. The excised spleens showed variable pathological changes but, the histological findings in the spleens did not indicate the presence of malignant lymphoma. However, some of these patients later developed and died of lymphoma.[1, 2] Tropical splenomegaly has been applied to the patients in a tropical environment who present with a large spleen of undetermined etiology.[4] It is usually found in malarious areas and it has been suggested that this condition represents an abnormal immunological response to malaria.

Skarin et al.,[5] Hermann et al.,[6] reported patients with splenomegaly and in whom malignant lymphoma diagnosis had been made after splenectomy. Long and Aisenberg also reviewed 25 patients with splenomegaly and pancytopenia for whom the diagnosis of lymphoma or idiopathic splenomegaly was made only by splenectomy.[7] Hepatomegaly was detected in 3 of these 10 patients with idiopathic splenomegaly. Knudson et al., reported 28 young patients with splenomegaly without an apparent cause.[8] All of these patients underwent splenectomy shortly after referral to the hospital. After splenectomy 3 patients were found to have splenic cysts. The length of follow-up study for these patients ranged from one to 14 years, an average period of 4.5 years. During the entire follow-up period 3 had hepatic cirrhosis and only one developed lymphoma.

Palpable spleens in 58 healthy male college students were reported.[9] These students were found to have normal hematocrits, reticulocyte counts, blood smears and heterophile titers. Ten years later, students were followed up with a mail survey and findings were compared with the control group.[10] The results indicated that there was a higher frequency of infection in the group with the palpable spleens than in the control group.

The present study is different from previous studies. All of our patients had enlargement of the liver as well as spleen, they had no history of any disease and all of the laboratory studies including the liver biopsy were found to be normal. All patients were followed for 2 to 10 years, and no clinical and laboratory changes were observed. Normal laboratory findings, endoscopic examination, liver biopsies and long term clinical follow-ups make us think that the idiopathic hepatosplenomegaly has a good prognosis and does not lead to the development of portal hypertension and/or organic disease.

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Pregnancy and Gallbladder Function

Ultrasonic Study

Şafak Reka, M.D.* / Şükran Karacadağ, M.D. / Hasan Telatar, M.D.** / Ömür Gönen, M.D.*****

Summary

In this study, ultrasonography was used on 30 pregnant women in the second and third trimester and on 14 nonpregnant controls to determine the motor function of the gallbladder. The gallbladder volume during fasting and residual volume after the maximum contraction in the second and third trimester were significantly larger than the controls. The maximum percent and the rate of emptying in the second and third trimester were singificantly lower than the controls. However, the differences of the volume and the maximum percent of emptying were not statistically significant between the second and third trimester of pregnancy. These findings suggest that the impairment of the gall-bladder's motor function in pregnancy may play a role in the development of gall-stones.

Key Words: Pregnancy, Ultrasonography, Gall-bladder, Gall-stone.

Introduction

The formation of gall-stones is complex.[1,2] The incidence is higher in women than in men; and pregnancy is an additional risk factor for cholelithiasis.[3] Although the prevalence of gall-stones is increased with pregnancy, a clear correlation has not been established between the incidence of gall-stones and the number of pregnancies. Changes in gallbladder function may contribute to gall-stone formation in pregnancy. Ultrasonography is an efficient method for the examination of the biliary tract.[4] In this study ultrasonography was used for evaluating the gallbladder motor function in pregnant women.

* Fellow, The Department of Gastroenterology, Faculty of Medicine Hacettepe University, Ankara - Turkey.
** Professor, The Department of Gastroenterology.
*** Associate Professor, The Department of Gastroenterology.

Materials and Methods

Thirty pregnant women and fourteen non-pregnant women volunteered for this study. Their ages ranged from 19 to 30 years, and all had either one or no pregnancies prior to this study. Fifteen of the pregnant women were in the second trimester, and 15 were in the third trimester. They had no history of medication or illness and all had normal physical examinations. The age, weight and height were similar in the pregnant and in the non-pregnant controls. They were non-obese women. Although the pregnant group was heavier than the control group, the difference was related to normal feto-placental development. Routine laboratory studies, including complete blood count, fasting blood sugar, liver function tests, and BUN were all within normal limits in both groups

B-Scan ultrasonography was used for the determination of gallbladder size. The transducer was placed in a sagittal projection in the right upper quadrant and positioned until the greatest length of the gallbladder was obtained. The transducer was then rotated 90 degrees and the greatest transverse and antero-posterior dimensions of the gallbladder were obtained. The volume of the gallbladder was calculated by the sum of cylinders method.[5] In some patients, the gallbladder was located under the right subcostal margin and a deep inspiration was required for adequate visualisation. The gallbladder size was determined in the morning after on overnight fast, and repeated after the 350 cc. liquid standart test meal[6] containing 420 calories (35 percent fat, 15 percent protein and 50 percent carbohydrate) serially every five-minutes for seventy minutes. The gallbladder function was expressed by the fasting volume, the rate of emptying, the maximum percent of emptying and the residual volume after the maximum contraction. During the active phase of contraction (20 to 45 minutes), the natural logarithm of the percent emptied plotted against time approximates a straight line. The rate of emptying is calculated by the linear-regression analysis.[6] The results were presented as means $\pm$ S. E. M. and groups were compared by the Student t-test.

Results

In pregnant women, the gallbladder volume during the fasting and residual volume after the maximum contraction was significantly larger ($p < 0.001$) than the control subjects (Figure 1). However, no significant difference was found between the second and third trimester of pregnancy.

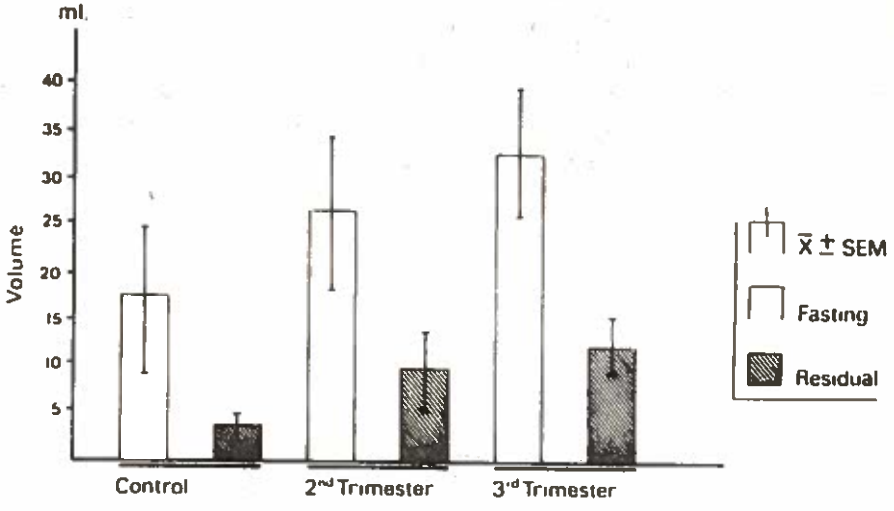

Figure 1
Gallbladder volume.

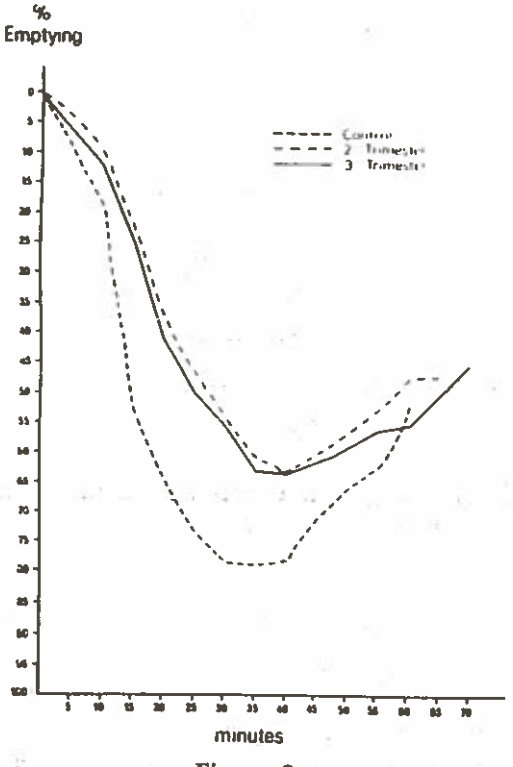

Figure 2
Contraction of gallbladder.

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Coital Injuries of the Vagina and the Perineum

Aytekin Altıntaş, M.D.* / Nihat Arıdoğan, M.D. / Oktay Kadayıfcı, M.D.** / İsmet Köker, M.D.** / Derya Ufuk Başaran, M.D.***

Summary

Minor injuries of the introitus during initial coitus are not uncommon, but injuries of the perineum and vagina which require surgical intervention are not rare either. 52 patients, with postcoital injuries of the perineum and vagina, came to the Department of Obstetrics and Gynecology at the hospital of Çukurova University Medical Faculty, between 1982-1984. Their age distribution, causes of postcoital injuries, symptoms, signs, their treatment and results of the treatment were evaluated. The predisposing factors in our series were almost entirely different from the data published in the United States and Europe which may be due to differences in sexual behavior. The primary predisposing factor was virginity and brutality of the male partner. There were no significant complications or deaths.

Key Words : Coital Injury, Vagina, Perineum.

Introduction

Postcoital rupture is the term generally used to describe laceration of the perineum and nearby tissue that occurs during intercourse. It is almost always encountered during the first coital attempt. Major predisposing factors are: a vagina which is not fully developed or with congenital malformations, coital attempt with a woman who is not fully prepared, and rape. The other possible factors are senile atrophy, insertion of a foreign body and a short vagina as a result of hysterectomy.[1, 2, 3]

* Instructor, The Department of Obstetrics and Gynecology, Çukurova University Medical School, Adana - Turkey.

** Associate Professor, The Department of Obstetrics and Gynecology, Çukurova University Medical School.

Postcoital ruptures are usually encountered around the introitus but it is not rare to see lacerations on the walls of the vagina and even up in the fornices.

The purpose of this paper is two fold:a) to identify the etiology and localization of the postcoital ruptures admitted to our clinic and b) to identify the structure of the genital tract and to evaluate the results of treatment.

Materials and Methods

This research is based on retrograde investigations of the case reports of patients admitted to the Department of Obstetrics and Gynecology at the hospital of Çukurova University Medical Faculty with the diagnosis of postcoital rupture.

Age, complaints, structure of the vagina, type and localization of the rupture and blood loss of the patients are evaluated and the treatment methods for the individual cases are discussed.

Analysis of Data

Fifty-two patients with postcoital rupture were admitted to our clinic between January 1982 and January 1984. The age distribution of our cases is shown in Table I.The youngest was 8 and the oldest was 43 years of age. The two youngest patients, ages 8 and 11, had been raped (Table I).

TABLE I
THE AGE DISTRIBUTION OF PATIENTS

Age (Yr)	No	%
7-10	1	1.92
11-14	1	1.92
15-18	22	42.30
19-22	17	32.70
23-26	9	17.22
Older than 26	2	3.94
Total	52	100.00

Almost all of the cases came to our clinic with complaints of persistent bleeding starting soon after coitus. The other complaints accompanying bleeding were coital difficulty, dispareunia and leakage of gas and stool through the vagina (Table II).

TABLE II
COMPLAINTS

Complaint	No	%
Bleeding	50	96.04
Pain	6	11.80
Coital difficulty	2	3.96
Leakage of gas	2	3.96

Of the rape cases, the 8 year old, had a wide rupture beginning from the perineum and extending up to the posterior fornix of the vagina and penetrating into the peritoneum. Therefore, the rupture could only be repaired with both transvaginal and transabdominal approaches.

The other rape case, age 11, had no vaginal penetration and there was no laceration of the hymen, but a huge hematoma was present beneath the perineum which was evacuated and sutured with 00 chromic catgut.

One of the cases had had surgery for the removal of a transverse vaginal septum 9 months before the first coitus. She presented with a laceration and postcoital rupture.

One of the two cases complaining of gas and stool leakage from the vagina had a sphincter ani rupture which extended 6 cm. along the rectal mucosa. In the other case, the sphincter ani and the hymen were intact, but there was a rectovaginal fistula 4 cm. beyond the sphincter. In this case the structure of hymen was fibrotic.

The injury sites of our cases are shown in Table III and the possible causes are shown in Table IV.

TABLE III
LOCATION OF COITAL INJURIES IN THE VAGINA

Site of Injury	No	%
Upper vagina		
posterior fornix	16	30.7
anterior fornix	1	1.92
left fornix	4	7.68
right fornix	7	15.36
Lower vagina and hymen	15	28.75
Perineum	12	23.10
Rectum	2	3.96
Rupture extending to the perineum	2	3.96

TABLE IV

PREDISPOSING FACTORS OF COITAL INJURIES OF THE VAGINA

Predisposing Factor	No
Virginity, brutality of male partner	42
Rape	2
Congenital anomalies	6
Previous vaginal septum operation	1
Overstretch	1
Total	52

Superficial lacerations with persistent bleeding of the hymen and introitus were treated with a gauze sponge. The bleeding stopped in a short time in all cases.

Ten of the cases with simple deep perineal lacerations were primarily sutured with 000 chromic catgut under local anesthesia.

The two cases with rupture of the rectal mucosa and perineum were repaired under general anesthesia. Edges of the mucosal wounds were debrided and closed with intermittent 000 chromic catgut sutures. Later, the surrounding tissues were stitched with 0 chromic catgut in order to support the mucosa.

In the case of rupture of the sphincter ani, the sphincter was sutured with intermittent 0 chromic catgut and the patient was given a soft diet and prophylaxis with amoxicillin 4 gr. daily for 6 days.

Patients with peritoneal penetration could only be sutured with both peritoneal and abdominal approach.

The remaining cases were primarily sutured with 000 chromic catgut under general anesthesia and were prescribed oral antibiotics and vaginal suppositories postoperatively. All were discharged within 24 hours. All patients were instructed to abstain from coitus for 30 days. There was no mortality in our series.

Another interesting observation encountered in our series was psychological disorders. There were 12 cases who developed psychological problems. The most common symptom was hysterical fainting on the day of discharge, from the hospital.

The seasonal distribution of our cases is shown in Table V.

TABLE V
SEASONAL DISTRIBUTION

Season	No	%
Spring	14	26.9
Summer	12	23.1
Autumn	13	25.0
Winter	13	25.0
Total	52	100.0

Discussion

Minor injuries of the introitus during the initial coitus are not uncommon, but injuries of the perineum and vagina which require surgical intervention are not rare either.[1] In our country and other societies where sexual education is lacking, postcoital ruptures are frequently encountered, because the first coitus is regarded as a marital duty where the important point is deflowering the hymen. Thus, often the girl is roughly forced to engage in intercourse without being adequately prepared.

Although in Wilson's study of 37 cases,[1] only 6 of them had the predisposing factor of virginity, in our series virginity was the primary predisposing factor. Fourty-two of our 52 patients (80.7 %) were virgins.

With the other 6 cases the vagina was either hypoplastic or fibrotic, and the injuries were attributed to their abnormal structure.

Two of our virgin cases were children and were subjected to rape. In one case, postcoital rupture was attributed to an unusual coital position.

While published data from U.S.A. and Europe indicate that the main causes of coital injuries are rape, alcohol, foreign body, short vagina (caused by either hysterectomy or radiotheraphy) and senile athropy,[1, 2, 3] our findings vary-with the exception of the two rape cases. The reasons for the difference are mainly custom, tradition, lack of sexual education and the practice of stopping intercourse after hysterectomy and menopause.

There are a number of theories which attempt to explain the mechanism and the localizations of postcoital injuries. Van de Velle claimed that disproportion of the male and female genital organs and brutal intercourse are the main factors.[4] Rahm, et al pointed out that shortening and narrowing of the vagina during the contraction of the vaginal muscles are the main factors, and unusual coital positions can only

predispose to injuries.[5] Krukierek found a relation between postcoital ruptures and annual seasons. According to his opinion, sexual desire is higher during the spring and early summer. This causes rough and brutal intercourse leading to lacerations.[6]

Dickinson has stated in his textbook of anatomy that the right vaginal fornix is larger than the left so that the penis frequently is inserted on this side, hence the right fornix is subjected to coital injury more often.[7] Speert has mentioned that atrophic vaginitis is an important factor in older women.[8]

Although there are a number of factors causing postcoital rupture, in our cases the main consistent factor was the absence of sexual stimulus to initiate arousal, and the lack of lubrication in the vagina.

We could not find any significant relationship between postcoital rupture and the seasons of the year. But the right fornix ruptures encountered in our series were slightly more numerous than the left fornix ruptures which could be explained by Dickinson's theory.

There has been no postcoital rupture attributable to senile atrophy of the vagina in our series. As has been mentioned above, this can be attributed to the tendency to stop intercourse at a certain period of life.

Rectal examination of the patients with postcoital rupture is compulsory since the rupture may extend into the rectum. There were various lacerations of the rectum in our two cases which were repaired and they healed properly without colostomy.

It is reported that postcoital rupture can cause vaginal eviscerations in elderly women. There was one vaginal evisceration in our series. The patient was just 8 years old with an urderdeveloped vagina and was raped. Laceration of the fornixes in this case were repaired transabdominally.

Although death caused by bleeding and shock has been reported, there was no mortality in our cases.[9]

The hysteric faintings noted in our series on the day of discharge was attributed to the fact that the patients felt safe in the hospital and were afraid to return to their home environment.

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Evisceration From a Previously Normal Umbilicus in Infants*

Two Case Reports

Melih Bulut, M.D. / Nebil Büyükpamukçu, M.D.*** / Akgün Hiçsönmez, M.D.*****

Summary

Extrusion of intestines from a previously normal umbilicus in infants is a rare entity and only two cases have been reported in the literature. We treated two other cases at Hacettepe University Medical Faculty, Department of Pediatric Surgery. We believe that these cases are distinctively different from other cases of infantile umbilical evisceration, and infection has an important role of the pathogenesis of this disease.

Key Words: Umbilical evisceration, Umbilical Hernia.

Introduction

Extrusion of intestines from a previously normal umbilicus in infants is a rare occurrence and it was first reported in a 7 week old baby by Metcalf and Prize.[1] Chochinov reported another infant and used the term"Spontaneous Umbilical Evisceration" for describing the condition.[2] Recently we encountered two such cases in our hospital. In this report we shall present our cases and discuss possible etiological factors.

Case Reports

Case 1: A two-month old female child was admitted to our department with two days history of diarrhea and vomiting and one-day history of white-coloured discharge from her umbilicus. The umbilicus was normal at birth and separated on the seventh day. There was no discharge or herniation from the umbilicus previously.

* The Department of Pediatric Surgery, Hacettepe University Medical Faculty, Ankara, Turkey.
** Research Assistant, Pediatric Surgery.
*** Professor, Pediatric Surgery.

On physical examination, it was observed that 10 cms of small bowel was protruding from the 1.5 cm in diameter umbilical defect which was not noted by the family. The colour of the bowel was normal (Figure 1).

Emergency operation was performed. The umbilical defect was extended transversely and abdominal exploration was performed. Patent omphalomesenteric duct, Meckel's diverticulum or another gut anomaly were not found. The skin and the fascia around the defect were inflamed. Wound culture was obtained and the abdomen was closed in layers (Figure 2). Although no bacteria grew from the wound culture, Penicillin, Tobramycin and Metranidazole were administered post-operatively. The baby made an uneventful recovery and was discharged on the seventh postoperative day.

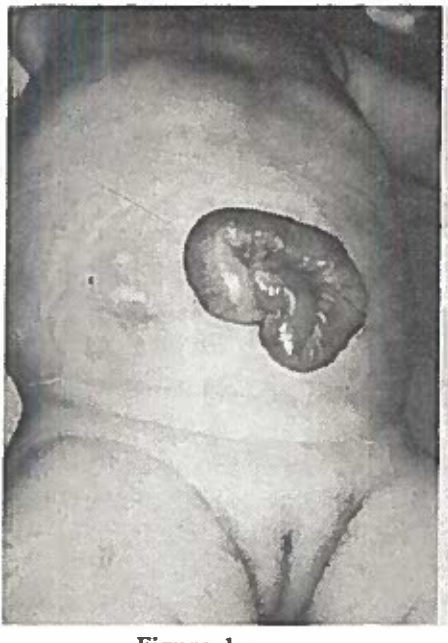

Figure 1
Small bowel extruding from the umbilicus.

