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ORIGINAL ARTICLE

# Malignancy and sarcoidosis: A single center experience from Turkey

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ABSTRACT

Objective: The relationship between cancer and sarcoidosis has been a research topic for a long time. An increased risk of sarcoidosis and sarcoid-like reactions is suggested in patients with malignant disease. The present study aimed to describe the clinical characteristics and the prognosis of 15 Turkish patients who had a diagnosis of both malignancy and sarcoidosis.

Methods: The patients admitted to our department between October 2013 and October 2018 were included in this study. Patient data including, the demographic data, clinical, radiological, pathological findings, and applied treatment modalities were retrieved from hospital database.

Results: The study included 14 females and 1 male with a mean age of 53.3±11.4 years. Malignancy was the preceding diagnosis in 13 patients. The mean interval time between two diagnoses was 4±3.6 years. Fourteen patients recovered from their cancer, only 1 patient with relapsed NHL was deceased. The most common type of malignancy was breast (n=7) and endometrium (n=3) carcinoma. Surgery was the primary therapeutic modality in 14 patients. Additionally patients received certain drugs which might contribute to onset of sarcoidosis such as Cyclophosphamide (n=8), Adriamycin (n=8), Trastuzumab (n=2), and Rituximab (n=1). Ten patients were asymptomatic for sarcoidosis and 7 patients had stage I pulmonary sarcoidosis. Two third of the patients (n=10) did not receive any therapy for sarcoidosis.

Conclusion: This study involves a few number of patients and according to the analysis of this group the presence of malignancy and sarcoidosis in the same patient might promote good prognosis for both entities. However the onset of sarcoidosis during the follow-up period is a challenging clinical condition and a biopsy is needed for differential diagnosis and management decision. Yet the biopsy might not be enough to differentiate between sarcoidosis and the sarcoid reactions related to malignancy. Future studies are needed to enlighten the underlying pathogenesis.

Keywords: cancer, diagnosis, drugs, malignancy, sarcoidosis.

## INTRODUCTION

Sarcoidosis is a chronic granulomatous disease which can affect any organ, mainly the lungs and intrathoracic lymph nodes [1]. Despite research for many decades, the etiology of disease is not clarified yet and both genetic and environmental factors have been accused to be responsible [2]. The unknown antigen/s start a Th1 response and cause release of various cytokines. The immune system which cannot get rid of the causative agent leads to formation and maintenance of granulomas which can either resolve, persist or progress to fibrosis leading to organ dysfunction [3].

Chronic inflammation has been linked to various steps involved in tumorigenesis. The possible relationship between malignancy and sarcoidosis was first hypothesized by Brincker in 1972, who showed an association of sarcoid reaction with lymphoma in 19 patients and later on proposed the sarcoidosis-lymphoma syndrome [4]. There have been several studies from different countries with contradictory findings which tried to explain a possible relationship between malignancy and sarcoidosis [5-12]. A meta-analysis of 16 observational cohort and case-control studies including more than 25,000 sarcoidosis patients suggested a moderate association between malignancy and sarcoidosis [5]. A study from Denmark denied such a relationship and proposed that the main reason for other studies which have shown such an association is most likely due to a misclassification and selection bias [6]. Another study from USA investigating the risk of malignancy in patients with sarcoidosis in a population based cohort demonstrated that the risk was similar among patients with sarcoidosis compared to non-sarcoidosis subjects. However there was an increased risk of hematological malignancies especially among sarcoidosis patients with the extra-thoracic involvement [7].

Another important issue which can explain the association of malignancy and sarcoidosis can be the systemic granulomatous reactions which are indistinguishable from sarcoidosis that occur after use of certain drugs including cancer specific treatments like immune checkpoint inhibitors (anti-PDL-1, CTLA-4), targeted therapies (MEK and BRAF inhibitors), anti-CD20 monoclonal antibody (rituximab) and cytotoxic agents like cyclophosphamide, bleomycin, adriamycin, etc. [8].

Apart from the enigmatic association of malignancy and sarcoidosis, the onset of sarcoidosis during the follow-up period of a patient with malignancy is a challenging clinical condition. The awareness of this situation and the differential diagnosis is of great importance for further management decisions. The present study aimed to describe the clinical characteristics of 15 Turkish patients who had a diagnosis of both malignancy and sarcoidosis.

## MATERIAL AND METHODS

### Patients

This is a retrospective study which was performed in the Department of Chest Diseases in Hacettepe University Hospital in Ankara/ Turkey. The study included 15 patients who were admitted between October 2013 and October 2018; and followed with the diagnosis of both malignancy and sarcoidosis. The study is approved by the Clinical Research Ethics Committee of Hacettepe University (06.07.2018; GO 18/621).

