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Sarcoidosis and lymphoma: case series and literature review

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Abstract. This is a case series and literature review of patients with various types of hematologic disorders and sarcoidosis. The patients were treated in the hematologic day care unit at Shaare Zedek medical center and at the hematology department of Chaim Sheba Medical Center hospital from 1990 until 2008. We report eight cases from two centers where both diseases were diagnosed at different time points. We have shown that there might be coincidence of two rare conditions and emphasize the importance of tissues sampling of lesions suspected to be a relapse of a former biopsy-proven disease, even in the presence of positive PET results.*(Sarcoidosis Vasc Diffuse Lung Dis 2011; 28: 146-152)*

Key words: sarcoidosis, lymphoma, recurrence, biopsy

Patient One

A generally healthy 16 year old male presented with lymphadenopathy found on routine physical examination. Biopsy of an inguinal lymph node revealed Hodgkin's lymphoma with lymphocytic predominance. CT scan showed stage III disease, with lymphadenopathy above and below the diaphragm. Complete remission was achieved with chemotherapy. Five and a half years later, routine follow up exam revealed again inguinal lymphadenopathy. CT scan showed mediastinal lymphadenopathy. Bronchoscopy with transbronchial biopsies showed non-caseating granulomas consistent with sarcoidosis. His clinical course was complicated by severe hypercalcemia with acute renal failure, which resolved with oral steroid treatment.

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Patient Two

A 57 year old female had known mild mediastinal lymphadenopathy for many years. Transbronchial biopsies did not reveal malignancy but showed reactive nodes. Three years later a CT showed enlarging of the known lymph nodes and a consolidation of the right upper lobe. A biopsy showed nodular sclerosis Hodkins lymphoma. The lymphoma was in stage IV with lymphadenopathy above and below the diaphragm and extranodal involvement. She was treated with aggressive chemotherapy and achieved complete remission. Several months later a follow up CT showed lymphadenopathy of the anterior mediastinum and a biopsy showed non-caseating granulomas consistent with sarcoidosis. She was asymptomatic and therefore, received no treatment.

Patient Three

A forty four year old female presented with an 8 month history of fatigue and a productive cough. The chest x-ray showed a left pleural effusion and a

subsequent CT scan showed a consolidation of the left upper lobe with large pleural effusion and retroperitoneal lymphadenopathy. Biopsy showed diffuse large B-cell lymphoma and complete remission was achieved with chemotherapy followed by radiation. A month later, while totally asymptomatic, she had a routine CT scan of the chest which showed new interstitial micronodular infiltrates in both lungs with scattered nodules. A transbronchial biopsy showed non-caseating granulomas and the diagnosis of sarcoidosis was made. She was treated with inhaled steroids with complete radiological and clinical recovery.

Patient Four

A 37 year old patient underwent an extensive work-up for lymphadenopathy and B-symptoms. A diagnostic spleenectomy revealed non caseating epitheloid granulomas consistent with sarcoidosis. She was treated with low dose steroids with a good clinical response. Approximately two years later, three necrotic wounds appeared on her skin. A biopsy revealed anaplastic lymphoma. CT-PET showed uptake of FDG above and below the diaphragm consistent with stage III disease. She was asymptomatic and therefore treated only with local radiation. Two and a half years after her original diagnosis of lymphoma, a transformation to aggressive lymphoma was diagnosed by biopsy of an enlarged lymph node. She received chemotherapy with a good clinical and radiological response.

Patient Five

A 31 year old female was diagnosed with sarcoidosis two years before referral to our center and treated with oral steroids. The diagnosis was made after undergoing a biopsy for suspicious lesions on the chest x-ray and she was treated with oral steroids for two years. At presentation to our center she complained about a weight loss of 10 kg. Gastroscopy showed diffuse infiltration of the stomach and biopsies revealed MALT lymphoma.

PET-CT showed uptake of FDG in the stomach and surrounding lymph nodes. She began treatment with chemotherapy with a good clinical and radiological response. Two years post treatment she was alive and undergoing evaluation for a possible relapse of lymphoma.

Patient six

A forty four year old female was referred to our center to continue treatment for relapsed non Hodgkins lymphoma. A year prior to her referral she underwent lumpectomy and axillary node dissection for intraductal breast carcinoma-stage I. After the surgery she underwent radiotherapy. Six months later a diagnosis of non-Hodgkin's lymphoma was made by biopsy of a cervical lymph node. The disease was in stage IIA with lymph nodes above the diaphragm only. She underwent chemotherapy and relapsed soon after she finished treatment.