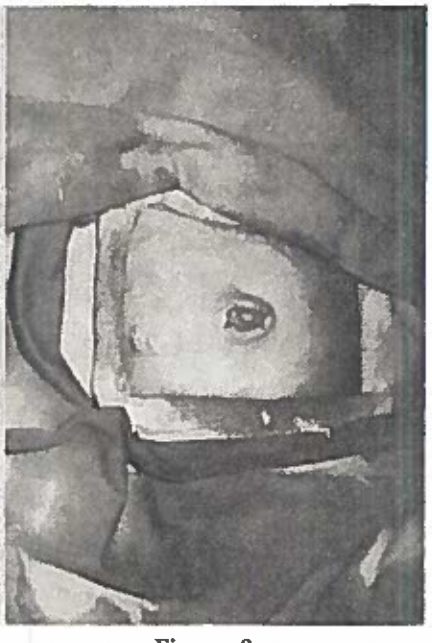

Figure 2
The appearance of the umbilicus after the operation.

Case 2: A three-month old female was admitted to our hospital with a one-hour history of extrusion of bowel from the umbilicus. Her umbilicus was normal at birth and separated on the sixth day. Umbilical discharge or herniation had not been noticed by the parents prior to admission.

On physical examination it was found that 15 cms of small bowel had herniated through the base of the umbilicus. Periumbilical skin was hyperemic. A median incision, including the umbilicus, was made and the abdomen was explored. No additional gut anomaly was found. The peritoneum and the fascia around the defect were not inflamed. The extruded gut was reduced and the laparotomy incision was immediately closed. No bacteria was isolated in wound, urine, stool and throat cultures. The baby had 38-39° C fever during the first four postoperative days in spite of the Penicillin, Tobramycin, Metranidazole therapy and the cause of the fever could not be explained. She made good progress. The abdominal wound healed satisfactorily and she was discharged from the hospital in good condition.

Discussion

Umbilical evisceration can occur in omphalocele, gastroschisis, patent omphalomesenteric duct and in the rupture of umbilical hernia.[1-4] Extrusion exists at birth in gastroschisis and omphalocele while the umbilicus is entirely normal at birth in "Spontaneous Umbilical Evisceration."

Herniation of the small intestine through a patent omphalomesenteric duct has been described.[3] Persistent umbilical discharge is a constant feature in patent omphalomesenteric duct. In addition, it is easily detected when the small bowel is examined. Patent omphalomesenteric duct or Meckel's diverticulum and other gut anomalies have not been found either in previously reported cases or in our cases.[1,2]

Rupture of an umbilical hernia was reported as a cause of umbilical evisceration in infants.[4] However, umbilical herniation had been noted before the rupture. We did not find a history of umbilical hernia in our cases as in the other two previously reported cases.[1,2]

Infection has been accepted as a possible predisposing or etiological factor in "Spontaneous Umbilical Evisceration."[1,2] In our first case as in Chochinov's case, umbilical discharge had started from a previously normal umbilicus and evisceration occured 24 hours later. Group A, beta hemolytic streptococci and E. coli were isolated from the wound culture in Chochinov's case.[2] No bacteria was isolated from the wound culture in Case 1, but obvious signs of infection in the umbilical skin, subcutaneous tissue and fascia were noticed. The most probable cause of the evisceration is infection in Chochinov's case and in Case 1. Since umbilical evisceration may occur during umbilical infection, omphalitis should be treated carefully in infants.

In Metcalf's case, as in our second case, there was no umbilical discharge, but hyperemia of the skin around the umbilicus was observed.[1] Although this hyperemia can be attributed to infection, neither evident inflamation in subcutaneous tissue nor fascia were detected in either case. It is difficult to explain the cause of the herniation when there is no obvious infection and when the umbilicus has previously been normal. We believe that the term "Spontaneous" Umbilical Evisceration is more appropriate for these cases.

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Intradural Herniated Lumbar Disc

Two Case Reports

Aydın Paşaoğlu, M.D.*

Summary

Two cases of intradural disc rupture are presented, and the literature on this subject is reviewed. Characteristics of the history, physical findings, and myelographic changes are highly suggestive of this clinical phenomenon. Despite relatively severe neurological defecits associated with lumbar lesions, the prognosis following surgery is good.

Key Words: Intervertebral disc displacement, intradural disc rupture, lumbar disc.

Introduction

The first case of intradural herniation of a lumbar disc was reported in 1942 by Dandy.[1] Recently, Smith reported two patients with intradural herniated lumbar disc and reviewed 43 additional cases found in the literature.[2] Since then, we have found 6 additional cases in the literature, one of them reported earlier but not included in Smith's review.[3-6] Of these, 42 cases were found to be lumbar lesions.

The following two case reports describe an uncommon L1-2 lesion and a more common L3-4 intradural disc herniation.

Case Reports

Case 1: A 70 year-old man presented with a 11-month history of fluctuating low-back pain. Four days before admission, he experienced acute lumbar and bilateral radicular pain, more severe on the right side, after lifting a heavy object. He had profound paraparesis and urinary and fecal retention. Pantopaque myelography revealed a block of round shape across the L1-2 interspace (Figure 1).

* Associate Professor of Neurosurgery, Department of Neurosurgery, Erciyes University Medical School, Kayseri, Turkey.

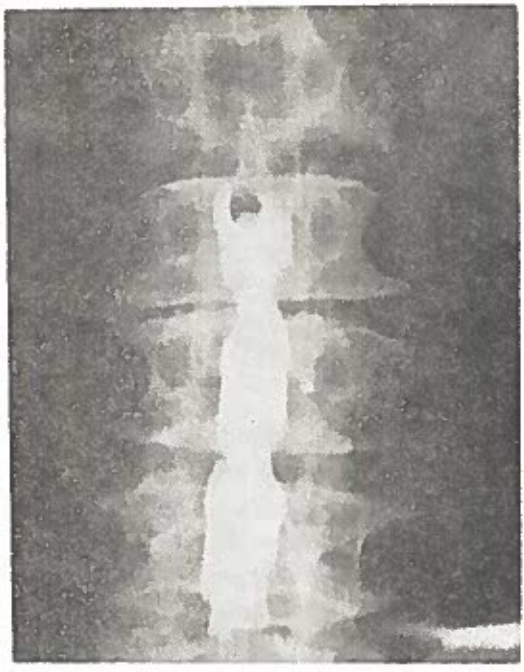

Figure 1

Pantopaque myelogram (case 1). Anteroposterior view demonstrating a block of round shape at L1-2.

An exploratory laminectomy was performed at L1-2. Dural opening revealed an intradural mass of disc material which compressed the conus medullaris to the left and posterior of the spinal canal and was surrounded by the cauda equina roots emerging from the conus. The conus was penetrated by the disc material anteriorly. After removal of the disc mass, approximately a 2.5x0.8 cm rent communicating with the L1-2 interspace was found in the anterior dura, but could not be closed. Epidural scar tissue was present at L1-2 and the dura was firmly adhered both to the underlying disc mass anteriorly and to the longitudinal ligament posteriorly. The patient's recovery was characterized by slow neurological improvement until he could walk unaided within 4 months. Bowel function returned within 4 months, and bladder function improved within 8 months of the operation (Figure 2).

Case 2: A 53 year-old man's history was very similar to that outlined in Case 1. But his neurological dysfunction was less severe. He had right leg weakness and atrophy, right radicular pain and L4 hypalgesia. There was no sphincter disturbance. Pantopaque myelography revealed an incomplete block across the L3-4 interspace (Figure 3).

Figure 2

Intraoperative photograph revealing a large intradural disc fragment (Left) and after removal of the disc mass the rent communicating with the L1-2 interspace in the anterior dura (Right).

Figure 3

Pantopaque myelogram demonstrating an incomplete block of round shape at L3-4 on the right side.

The exploration revealed an intradural disc rupture. A 1.5x0.5 cm rent communicating with the L3-4 interspace was found in the anteriolateral dura. Epidural scar tissue was less prominent compared to that seen in case 1. The patient's postoperative recovery was excellent. The radicular pain resolved, and sensory deficit and leg weakness improved within 6 weeks.

Discussion

In the lumbar cases reviewed in the literature and the present cases, the histories were chronic regarding back pain, and acute in regard to severe radicular pain and progressive neurological deficit. The significance of this phenomenon is that it must be considered as a surgical emergency. If incontinence is present, only prompt surgery can offer a chance for recovery. Operation microscope is invaluable during surgery, particularly when removing the disc mass at the conus level.

The most common myelographic finding in cases with intradural herniated disc was a complete block of the contrast medium.[2,7,8] It should be stressed that an irregularly marginated filling defect or an appearance of a circumscribed mass at the level of disc space is highly suggestive of intradural disc herniation.

Adhesions between the dura mater and the posterior longitudinal ligament have been demonstrated and thought to be the main cause of intradural herniation.[2,5,9] These adhesions would favor the gradual erosion of the overlying dura mater, with its possible rupture in a later stage, caused by the compressive mechanism of a protruded disc. The relatively frequent occurrence of intradural ruptures at L3-4 may be explained by the frequent involvement of this level. A recent study on biomechanics of the lumbosacral dural sac using flexion-extension myelography, showed that dural sac changes are variable at different levels. Most stretch occurs between L4 and L5, which over years may lead to weakening of the dura at this level.[10] But this does not explain the rarity of intradural disc herniation at L5-S1 level. Although none of our two patients have had previous surgery or spinal infection, it seems reasonable to assume that with a localized nonspecific inflammatory process which could not be detected clinically or a previous surgery causing adhesions between the ventral dura and posterior longitudinal ligament, the disc fragment has a greater chance of penetrating the dura at a certain level.

Despite its infrequent occurrence, preoperative diagnosis of an intradural disc herniation should be considered when the appropriate

history, and neurological and radiological findings exist. By utilizing metrizamide enhancement of spinal computerized tomography,[8] and by observing the presence of macrophages in the cerebrospinal fluid obtained at myelography,[2] the diagnosis may be determined preoperatively.

Although the radicular pain and neurological deficit are relatively severe, intradural disc herniation at L1 and below carries a good prognosis, with somewhat slow but excellent functional recovery being the rule.

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Multiple Metachronous Osteogenic Sarcoma*

A Case Report

Münevver Büyükpamukcu, M.D. / Talat Göğüş, M.D.*** / Faik Sarıalioğlu, M.D.**** / Sinan Kejanlıoğlu, M.D.***** / Namık Çevik, M.D.******

Summary

A case of multiple-metachronous osteogenic sarcoma involving the right femur, the left scapula and the right humerus is reported. Clinical, X-ray, scintographic and pathologic studies were confirmatory of the tumors arising separately in the femur, scapula and humerus and were not instances of metastatic involvement of one bone to another.

Key Words: Osteosarcoma Syndromes, Metachronous, Synchronous Osteosarcoma.

Introduction

A very small percentage of patients with osteogenic sarcoma, especially those without pulmonary metastases, appear with multifocal skeletal lesions. It has not yet been estabilised that these sarcomas either arise in multiple sites, or that one of the lesions spreads rapidly to other areas. The almost simultaneus appearance of pulmonary metastases or their relatively late radiographic appearance suggests that the multiple lesions were independent primary tumors.[1-5]

Among 63 osteogenic sarcoma cases seen in the Hacettepe Children's Center during the last eleven years, we found only one patient who exhibited multiple osteogenic sarcoma primarily.

The case reported here is an example of the syndrome of multiple metachronous osteosarcoma where the scintographic screening of the patient has also been emphasized.

* From the Departments of Pediatrics (Oncology) and Orthopedics, Medical School of Hacettepe University, Ankara-Turkey.
** Associate Professor of Pediatrics, Division of Oncology.
*** Professor of Orthopedics.
**** Fellow, Pediatric Oncology.
***** Resident, Orthopedics.
****** Professor of Pediatrics, Division of Oncology.

Case Report

A girl of thirteen years of age was complaining from a swelling of the lower right thigh for three months. There was neither a history of any injury, or pain,nor a general emotional disorder before. There was also no exposure to intrauterine irradiation or afterwards. Physical examination revealed a hard circumferential swelling of the lowest third of the right femur. Extention of the right knee was painful and not complete. The girl was examined in another hospital before where a biopsy was taken from the swelling three weeks ago. The histologic diagnosis was sclerotic osteogenic sarcoma. At that time radiogramms of the right femur and the knee showed sclerosis and destruction of the lower third of the femoral shaft above the epiphyseal line, erosion of the cortex and irregular new bone formation extending into the soft tissue (Figure 1). There was also periostal reaction above the sclerotic destruction area of the femur; the appearance being typical of a sclerotic osteosarcoma. No radiological abnormality was noticed in X-rays of the spine, pelvis or other long bones which were taken in our hospital. The affected bone radiographies were the same as before. The chest X-ray revealed clear lung and mediastinal shadows (Figure 2). There was no metastatic appearance in the tomographies of the lungs. On the (10 milicurie 99 Technetium-Methilen-Diphosphate) scintographic examination, there was hyperactive uptake at the left scapular crista and at the head of the right humerus and the lower part of the right knee (Figure 3).

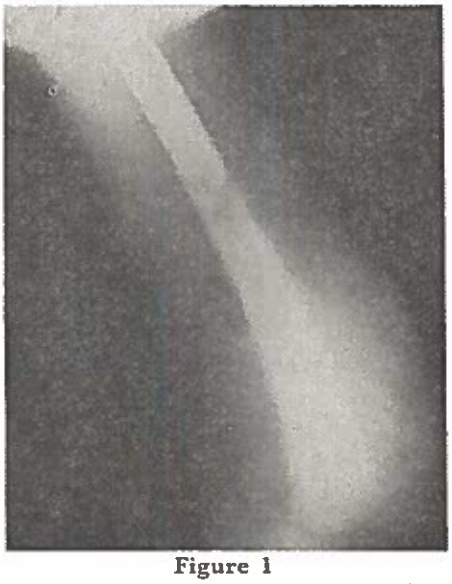

Figure 1

Radiographie of the right femur shows sclerosis and destruction of the lowest third of the femur and irregular new bone formation.

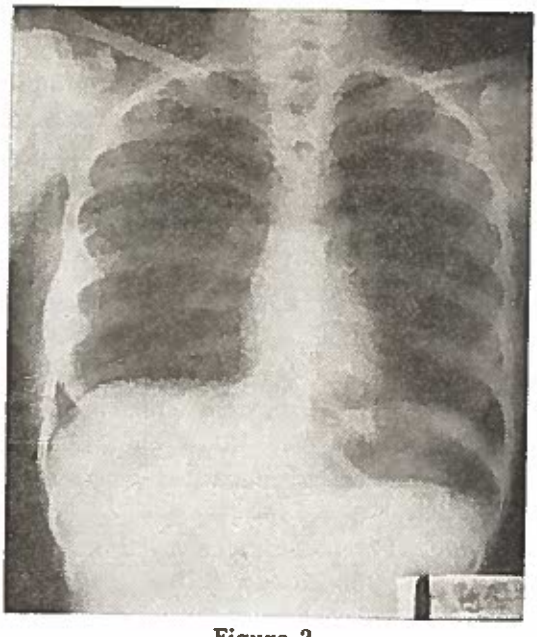

Figure 2
Radiographic of the chest shows clear lung and mediastinal shadow.

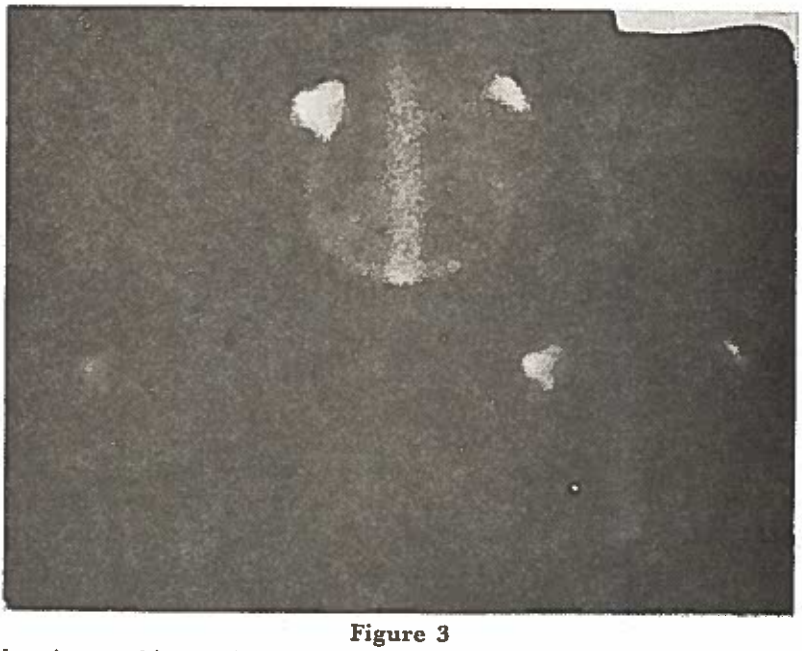

Figure 3
On the scintographic examination there were hyperactive uptake at left scapular crista and head of right humerus.

Laboratory investigations: Hemoglobin was 12,9 grammes and blood white cells were 5.000 per cubic milimeter, with normal morphology of both white and red cell series, and adequate number of platelets. The erythrocyte sedimentation rate was 43 milimetres in the first hour. Serum calcium was 9,6 miligrams percent, inorganic phospate 5,6 miligrams percent; alkaline phosphatase 17 King Armstrong Units (Normal 4-15 K.A) blood urea nitrogen was 13 miligrams percent, blood kreatinin was 1,2 miligrams percent.

Treatment and progress: Multiple combined chemotherapy (Cyclophoshamide + Vincristine + Bleomycin + Actinomycin-D) were given as preoperative treatment. One and a half months later right hip desarticulation was performed. Histopathological examination confirmed the diagnosis of sclerotic osteosarcoma. Two months later another skeletal scintography was done which demonstrated increased radioactivity at the previous sites, however there were no signs of skeletal metastasis on the plain radiographies. The patient received three courses of combined chemotherapy during five months which was complicated by alopecia and severe asthenia. She used a wheel chair and the site of the amputation was free of new tumor formation. In the fifth month, she came in complaining of pain in the left and right shoulders. A swelling could be noticed on the left scapula. Radioactive uptake was the same as it had been three months ago, but contrary to the previous findings, destruction and sclerosis of the left scapula and the head of right humerus were apparent on the roentgenograms(Figures 4 and 5). Further radiologic investigations like tomograms and technetium scans did not identify any tumor involvement of lung, liver or other bones. However additional tumor tissue was obtained by biopsy from the left scapular mass. Histological examination of this tissue confirmed the diagnosis of osteosarcoma. The previously determined alkaline phosphatase level was still as high (25 King Armstrong Units). The patient was placed on a high dose Cis-platinum (100 mgr/m^2) treatment. Begining from the onset of therapy, for nine months neither pulmonary nor other visceral metastases were noticed, but no regression of the tumoral lesion has yet been observed.

The sequence and source of the multiple lesions in this patient are not definitely known. The lesions could be hematogenous metastases of the original femoral lesions, extending very slowly, but there was a high radioactive uptake on the secondary sites. It seems most likely that there is independent development of tumors at multiple sites, as the course of the patient's disease is that of the osteosarcoma syndrome, known as multiple metachronous osteosarcoma.

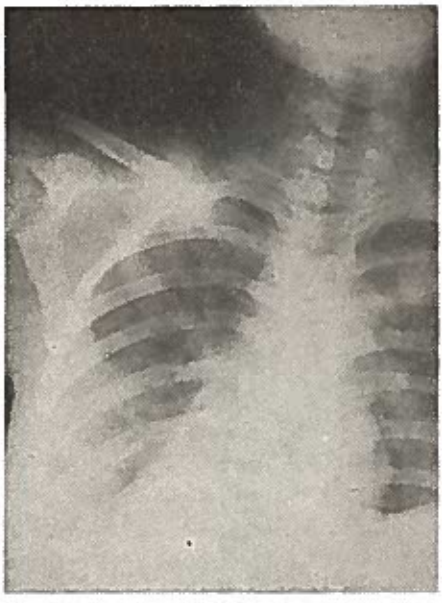

Figure 4
Roentgenogram of left scapula shows destruction and sclerotic appearance.

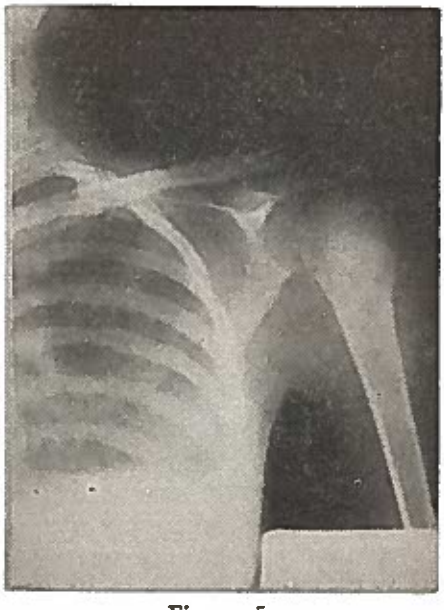

Figure 5
Roentgenogram of head of right humerus shows sclerosis and new bone formation.