A study form including the demographic data (age, gender, smoking status); medical history (history of malignant disease, medications); physical examination findings; angiotensin converting enzyme (ACE) levels; spirometry results; and radiological findings (computed tomography (CT) of thorax and/or positron emission tomography/ computed tomography (PET/CT) scan) was filled for each patient. The data were retrieved from hospital database.

The diagnosis of sarcoidosis was confirmed according to the ATS/ERS/WASOG statement (1). Only patients who belong to "highly probable" and "probable" categories were included. All the patients had a biopsy demonstrating non-caseating granulomas. Mediastinal lymph nodes (conventional transbronchial needle aspiration: 8, endobronchial ultrasonography guided transbronchial needle aspiration: 3) were sampled in 11 (73.3%) patients and extra-thoracic lymph nodes were sampled in 4 (26.7%) patients.

### Statistical Analysis

Statistical analysis was conducted using the SPSS 23.0 package for Windows. Categorical variables

were shown as frequencies and percentages. Numerical variables with a normal distribution were given as mean ± standard deviation; with abnormal distribution as median and minimum-maximum.

## RESULTS

The characteristics of study patients are summarized in Table 1. The study included 15 patients (14 female/ 1 male) with a mean age of 53.3±11.4 years. While malignancy was the preceding diagnosis in 13 patients, sarcoidosis was the preceding diagnosis in only 1 patient. Malignancy and sarcoidosis were diagnosed concurrently in 1 patient with endometrium carcinoma. The patient with the preceding diagnosis of sarcoidosis had both mediastinal lymphadenopathies and breast involvement (Figure 1). A biopsy of breast revealed granulomatous mastitis and one year later she was diagnosed with breast carcinoma.

Other than a patient who were actively treated with the diagnosis of relapsed Non-Hodgkin lymphoma (NHL), 14 patients were all recovered from their malignant disease and were in regular follow-up in medical oncology department. They were referred

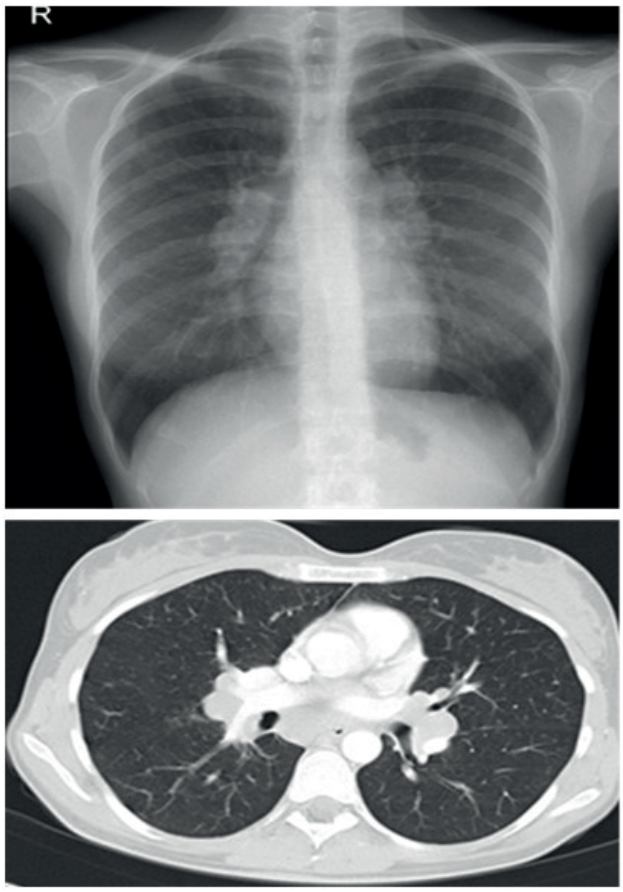


**Figure 1.** The x-ray and computed tomography of thorax in a patient presenting with bilateral hilar lymphadenopathy (stage 1 sarcoidosis) and also breast involvement