She received three cycles of salvage treatment DVIP dexamethasone, etoposide, ifosfamide cisplatin and then autologous bone marrow transplantation (ABMT) with high dose chemotherapy BEAM (BCNU, etoposide, cytosar, melphalan) protocol.

A second relapse two months after ABMT was treated with interferon and IL-2 blood (1). She again, achieved complete remission. Two years after completion of treatment, mediastinal lymphadenopathy was observed again and a biopsy revealed sarcoidosis. She was treated with inhaled and low doses of oral steroids, with complete clinical and radiologic remission.

Patients seven and eight are presented in table 1.

Materials and Methods

Review of patient files between 1990-2008 from Chaim Sheba Medical Center and Share Zedek Medical center hematology departments. All patients in the series were diagnosed with malignant lymphoma and sarcoidosis over this time period.

We received a statement (P46/10) from our local Helsinki committee noting that IRB approval was not necessary due to the fact that no patient had any intervention or treatment performed as part of this retrospective study and the study did not, at any time, revealed patient identity or cause any privacy violation of the patients.

Table 1. Characteristics of 8 patients diagnosed with lymphoma before or after sarcoidosis

Patient #	Age at diagnosis of lymphoma	Gender	Tx of sarcoidosis of sarcoidosis	Outcome	Diagnosis	Clinical presentation	Sarcoidosis	Tx for malignancy	Hematologic disorder
1	16	M	Oral steroids	Alive	PET-CT and LN biopsy	Lymphadenopathy Hypercalcemia	7 years after HD	Esc. BEACOPP+ ABVD	HD
2	57	F	No treatment	Alive	Galium scan and transbronchial biopsy	Mediastinal lymphadenopathy	6 Mts. After HD	Esc. BEACOPP	HD
3	44	F	Inhaled steroids	Alive	CT-Scan and transbronchial biopsy	Pulmonary infiltrates	1 year after Ly	R-CHOP	DLBCLY
4	39	F	Oral steroids	Died of JC virus encephalitis	Spleenectomy	Spleen	2.5 years prior to Ly	R-CHOP	FDG uptake above and below diaphragm Anaplastic Ly-transformed from low grade
5	31	F	Steroids inhaled and oral	Alive	LN biopsy	Pulmonary infiltrates	M2 years prior to Ly	R-CHOP	Malt Ly FDG uptake in the stomach and surrounding LN nodes
6	60	F	Oral steroids	Alive	LN biopsy	No information no more info	Many years prior the Ly radiation	Surgical excision and	Cutaneous t-cell Ly
7	47	F	Steroids inhaled and oral	Alive	LN biopsy	Mediastinal lymphadenopathy	2.5 years after remission	Many courses of chemotherapy including ASCT	DLBCLY
8	60	F	Steroids inhaled and oral	Alive	Lung biopsy	No information	15 years prior to sarcoid	Spleenectomy	Marginal zone Ly

M - male
F - female
Ly - lymphoma
Abvd - combination chemotherapy-adriamycin, vinblastine, DTIC, bleomycin
Esc. BEACOPP - combination of chemotherapy: bleomycin , adriamycin, vincristine, procarbazine, prednisone, cyclophophamide
R – Rituximab
CHOP - combination chemotherapy , adriamycin, vincristine, prednisone, cyclophophamide
Tx - treatment
PET-positron emission tomography
CT - computed tomography
LN - lymph node
DLBCLY-diffuse large b-cell lymphoma
ASCT - autologous stem cell transplant
HD - Hodgkin's disease

Table 2.