Discussion

The medical literature records very few cases of multiple osteogenic sarcoma. Osteogenic sarcoma is, in the experience of most observers, a solitary bone tumor. It is disseminated through the blood stream and is much more prone to producing pulmonary metastases than distant bone lesions without the intervening involvement of the lung.[1-5]

After White (1922) and Silverman's (1936) two cases with multiple foci of osteosarcoma, in 1948, Ackerman described two patients with multifocal osteosarcoma.[1] In these cases, he noted that the osseous lesions were limited to the metaphyses of the involved long bones. He thought they were of multicentric origin because of the absence of involvement in other regions of the long bones (characteristic of bone metastases) as well as the simultaneous appearance of the lesions. Mauck and Carpenter described one patient in 1959 with multi-osseous sclerotic osteogenic sarcoma: the authors believed the tumor to represent a neoplasm of similar cytological appearance occuring simultaneously in multifocal fashion.[2] In 1961 Smithers and Gowing, in 1965 Singh and Scudder, in 1965 Davidson, Chache and James reported multifocal osteogenic sarcoma without pulmonary metastases.[3-5] They discussed bone-to-bone metastases and multicentric origin.

Amstutz reported two additional cases of multifocal osteosarcoma and reviewed the literature in 1969.[6] He classified this disorder into three categories; Type I, occuring in childhood and adolescence with symmetric or asymmetric lesions; appearing simultaneously (or nearly so). Type II, in adults with low grade multiple bone lesions and no pulmonary metastases and Type III in adolescents or adults with metachronous lesions. He considered these various types of multiple lesions to be metastatic deposits from a single primary focus because there were insufficient criteria for a multicentric hypothesis even in the absence of pulmonary lesions.

Fitzgerald et al, reported 12 patients with multiple metachronous osteogenic sarcoma without intervening visceral lesions, among nearly 800 cases in the files of the Mayo Clinic in which the patients were followed up after treatment of an osteosarcoma.[7] They suggested the influence of host factors on the development and extent of such tumors. It was not possible to determine whether the metachronous sarcomas represented late metastases or new primary tumors. A significant observation was that patients who had a new lesion were potentially curable.

The latest report came from Simodynes et al in which they reported a patient with the syndrome of multiple metachronous osteosarcoma who had had an eleven-year survival record.[8] They believed that different observations supporting multicentric rather than metastatic origins of the many lesions are similer patterns of growth, with similar histologic appearances and present in areas not characteristic of metastases. They suggested two types of multicentric osteosarcomas; the first one is multiple synchronous osteosarcoma. The Amstutz type I represents this type. Onset is in childhood or early adolescence. Pulmonary metastases are absent or occur very late, but there are multiple metaphyseal lesions which are nearly symmetrical in long bones. As the process is very rapidly fatal, aggressive treatment may not be justified. The second is multiple metachronous osteosarcoma which occurs only one-fifth as often as multiple synchronous osteosarcoma. The Amstutz type II represents this group. Onset is later, often in middle age. Pulmonary metastases are absent or very late. Multiple lesions in both long and flat bones are noted at presentation, or they develop periodically thereafter. The lesions are asymmetrical and are either lytic or sclerotic. The patients have relatively long survival records, even without treatment.

We believe that the number of cases in the literature is probably still too small to distinguish such so-called syndromes from the variations which occur by chance: nonetheless, it appears that distinct patterns are

emerging. Identification of syndromes is of value as it can lead to an increased understanding of prognosis, treatment and tumor etiology.

We also believe that our case is an example of osteosarcoma syndrome known as multiple metachronous osteosarcoma. The patient bone scans showed abnormal uptake, three months before plain roentgenograms could identify lesions in the head of the right humerus and left scapular crista. Therefore, we recomend that one should obtain skeletal scintographies periodically in every patient with osteogonic sarcoma.

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Transient Monocular Blindness in Cerebro Vascular Diseases (Amaurosis Fugax)

James A. Goodwin, M.D.*

Amaurosis fugax refers to transient monocular visual loss due to atherosclerosis of the ipsilateral internal carotid artery, but the differential diagnosis usually includes retinal migraine. The importance of distinguishing these two conditions is obvious since symptomatic carotid stenosis requires invasive studies as a prelude to possible surgical treatment while a diagnosis of migraine should lead to conservative management.

Differentiation of amaurosis fugax from migraine is based mainly on the clinical characteristics of the attacks. Most publications on amaurosis fugax indicate that the spells typically last only two or three minutes and that "positive" visual phenomena such as scintillations are uncommon.[1-6]

The clinical characteristics of retinal migraine attacks, on the other hand, are not clearly set forth in the medical literature. Nevertheless, migraine episodes are commonly regarded as distinct from those of amaurosis fugax in that the attacks last longer, typically between 15 and 60 minutes, and are often accompanied by scintillations or other "positive" visual phenomena. The occurrence of headache or orbital pain with retinal migraine must be considered variable; some authors find that it is common while others say it is rare.

* Associate Professor of Neurology and Ophthalmology University of Illinois, Eye and Ear Infirmary, Chicago, Illinois, U.S.A.

Review of the Literature

Virchow (1856) is given credit for the first pathologic description of carotid thrombosis ipsilateral to an eye that had been blinded by ischemia.[7] In 1875, Gowers briefly described clinical cases in which transient monocular blindness was associated with contraletaral hemiplegia due to stroke.[8] Interest in the relation between the carotid artery and the eye slackened for 50 years after Elschnig's statement in 1893 saying collateral circulation is so great that any visual dysfunction in carotid thrombosis is always temporary.[9] The following decades produced scattered reports of carotid artery thrombosis with mention of visual symptoms though none drew attention to a clearcut monocular syndrome ipsilateral to the vascular lesion.

In 1937 Egas Moniz published 4 cases of internal carotid artery occlusion that had been discovered in the course of studying 537 patients with positive contrast carotid angiography, a technique he had just recently developed.[10] One patient had a fixed visual loss in the eye ipsilateral to the occluded carotid but this had been noted 17 years prior to the stroke and the patient had syphilis. Another patient had "transient obscurations of vision" (obnubilations de la vision) but it was not specified whether this was monocular or binocular.

Andrell in 1943 reported 9 cases of angiographically documented internal carotid artery occlusion.[11] Two had transient homonymous hemianopsia. Case 5 had thrombosis of the right internal carotid siphon with associated occlusion of the ipsilateral central retinal artery but no visual symptoms were quoted and the fundus was not described! Case 7 had "seizures of left eye blindness" but the patient was described as being on the verge of fainting when "everything blurred for a few minutes". It is doubtful that this represents true amaurosis fugax.

It was not until 1951 that the importance of transient visual attacks in the diagnosis of carotid artery disease was reemphasized by Fisher in his major study of carotid thrombosis.[1,2] He carefully described the clinical profile of these monocular attacks and demonstrated the relationship of amaurosis fugax to carotid atherosclerosis. Fisher argued that the mechanism of the attack is flow crisis in the retinal circulation due either to high grade stenosis of the internal carotid artery or to embolisation of the retinal artery from an ulcerated atheroma at the carotid bifurcation. In this and subsequent publications Fisher and others have repeatedly emphasized that amaurosis fugax attacks are quite stereotyped lasting between 1 and 5 minutes with little in the way of "positive" visual phenomena.[1-5]

Many basic Neurology texts pass over the topic with scant description of amaurosis fugax attacks. Merritt, however, gives the following account contrasting amaurosis fugax with migraine:

The usual ischemic attacks of transitory blindness (amaurosis fugax) are shorter in duration (seconds to minutes), usually monocular, rarely hemianopic, and are not accompanied by a hemianopic fortification spectrum. The monocular visual loss may be total or partial. Occassionally, photopsias, consisting of showers of stationary flecks of light that disappear quickly, occur. Other types of scotomata may also be observed.[12]

Cogan in 1961 was the first to report a survey of the causes for transient monocular blindness other than carotid atherosclerosis.[13] This study was limited by the fact that the major criterion for excluding carotid artery disease was symmetric ophthalmic artery pressures as measured by ophthalmodynamometry. Most of the patients did not have carotid angiography which today is considered the only definitive way to rule out carotid atherosclerosis. The study group consisted of 25 cases and the final diagnoses were as follows:3 cases of tumor pressing on the symptomatic optic nerve, 5 of papilledema, 5 of primary vascular disease in the ophthalmic or retinal arteries, 6 "psychogenic", and 5 miscellaneous. Most of these other conditions can be easily distinguished from amaurosis fugax on clinical grounds. The blackouts due to papilledema usually affected either eye alternately or both at once. They generally lasted only seconds but some of the patients described episodes lasting 2-3 minutes. Cogan's cases that were ascribed to local vascular disease in the orbit or eye were put in that category on questionable grounds. Also, those dubbed "psychogenic" consisted of a heterogeneous group that were difficult to define and this categorization was based on admittedly weak criteria. The miscellaneous cases were also poorly characterised but it was in this group that Cogan chose to discuss the possibility of migraine as a mechanism. These patients' attacks lasted seconds to 15 minutes and one described seeing light in the center of the involved field as vision was coming back. One patient had headache associated with some attacks. Other than this there were no features listed in any of the case reports that would point specifically to migraine as the cause.

The most commonly recognized migraine attacks are characterised by binocular scintillating scotomata called "fortification spectra". These migrate and change size within homonymous half fields during symptomatic episodes that typically last 30 to 60 minutes.[14] The visual symptoms are classically followed by a unilateral throbbing headache accompanied by nausea, vomiting and diaphoresis. Most neurologists accept

that on occasion the visual aura in migraine can be confined to one eye and may be accompanied by pain in the ipsilateral orbit or a unilateral headache. It is also commonly held that these monocular migraine auras may last up to 60 minutes or longer just as the more common homonymous auras do (informal personal survey). Review of the literature, however, gives little support to these ideas since the published descriptions of monocular or "retinal" migraine are often contradictory.

Among the earliest clear statements on the subject is the following from Ormond in 1913: That a local spasm of arteries can occur is well known to ophthalmic surgeons, many of whom have had opportunities of seeing the fundus oculi during these attack in which the retinal arteries are reduced to mere threads. At the same time the vision is profoundly affected.[15]

McMullen, in a review of ophthalmic aspects of migraine, cited a case reported from the German literature in 1917.[16] This involved a 51 year old woman who had had classic migraine for many years. Among the usual binocular attacks she had some in which "...the visual aura took the form of a network with hexagonal meshes appearing before one eye."

Valery-Radot in his 1936 book on migraine comments that there are cases in which the visual troubles are monocular involving either "banal" or scintillating scotomata.[17] He noted that "these cases are very rare." Later on he cites the self observation of Meyer in which unilateral transient blindness took the place of his previous migraines but were unaccompanied by his customary unilateral headache.

That these monocular migrainous attacks can lead to permanent visual loss from retinal infarction was emphasized by Graveson in 1949.[18] He provided case reports on 4 patients and reviewed 9 similar cases from the literature. Three of his patients had transient visual spells either before or after the permanent deficit developed. The duration of episodes varied from 1 minute to 3 hours. One patient had attacks with teichopsia consisting of flashes, spots and zigzag formations but migration of the positive scotomata in the affected field was not mentioned. Only 1 of the 3 had pain associated with the attacks; she described sharp stabbing pain first above the eye and then in the eyeball lasting several minutes. The visual deficit started at the same time as the pain and lasted 3 hours.

Carroll profiled the typical case as occurring in a young adult with background history of migraine type headaches.[19] The attacks are typically short, lasting under 10 minutes and are without fortification spectra or scintillations. Carroll also remarked that there is invariable absence of headache with the attacks. Walsh and Hoyt, on the other

hand, considered visual sensations of "sparkling showers of flickering specks" as not uncommon.[20] They agreed with Carroll that most attacks last under 10 minutes but found that ipsilateral headache may follow the monocular visual attacks. Lance describes monocular attacks as lasting "some minutes" and notes that a dull ache usually develops behind the involved eye with the attacks.[21]

Comments

One is forced to conclude from published accounts that the clinical characteristics of retinal migraine are far from being firmly established. The cases are few and the symptoms are varied so the degree of overlap with amaurosis fugax is difficult to specify. Because of this, together with the fact that we could find no published series that emphasized description of the symptomatology in amaurosis fugax, we decided to critically assess the clinical characteristics of the visual attacks in a series of angiographically documented carotid artery cases. We felt that the critical issues involved the duration of attacks, the presence of positive visual sensations, and the association of visual symptoms with ipsilateral head or eye pain. We were encouraged by finding some isolated case reports of amaurosis fugax that documented long duration visual attacks.[6, 22] In fact, Fisher, in his paper on fundus observations during an attack of amaurosis fugax, clearly described the fact that his patient's visual symptoms lasted 65 minutes under observation and that many of the previous ones had lasted up to 45 minutes.[4]

We studied 38 patients with amaurosis fugax due to carotid artery atherosclerosis in an effort to determine to what extent the episodes differ from those thought to be typical of migraine, namely long duration attacks with "positive" visual phenomena. Our study comprised 38 patients with monocular visual attacks due to angiographically documented internal carotid artery atheromata.[23] (Table I,II). The patients were typical of those with symptomatic carotid artery disease in general; the mean age was 62 with a range of 42 to 77 years. There was a male predominance (25:12) and most of the patients were caucasian. The number of reported monocular visual attacks was highly variable, ranging from 1 to "many". Most patients underwent workup and treatment after only 2 attacks, however. The frequency of attacks ranged from 3 in 4 years to 4 in a single week.

We found that in our 38 patients with amaurosis fugax the duration of episodes varied greatly from seconds to hours both across individuals and from one attack to another in a given patient. Positive visual symp-

toms and long attack duration do not correlate with a background history of migraine but they do correlate with observed emboli in the retinal circulation. Actually, these features may relate more directly to the acuteness of blood flow crisis than to the exact mechanism of blood flow arrest. Our one patient with carotid artery dissection also had visual scintillations and his visual attack lasted several hours. We suggest that the underlying factor common to embolic attacks and this presumed non-embolic carotid occlusive syndrome is the acuteness with which it evolves and that this is the aspect which predisposes to long duratin and positive symptoms.

TABLE I

Age 42-77 mean = 61		
Sex 25 male	12 female	Total 37
History of	Hypertension	9
	Diabetes mell.	3
	Stroke	13
	TIA	8

TABLE II

Pts(N)	Duration (minutes)	Positive vis Sympt	Migraine History	Mechanism Low Flow*	Emboli**
3	<1	0	1 (0.33)***	3 (1.00)	0
20	1–5	4 (0.20)	5 (0.25)	17 (0.85)	1 (0.05)
9	6–15	4 (0.44)	2 (0.23)	7 (0.78)	1 (0.11)
6	16-hrs	4 (0.67)	2 (0.33)	2 (0.33)	2 (0.43)
38		12	10	29	4

* Patients with particular evidence for low flow in the ophhalmic artery; carotid occlusion or high grade stenosis, low ODM, reversal of flow in the opthalmic artery.

** Patients with visualized retinal artery emboli or angiograms which failed to reveal a hemodynamically significant stenosis, or presence of a cardiac embolic source.

*** Numbers in parentheses are fraction of total patients in the particular duration category expressed as decimals.

The patients with retinal emboli tended to have visual episodes restricted to either the upper or lower half field in the affected eye while those with hemodynamic crises due to high grade carotid stenosis tended to describe diffuse or total field involvement.

None of our patients with positive visual symptoms described slow migration or change in size of the scotomata during the attack. While this sort of migration is common and has been thoroughly studied in

typical homonymous migraine auras[14] it has not been clearly described in any published account of retinal migraine. Thus, its absence in these amaurosis fugax cases is not of clear differential diagnostic value.

The literature and common opinion in the medical community suggests that amaurosis fugax is always a painless condition while retinal migraine is often accompanied by ipsilateral orbital pain.[18, 20, 21] We had a single patient who experienced severe orbital pain ipsilateral to the symptomatic eye during one of her amaurosis fugax attacks. The pain was steady and non throbbing with radiation to the frontal and temporal area on the same side. It came after several hours of visual symptoms and lasted about 30 minutes. This patient had a non-stenosing ulcerated carotid plaque. In a subsequent painless episode she developed permanent upper half field loss caused by a fibrin platelet embolus to the lower retinal artery branch. At carotid surgery it was observed that the atheromatous plaque had fibrinplatelet debris loosely adherent to its surface. The mechanism of orbital pain in this case is unclear through the patient had a background history consistent with common migraine. It seems conceivable that embolisation to the retinal circulation interacted with a tendency to vascular spasm predicated on the presence of migraine diathesis and that this caused ischemic pain in the orbit. Against this interpretation, however, is the fact that background migraine did not seem to modify the clinical manifestations of amaurosis fugax in our other patients. We could find no mention of orbital pain in any other reported case of amourosis fugax and it must be considered extremely rare.

We wish to emphasize that 6 of our patients with amaurosis fugax had attacks lasting between 16 minutes and several hours, 12 patients had positive visual symptoms, and one even experienced severe orbital pain during an episode.

Based on these studies we feel that the syndrome of amaurosis fugax is so varied that definitive differentiation from retinal migraine using the clinical characteristics of the attacks is not possible. Since significant atherosclerosis has been demonstrated at relatively early age, it may be advisable to perform carotid angiography even in some young people who present with recurrent monocular visual attacks.

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The Effect of Vitamin E on Hypervitaminosis A*

Murat Yurdakök, M.D. / Melda Çağlar, M.D.*** / İmran Özalp, M.D.**** / Olcay Oran, M.D.**** / Kadriye Yurdakök, M.D.*****

Summary

The effect of vitamin E on the hepatotoxic effects of hypervitaminosis A was determined in rats. Animals received vitamin A orally in a dose of 150000 U per day for fourteen days. Some of them also received a single intraperitoneal dose of 50 mg vitamin E on the first day of the study. Serum vitamin A and alanine aminotransferase (SGPT) levels were less elevated in the group treated with vitamin E than the group receiving vitamin A alone (vitamin A 39.37 $\pm$ 2.34 µg/dl and 70.31 $\pm$ 7.63 µg/dl, $p < 0.01$; SGPT 91.0 $\pm$ 11.1 U and 145.8 $\pm$ 18.0 U, $p < 0.05$ respectively). Histopathological changes in liver due to hypervitaminosis A were also prevented by vitamin E treatment.

Key Words: Hepatotoxicity, Hypervitaminosis A, Vitamin E.

Introduction

Hepatotoxic effects of chronic vitamin A intoxication are well known both in humans and laboratory animals.[1-7] Vitamin E is needed for efficient vitamin A utilization and liver storage. It may also lessen the hepatocellular damage of hypervitaminosis A.[8-13] The present study was conducted to determine the value of vitamin E on the hepatotoxic

* The Institute of Child Health, Hacettepe University, and Turkish Health and Therapy Foundation, Ankara-Turkey.
** Pediatrician, S.S.K. Ulus Hospital and the Institute of Child Health Hacettepe University, Ankara-Turkey.
*** Professor of Pediatrics and Pathologist, the Institute of Child Health, Hacettepe University, Ankara-Turkey.
**** Professor of Pediatrics, the Institute of Child Health, Hacettepe University, Ankara-Turkey.
***** Resident in Pediatrics, Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara-Turkey.

effects of hypervitaminosis A and also to compare the hepatic functions and morphology in rats which received large doses of vitamin A with or without vitamin E.

Materials and Methods

Adult male albino rats obtained from Laboratory Animals Breeding Unit, Ministry of Health and Social Welfare were used in this study. Thirty rats were divided at random into three equal groups, were housed five per cage and were fed on standart diet and water ad libitum. Groups one and two consisted of animals which received vitamin A (Afortin^R) orally in a dose of 150000 U per day for fourteen days. Vitamin E (Evigen^R) was injected intraperitoneally in a single dose of 50 mg on the first day of the study in group one.[14, 15] Group three consisted of controls.

All animals were weighed initially and then on the day of sacrifice. On the fourteenth day, blood samples were obtained by cardiac puncture while animals were under light ether anesthesia. Sections from the liver and kidney were randomly, taken from different lobes, embedded in paraffin, cut into four micron thick sections and stained with haematoxylin and eosin. Serum carotene and vitamin A were measured by micro method.[16] Transaminases[17] and BUN[18] levels were determined. Results were expressed as the mean $\pm$ SEM. Student's t-test was used to compare the means between groups.