**Table 1.** The characteristics of study patients

| | | |
|---|---|---|
| Age | 53.3 ± 11.4 years (Range:35-75) | |
| Gender | 14 Female/ 1 Male | |
| Smoking history | Ex-smoker, N=7 (46.7%) | |
| | Non-smoker, N=8 (53.3%) | |
| Preceding diagnosis malignancy | N=13 (86.7%) | |
| Preceding diagnosis sarcoidosis | N=1 (6.7%) | |
| Concurrent diagnosis of malignancy and sarcoidosis | N=1 (6.7%) | |
| Time interval between the diagnosis of malignancy and sarcoidosis | 4±3.6 years (Median: 3 years, Range: 1-12) | |
| History of familial sarcoidosis | None | |
| Mortality rate | N=1 (6.7%) | |
| Spirometry at diagnosis | FEV1% | FEV1% |
| | FVC% | FVC% |
| | FEV1/FVC | FEV1/FVC |
| Malignancy types | Breast | N=7 (46.7%) |
| | Endometrium | N=3 (20%) |
| | Rectum | N=1 (6.7%) |
| | Prostate | N=1 (6.7%) |
| | Renal cell carcinoma | N=1 (6.7%) |
| | Non-Hodgkin lymphoma | N=1 (6.7%) |
| | Adenoid cystic carcinoma | N=1 (6.7%) |
| Malignant disease outcome | Cured | N=14 (93.3%) |
| | Relapse | N=1 (6.7%) |

to chest diseases department for further evaluation of new pulmonary lesions and/or mediastinal lymphadenopathies. The mean interval time between two diagnoses was 4±3.6 years (Median: 3 years, Range: 1-12 years). Only the patient with relapsed NHL died and mortality rate was 6.7% in the study population. The most common type of malignancy was breast cancer (n=7, 46.7%) and endometrium (n=3, 20%) carcinoma was the second common type. Ten patients had a PET/CT evaluation and pathological FDG uptakes ranging between 5.3 and 33 were reported in pulmonary parenchymal lesions and/or mediastinal lymphadenopathies. These high uptakes were all reported to be a possible recurrence of the previous malignant disease.

The therapeutic approaches for the malignant diseases are depicted in Table 2. Fourteen patients had undergone surgery, 7 received radiotherapy, and 9 received chemotherapy. Cyclophosphamide (n=8), adriamycin (n=8) and taxanes (paclitaxel, docetaxel) (n=5) were the most commonly used cytotoxic drugs. There were 2 patients who used trastuzumab, a monoclonal antibody used for HER2+ breast carcinoma. There was 1 patient who used rituximab, a monoclonal antibody targeting CD20 on the surface of lymphoma cells.

The clinical aspects of sarcoidosis are summarized in Table 3. Pulmonary sarcoidosis was the most common presentation, 10 patients were asymptomatic for sarcoidosis, 7 patients have stage I pulmonary sarcoidosis. Main thoracic CT findings were mediastinal lymphadenopathies and parenchymal nodules. Extra-thoracic lymphadenopathy (n=6) were the most commonly involved extrapulmonary site of sarcoidosis. Two third of the patients (n=10) did not receive any therapy for sarcoidosis. While 4 out of 10 patients who did not receive any therapy had spontaneous remission, 6 patients had a stable disease.

**Table 2.** The therapeutic approaches for the malignant diseases

| Therapeutic approach | | | |
|---|---|---|---|
| Surgery | N=14 | | |
| Radiotherapy | N=7 | | |
| Chemotherapy | N=9 | | |
| Chemotherapeutic agents | | | |
| Cyclophosphamide | | Hormone therapy | |
| Adriamycin | N=8 | Tamoxifen | N=1 |
| Paclitaxel | N=8 | Anastrozole | N=2 |
| Docetaxel | N=4 | | |
| Vincristine | N=1 | | |
| 5-Fluorouracil | N=1 | | |
| Trastuzumab | N=1 | | |
| Rituximab | N=2 | | |

## DISCUSSION

This study describes the clinical features of 15 Turkish patients diagnosed with both malignancy and sarcoidosis. The majority of patients were female (n=14) and the most common type of malignancies were breast and endometrium carcinoma. Malignancy was the preceding diagnosis in most of the patients (n=13) and the mean interval between the two diagnoses was 4±3.6 years. Most of the malignancies were cured (n=14). Majority of the patients (n=10) had asymptomatic sarcoidosis. Nearly half of the patients had stage I pulmonary