Reference	Number of patients	Age sarcoidosis diagnosed*	Sarcoidosis confirmed by biopsy	How was the biopsy taken	Treatment of sarcoidosis	PET scan	Average latency period to second diagnosis	Outcome
Brinker 1986 (8)	17	41	14/17	NA	9/17	no	125 mts	8/17 alive
Karakantza 1996 (20)	5	37	yes	2 mediastinal/2 LN/1 lung	3/5 oral steroids	no	8.5 years	4/5 CR
Kornacker 2002 (14)	2	44/41	yes	transbronchial/ mediastinoscopy	oral steroids	no	during tx to 4 mts after tx for Ly	1 PD/1 CR
Hollister 2005 (21)	1	56	yes	mediastinoscopy	no	yes	During tx for Ly	NA
Suvajdzic 2007 (9)	2	46/58	yes	NA	one patient with oral methotrexate	NA	12 years	CR
Subbiah 2007 (7)	1	32	yes	LN biopsy	oral steroids	yes	5 mts prior to tx	CR
Sonnet 2007 (16)	1	68	yes	LN biopsy	NA	yes	27 mts after Ly	CR
Ozer 2009 (18)	2	49/56	yes	mediastinoscopy	oral steroids (X/56)	yes	mts. prior to diagnosis of sarcoidosis	CR
Papanikolaou 2010 (11)	79	44	yes	NA	NA	no	38 mts.	65/79 alive
Alexandrescu 2011 (10)	2	37/46	yes	NA	NA	no	2.5 years	NA
Our article	8	39	yes	various	6 oral st./ 1 inhaled/1 no tx	2/8	4.3 years	7/8 alive

* Age is expressed in years (mean)
NA - not available
Tx - treatment
Mts - months
LN - lymph node
CR - complete remission
St - Steroids
PD - progressive disease
Ly - limphoma

Results

In this case series we present eight patients with various types of malignant lymphoma and a diagnosis of sarcoidosis. Characteristics of the 8 patients are shown in table 1. Both diagnoses were histologically confirmed in all patients. The median age of the patients was 39 years (range, 16-60) at the time of the lymphoma. All but one of the patients were female. Two patients were diagnosed with Hodgkins lymphoma, two with diffuse large B-cell lymphoma, one with aggressive lymphoma transformed from low grade lymphoma, one with a MALToma one with low grade lymphoma and one with T-cell lymphoma. All achieved complete remission from lymphoma with chemotherapy and steroids. The course of the sarcoidosis was benign in these patients. The latency period between conditions was an average of 4.3 years. Sarcoidosis was treated with oral steroids in 3 cases with inhaled in 1 case, with both in 3 cas-

es and not treated at all in one case. All patients except one were alive at the time of the study.

Discussion

Sarcoidosis is an autoimmune disease most common in women in their third and fourth decade of life (2). The incidence of sarcoidosis varies throughout the world. The highest annual incidence is in northern Europe with 5-40 cases per 100,000 people while the lowest is in Japan (2). Sarcoidosis is characterized by non caseating granulomas infiltrating various organs without evidence of infectious (tuberculosis, ricketsia, borrelia) or other agents (clay, talc, pine tree pollen) known to cause sarcoid-like granulomatous disorders (3). The disease predominantly involves the lungs, lymph nodes and skin which are portals of entry for many immunologically active factors

The cause of the disease is unknown. It is believed that there is a specific etiologic antigen in sarcoidosis which triggers the disease in genetically predisposed individuals (3). There have been reports of occupational clusters with possible toxic or infectious exposures: i.e. firefighters (2), teachers, automobile manufacturers and others (5).

The diagnosis is usually suspected by the clinical presentation and the radiological imaging and confirmed by histologic evidence in one or more organs of non-caseating epitheliod cell granulomas in the absence of other organisms or particles known to cause sarcoid-like granulomas (2). Several reports suggest that 18F-flurorodeoxyglucose positron emission tomography (18 FDG PET) may be useful in the assessment of organ involvement (6). The association between sarcoidosis and lymphoma has been described[7] with, according to some reports, an incidence of lymphoma at least 5.5-11 times higher in patients with sarcoidosis (7).

The sarcoidosis lymphoma syndrome was first described in 1986. In this observational study of 17 patients, the diagnosis of lymphoid malignancy was made in average 10 years after the diagnosis of sarcoidosis (8). In our study ilymphoma was diagnosed 2.5 years (average) after sarcoidosis, in 4 patients and in 3 other patients sarcoidosis was diagnosed an average of 6.5 years before lymphoma. Only in one patient sarcoidosis was diagnosed more then 10 years before lymphoma. Suvajdzic et. al described the occurrence of lymphoid malignancies in two patients with well documented sarcoidosis (9). In recent years larger studies have addressed this connection. 110 cases of sarcoidosis associated with malignancy were reviewed: 10 from center experience and 100 from a review of the literature . The authors found that 73% of patients with non cutaneous sarcoidosis who developed malignancy-developed hematological malignancy (10). They noted that patients with chronic sarcoidosis have a 5.5 higher risk of developing a lymphoproliferative disorder (8). Out of the 10 patients recruited over 20 years in their center, 4 had sole cutaneous sarcoidosis. those four developed solid tumors with an average of two carcinomas each.