Results

The rats which received a high levels of vitamin A gradually developed the signs of vitamin A intoxication, such as lassitude, fur discoloration and alopecia.[6] However we did not observe weight loss.

The livers of the rats receiving a high levels of vitamin A without vitamin E were not enlarged; there was not a statistically significant difference between the groups in liver weight and the ratios of liver weight to body weight ($p > 0.05$) (Table I).

Serum vitamin A levels were markedly elevated in the group two ($p < 0.01$). In group one vitamin A levels were the same as in the control group ($p > 0.05$) (Table I).

In animals receiving vitamin A only there was a striking elevation of SGPT (serum alanine aminotransferase) ($p < 0.01$), however in the group treated with vitamin E, the mean SGPT level was less elevated than the group receiving vitamin A alone ($p < 0.05$), but higher than the control group ($p < 0.05$) (Table I).

TABLE I

BODY AND LIVER WEIGHTS, AND SERUM TRANSAMINASES, BUN, CAROTENE AND VITAMIN A LEVELS IN THE STUDY AND CONTROL GROUPS

Group	Body w. (g)	Liver w. (g)	L/B* (%)	SGOT (U)	SGPT (U)	BUN (mg/dl)	SGPT/SGOT	Serum Carotene (μg/ml)	Serum Vit. A (μg/dl)
I	243.7**	8.7	3.57	313.0	91.0	24.4	0.29	1.18	39.37
	6.8	0.4	0.11	17.3	11.1	0.7	0.03	0.09	2.34
II	237.0	7.9	3.35	360.0	145.8	23.0	0.39	1.72	70.31
	6.7	0.1	0.09	13.4	18.0	0.8	0.01	0.13	7.63
III	233.6	7.8	3.40	352.0	49.4	19.3	0.14	1.44	36.95
	11.8	0.3	0.12	14.3	3.6	0.9	0.01	0.13	3.25
I- II	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p < 0.05$	$p < 0.05$	$p > 0.05$	$p < 0.01$	$p < 0.01$	$p < 0.01$
I-III	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p > 0.05$	$p > 0.05$
II-III	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p < 0.05$	$p < 0.01$	$p < 0.01$	$p > 0.05$	$p < 0.01$

* L/B : The ratio of liver weight to body weight.
** Mean ± SEM

Although BUN levels were higher in the study groups than in the control group ($p < 0.01$), there was not a statistically significant difference between groups one and two ($p > 0.05$) (Table I).

Figure 1

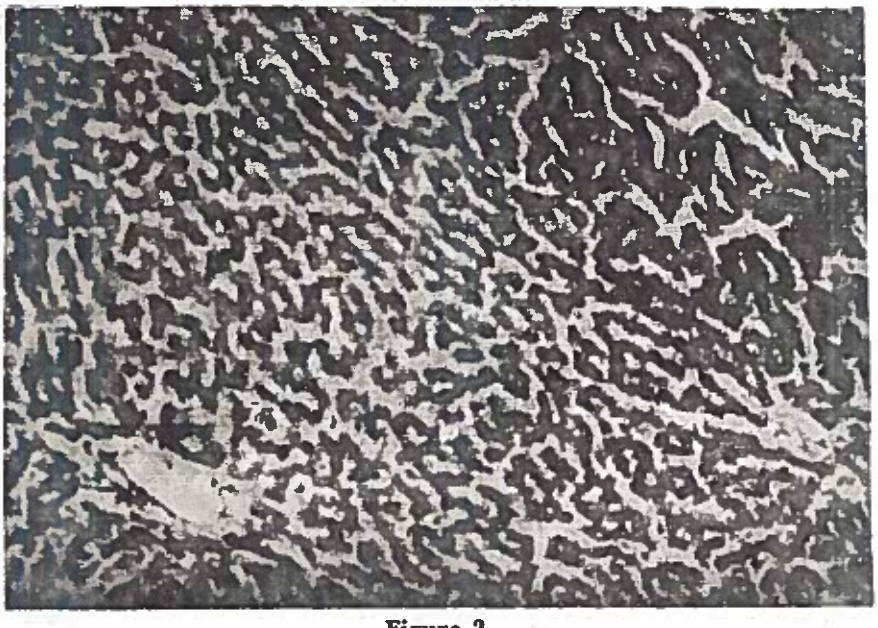

Figure 2

Light microscopic examination of the livers of the rats which received vitamin A showed the lobular architecture to be intact with normal tracts and central canals. The liver cell plates were regularly arranged. There were tiny vacuoles in the cytoplasm of hepatic cells which were predominantly in the portal tracts. A small number of minute droplets were seen in scattered liver cells as well. Furthermore, there were varying degrees of localized necrosis of liver cells. These necrotic areas were replaced by aggregates of mononuclear cells, consisting mostly of lymphocytes, macrophages, and a few plasma cells (Figures 1 and 2). There was no pathological finding in the livers of rats treated with vitamin E. Microscopic examination of the kidneys of rats which treceived vitamin A with or without vitamin E showed no pathological sign.

Discussion

Regardless of whether it is ingested as retinol, retinen or retinyl ester, vitamin A undergoes esterification by the intestinal mucosa before being released into the lymphatic system. Liver stores are primarily composed of biologically inactive palmitate ester, although some vitamin A alcohol is considered to be stored in hepatocytes. Enzymes responsible for esterifying the alcohol and cleaving the ester are both found in liver microsomes. Hepatic esterases convert the ester to biologicaly active alcohol, which is released into the blood.[1, 19] There is no evidence that the palmitate ester is toxic to the liver in man when present in excessive amounts, although large doses of free vitamin A produce lysosomal and mitochondrial damage.[1, 19]

Vitamin A is released into the blood as retinol in association with retinol-binding protein and prealbumin. Retinol-binding protein is a protein of low molecular weight secreted by the liver. However, this protein, on entry into the circulation, immediately complexes with free albumin so that vitamin A in blood is found largely in combination with this protein complex. Vitamin A esters and carotene are not carried by this complex, but appear to be in weak association with the various lipoproteins and albumin.[20] During hypervitaminosis A there are disturbances in this retinol transport system. The ability of the liver to take up retinol may be exceeded and retinol-binding protein secretion may be suppressed by as much as 50 percent.[1]

Hepatomegaly and abnormal liver function tests have been described both in animals and in humans who chronically ingest large quantities of vitamin A.[1-5] Fatty infiltration with vacuolated cells in the liver of the rats have also been reported before.[6-8] We have observed the same effects. In humans, although many patients with chronic hypervitami-

nosis A have hepatomegaly, liver biopsies have been obtained in only a few instances.[1-5] On light microscopic examination, the liver may appear normal or show minor changes. Although portal hypertension has been reported, hepatic fibrosis and cirrhosis have been documented in only two cases.[21]

The most striking and probably the primary ultrastructural change observed in the livers of humans and laboratory animals with hypervitaminosis A is the massive accumulation of lipid (which may actually be vitamin A) in perisinusoidal cells.[22-25] Accumulation of numerous lipid-storing perisinusoidal cells and perisinusoidal fibrosis were observed in the second stage. Perisinusoidal cells (Ito cells) or lipocytes are located in the space of Disse between the sinusoidal endothelium and hepatocytes.[24, 25] Ito cells are thought to be specific storage cells for vitamin A and can be distinguished from Kuppfer cells by their location in the perisinusoidal space of Disse or intercellular space, and by the absence of phagocytic activity. Under certain experimental conditions, they transform into fibroblasts which have the capacity to produce type III collagen. The excessive accumulation of vitamin A within the Ito cells stimulates these cells to produce collagen. Perisinusoidal fibrosis, obliteration of sinusoidal lumina and ingrowth of small arterioles probably impair blood flow and appear to lead to secondary alterations in hepatocytes.[22-28] Vitamin A is known to accumulate in hepatocytes as well.[26] However, hepatic droplets are very rare, and there is no evidence for a direct toxic effect of vitamin A on the cytoplasm of hepatocytes.[23] The major alterations in hepatocytes such as cellular atrophy and formation of bullae can be explained as consequences of an altered blood supply.

There is a correlation between vitamin A and vitamin E metabolism. In experimental animals vitamin E has been shown to have a beneficial effect on the protection of vitamin A from oxidation in the gut, increasing vitamin A absorption, utilization, and storage in liver.[8-13] It has been shown that rats given vitamin E in their diet stored up to ten times as much vitamin A in their liver as those without additional vitamin E. Vitamin E slows the decline of hepatic deposits of vitamin A. In the livers of rats maintained on a diet deficient in both vitamin A and E, vitamin A stores disappeared much more rapidly than in animals receiving vitamin E. The liver storage of vitamin E is less in rats concurrently receiving high oral doses of vitamin A than rats receiving vitamin E alone. Furthermore, when high doses of vitamin A were given to rats, rabbits or guinea pigs, the animals became deficient in vitamin E faster. Therefore, it has been suggested that administration of vitamin

E along with massive doses of vitamin A may facilitate the accumulation of larger stores of vitamin A.[8-13] Low serum vitamin A levels found in animals treated with vitamin E in this study can be explained by the effects of vitamin E on the metabolism of vitamin A described above. However, the amount of vitamin E used in this study and in previous experiments was high. Using smaller doses, others have failed to demonstrate any effect of vitamin E on vitamin A metabolism in rats and man.[8-13]

It has been shown that there is increased permeability or fragility in membranes of subcellular particles of liver tissue in vitamin A-deficient rats. Vitamin A also influences the stability and permeability of biological membranes, but high doses may disrupt their lipoprotein structure.[29, 30] Vitamin E protects against distruption of membranes due to hypervitaminosis A through its free radical quenching ability.[31] In this study, it has also been shown that vitamin E reduces the hepatotoxic effects of hypervitaminosis A both biochemically and morphologically.

In areas of the world where protein-calorie and vitamin A deficiency abounds, vitamin E deficiency, particularly in children, also occurs sporadically.[32, 33] When massive oral or intramuscular vitamin A doses are administered to children who are severely malnourished it would seem judicious to also administer some vitamin E simultaneously.

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Phenotypic Characterization of Convoluted T-Cell Lymphoma/Leukemia in Lymphoid Tissues*

Immunohistochemical staining of frozen sections with monoclonal antibodies

Nükhet Tüzüner, M.D.

Summary

Frozen sections of 5 cases with the typical morphologic features of convoluted T cell lymphoma/leukemia, as described by Barcos and Lukes, were stained with a panel of monoclonal antibodies (MoAb) including reagents reactive with subpopulations of T cells and the common acute lymphoblastic leukemia antigen (CALLA). The enzyme terminal deoxynucleodityl transferase (TdT) was detected in the neoplastic cells from each case by immunoperoxidase (IPX) staining of paraffin sections.

Two of the five cases appeared to be analogous to the early thymocyte population; while the other two cases were related to the common thymocyte population. In the remaining case tumour cells were stained for Leu1 but could not be stained with other monoclonal antibodies, either specific for T cells or CALLA.

Key Words: Convoluted T cell lymphoma; monoclonal antibodies; lymphocyte subsets; immunoperoxidase technique.

Introduction

Human T cell lymphomas and leukemias display heterogeneous clinical behavior and diverse histopathological characteristics.[1-3] It is

* This study was conducted in the University of Southern California Medical Center. Department of Hemotopathology.

** Associate Professor, Department of Pathology, University of Istanbul Cerrahpaşa Medical Faculty, Istanbul-Turkey.

also clear by now that apparently histologically homogeneous T cell proliferations may express different antigenic phenotypes and are revealed by flow cytometry studies using monoclonal antibodies (MoAb) to T cell antigens. Reinhertz et al[4] proposed, on the basis of flow cytometry studies with monoclonal antibodies raised against thymocytes, that there are three stages of differentiation in the cell distribution and expression of surface antigens.

It is now apparent that some of the antibodies identify antigens that are not cell lineage specific ie. OKT 9 and OKT 10 which are found in non T cells and myeloid cells.[5] However, when these antibodies are applied to the study of T cell leukemia/lymphomas different phenotypic patterns are expressed by the neoplastic cells from different patients[1-3,6-9]

Our own flow cytometry studies of human lymphomas and leukemias have demonstrated that because of the variation in the degree of involvement of lymphoid tissues by neoplastic cells, and because of sampling differences, it is frequently difficult to demonstrate a clear cut pattern which can be said to represent the phenotype of the lymphoma cell. There are always varying numbers of residual normal/reactive ymphocytes present in the suspension.

The study reported here presents the results of immunohistochemical staining patterns of lymphoid material from 5 cases diagnosed as convoluted T cell lymphoma/leukemia. The staining patterns are quite different between cases with the same morphological cell type and the effect of focal or localized involvement of the tissue is demonstrated.

Materials and Methods

The five patients in this study ranged in ages from 17 to 42 years, 3 were males and 2 were females. An anterior mediastinal mass was detected radiologically in 3 patients at the time of diagnosis. The mediastinum and/or lymph nodes were the initial presentation sites of the disease in two patients, and these two patients showed no marrow involvement at the time of diagnosis. The leukocyte counts ranged between 5400-37.00 mm/cu in 4 of the patients and 170.000 cu/mm in the remaining one (Table I).

Frozen tissue from 8 patients who were diagnosed as convoluted T cell lymphoma/leukemia confirmed in paraffin sections were available for study. In all the cases the tissue had been obtained prior to therapy.

TABLE I

CLINICAL AND LABORATORY FEATURES OF CASES STUDIED

Cases	Age/ Sex	WBC	E-R	P-ACP	TdT	Mediastinal Mass	Lympha-denopathy	Survival
1	20/M	5400	24 %	35 %	+	+	+	20 +
2	17/M	170000	33 %	20 %	+	-	+	10 +
3	43/M	12100	28 %	65 %	+	-	+	9 +
4	30/F	12600	ND	85 %	+	+	+	8 +
5	27/F	37600	90 %	95 %	+	+	-	7 +

In 3 out of 8 cases fresh material could not be studied due to freezing artefacts. In the remaining 5 cases cryostat sections (8 micron thick) were dried overnight at room temperature prior to staining. Following acetone fixation the sections were washed with modified PBS[10] for 15 minutes, followed by staining of different sections with a panel of mouse antihuman MoAb's (Table II): Leu1, Leu2, and Leu3 (Becton and Dickinson) at 1:60 dilution, OKT3, OKT6, OKT11 and OKT10 (Ortho diagnostic) at 1:50 dilution, B1 (coulter) at 1:50 dilution, BA1 (Hybritech) at 1:50 dilution, J5 (Schlossman) at 1:50 dilution and HLA-DR at 1:2000 dilution. Following the initial incubation with primary antibody the sections were washed in multiple changes of modified PBS for 5 minutes and then incubated with biotinylated affinity purified mouse IgG(BAHAM) for 15 minutes. Sections were finally washed in modified PBS and incubated in ABC complex (Vector Lab) for 20 minutes. Peroxidase reaction was performed using a preparation of 3-amino, 9-ethyl carbozole (AEC) in 5 ml of N, N-dimethylformamide, 50 ml of acetate buffer (pH 5.2) and 200 microliters of hydrogen peroxide. Color reaction was developed for 10 minutes and terminated by washing the slides with PBS for 5 minutes. The sections were counterstained with fresh Mayer's hematoxylin for 15 minutes.

Paraffin sections were also stained with anti TdT and heterologous Fab_2 antibodies to kappa and lambda light chains as described previously.[11]

Surface marker studies, including immunofluoresence staining for surface Ig and sheep erythrocyte rosette formation, were performed as described previously.[12] Wright stained cytocentrifuge preparations of suspensions were also examined to demonstrate that the neoplastic convoluted T cells formed sheep erythrocyte rosettes.

Direct immunofluoresence staining with the MoAb's OKT 3,4,6, 8,11 was performed and indirect immunofluoresence staining with the

TABLE II
MONOCLONAL ANTIBODIES USED IN THE STUDY

Antibody	Source	Specificity
Leu 1	Becton-Dickinson	Anti-human T cell (pan T)
Leu 2	Becton-Dickinson	Anti-human T cell (suppressor)
Leu 3	Becton-Dickinson	Anti-human T cell (helper)
OKT3	Ortho Diagnostics	Anti-human T cell (pan T)
OKT4	Ortho Diagnostics	Anti-human T cell (helper)
OKT8	Ortho Diagnostics	Anti-human T cell (suppressor)
OKT6	Ortho Diagnostics	Anti-human thymocytes, Langerhans cells
OKT10	Ortho Diagnostics	Activated T cell, some B cells, Plasma cells, NK cells
OKT11	Ortho Diagnostics	Anti-human T cell (E receptor)
B1	Coulter Immunology	Anti-human B cell (pan B)
BA1	Hybritech	Anti-human B cell, neutrophiles
J5	Schlossman	Common acute leukemia antigen (CALLA)

MoAb's OKT 10, anti-CALLA and anti-Ia as described previously.[2,6] Cells were analysed for fluoresence in an Ortho Spectrum III Flow cytometer.

Results

Clinical and laboratory features of the 5 cases studied has been summarized in Table I.

Cell Suspension Studies: Cells from lymph nodes or mediastinal masses formed spontaneous sheep erythrocyte rosettes (65-90 % in three of the patients, and 24-33 % in the other two cases). In each case rosetting cells appeared to be typical convoluted T cells of this lesion.

Immunohistology: Representative sections of lymph nodes from 3 of the patients showed partial involvement by lymphoma whereas biopsies of the 2 mediastinal masses showed diffuse replacement of the parenchyma by lymphoma. However, in all the cases the involved areas showed the same cytological appearance with neoplastic cells i.e. irregular nuclei with deep indentations and fine stippled chromatin.[13]

T-Cell Antibodies: In the 3 partially involved lymph nodes, lymphoid cells in the uninvolved areas were stained with antibodies Leu1, Leu2, Leu3, and OKT 11. The positive cells were concentrated in and arround the residual follicles and in the T dependent areas. OKT3 staining showed the same distribution but fewer cells stained then with Leu1 (Figure 1,2).

There was no staining of uninvolved areas of the lymph node by OKT6 or OKT 10. The portions of lymph nodes which were infiltrated with the convoluted T cell lymphoma presented different patterns (Table III). The cells in all 3 cases stained with Leu1 or OKT3, but there was variation in the intensity of staining. There were no stained cells with Leu2 or Leu3 antibodies in any of these cases. In case 1, tumour cells stained with OKT 11 but the lymphoma areas in other two lymph nodes were negative with this antibody. In contrast the lymphoma cells in case 1 and 2 stained intensely with OKT 10 (Figure 3), whereas case 3 showed no staining with this antibody. The lymphoma areas in all 3 cases showed no staining with OKT6, except for one small area of OKT6+ cells in case 2.

TABLE III
CYTOFLOWMETRY RESULTS

			Monoclonal Antibodies (%)					
Cases	OKT3	OKT4	OKT8	OKT11	OKT6	OKT10	CALLA	Ia
1	5	4	4	87	5	77	5	12
2	10	4	7	3	0	82	5	72
5	82	82	88	85	83	8	5	2

Sections from the mediastinal masses of cases 4 and 5 were diffusely replaced with convoluted T cell lymphoma. The lymphoma cells stained with Leu1, Leu3, OKT11, OKT6 and OKT10 in case 4. There was a diffuse staining pattern with Leu1, but irregular staining in terms of number of cells stained and intensity with the other antibodies (Figure 4). In case 5 the lymphoma cells stained diffusely with Leu1, Leu2, Leu3, OKT11 and OKT6.

Common Acute Lymphoblastic Leukemia Antigen (CALLA): In case 1 CALLA was present in most of the lymphoma cells (Figure 5), but there was no antigen observed in the uninvolved portions of these lymph nodes. In case 2 a small lymphomatous area showed lymphoma cells devoid of CALLA. Although scattered lymphoma cells express the CALLA in this area, the remaining tissues from the other cases were negative for CALLA.

B-Cell Antibodies: The three partially involved lymph nodes demonstrated polyclonal staining for kappa and lambda light chains in uninvolved areas. Lymphoma cells did not stain for light chains in diffusely involved mediastinal masses. The BA1 antibody stained cells in follicular centers and scattered lymphocytes in the interfollicular areas. Neither antibody stained in the areas involved by lymphoma in lymph nodes or in the sections of the mediastinal masses in 4 cases. However, in case 2 the lymphoma cells stained with BA1 diffusely (Figure 6).