**Table 3.** The clinical aspects of sarcoidosis in the study patients

| Clinical aspect | | N (%) |
|---|---|---|
| Involved systems | Pulmonary | 14 (93.3) |
| | Extra-pulmonary | 7 (46.7) |
| Pulmonary sarcoidosis stage | I | 7 (46.7) |
| | II | 6 (40) |
| | III | 1 (6.7) |
| Involved extra pulmonary sites | Extra-thoracic lymphadenopathy | 6 (40) |
| | Liver | 1 (6.7) |
| | Spleen | 1 (6.7) |
| | Breast | 1 (6.7) |
| Thorax CT findings | Lymphadenopathies | 13 (86.7) |
| | Nodules | 6 (40) |
| | Micro nodules | 2 (13.3) |
| | Bronchiectasis | 1 (6.7) |
| Symptoms | Asymptomatic | 10 (66.7) |
| | Symptomatic | 5 (33.3) |
| Laboratory | Elevated ACE | 4 (26.7) |
| Treatment | No treatment | 10 (66.7) |
| | Steroid | 4 (26.7) |
| | Steroid + methotrexate | 1 (6.7) |
| Treatment response | Remission | 2 (13.3) |
| | Stable disease | 1 (6.7) |
| | Relapse | 2 (13.3) |
| Follow-up of untreated patients | Spontaneous remission | 4 (26.7) |
| | Stable disease | 6 (40) |

sarcoidosis. The main thoracic CT findings were mediastinal lymphadenopathies and parenchymal nodules. The prognosis of sarcoidosis was good and two third of the patients (n=10) did not receive any therapy.

The relationship between malignancy and sarcoidosis has been described in various publications [5-13]. However it is still unclarified whether this relationship is by chance, by an underlying mechanism such as chronic inflammation and dysregulated immune surveillance, or by a genetic predisposition that can explain the concurrent presence of two diagnoses in the same patient. Sarcoidosis and sarcoid like reactions have been encountered in different types of malignancies and both the distribution and frequency vary among different countries. Lymphoma, breast, testicular, gastrointestinal and lung carcinoma are the most common types of malignancies that are related with higher frequency of sarcoidosis [14-18]. In most of the studies, the diagnosis of sarcoidosis was usually made after a long period (more than 5 years) of malignancy diagnosis [9]. However, in a recent study 66% of sarcoidosis cases were diagnosed within the first year of malignancy diagnosis [19]. In the present study, breast (46.7%) and endometrium carcinoma (20%) were the most common malignancies and the mean time interval between two diagnoses was 4±3.6 years ranging between 1 to 12 years. The main reason that might influence the type of malignancy can be the gender differences among different studies as seen in the present study with female predominance and breast carcinoma relatedly. The incidence of sarcoidosis in females has a biphasic pattern with the first peak at 25-39 years and the other in 50-60s. The mean age of the patients in our study was 53.3 years which is similar to the literature and compatible with the second peak observed in females in general population supporting the coincidence of sarcoidosis and malignancy.

In cancer patients granulomas can be detected mainly in 2 clinical scenarios. The first one is the sarcoid reactions most commonly occurred in the lymph nodes draining the tumor and other organs such as spleen, skin and bone marrow. The second is the typical sarcoidosis presentation. While the first scenario is usually asymptomatic, the second can be symptomatic. The mechanism of tumor associated sarcoid reactions in regional nodes has not been elucidated, although some authors have suggested that the relationship between a malignancy and a sarcoid reaction is a reaction of host resistance to the tumor or a reaction to metabolic disintegration substances released from the tumor cells [20]. Interestingly all the cases of the study except one had their cancer in remission thus questioning the possibility of host immunity against a cancer that was not active and supporting the typical sarcoidosis presentation. On the other hand it should not be underestimated the fact that malignancies can relapse even after a long period of time and this study included at most a 12-year long period of follow-up.

Another issue which might explain the relationship are the treatment modalities used for the malignant disease. Several chemotherapeutics (bleomycin, vinblastine, cyclophosphamide, adriamycin), immune checkpoint inhibitors (nivolumab, pembrolizumab), targeted therapies (BRAF and MEK inhibitors), and monoclonal antibodies (rituximab, trastuzumab) can cause sarcoidosis and sarcoid like reactions [8,21-23]. In the present study, similar to the Japanese series, surgery was the primary therapeutic modality in 14 patients [14]. Additionally patients received certain drugs which might contribute to onset of sarcoidosis such as cyclophosphamide (n=8), adriamycin (n=8), trastuzumab (n=2), and rituximab (n=1). None of the patients used immune check point inhibitors.