In another recent, retrospective study, 79 cases from the literature were analyzed. In 70% of those cases sarcoidosis preceded lymphoma. In these cases the interval between both diseases was on average 96 months . Non Hodgkin's Lymphoma was more common than Hodgkin's lymphoma. Presentation of lymphoma was significantly more common as new or worsening spleenomegaly and lymphadenopathy. In approximately 30% of cases reviewed sarcoidosis developed after the lymphoma. In this cohort the interval between diseases was on average 36 months .

A large study conducted in the Netherlands observed 7476 patients with Hodgkins lymphoma and compared them to 18,573 matched controls and 86,000 first degree relatives of matched controls (12). They concluded that a personal or family history of autoimmune conditions-including sarcoidosis is strongly associated with an increased risk of Hodgkins lymphoma. The opposite was also shown – that personal and family histories of sarcoidosis are significant risk factors in the development of Hodgkins lymphoma. On the other hand, a pooled analysis of data from 12 case controlled studies did not show a higher risk of non-Hodgkins lymphoma in patients with self reported sarcoidosis (13).

The appearance of lymphoma after sarcoidosis may be attributed to the underlying immunological abnormalities that occur in the disease process such as a decrease in CD-8 positive T-Cell suppressor/cytotoxic cells or an activation of CD4 positive T-cell helper/inducer cells (9). There has also been a report of the reduction or possible absence of a subset

of T-regulatory cells, the CD1d-restricted natural killer T-cells (NKT) in the peripheral blood of patients with sarcoidosis. Theses NKT cells mediate anti-tumor effects-15 (9). Other hypothesis includes abnormal cytokine production, cutaneous anergy to particular antigens and hypergammaglobulinemia (9).

Sarcoidosis has also been described after lymphoma and treatment with chemotherapy (7). Kornacker et. al described two patients who developed sarcoidosis during or soon after treatment for non-Hodgkins lymphoma (14). They hypothesized, that in some cases the exposure to chemotherapy itself (bleomycin and others) might precipitate a granulomatous reaction (14). They also suggested that chemotherapy may eliminate immunosuppressive cells which are able to inhibit the immune activation in sarcoidosis (14).

A retrospective review of over 3000 patients treated for hematological malignancies revealed only ten (0.3%) patients with concurrent sarcoidosis five of these patients had lymphoma and the other five myeloid malignancies (15).

Beyond the aforementioned connection between sarcoidosis and lymphoma another important point to be learned from our study is the value of a biopsy when relapse is suspected. In this series patients would probably have been misdiagnosed and not treated adequately if tissue was not examined.

Although less relevant to our series, PET-CT is now thought to be the state of the art method to diagnose and follow patients with lymphoid and other malignancies. However, this method is associated with a number of false positive findings which have major therapeutic implications. The most frequent false positive findings are bone marrow activation by chemotherapy and/or cytokines and thymus hyperplasia (16). PET-CT might also show uptake in many inflammatory disease such as sarcoidosis (16). Although there is some evidence to suggest that FDG uptake SUV max is less in benign disease (mean 5.02) than in malignant (mean 10.8) (17), there is no definitive way to differentiate between benign and malignanat condition other than a tissue diagnosis (17, 18). In 2006 (16) a case series of seven patients with lymphoma reported positive uptake on follow up PET-scan. Biopsies were done on all patients and two had non malignant lesions - one of which was sarcoidosis. A much larger study (19) described 151 patients with lymphoma after first line chemotherapy. Biopsies were performed on all patients with positive PET scans (30 patients). Fifty-seven percent of the biopsies confirmed relapse of the lymphoma. All others (43%) showed a benign diagnosis with three patients having sarcoidosis.

Thus, without pathological analysis it is impossible to distinguish, based on FDG-PET, between malignancy and inflammatory diseases. In conclusion we present a series of 8 patients with two relatively rare illnesses.

Both these conditions might show positive FDG uptake on PET-CT scan and tissue biopsy is therefore necessary to confirm the diagnosis. Even in the presence of an established diagnosis (and a good explanation for the lymphadenopathy) one should always raise the differential diagnosis and consider tissue biopsy in order to confirm or infirm the diagnosis. In addition a connection between sarcoidosis and hematological malignancies has been reported and is confirmed in this study, raising many interesting question regarding a common etiology of these two conditions.

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