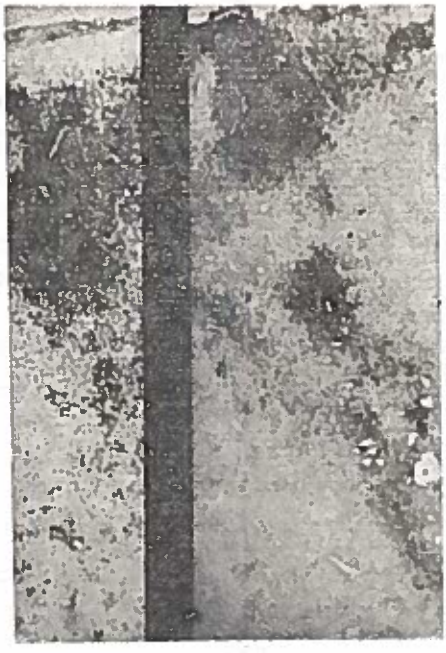

Figure 1

Staining with Leu1 (left) and OKT11 (right) in convoluted T cell lymphoma (case 2), positive cells are concentrated in and arround the residual follicles and in the T zones (Hematoxylin counterstain X 64).

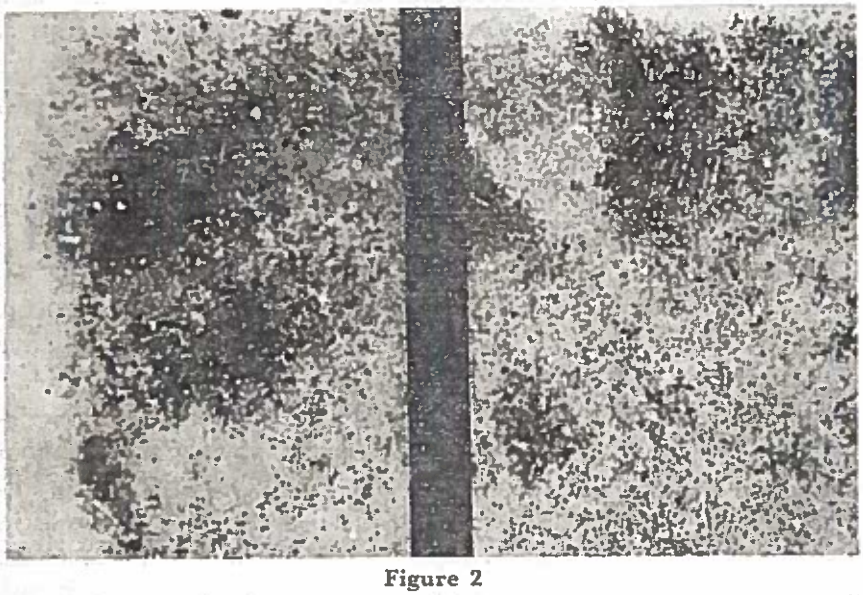

Figure 2

Staining with Leu1 (left) and OKT3 (right) in convoluted T cell lymphoma (case 3); distribution of staining is similar but fewer cells stained with OKT3 than with Leu1 (Hematoxylin counterstain X 64).

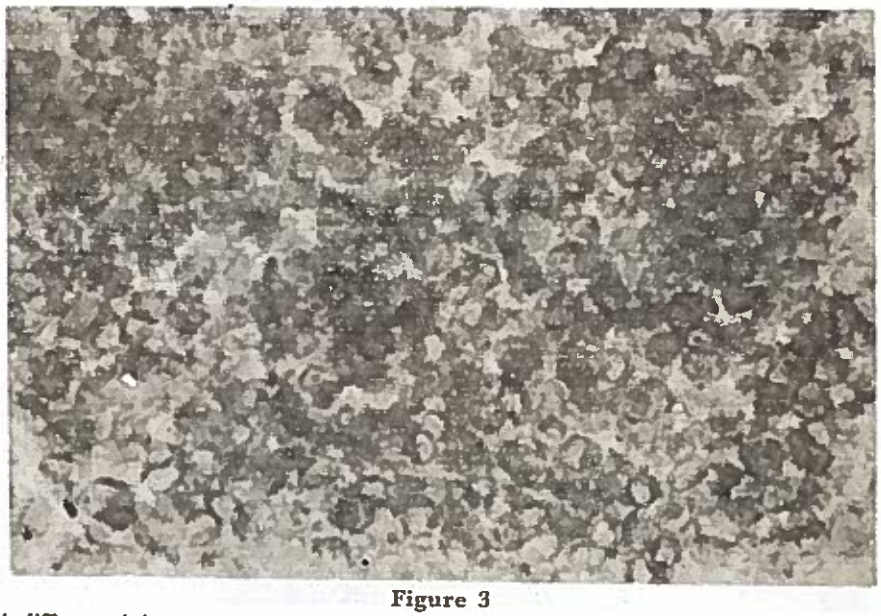

Figure 3
A diffuse staining pattern with OKT10 (case 2), a narrow rim of color surrounds each cell, indicating membrane staining (Hematoxylin counterstain X 640).

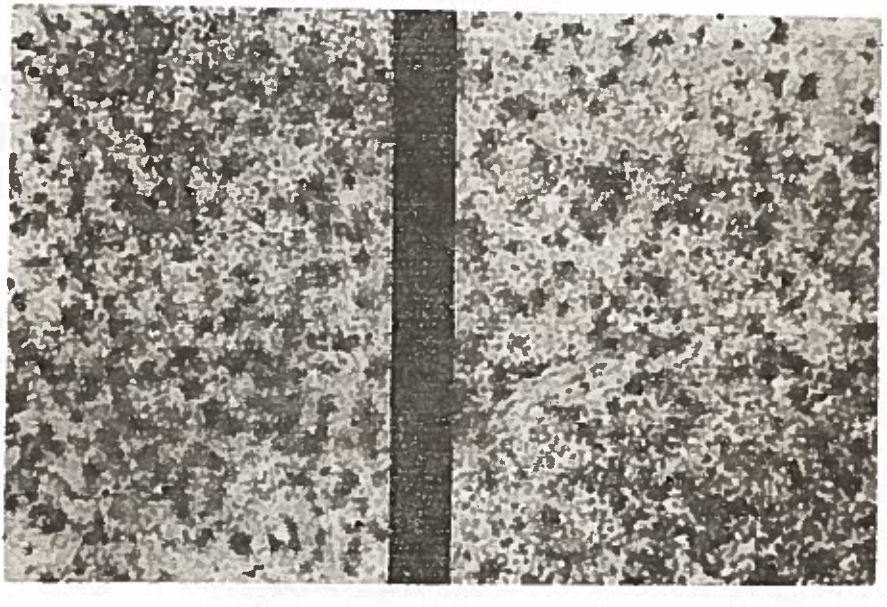

Figure 4
Irregular staining in terms of number of cells stained and intensity with OKT3 (left) and OKT6 (right) (case 4) (Hematoxylin counterstain X 160).

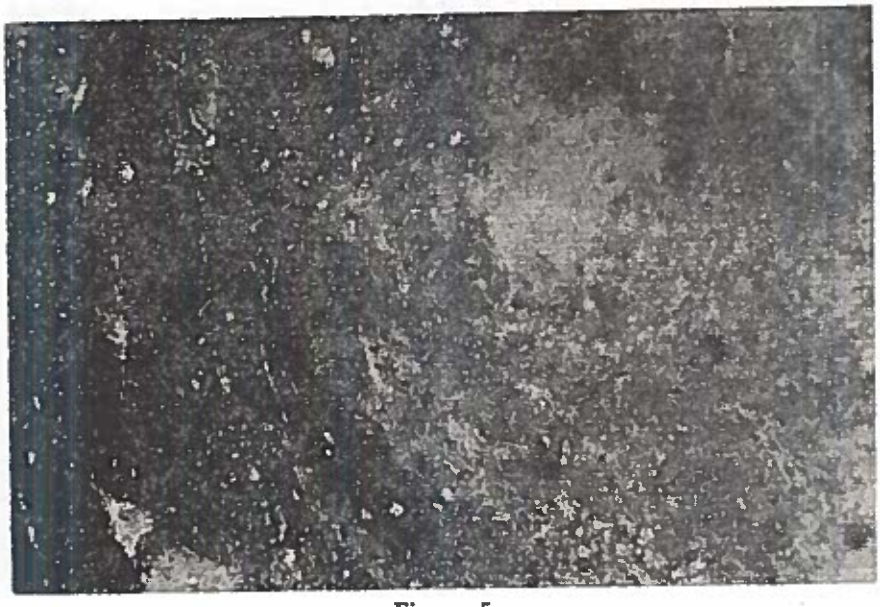

Figure 5
A diffuse staining pattern with CALLA (case 1); no staining is seen in the uninvolved portions of node (Hematoxylin counterstain X 64).

Figure 6
A diffuse staining pattern with BA1 (case 2) (Hematoxylin counterstain X 640).

TABLE IV

STAINING PATTERNS OF TUMOUR AND RESIDUAL LYMPHOID TISSUES WITH MONOCLONAL ANTIBODIES

Case		Leu1	Leu2	Leu3	OKT3	OKT11	OKT6	OKT10	CALLA	Kappa	Lambda	B1	BA1
	Tumour Tissue	2+	0	1+	1+	4+	0	3+	3+	0	0	0	0
1	Residual Lymphoid Tissue	4+	2+	3+	3+	3+	0	0	0	4+	4+	3+	3+
	Tumour Tissue	0	0	0	0	0	0	4+	4+	0	0	0	3+
2	Residual Lymphoid Tissue	4+	2+	3+	3+	3+	0	0	0	3+	4+	2+	1+
	Tumour Tissue	3+	0	0	0	0	0	1+	0	0	0	0	0
3	Residual Lymphoid Tissue	3+	1+	2+	2+	3+	0	●	0	3+	3+	2+	2+
	Tumour Tissue	3+	0	2+	2+	1+	3+	2+	0	0	0	0	0
4	Residual Lymphoid Tissue					N O N E							
	Tumour Tissue	4+	3+	3+	3+	3+	4+	0	0	0	0	0	0
5	Residual Lymphoid Tissue					N O N E							

Flow Cytometry: The results of the flow cytometry studies are given in Table IV. The correlation between the results of IPX staining with the same or comparable antibodies was excellent. In both case 1 and 2 the lymphoma cells possesed the CALLA antigen by IPX staining but were negative by cytofluoragraphy.

Discussion

It is clear from examining sections of lymphoid tissues involved with lymphomas that even with extensive replacement of normal lymphoid tissue by the lymphoma cells some residual normal or reactive lymphoid cells and stromal structures remain. This has become more apparent from immunohistochemical studies and surface marker studies performed on lymph node suspensions. In the case of partial or incomplete involvement of the lymphoid tissue by lymphoma, this is even more evident. Flow cytometry studies of blood and lymphoid tissue cells suspensions are complicated by this factor since the lymphoma or leukemia cells are mixed in various degrees with the residual lymphoid and other cells, homogeneous phenotypes are frequently obscured. The study reported here clearly illustrates the difference in phenotypes between lymphoma cell areas in partially involved lymph nodes and residual lymphoid tissue. It is not surprising that flow cytometry studies might not reflect the lymphoma phenotype because of this mixture.

In the present study, we utilized a panel of monoclonal antibodies to phenotype the lymphoma cells of convoluted T cell lymphoma/leukemia from five patients. A diagnosis of convoluted lymphoma was made from paraffin sections using the morphologic criteria described by Barcos and Lukes.[13] The clinical features, presence of TdT, the lack of surface Ig, and the demonstration of punctate acid phosphatase activity and spontaneous rosette formation with sheep erythrocytes confirmed the diagnosis. In spite of this degree of homogeneity, the cases demonstrated different immunological phenotypes.

In cases 2 and 3, OKT10 and CALLA were expressed possibly suggesting that these represented earlier stages of differentiation. The expression of Leu1 is not consistent with this, but does suggest as have others, that the Leu1 antibody identifies a different antigen than the OKT3 and other pan-T antigens. Foon et al, have reported that 100 % of thymocytes and ALL cells stained with Leu1.[7] On the other hand, Burns et al, have demonstrated that Leu1 antigen may also be expressed on a small number of lymphomas of B cell origin.[14] However, the apparent discrepancy in the expression of Leu1 on these cells may reflect asynchronous gene expression as postulated by Greaves et al.[1]

Case 3 would appear to reflect early progenitors with few differentiation antigens. In case 2, lymphoma cells expressed T3$^-$, T4$^-$, T6$^-$, T8$^-$, T 10$^+$, CALLA$^+$, BA1$^+$ phenotype so it may best fit pre-B cell phenotype. Case 1 showed the expression of more antigens but T10 and CALLA still expressed. This would appear to reflect a latter stage in differentiation as due to cases 4 and 5 which were biopsies of mediastinal masses. These both showed T6 antigen as well as other evidence of a more differentiated phenotype with expression of helper and supressor phenotypes. The so called common thymocyte antigen T6 was not expressed in the lymph nodes.

Cases 1 and 2 stained positively with CALLA by the immunoperoxidase technique but flow cytometry did not demonstrate this antigen. Whether or not this is due to technical difference or reflects the ability of immunocytochemical approach to detect cytoplasmic as well as surface antigen is not clear from this study. The CALLA has been reported on convoluted T cell lymphoma.[6, 15] However, it is also clear from our results and others that CALLA is neither cell line specific or specific for neoplastic lymphoid cells.

An important feature of this study is that the 3 lymph nodes were only partially involved by the lymphoma. In the areas residual lymphoid tissue, follicles were recognizable and when stained with these antibodies showed a different phenotype than that of the lymphoma cells. The expected distribution of the T and B cells and their subsets were seen topographically. These findings point out the reason why flowcytometry results may show significant numbers of more mature T cells with helper and suppressor antigens or B cells with polyclonal surface Ig pattern.

This study demonstrated that cells with similar morphological features may have different immunologic phenotypes. It also proved the superiority of immunohistochemical staining of sections in showing foci of the lymph nodes involved by lymphoma. Through the use of this technique one can phenotype only the neoplastic cells. This approach also has the potential for evaluating the host immunological response to the lymphoma cells. A major disadvantage of this approach is that it is difficult to quantitate the precise number of cells and the intensity of staining.

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Diagnostic Significance of Ascitic Fluid

Şafak Reka, M.D.* / Şükran Karacadağ, M.D. / Hasan Telatar, M.D.****

Summary

Five-hundred patients with ascites were studied and protein values of the ascitic fluid and serum were determined in various diseases. It was shown that the high-protein ascites may be found in hepatic cirrhosis, nephrotic syndrome, and congestive heart failure. Also, low-protein ascites may be found in peritonitis and peritoneal carcinomatosis. These findings indicate that ascitic fluid protein values may occasionally be found to be different from those expected.

Key Words: Ascites, Ascitic fluid, Exudate, Transudate.

Introduction

Ascitic fluid analyses are frequently performed for the differential diagnosis of various diseases. In hepatic cirrhosis, congestive heart failure and nephrotic syndrome, low-protein values, and in peritonitis and peritoneal carcinomatosis, high-protein values are expected. However, unexpected protein concentrations of the ascitic fluid may occur in these diseases.[1-3] In the present study, the protein concentrations of the ascitic fluid were determined in 500 patients with various diseases and the correlation between the ascitic fluid and serum total protein concentration was investigated.

Materials and Methods

Five-hundred patients were studied in Hacettepe University Medical Center. Their ages ranged from 18 to 76 years. The diagnosis of hepatic cirrhosis was made by physical examination, liver function tests,

* Fellow in Gastroenterology, Hacettepe University Faculty of Medicine Ankara, Turkey.

** Professor in Gastroenterology, Hacettepe University Faculty of Medicine Ankara, Turkey.

scanning of the liver and spleen, peritonoscopy and/or liver biopsy in 258 patients. Twenty-five patients had nephrotic syndrome and the diagnosis was made by physical examination, serum and urine protein analyses. The diagnosis of peritoneal carcinomatosis was established by biopsy obtained during peritonoscopy and/or laparotomy in 145 patients. Thirty-three patients had tuberculous peritonitis and 4 patients pyogenic peritonitis and the diagnosis was made by culture and peritoneal biopsy. The remaining 35 patients had congestive heart failure.

Ascitic fluid and serum samples were simultaneously collected from all patients. Specific gravity, glucose, total protein, cytologic examination, and bacterial cultures were performed. The ascitic fluid and the serum proteins were determined by the Autoanalyser SMA, with SD being 0.2 %.

Protein concentration of the ascitic fluid greater than 3 gm/ml. was interpreted as exudate. Ascitic fluid to serum ratios of total protein were determined in all patients. Ascitic fluid total protein concentration was also compared with serum total protein concentration in all groups.

Results

Table I shows the incidence of transudate and exudate of the ascitic fluid in all patients.

TABLE I

Disease	Number of patients	Ascitic Fluid	
		Transudate	Exudate
Hepatic Cirrhosis	258	299 (89 %)	29 (11 %)
Nephrotic Syndrome	25	21 (84 %)	4 (16 %)
Congestive Heart Failure	35	27 (77 %)	8 (23 %)
Tuberculous Peritonitis	33	15 (45 %)	18 (55 %)
Pyogenic Peritonitis	4	4 (100 %)	–
Peritoneal Carcinomatosis	145	106 (73 %)	39 (27 %)
	500		

Hepatoma and spontaneous peritonitis were eliminated in 29 patients with hepatic cirrhosis and high-protein ascites.

Table II shows the protein concentration of serum and ascitic fluid and the rations in all groups.

There was a significant correlation between the ascitic fluid and the serum total protein concentration (r: 0.15 $p < 0.05$) in patients with cirrhosis of the liver. Figure 1 shows the protein concentration of serum and ascitic fluid in each patient.

TABLE II

Disease	Ascitic Fluid (gm/100 ml)		Serum (gm/100 ml)		Ascitic fluid/Serum	
	Mean±SD	Renge	Mean±SD	Range	Mean±SD	Range
Hepatic Cirrhosis	1.4 ± 1.3	0.03–8.6	6.5 ± 1.0	4.2–9.0	0.20 ± 0.19	0.004–0.93
Nephrotic Syndrome	1.2 ± 1.2	0.05–4.2	4.9 ± 1.1	3.5–6.7	0.22 ± 0.20	0.010–0.67
Congestive Heart Failure	1.9 ± 1.4	0.24–7.1	6.7 ± 0.8	5.4–9.4	0.28 ± 0.19	0.033–0.82
Tuberculous Peritonitis	3.2 ± 2.3	0.04–8.6	6.8 ± 1.0	4.5–8.3	0.46 ± 0.33	0.007–1.14
Peritoneal Carcinomatosis	2.2 ± 1.7	0.11–9.2	6.2 ± 0.3	4.3–8.3	0.35 ± 0.28	0.010–1.73

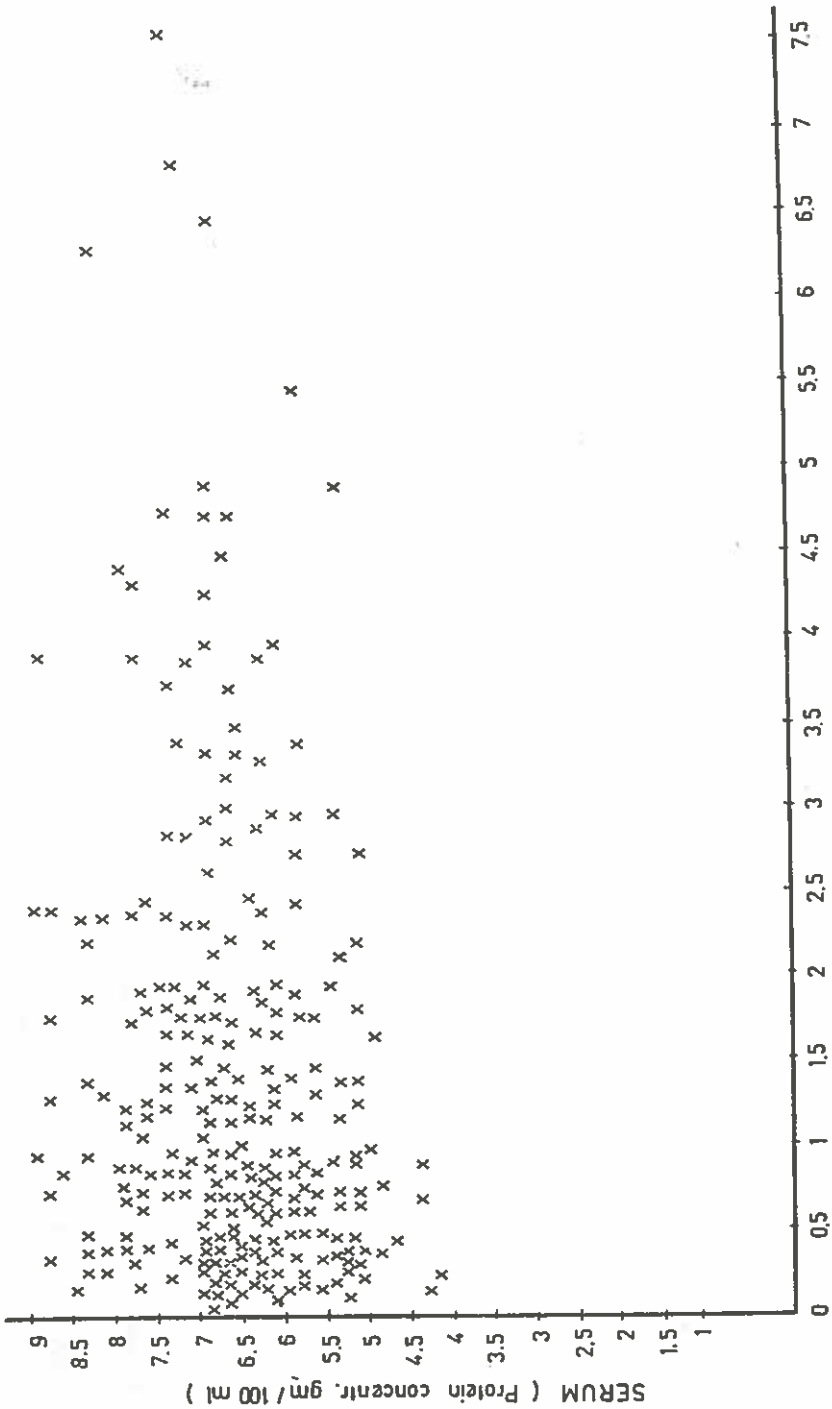

Figure 1
Hepatic Cirrhosis (258 patients).

