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Early View

Research letter

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Clinical differences in sarcoidosis patients with and without lymphoma: a single-center retrospective cohort analysis

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Sarcoidosis is a systemic disease of unknown origin, characterized by the presence of non-caseating granulomas at disease sites[1]. A relevant clinical problem in the management of this disease is the co-existence of other clinical conditions, such as solid tumors or lymphomas, that may occur before or following the diagnosis of sarcoidosis as well as simultaneously[2]. Particularly, the association of sarcoidosis and lymphoma is well established and was named the "sarcoidosis-lymphoma syndrome" by Brincker and colleagues in 1986[3]. In this syndrome, lymphoma occurs mainly in patients with a chronic active form of sarcoidosis, suggesting that chronic disease could be a risk factor for lymphoma. However, the distinctive clinical features of patients with sarcoidosis and lymphoma, and the precise mechanism underlying this association remain unclear.

We retrospectively reviewed the database of the "Center for Rare Lung Diseases" at the University Hospital of Modena to identify all subjects with a diagnosis of sarcoidosis between 1990 and 2013, with the aim to evaluate clinical, functional and serological differences related to the presence of lymphoma in sarcoidosis patients, as well as differences in survival.

We recorded the following clinical data: gender, age, radiographic (i.e., Scadding) disease staging, organ involvement and treatment of both conditions, stage of lymphoma, sarcoidosis and lymphoma relapses, pulmonary function tests (PFTs), serology and haematology data as well as serum angiotensin-converting enzyme (ACE) levels at the time of diagnosis. These parameters were compared between patients with and without lymphoma (Table 1).

We retrieved 209 sarcoidosis patients and found 10 cases (4,8%) with a previous or subsequent diagnosis of lymphoproliferative disorder and a mean follow-up of 6.7 years and 9.5 years, respectively.

Differences between groups were tested with a two-sample Student's T test in continuous variables normally distributed with equal variances. The Chi-squared test was used to compare the distribution of categorical variables between the two groups, and the Fisher exact test when appropriate. Survival was estimated using the Kaplan-Meier method and compared between groups with the log-rank test.

There was no difference in patients' median age between the sarcoidosis and the sarcoidosis-lymphoma syndrome group (48.7 *vs* 46 years, p=0.578); the majority of subjects within the sarcoidosis group were females; in contrast, a slightly, not significant male predominance was observed in the sarcoidosis-lymphoma syndrome group (p=0.344).

Most of the patients in the two groups were non-smokers (60.7% and 85.7% in the sarcoidosis and sarcoidosis-lymphoma groups, respectively). A difference was found in terms of

chest X-ray staging, specifically a milder disease extent/severity in patients with lymphoma. In fact, stage II was the most common stage in the sarcoidosis group, whilst stage I was more frequently observed in the sarcoidosis-lymphoma group. PFTs trended towards worsening in the sarcoidosis group, wherein functional abnormalities were more likely to be present, although this difference did not reach statistical significance (FVC: 3,3 vs 4,2 liters, p=0.052). In addition, 36 relapses (18,9%) of sarcoidosis were reported in the sarcoidosis group, while no relapse was observed in the sarcoidosis-lymphoma group.

We also detected a statistically significant difference in ACE serum levels between groups. Indeed, in the sarcoidosis-lymphoma syndrome group, serum ACE level was significantly higher compared to patients without lymphoma, both at the time of the diagnosis of sarcoidosis (94.9 UI/L *vs* 55.8 UI/L, p = 0.02) and at the last measurement available (83.3 UI/L *vs* 50.7 UI/L, p = 0.047).

However, survival did not differ between the two groups (log-rank test p=0.3724).

In the present study, we investigated whether serological, clinical, functional or radiological features may help differentiate patients with sarcoidosis from those with sarcoidosis-lymphoma syndrome. We showed that lung involvement as assessed by chest X-ray (Scadding radiographic stage II), a restrictive ventilatory defect and a higher rate of relapse were more common among patients with sarcoidosis alone. Furthermore, and perhaps more interestingly, serum ACE levels were higher in patients with sarcoidosis-lymphoma syndrome both at the time of the diagnosis and at the last follow-up measurement available, indicating that patients with persistently elevated serum ACE levels should probably be carefully monitored over longer periods, despite the similar outcomes in term of mortality observed in the two groups.

Previous epidemiological studies showed an increased incidence of various types of cancers in patients with sarcoidosis[4], but this association does not seem to be cancer-specific. However, breast and testicular tumors are more frequently described in association with sarcoidosis[5], and may occur either before, concurrently or after onset of sarcoidosis[2,6]. In patients with either hematological malignancies or solid tumors, granulomatous inflammation is a frequent finding mainly in the local lymph nodes draining the cancer site[7]. However, these “sarcoid-like reactions” have limited clinical relevance and should not be regarded as sarcoidosis.