Sarcoidosis subsequent to diagnosis of malignancy has been related to a favorable prognosis, remission of cancer, and low frequency of relapse thus suggesting an immune response that might help to keep the malignancy under control in these patients [15-16,24]. A retrospective multicenter observational study enrolling 133 patients with a confirmed diagnosis of cancer and subsequently developed granulomas in different organs have shown that there is a significant association between the presence of granulomas and reduced metastasis and increased survival [25]. The present study even though including a few number of patients also supports these findings by demonstrating recovery from malignant disease in 14 patients. In the current literature, there is insufficient data related to the clinical presentation and prognosis of sarcoidosis in patients with a preceding diagnosis of malignancy. In our series,

 

most of the patients (n=10) had asymptomatic sarcoidosis. Nearly half of the patients had stage I pulmonary sarcoidosis. The clinical outcome of sarcoidosis was similar to the general population and two third of the patients (n=10) did not receive any therapy for sarcoidosis. Whether the presence of a previous malignancy serves as a protection and results with a mild clinical presentation for sarcoidosis is a matter that needs to be clarified.

FDG-PET/CT is a widely used imaging modality for staging and follow-up of various tumors [26]. It is useful for the detection of lymph node metastasis, but false-positive results can occur due to sarcoidosis. Therefore sarcoidosis should be considered in differential diagnosis when newly emerging lymphadenopathies or lung lesions appear, and a biopsy should be performed for differential diagnosis and further management decisions. Endobronchial ultrasonography guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive way for demonstrating non-caseating granulomas in mediastinal lymph nodes [25]. Retrospective studies have shown that sarcoidosis/ sarcoid-like reactions are seen more commonly in restaging PET/CT in patients with suspected relapse rather than initial staging. This observation suggest that this phenomenon may be related to an anti-neoplastic immune response that represents a host defense mechanism against the spread of tumor cells. This theory is supported by the finding that sarcoid-like reactions are associated with better prognosis in patients with gastric cancer and Hodgkin's lymphoma [27]. The present study also supports this finding with 14 patients who recovered from their cancer. All PET/CTs were performed for regular follow-up or suspected relapse. Conventional or EBUS-TBNA were the most commonly used biopsy methods for differential diagnosis.

The class II major histocompatibility complex (MHC) molecules encoded by human leukocyte antigens (HLA) play an important role in antigen presentation. It has been shown by many studies from different countries including Turkey that HLA alleles are closely related to the risk of developing sarcoidosis, the type of clinical presentation, extra-pulmonary involvement and the outcome of disease [28-29]. To our knowledge there has been no study that has investigated the relationship of HLA and the risk of cancer in sarcoidosis patients, which could also enlighten the genetic effect that might play a role in pathogenesis. According to the data of some cancer patients (n=13) who were included in our previous study HLA-DQB1*03 was the most common allele in cancer patients (unpublished data). Further studies including the HLA genotyping of the cancer-sarcoidosis entity should be performed in order to enlighten the mystery beyond the relationship of the two diseases and the pathogenesis of sarcoidosis which up-to-date is still unknown.

The major limitations of the study are the retrospective nature of the study, the low number of patients included and the absence of a control group. However the present study is the first case series from Turkey with 15 patients who had a diagnosis of both malignancy and sarcoidosis. Moreover this study represents a comprehensive examination of whole study patients with a long follow up period. Yet it is still not very clear the cut off criteria for the differentiation of the sarcoidosis and the sarcoid-like reactions in patients with malignancy which might be a subject of changes in evaluation of the entities in the future. Bonifazi et al. proposed a diagnostic work-up for cancer patients with an identification of granuloma on biopsy and stated that elevated ACE, granulomas in areas remote from cancer, previous diagnosis of sarcoidosis, atypical involvement for cancer ( ocular, skin, parenchymal lung disease and cardiac) and hypercalcemia with high vitamin D1,25 and low vitamin D25 and PTH are features that favor sarcoidosis rather than a relapse of the malignancy [30].

## CONCLUSION

By analyzing the data of the 15 patients that have been followed up in our center for 5 years we have demonstrated that the presence of cancer and sarcoidosis in the same patient might promote good prognosis for both entities. Although the onset of sarcoidosis during the follow-up period is a challenging clinical condition, the awareness of this coexistence and appropriate differential diagnosis are of great importance for further management

decisions. Usage of certain drugs can be a clue for onset of sarcoid reactions. Future studies are needed to enlighten the exact pathogenesis and probable role of HLA alleles.

## Author contribution

Study conception and design: DE, SE; data collection: DE, SSU, DK; analysis and interpretation of results: DE and DK; draft manuscript preparation: all the authors. All authors reviewed the results and approved the final version of the manuscript.

## Ethical approval

The study was approved by the Clinical Research Ethics Committee of Hacettepe University (Protocol no. 18/621 / 06.07.2018).

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## Conflict of interest

The authors declare that there is no conflict of interest.

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