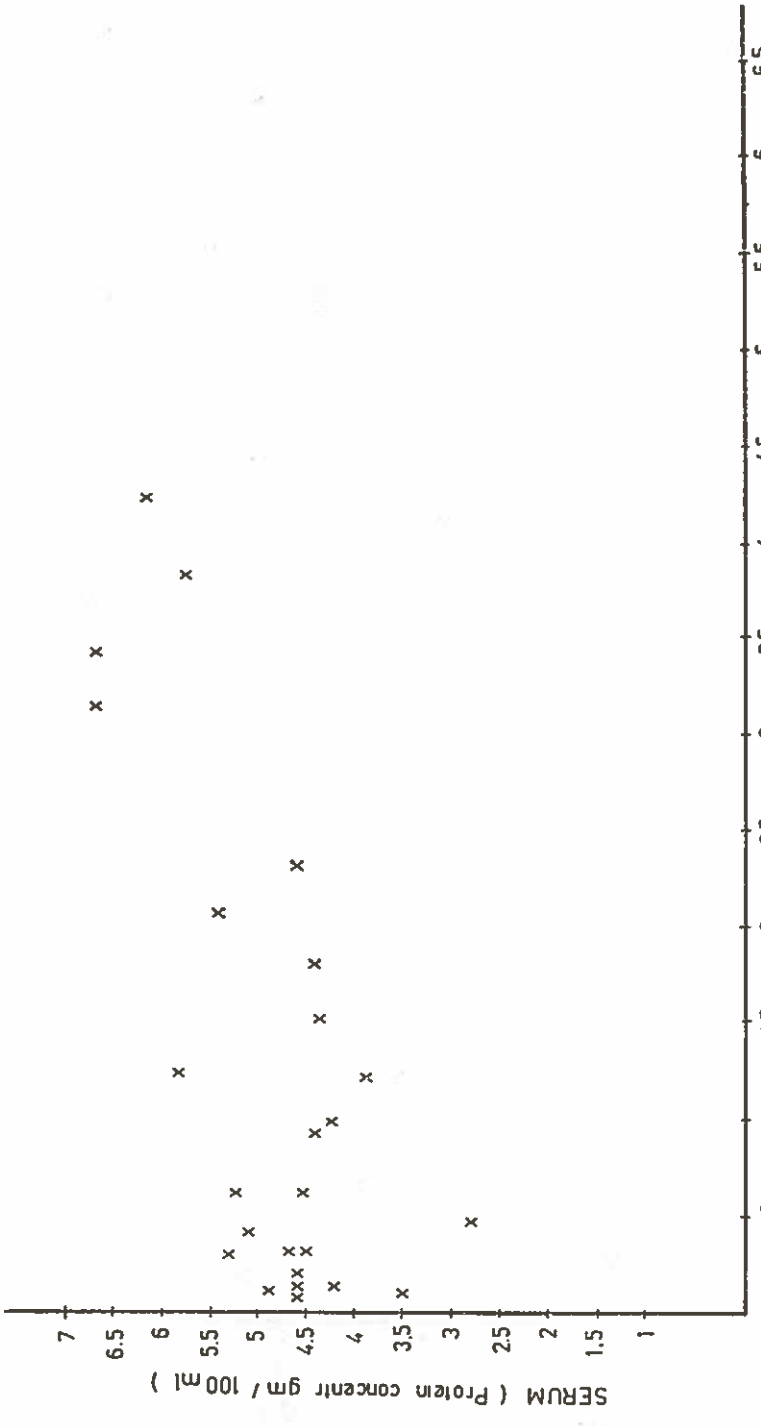

Figure 2
Nephrotic Syndrome (25 patients).

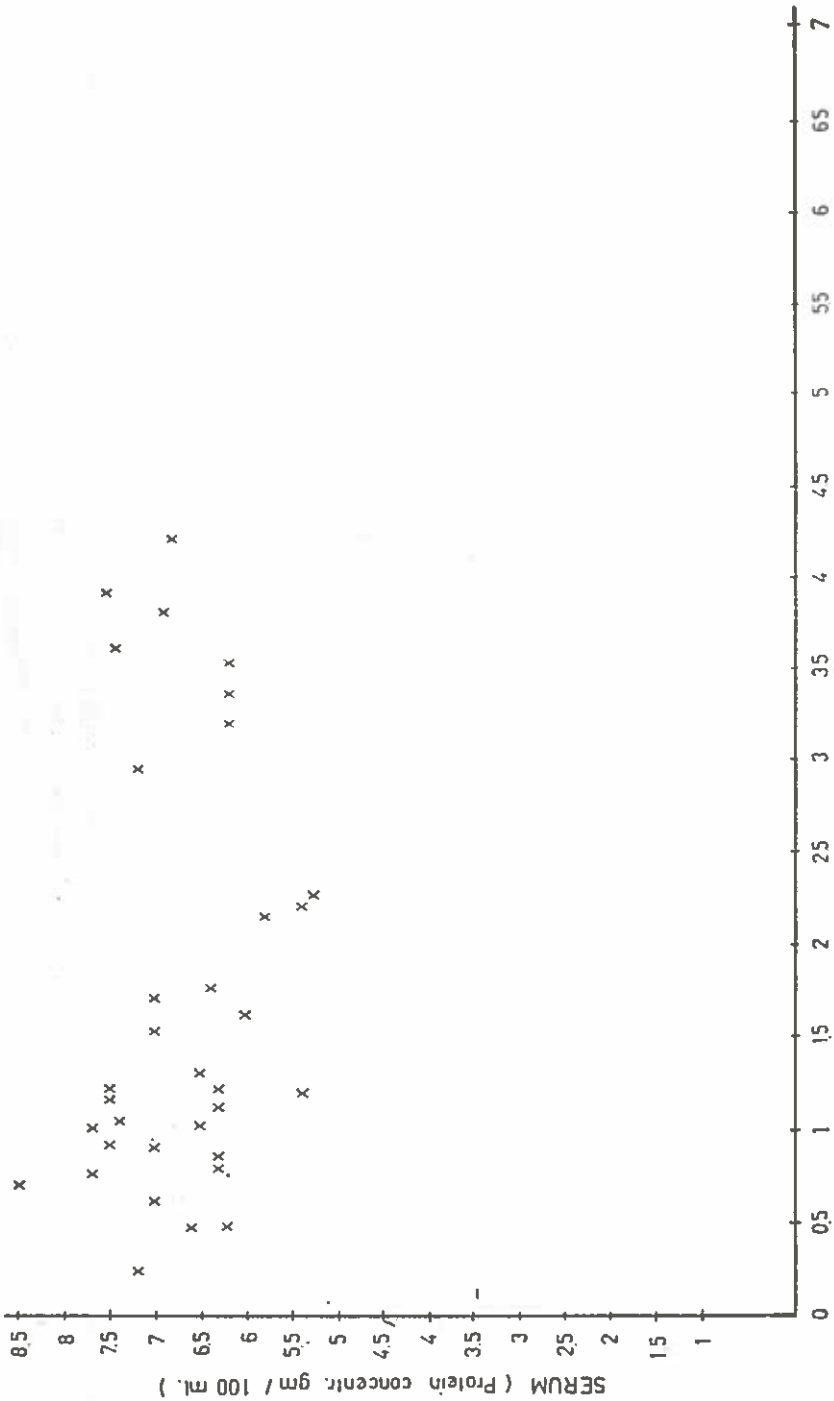

Figure 3
Congestive Heart Failure (35 patients).

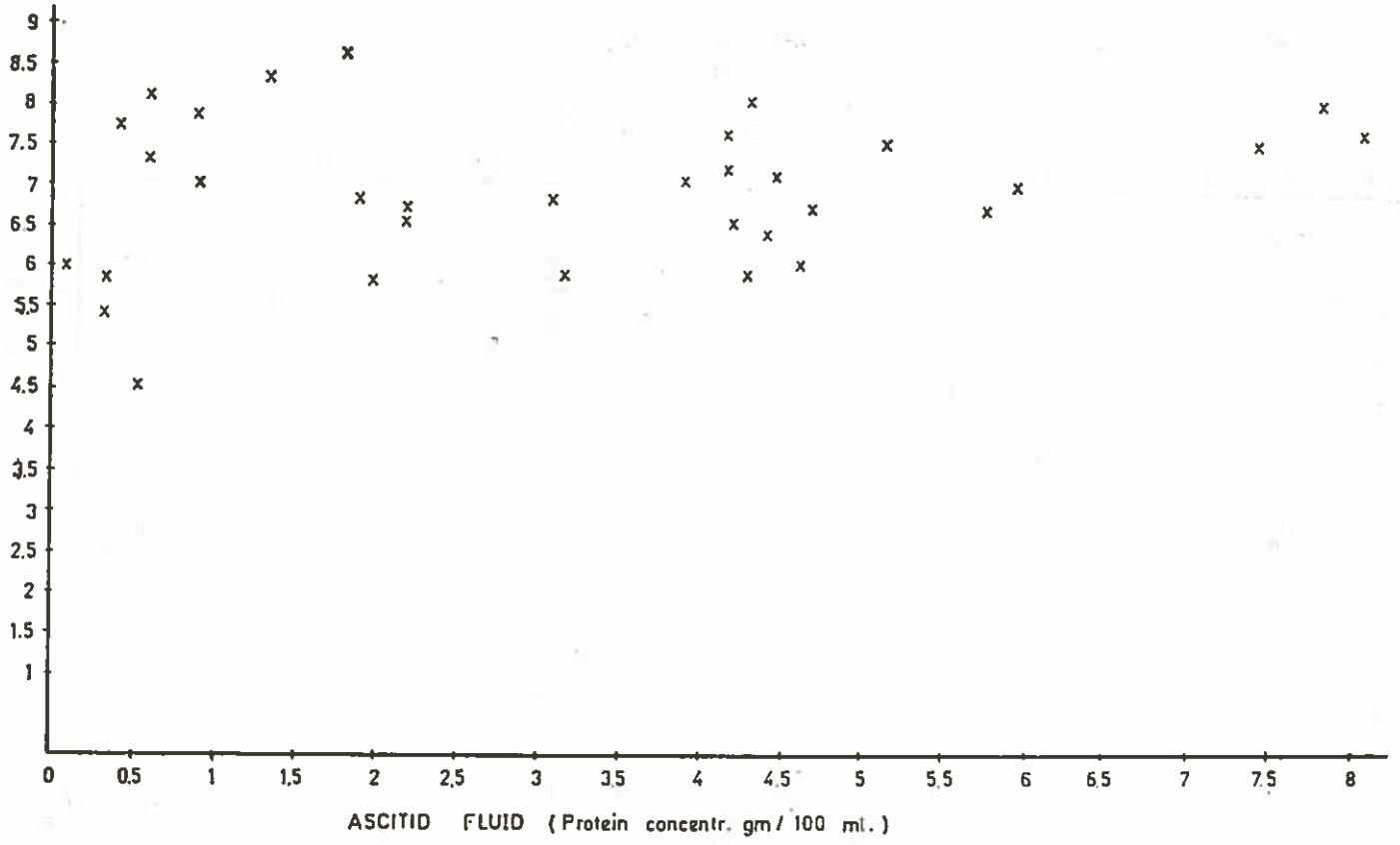

Figure 4
Tuberculous Peritonitis (33 patients).

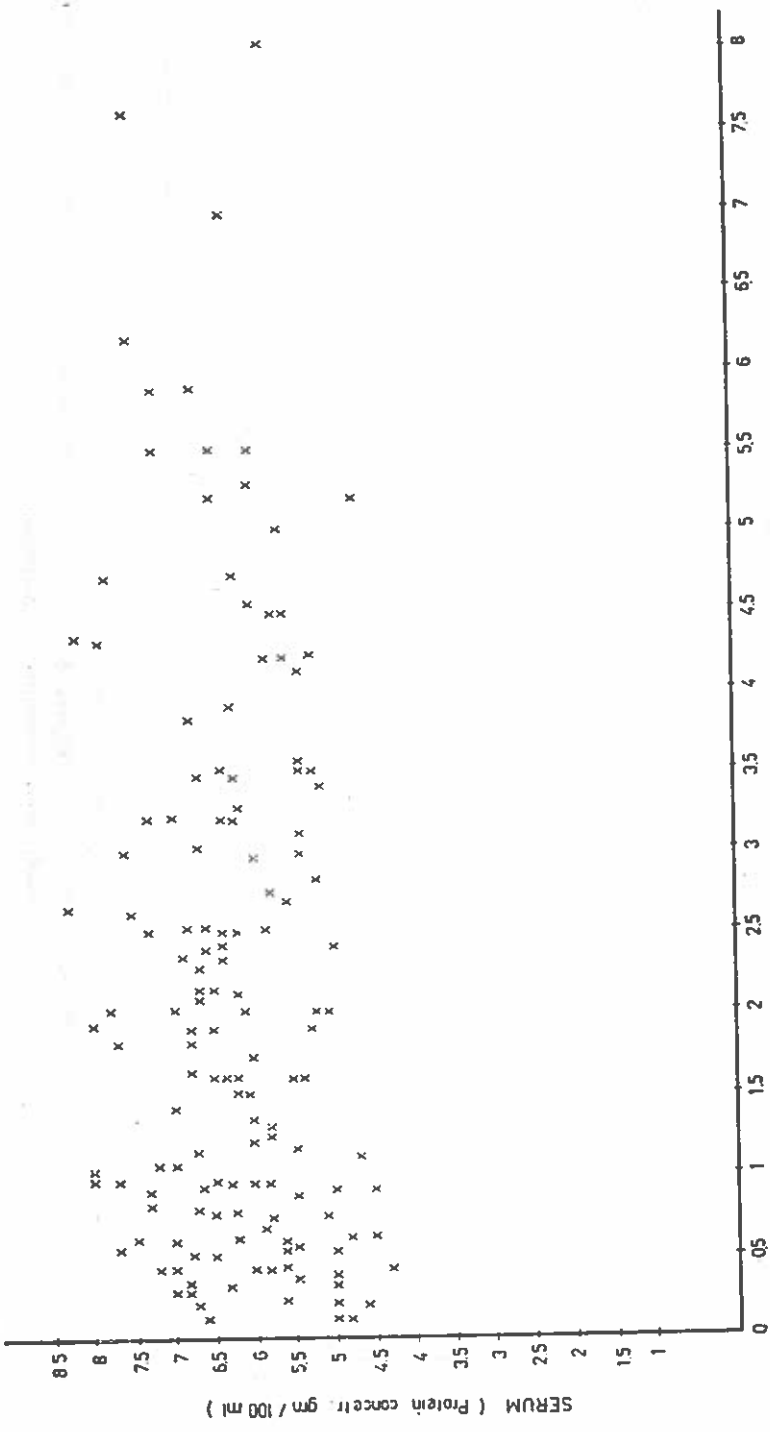

Figure 5
Peritoneal Carcinomatosis (145 patients).

Such a correlation (r: 0.06 $p < 0.05$) was also present in patients with nephrotic syndrome (Figure 2).

But, there was not a significant correlation between the ascitic fluid and the serum total protein concentration in patients with congestive heart failure (r: 0.11 $p > 0.05$), tuberculous peritonitis (r: 0.05 $p > 0.05$) and peritoneal carcinomatosis (r: 0.13 $p > 0.05$) as shown in (Figures 3,4 and 5).

Discussion

In hepatic cirrhosis, congestive heart failure andnephrotic syndrome, ascitic fluids are expected to be transudative. However high-protein values have been reported in some patients. In the present study 11 percent of the patients with hepatic cirrhosis had exudate and there was a significant correlation between the ascitic fluid and the serum protein. Similar studies were reported by Pillay[1], Sampliner[2], Wilson[3], Boyer[4] and Pare[5], and the incidence of exudate was found to be 26 %, 12 %, 24 %, 17 % and 17 %, respectively. Conn[6] also reported high-protein ascites in hepatic cirrhosis.

The unexpected values of the ascitic fluid protein cannot be explained easily. There was no evidence of a complicating disease such as spontaneous peritonitis which may cause highprotein levels. It has been pointed out that diuresis may result in a rise of protein concentration of the ascitic fluid.[7, 8, 9] However, Wilson[2] found no significant difference between the diuretic-treated and nontreated patients with hepatic cirrhosis. In a few reports, high-protein ascites in patients with hepatic cirrhosis was explained by the low portal pressure.[5, 10, 11] However, the mechanisms of the elevated ascitic fluid protein remain unexplained.

In the present study twenty-three percent of the patients with congestive heart failure had exudate but there was no significant correlation between the ascitic fluid and the serum protein. In Pillay's study[1] 31 percent of the patients had exudate. Similar results were reported by Witte.[12]

There have been a few reports about low-protein values in ascitic fluids of patients with peritoneal carcinomatosis and peritonitis.[4, 5, 13, 14] It was reported in three independent studies that 40 %, 74 % and 27 % of the patients with peritoneal carcinomatosis[4, 5, 14] and 70 % of the patients with peritonitis[14] had low-protein ascites. It was stated that low-protein values in peritoneal carcinomatosis and peritonitis might by explained by portal pressure.[5, 14]

In conclusion it can be said that the ascitic fluid protein values may be found different from those expected. No definite reason was established for this and further investigations may elucidate the pathophysiology.

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Congenital Heart Disease in Patients who are Over 40 Years of Age

Operative Results and Long-term Postoperative Follow-up

Seydi V. Aksüt, M.D.* / Nasıh Nazlı, M.D. / Ferhan Özmen, M.D.** / Erdem Oram, M.D.*****

Summary

To determine indications and optimum opportunities for cardiac surgery in patients over 40 years of age who have congenital heart diseases, we reviewed the histories and medical courses of 51 patients who had come to the Adult Cardiology section of the Hacettepe University Hospital between the years 1974-1984, and who underwent cardiac catheterization, angiography and surgery for diagnosis. Thirty-seven cases were confirmed by surgery.

In this study the cases have been classified according to the final diagnoses and their various characteristics have been discussed.

Atrial septal defect constituted the largest group (68.6 %) and no correlation was found between the patient's age and systolic pulmonary artery pressure. Twenty-six patients (73.6 %) over 37 who were followed-up for 1 to 8 years (average 2.9 years) proved to be in good condition. Surgical mortality was 2.7 percent in early postoperative period.

Congestive heart failure was found in 41.1 percent of the cases and arrhythmia was observed in 15.7 percent. However, their clinical conditions were good in postoperative follow-ups. The ratio of the pulmonary flow to systemic flow averaged 3.

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

According to these results, surgical operation should be performed particularly in cases with ASD, regardless of age, pulmonary arterial pressure and clinical conditions (including functional class IV).

Key Words: Congenital heart disease (CHD), Atrial septal defect (ASD), Patent ductus arteriosus (PDA), Ventricular septal defect (VSD), Tetralogy of Fallot (TOF).