Coexistence of sarcoidosis and lymphoma is well known. Indeed, patients with sarcoidosis are up to 11 times more likely to develop lymphoma as compared to the general population[8]. Specifically, an increased risk of Hodgkin lymphoma was observed in patients with sarcoidosis in a

population-based case-control study in Scandinavia[4]. In the majority of cases, lymphoma occurred after sarcoidosis, usually within a short time interval[9]. Patients with sarcoidosis-lymphoma syndrome tend to be significantly older than unselected individuals with sarcoidosis[10]. In contrast, in our study, no differences were observed in the median age of patients with or without lymphoma. Different genetic background or environmental exposures may account for this inconsistent finding[1]. Similar to our study, *Blank and colleagues*[11] performed a retrospective study analyzing the incidence and type of malignancies in a large cohort of patients with sarcoidosis, showing a similar rate of lymphoproliferative disorders (4.1% *vs* 4.8 % in our study), thus confirming the generalizability of our findings.

In our study, a number of limitations should also be acknowledged, the main being the small number of patients with sarcoidosis-lymphoma syndrome, although, reassuringly, a comparable prevalence of sarcoidosis-lymphoma syndrome was found in previous similar studies[11]. Moreover, the retrospective design is prone to incomplete or missing data. Finally, the lack of a control population without sarcoidosis followed over the same period of time precludes us from identifying sarcoidosis as a risk factor for malignancy. These limitations notwithstanding, our data suggest that in patients with sarcoidosis persistently elevated serum ACE levels should raise the suspicion of supervening lymphoma. ACE is generally used to monitor disease behaviour during follow-up[1]. Thus, we argue that serum ACE levels may reflect the intensity of the lymphocytic activation occurring in patients with sarcoidosis, and that an exuberant and uncontrolled lymphocytic activation, perhaps not counterbalanced by T-regulatory cell activity[12], may trigger the development of lymphoma. In support of our hypothesis, evidence suggests that serum ACE is lower in patients with lymphoma alone[13]. Interestingly, we also observed that the CD4/CD8 lymphocyte ratio in bronco-alveolar lavage was higher among patients with sarcoidosis-lymphoma syndrome (data not shown), further supporting the hypothesis of an aberrant lymphocytic activation (T-helper) in patients with both conditions.

In conclusion, our study suggests the existence of clinical, radiological and serological differences in sarcoidosis with or without lymphoma syndrome. Larger prospective studies are required to confirm and expand on these observations.

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Table 1. Demographic and clinical characteristics of the study population

	Sarcoidosis	**Sarcoidosis + Lymphoma**	**P**
Patients, n	199	10	
Age, years	48.7 (± 14.8)	46 (± 12)	0.578
Gender			
Male	89 (44.7)	6 (60)	0.344
Female	110 (55.3)	4 (40)	
Smokers:			
No	105 (60.7)	6 (85.7)	
Ex	26 (15)	0 (0)	0.630
C	42 (24.3)	1 (14.3)	
FVC, litres	3.3 (± 1,1)	4.2 (± 0,8)	0.052
FVC, % predicted	96.2 (± 18.0)	100.1 (± 19,2)	0.583
FEV1, litres	2.7 (± 0,9)	3.3 (± 0,6)	0.92
FEV1, % predicted	94.4 (± 19,1)	97.1 (± 18.0)	0.720
DLCO, ml min kPa	6.2 (± 2,6)	7.4 (± 1,8)	0.234
DLCO, % predicted	73.9 (± 23,8)	75.3 (± 15,3)	0.881
Chest X-rays stage (%)			
Stage 0	15 (7.5)	0 (0)	
Stage 1	59 (29.7)	5 (50)	
Stage II	89 (44.7)	3 (30)	0.671
Stage III	30 (15.1)	2 (20)	
Stage IV	6 (3.0)	0 (0)	
ACE (U/L)			
At diagnosis	55.1 (± 36,7)	94.9 (± 43,9)	0.02
First relapse	86.0 (± 56,4)	-	N/A
Last follow up	50.7 (± 41,7)	83.3 (± 42,5)	0.04
Relapses	36 (18.9%)	0 (0%)	N/A
Organ involvement			
Mediastinum	159 (79.9)	8 (80)	0.994
Lungs	137 (68.8)	7 (70)	0.939
Skin	53 (26.6)	4 (40)	0.354
Lymph-nodes	34 (17.6)	3 (30)	0.321
Eyes	12 (6.0)	1 (10)	0.612
Spleen	12 (6.0)	1 (10)	0.612
Liver	17 (8.5)	0 (0)	0.335
Salivary glands	5 (2.5)	0 (0)	0.999
Nervous system	7 (3.5)	0 (0)	0.999
Hypercalcemia	1 (0.5)	0 (0)	0.999
Bones	2 (1.0)	1 (10)	0.137
ORL	1 (0.5)	0 (0)	0.999
Gastrointestinal	2 (1.0)	0 (0)	0.999
Lacrimal glands	1 (0.5)	1 (10)	0.094
Bone marrow	2 (1.0)	0 (0)	0.999
Heart	1 (0.5)	0 (0)	0.999
Testis	1 (0.5)	0 (0)	0.999

Continuous variables are expressed as mean±SD if normally distributed, as median (min, max) if non-normally distributed; categorical variables are expressed as absolute numbers and percentages
N/A = not applicable

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