Introduction

It is sometimes difficult to determine indications and optimum oppurtunities for cardiac surgery in patients with congenital heart disease. In this study, our aim is to contribute to the above issue in the case of elderly patients. It is generally believed that with middle-aged patients who have uncomplicated congenital heart diseases, surgical operation is the standart treatment.[1] However, reports concerning older patients are sparse, and conclusions are contradictory.[2,3]

In this paper, we review and discuss various characteristics of 51 cases with CHD who were over 40 years-old and were diagnosed by cardiac catheterization, angiography and surgery between 1974 and 1984.

Materials and Methods

From January 1974 to December 1984, 51 patients with CHD who were over 40 years of age underwent cardiac catheterization and angiography, for diagnosis. They formed a study group of 37 cases. The diagnoses were confirmed by surgery. The age of patients varied between 40 and 61 years; 33 were female and 18 male.

Results

Age and Congenital Heart Disease: 2814 cardiac catheterizations and angiographies (except coronary angiography) were performed in the last ten years at Hacettepe University Hospital, Department of Adult Cardiology, fifty-one patients had congenital heart disease (1.8 %) and were over 40 years old; 32 of these belonged to the 40-49 age group and 18 were in their fifties. The oldest patient was a 61 year-old female who suffered from atrial septal defect.

The largest group was ASD with 35 cases (68.6 %). The other groups were PDA, 5 cases (9.8 %); VSD, 3 cases (5.8 %); TOF, 2 cases (3.9 %); pulmonary stenosis (PS), 2 cases (3.9 %); aortic coarctation (AO-CO), 2 cases (3.9 %), subclavian artery - vena cava superior fistula and aneurysm of main pulmonary artery; one cases each (4.1 %) (Table I).

TABLE I

AGE DISTRIBUTION OF CHD PATIENTS OVER 40 YEAR OLD

CHD	Age (Years) 40-49	50-59	60+	Total
ASD	22	12	1	35 (68.6 %)
PDA	4	1	–	5 (9.8 %)
VSD	–	3	–	3 (5.8 %)
TOF	2	–	–	2 (3.9 %)
PS	2	–	–	2 (3.9 %)
Ao . Co.	1	1	–	2 (3.9 %)
A.Subcl.-VCS A-V Fis.	1	–	–	1 (2.05 %)
Anev. PA.	–	1	–	1 (2.05 %)
Total	32	18	1	51

Congenital Heart Disease (CHD), Atrial Septal Defect (ASD), Patent Ductus Arteriosus (PDA), Ventricular Septal Defect (VSD), Tetralogy of Fallot (TOF), Pulmoner Stenosis (PS), Aorta Coarctation (Ao.Co.), Arteria subclavia-vena cava superior A-V fistul (A.Subl.-VCS A-V Fis.), Anourysm of main pulmonary artery (Anev. PA).

Clinical Symptoms and Findings: (Table II) Subjective symptoms, such as palpitation and shortness of breath were found in 38 cases (74.5 %); 34.3 percent of ASD and all PDA patients showed no symptoms. Congestive heart failure was found most commonly in ASD (45,7 %) and secondly in PDA (40 %). Cyanosis was confirmed in one ASD, one VSD and naturally in all TOF cases.

TABLE II

CLINICAL SYMPTOMS AND FINDINGS OF CHD PATIENTS

CHD	No.	Symptom	Cyanosis	CHF*	Arrhythmia
ASD	35	23	1	16	6
PDA	5	3	–	2	–
VSD	3	3	1	1	–
TOF	2	2	2	1	–
Others	6	5	–	1	2
Total	51	38	4	21	8

*Congestive heart failure (CHF)

Eight patients had various arrhythmias (15.7 %), atrial fibrilation, atrial and ventricular premature beats.

Hemodynamic Data (Pulmonary Artery Systolic Pressure): Systolic pulmonary arterial pressure of 42 patients with left-to-right shunt ranged from 10 to 155 mm Hg and the average was 40.8 mm Hg. There was no difference between the age groups 40-50 and 50-60 (Figures 1 and 2).

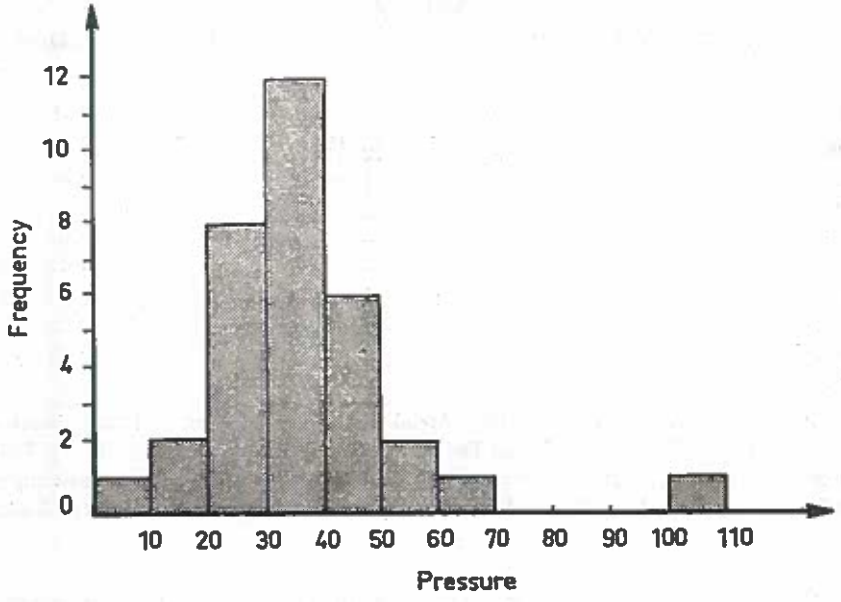

Figure 1
Frequency of patients in each pulmonary artery pressure group.

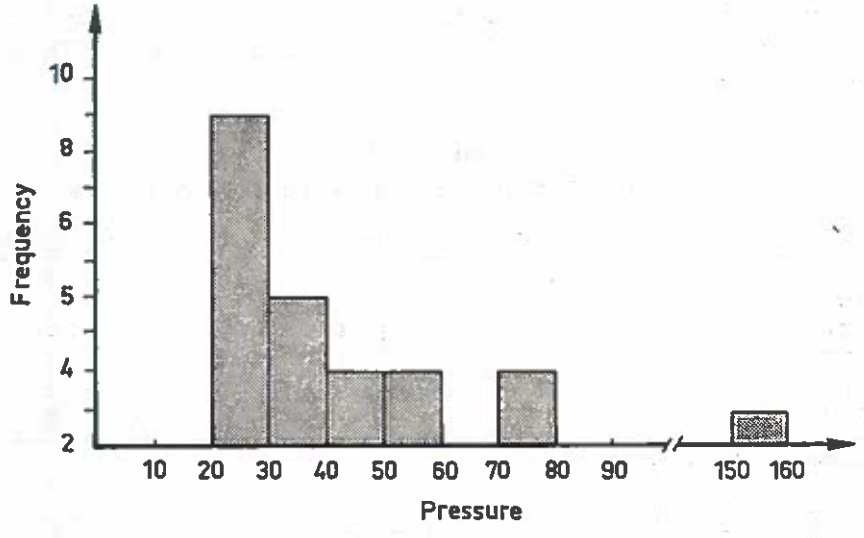

Figure 2
Frequency of patients in each pulmonary artery pressure group.

The ratio of pulmonary blood flow to systemic blood flow (Q_p/Q_s) ranged from 1.1 to 6 and the average was 3. The relationship between Q_p/Q_s and systolic pulmonary arterial pressure is shown in Figure 3.

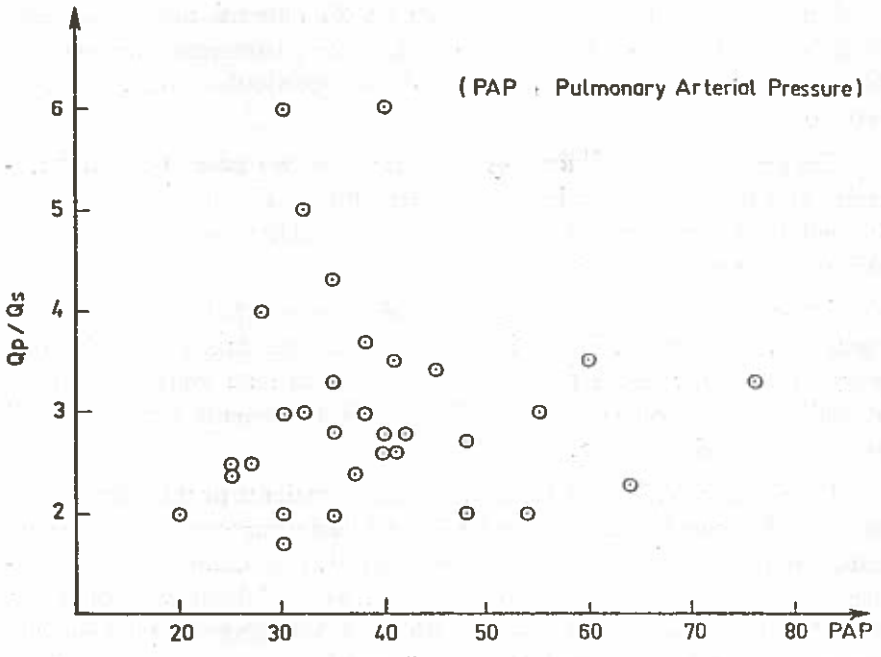

Figure 3

Relationship between the ratio of pulmonary blood flow (Qp) to systemic blood flow (Qs) and pulmonary arterial pressure (PAP).

Age and Clinical Hemodynamic Characteristics of Groups: Atrial Septal Defect (ASD): There were 35 patients in this group, 25 of whom were female (71.4 %) and 10 male (29.6 %).

There were 26 patients in age group 40-50, 18 females (51.4 %), 8 males (22.9 %). In age group 50-60 there were 6 females (17 %) and 2 males; and one female patient was over 60 years old. 6 patients had partial anomalous pulmonary venous drainage (17 %), ten patients (28.5 %) had mitral valve prolapsus and 2 patients had tricuspid regurgitation and their tricuspid valves were replaced. Twenty-three cases (65.7 %) were symptomatic, 16 patients (45.7 %) had congestive heart failure, 6 patients (17 %) had arrhythma, three atrial fibrilation, two atrial premature beats and one ventricular premature beat. EKG analyses revealed that seven patients (20 %) had right ventricular hypertrophy and one patient was cyanotic. The average pulmonary arterial systolic pressure was 37.8 mm Hg. The ratio of the pulmonary flow to systemic flow was an average of 3.

Secundum type defects were found in 33 patients. Primum and sinus venosus types of defects were found in two patients. These were confirmed by surgery.

Surgical operation was performed on 26 patients out of 35 cases (74.3 %). In early postoperative period, three paroxysmal supraventricular tachycardia, one atrial flutter and one ventricular premature beat were found.

Congestive heart failure was confirmed in two patients, postoperatively, and was controlled by medical treatment. The patients were discharged from the hospital in good condition. There was no mortality during the operation or in the hospital.

Patient Ductus Arteriousus (PDA): There were 5 patients (3 females, 2 males) in this group. Four of the were in the age group of 40-50, one patient was in the age group of 50-60. Three patients were symptomatic and two had congestive heart failure. Four patients were operated on with no complications.

Ventricular Septal Defect (VSD): All three patients in this group were male and belonged to age group 50-60. All had symptoms, one had cyanosis, one had congestive heart failure. Systolic pulmonary arterial pressures were 55,76,155 mm Hg. respectively. Two of them were operated on and were discharged in good condition. Eisenmenger's syndrome developed in one patient, and he was followed.

Tetralogy of Fallot (TOF): There were two patients, one female and one male, belonging to the age group 50-60. Both had cyanosis and subjective symptoms. Congestive heart failure developed in one patient. Corrective surgery was performed on one patient who died in early postoperative period. The other patient was followed.

Prognosis: Thirty seven patients out of 51 were operated on. One patient with TOF died in the early postoperative period. Surgical mortality was found to be 2.7 percent.

It was possible to follow 27 of the 36 patients for a period of 1-8 years (average 2.9 years). They were in good cilinical condition and functionally belonged to classes I-II. In 14 of the cases, surgery was planned but not performed for various reasons. No records were found about their follow-up (Figure 4).

Discussion

Controversy over medical versus surgical treatment of elderly patients with CHD has remained unresolved. There are many reasons for this. The number of cases is small; operations have been performed by various surgeons; data concerning medical treatment are inadequate and there is no data in detail on the long-term follow-up studies of a large number of patients that have undergone operation.

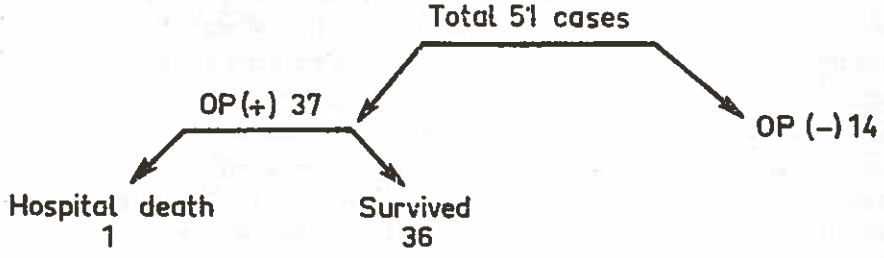

Figure 4
Follow-up results of CHD over 40 years of age.

Formerly, pulmonary hypertension, large left-to-right shunts, high right atrial pressure, atrial fibrilation, congestive heart failure and other cardiac or pulmonary diseases were regarded as contraindications to surgical intervention. This was because of high mortality and morbidity. It was believed that there was little likelihood of symptomatic benefit or prolongation of life.[3,4]

Consequently, these strict criteria discouraged surgical repair of congenital heart disease in many symptomatic elderly patients. Due to these restricted criteria, data collection on this issue declined. As is known, the relative incidence of various CHD in children and adults is different. Figure 5 compares the relative incidence of CHD in children studied by Keith et al[5] and in the adult patients by us.

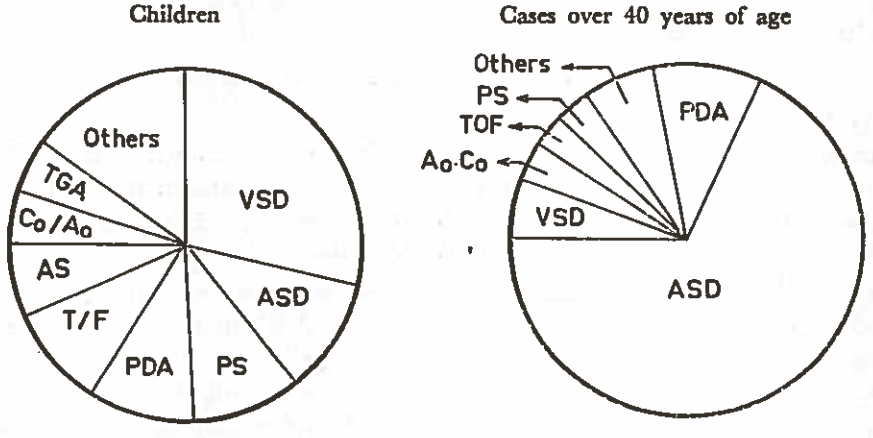

Figure 5
Incidence of various CHD.

VSD is most common in children,[5,6] while ASD is most frequently found (68.6 %) in patients over 40. This result confirms the findings of Kusumoto et al.[7] In adults, particularly in patients over 40 years of age, the incidence of ASD increases but that of VSD markedly decreases. Many factors have been put forward to explain this inversion. Generally, ASD patients may be asymptomatic and diagnosed only after they have reached the third and fourth decades. Moreover; VSD patients without treatment frequently die of heart failure and/or are operated on during infancy and childhood.

Also, natural closure of defects occurs more frequently in VSD than in ASD.[8] Infective endocarditis and aortic regurgitation occur more frequently in VSD and such complications effect prognosis.

It is known that the incidence of arrhythmia increases with age and this incidence in ASD is higher than that in the general population. Arrhythmia was found in 17.3 % of our cases.In adults with ASD, arrhythmia complications are more common after cardiac surgery.[6,9] Arrhythmia was confirmed in 19.2 % of our patients postoperatively and was controlled by medical treatment.

One of the most important factors which affect prognosis in left-to-right shunt cases is pulmonary vascular changes In our study we found no correlation between the age groups 40-50 and 50-60. These results are consistent with those of Kusumoto et al.[7] These authors found that the prognosis of patients who underwent surgery is better than those which have been followed with medical treatment.

Cooley et al found that of age, the presence of pulmonary hypertension with moderate increase of pulmonary vascular resistance, a large left-to-right shunt, congestive heart failure and/or atrial fibrilation do not affect the results of surgical treatment and stated that surgical operation could be performed with low mortality and morbidity.[10] However, despite adequate medical treatment, most patients over the age of 60 with ASD had disabling and often progressive symptoms. Therefore they claimed that surgical closure of ASD in patients over the age of 60 was safe and had low morbidity even in patients with moderate pulmonary vascular resistance and large left-to-right shunt or congestive heart failure. The same results were found by Sutton et al.[11] They stated that elderly patients with ASD should be operated on.

Breyer et al, found that operative risk is high but still acceptable for severely ill functional class IV patients and woult prolong their lives.[12]

We were unable to get any records concerning patients who did not undergo surgery; but 26 patients who had surgery and came for a check-up after 1-8 years were found to be in good condition.

Surgical mortality was 2.7 percent. Corrective surgery was performed in one case because of Tetralogy of Fallot; and the patient died in the early postoperative period. It is certain that the risk in corrective surgery is very high in older patients.

Although at least half of the patients of the ASD, VSD, PDA groups who underwent surgery had factors which increased surgical risk; we had no mortality in these groups. For this reason, surgery should be performed on patients over 40 or even 60 even if they have moderate pulmonary hypertension, atrial fibrilation, congestive heart failure and large left-to-right shunt.

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primary peritonitis and hepatic lesions, intestinal obstructions are the most common form of complication.[2-8] The intestinal obstructions are mainly caused by the bolus of the ascarids obstructing the lumen. Besides, inflammation, spasm, volvulus or invagination can be the obstructive mechanisms.[3]

According to the clinical picture, ascariasis complicated intestinal obstructions are classified as acute and subacute.[3] The subacute form is treated conservatively.[2, 3, 9] Patients who have fever, dehydration, signs of acute abdomen and many air fluid levels on the plain radiographs display the acute form, and they are treated surgically.[3, 9]

Surgical intervention for the acute group of patients must be carried out promptly, because volvulus leading to intestinal infarction is one of the probable obstructive mechanisms. Intestinal infarction results in severe peritonitis and high morbidity and mortality.

Materials and Methods

During a two-year period, from the January 1st 1982 to January 1st 1984, 6 patients with ascariasis complicated intestinal obstructions were treated in the Dr. Sami Ulus Children's Hospital. The hospital records of the patients were evaluated and analysed retrospectively.

Clinical Data: Four of the cases were male and 2 were female. The youngest patient was 2.5 and the oldest was 6 years old. They were admitted to the hospital from 12 to 144 hours after the onset of the obstructive symptoms. All of the patients had abdominal pain and bilious vomiting. The patients with delayed admittance also had abdominal distensions and failure to pass stool. Only one patient had a previous ascariasis diagnosis, but after the onset of the obstructive symptoms, three had passed ascarids. The passages were oral in one, anal in one and both oral and anal in the third patient.

All of the patients had varying degrees of dehydration and electrolyte imbalances. Abdominal examinations revealed signs of acute abdomen. The masses which were located in the right lower quadrants were palpated in two patients. The other physical finding was the palpation of ascarids with rectal examination in one patient.

The plain radiographs of abdomen revealed air fluid levels. In 3 patients, the radiographs revealed not only evidence of obstruction but also presence of wisp-like radioluscent lines (Figures 1,2). The diagnostic clues had been the passage of ascarids, ascarids with rectal examination, and the evidence of ascarids on plain radiographs.

Figure 1
Plain radiograph of our 3rd patient in erect position.

The patients had undergone laparatomy with right upper quadrant transverse incisions. Volvulus of an intestinal loop full of ascarids was the common finding. The obstruction levels were terminal ileum in 5 and mid-ileum in the remaining patient. Volvuluses varied from a half turn to three complete turns. After derotating, the intestines were found to be infarcted in four and viable in two patients. The infarcted intestines were resected and anastomosed in three but ileostomysed in one patient because of severe peritonitis. In one of the patients with viable intestines, milking the ascarids bolus into the caecum was successful. The milking procedure failed in one, and extraction of the ascarids after ileotomy was performed.

One of the patients expired because of sepsis while others including the ileostomysed patient made an uneventful recovery (Table I).

TABLE I
THE CLINICAL FINDINGS AND COURSES OF OUR CASES

Case	Age	Sex	Duration of Symptoms	Complaints	Previous Ascariasis Diagnosis	Ascarids After the Onset	Abdominal Examination	Radiography	Operative Finding	Operative Procedure	Outcome
I Y.K.	3	M	48 hours	Abd. pain vomiting failure to pass stoll distention	No	No	Distention tenderness rigidity, rebound	Wisp-like radiolusc. obst. patt.	Midintest. 720° volv. Infarction	Resection anastomosis	Excitus
II A.B.	3	M	12 h.	Abd. pain vomiting	Yes	No	Tenderness Rigidity rebound	Obst.pattern	Term. ileal 270° volv.	Milking	Recovery
III D.Ö.	2.5	M	72 h.	Convulsion Fever Abd. pain vomiting distention	No	No	Stupor distention tenderness rigidity mass	Wisp-like radiolusc. obst.patt.	Term.ileal 1080° volv. Infarction	Ileostomy	Recovery
IV G.Ö.	6	F	24 h.	Abd. pain vomiting	No	One anal ascarid	Tenderness Rigidity Rebound Mass Rectal asc.	Obst.patt.	Term. ileal 180° volv.	İleotomy extraction	Recovery
V D.Y.	4	M	144 h.	Abd. pain vomiting failure to pass stool distention	No	Two oral ascarids	Distention Tenderness Rigidity Rebound	Obst. patt.	Term. ileal 720° volv. Infarction	Resect. anastomosis	Recovery
VI E.S.	2.5	F	48 h.	Abd. pain vomiting Failure to pass stool	No	One oral one anal ascarids	Distention Tenderness Rigidity Rebound	Wisp-like radiolusc. Obst. patt.	Term, ileal 1080° volv. Infarction	Resection anastomosis	Recovery

Figure 2
Plain radiograph of our 6th patient in supine position.

Discussion

Ascariasis infects people of countries where standards of public health and personal hygiene are low. It is common in South Africa, far East, and Latin America.[3, 10] It is also known to be prevalent in Turkey. Increased movement and migration of the people make the disease a worldwide condition. The infestation is often asymptomatic or may cause only mild symptoms, but life threatening complications such as intestinal obstructions are well known. These are the main reasons why the disease must be considered in the differential diagnosis of intestinal obstructions.

In the endemic areas ascariasis was reported to be responsible for 12.8 % of all acute abdomens and 27 % of the childhood intestinal obstructions. On the other hand, our patients had accounted for 3 % of our acute abdomens and 5 % of intestinal obstructions.[3]

After diagnosis, the important point was to differentiate whether the case may respond to a conservative treatment or requires surgical intervention. Surgical therapy is applied to patients with the acute form of the disease.[3, 9]

Following fluid and electrolyte resuscitations and administration of the proper chemotherapeutic agents, surgical interventions were performed on our patients. Volvulus of an intestinal loop which was full of ascarids was a constant finding. The weight of ascarids mass and the hyperperistaltis were the major causes of the volvulus.

Following derotating the volvulus, the next step was to assess the viability of the intestine. We have found the intestines to be viable in 2 cases and infarcted in 4 cases. If the intestines are viable the preferred method is milking the ascarids bolus into the caecum where they are harmless.[2, 3, 8, 10] If the milking is not possible enterotomy and extraction of ascarids or resection and anastomosis may be preferred.[3 11] The infarcted intestines are also resected and anastomosed. In cases with severe peritonitis due to perforation, ileostomy may be a life saving procedure.

If the ascariasis complicated intestinal obstruction is in the acute form, surgical intervention must not be delayed.

Volvulus as an obstructive mechanism is reported to be responsible in 18 % to 84 % of the cases and infarction had already supervened in 60 % to 80 % of them.[2, 3] In our series volvulus was responsible in 100 % and infarction supervened in 66 %. Volvulus leading to the intestinal infarction rises the mortality rate from 3 % to 50 %.[3, 11] In our series we have a mortality rate of 17 %.

The complications of ascariasis are best treated with preventive measures. Sanitation and high index of suspicion for ascariasis may lower the frequency of this life threatening complication.

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Idiopathic Edema

Şali Çağlar, M.D.* / Volkan Korten, M.D. / Çetin Turgan, M.D.*** / Ilgar Taşdemir, M.D.****

Summary

Idiopathic edema is the term applied to a group of disorders which do not fit the many known types of edema. There are some recent reports which suggest that the majority of cases are caused by the use of diuretics. The history, clinical course and follow-up of the patient are presented in support of this view.

Key Words: Idiopathic edema.

Introduction

Before making a diagnosis of idiopathic edema, it is necessary to show that the disorder is not due to nephrotic syndrome, renal insufficiency, congestive heart failure, hepatic cirrhosis with ascites, venous or lymphatic obstruction or other known causes of edema.[1,2,3] Typically, idiopathic edema occurs in females between 20 and 45 years of age. The disorder has never been reported before puberty and it occasionally may first be observed after menopause.

There is diurnal periodicity, for which a postural component is considered to be responsible. The edema is worst at the end of activity (day or night). In some women there is premenstrual aggravation of the edema. The edema is worst in the feet, ankles, legs, abdomen and breasts. It is often noticed in the eyelids, the face and the fingers at the beginning of the day.[3]

The cause of this condition remains obscure. One hypothesis suggests that it results from reduced blood volume caused by a capillary leak of albumin. It is associated with elevated plasma renin activity and aldosterone levels. There is also a tendency toward sodium and water retention especially when the patient is standing. Some of these patients are not able to excrete a water load, particularly on standing up.[4,5]

* Professor in Medicine Hacettepe University Medical School Ankara, Turkey.
** Instructor in Medicine Hacettepe University Medical School.
*** Associate Professor in Medicine Hacettepe University Medical School.

Mac Gregor et al., suggest that the majority of cases are due initially to diuretics or a sudden increase in sodium and carbohydrate intake following periods of marked selfimposed starvation.[8,9]

Case Report

An obese 50-year-old woman was admitted to the Hacettepe University Hospital with edema of unknown cause from which she suffered for three years. Six years earlier, the patient had weighed 87 kg. In 1979, she began to experience a precordial pain after exerting an effort, radiating to the left arm. The pain lasted 3-5 minutes and was relieved by rest. She consulted a local doctor and was given isosorbide dinitrate 10 mg tid. She used this drug for 4 months, after which the doctor stopped the treatment. After that time she did not experience angina pectoris. She was given Brinerdin (0.5 mg dihydroergocristine + 5 mg clopamide + 0.1 mg reserpine) one tablet per day and furosemide 40 mg per day for hypertension. She attempted to lose weight and reduced her weight to 63 kg in 6 months. She felt weak and allowed her weight to increase to 68 kg. During the period of weight reduction, she noticed pitting edema in her legs. She reported that her urine output had decreased and the doctor told her to take 80 mg of furosemide per day. Because of the persistent edema, she gradually increased the dose of furosemide on her own initiative to 800 mg per day. During the three years preceding her admission to our hospital she was taking 800-1440 mg of furosemide daily. She described abdominal distention when she was edematous. She complained of constant thirst, polydipsia, polyuria, nocturia (2 times), dizziness on standing and tiredness. She described leg cramps and carpopedal spasms. She said she consumed 10 kg of grapefruit and a great number of lemons in a week. She also described tinnutus in both ears which persisted for one year. Her menopause had started two years ago. She did not notice premenstrual edema aggravation. She smoked 40 cigarettes per day for 15 years. She had undergone an appendectemy 35 years ago.

On examination, the patient was cooperative. Her height was 1.65 m, and she weighed 68 kg. Her blood pressure was 120/70 mm Hg and her pulse was 88. Mild pitting edema of both legs was present. The liver was 6 cm palpable below the right costal margin with a vertical span of 12 cm. No other abnormal physical signs were present. She had no proteinuria and no red or white cells in her urine. A chest X-ray was normal. Laboratory tests included hemoglobin 14.3 g/dl, plasma sodium 136 mEq/L, potassium 2.7 mEq/L, chloride 98 mEq/L, BUN 14 mg/dl, creatinine 1.1 mg/dl, plasma total protein 6.0 g/dl, albumin 3.8 g/dl

and bilirubin 0.6 mg/dl, total lipid 950 mg/dl, cholesterol 280 mg/dl, alkaline phosphatase 6 KA μ/dl. The plasma volume was 1.70 liter, calculated total blood volume was 3,365 liter. The intravenous pyelogram was normal. The electrocardiogram and echocardiographic examination were normal. The HB_s Ag and HB_s Ab were negative. A liver-spleen radionuclide scan revealed no abnormality. Audiologic tests revealed a mild cochlear pathology.

The plasma thyroxine level was 10.5 μg/dl and the thyroid stimulating hormone was measured as 1.4 μu/liter.

In the hospital course, her diet corresponded to her preadmission intake, containing 200 m mol sodium per day and she was given 800 mg of furosemide per day for eleven days. Before the diuretic was discontinued, plasma renin activities were 65.0 ng/ml/h in a supine position at 8 a.m. (Normal 1.67 $\pm$ 0.83) and 85.0 ng/ml/h in an upright position at noon (Normal 3,3 $\pm$ 1.85); plasma aldosterone activities were 330 pg/ml in a supine position (Normal 65 $\pm$ 30) and 570 pg/ml in an upright position (Normal 170 $\pm$ 58) at the same hours.

When she stopped taking the diuretic, she gained 8.2 kg in 6 days, her weight went up to 76.2 kg. The weight gain was accompanied by a marked increase in leg and facial edema, and discomfort in the abdomen. Her blood pressure did not rise. At her heaviest weight, the plasma volume was 3.12 liters, the plasma renin activity fell to 0.7 ng/ml/h in a supine position at 8 a.m. and to 0.2 ng/ml/h in an upright position at noon and the aldosterone activity 90 pg/ml in a supine position at 8 a.m. and 185 pg/ml upright at noon.

Sixteen days following cessation of diuretics, her weight was 70.3 kg. The ankle and facial edema had disappeared. Although she lost some weight during this time, her weight remained at more than 68 kg. Because her weight had not returned to the baseline, sodium intake was reduced to 80 m mol/day. This reduction in dietary sodium resulted in a gradual loss of weight to 68 kg over the next month. On repeated follow-up visits as an outpatient, she reported no ankle edema, dizziness or tiredness. She was advised to follow a 1600 calorie diet, containing 80 mmol sodium per day.

Discussion

Patients with idiopathic edema show all the characteristics of chronic volume depletion, but the view that the low blood volume is due to a leak of albumin from the capillaries has not been confirmed. In the isotopically labeled albumin studies that have been undertaken to support

this view, it is not clear whether the prolonged retention of albumin in the extravascular compartment was a consequence of the edema or its cause.[6,7]

Mac Gregor et al suggest that whatever the initial reason for starting diuretics may be, the continued use of diuretics causes a persistent rise in plasma renin activity and secondary aldosteronism. The juxtaglomerular apparatus and the adrenal glands of patients become enlarged.[7] Irregularity in the dose of diuretics may cause a sharp fall in urinary sodium excretion, a weight gain and the rapid onset of the edema. A vicious cycle ensues. The patient quickly returns to the use of diuretics because of edema.

On the other hand, sudden increases in sodium and carbohydrate intake after periods of sodium deprivation combined with fasting can each cause sodium and water retention.[7,10] De Wardener et al., also suggested that some patients with idiopathic edema might have an impaired ability to secrete natriuretic hormone. This might be either a primary condition, due to prolonged use of diuretics or perhaps the tubules do not respond appropriately to a rise in natriuretic hormone concentration.[7,11] They demonstrated that following an initial period of weight gain, stopping diuretics or placing the patient on a low salt diet led to a permanent remission in these patients. After stopping diuretics, weight and edema increased transiently, but within the next 2-3 weeks, the weight returned to baseline and the edema cleared. Nine of their 12 patients responded in this way. In the other 3 patients, 3 weeks later, the weight was still higher than baseline values. Reduction of the sodium intake to about 50 mEq/day in these 3 patients caused the edema to disappear in 2 patients. When they allowed the sodium intake to increase gradually, these 2 patients were able to tolerate a normal sodium intake. The third patient was not able to control her sodium and calorie intake and had intermittent edema.

The 3 patients in whom edema persisted had taken the largest quantities of diuretics. The authors postulated the unresponsiveness of the kidneys to the raised levels of natriuretic hormone was related to the previous administration of diuretics.[7]

Our case is very similar to those 3 patients of Mac Gregor et al. She had begun taking diuretics for reasons that are not clear and admitted that in attempting to control her weight there were large fluctuations in her carbohydrate and salt intake. Three weeks after stopping the diuretics, she still weighed 2 kilograms higher than the baseline value. After reduction of salt intake it took two weeks for her weight to return

to the baseline vaule. She had also taken the largest quantity of furosemide reported in the literature. This case also showed that diuretics-induced edema is not infrequently an iatrogenic condition.

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Polyorchism

A Case Report

Atıf Akdaş, M.D.* / Reşit Tokuç, M.D. / Bedri Uzunalimoğlu, M.D.*** / Şevket Ruacan, M.D.******

Summary

Histologically-confirmed polyorchism was demonstrated in a 33 year-old man. The patient's chief complaint was infertility. The extra testis was found in the left hemiscrotum. No other urogenital anomaly was diagnosed. The significance and associations of this rare congenital anomaly are discussed.

Key Words: Polyorchism, Supernumerary testis.

Introduction

Polyorchism is one of the very rare anomalies of the urogenital tract. Fifty seven histologically proven cases have been reported.[1] Embryology of the supernumerary testes has been well explained by Wescott in 1967.[2] There have been two reports of unilateral duplication with absence of the contralateral testicle.[3] Spermatogenetic activity was found to be decreased in some polyorchids.[4] Brief reviews were made by Mehan in 1976, and Pelander in 1978.[3,5] We, herein report a new case of a histologically proven triorchism.

Case Report

KK., a 33 year-old man, was admitted to the hospital with the complaint of infertility. He had been married for 5 years. During the first 2 years his wife had used vaginal ovuls for contraception. Three years ago, he had used mesterolon for 3 months. After that, his wife became pregnant twice, but both times had a spontaneous abortion. Pertinent history revealed nothing about genitourinary tuberculosis,

* Associate Professor, The Department of Urology, Faculty of Medicine Hacettepe University, Ankara, Turkey.
** Fellow, The Department of Urology.
*** Professor, The Department of Pathology.
**** Associate Professor, The Department of Pathology.

gonorrhea, scrotal trauma, or mumps. The patient had no other urogenital complaints, and was not aware of any mass in the scrotum.

On physical examination, both testes were found to be normal in size and consistency; and a small mass, about 1 cm. in diameter was palpated in the left hemi-scrotum that felt like the continuation of the normal testis. Transillumination of this particular mass was positive. The right epididymis was normal but the left one was difficult to palpate. Further, grade I varicocele was noticed on the left side. Both spermatic cords and vasa deferentia were normal on palpation.

Laboratory examinations were within the normal range including serum FSH, LH, Testosterone levels, and excretory urography. Three consecutive semen analyses revealed 20, 29, and 12 million sperms per cc. with normal motility and morphology.

After a high inguinal left spermatic vein ligation, the left hemi-scrotum was explored. The mass was found to be an accessory testicle. Both the normal and the accessory testes had their own blood supplies. There was a single epididymis arising from the primary testis, with its corpus bridging the two testes, and the cauda was fixed to the accessory one. Also a single vas deferens arose from the caput epididymis, and its proximal portion was obliterated. Five cm. distal part of it was found to be normal, and a side-to-side epididymo-vasostomy was performed (Figure 1).

Figure 1
Intraoperative photographs showing left hemiscrotal contents and supernumerary testis.

Biopsy of the primary testis revealed normal testicular tissue. In contrast patchy tubular hyalinization and spermatogenetic arrest at spermatid level was observed in the accessory one. (Figure 2).

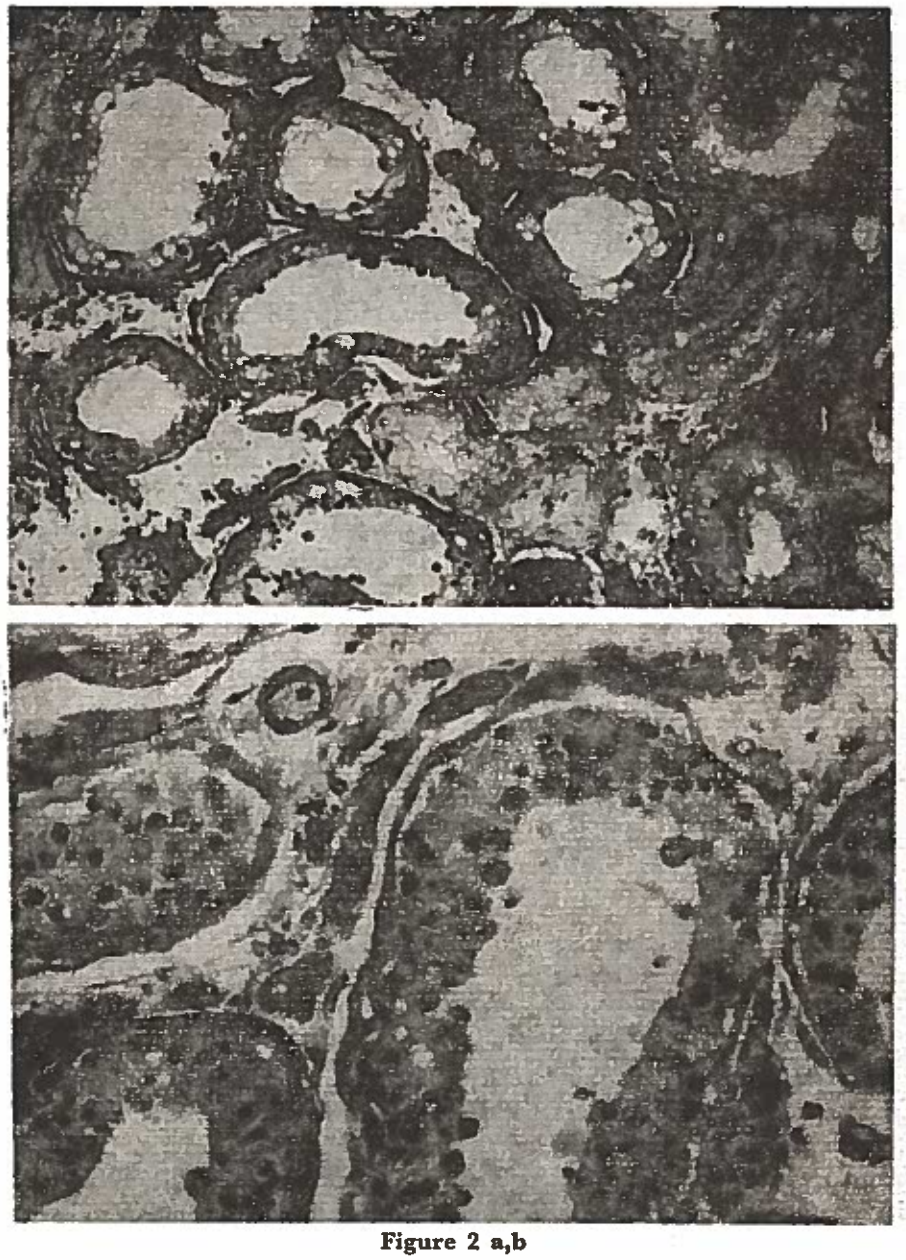

Figure 2 a,b
Histopathological specimens showing patchy tubular hyalinization and spermatogenic arrest.

Discussion

The earliest demonstration of polyorchism was an autopsy finding in 1670, but the first case report was made in 1895.[1,5] Since then, a total of 57 cases have been reported.[1]

In most of these cases spermatogenesis was absent, and in some cases there were complaints of infertility.[4,5] In a case reported by Smart in 1972, a pregnancy wihch had resulted in spontaneous abortion was involved.[6] There is a similar history with our patient. Five cases of complete duplication have been reported.[1] There have been 2 reports of unilateral duplication with absence of the contralateral testicle.[6]

The anatomical variations and embryological etiologies of polyorchidism have been widely discussed by some authors.[2,8] The two most-commonly associated anomalies are maldescent and inguinal hernia. Other associated findings are torsion, hydrocele, epididymitis, varicocele, and cancer.[5,7] Three cases of accessory testicular cancer have been reported namely, 2 teratomas and one anaplastic seminoma.[9,10,11]

Frequent association of other congenital anomalies, and the higher risk of torsion and malignancy makes surgical exploration necessary for an accessory testis.

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