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The association between sarcoidosis and lymphoma: A retrospective and multicentre study of 46 patients

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Introduction

Sarcoidosis is a systemic granulomatous disease of unknown origin in which various organs are infiltrated by non-caseating epithelioid giant-cell granulomas (1). Its diagnosis is based on three major criteria: a compatible clinical/radiological presentation as well as evidence of granulomas on a histological examination and the exclusion of differential diagnoses (2). In some patients, sarcoidosis may coexist with other clinical conditions, such as lymphoma that may occur before, after, or simultaneously with the sarcoidosis diagnosis (3). Brinker et al. reported an increased incidence of lymphoma in patients with sarcoidosis (4). The same author later defined the sarcoidosis-lymphoma syndrome (SLS) as a condition in which the onset of lymphoma occurs several years after the diagnosis of sarcoidosis in the same patient (5). Moreover, the coexistence of the two diseases within the same year has also been described, as well as a sarcoidosis diagnosis occurring at least one year after the lymphoma diagnosis (6). However, few studies have described and compared these three types of sarcoidosis-lymphoma association (SLA). To further elucidate this association, the aim of this study was to compare the clinical, laboratory, and radiological features of patients with SLA to those of patients with sarcoidosis alone (SA). Then, these features were compared between the three types of SLA. In addition, in order to identify predictive factors of lymphoma development the features of patients with SA were compared to those of patients with SLS.

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Patients and methods

Study design and patients

This retrospective multicentre study reviewed the records of patients hospitalised between 1999 and 2022 in at least one of the following hospitals: Université Claude Bernard Lyon I, Lyon, France Hospices civiles de Lyon, Centre Léon Berard and Centre Hospitalo-universitaire de Saint-Etienne. Patients were identified on the Lyon University Hospitals and the Saint-Etienne University Hospital databases using the keywords "sarcoidosis" and "lymphoma". For patients who have been followed up for lymphoma at the Centre Léon Berard, the records were previously transmitted to the Lyon University Hospitals database. The inclusion criteria were: i) age ≥18 years at the time of initial sarcoidosis or lymphoma diagnosis; ii) a biopsy-proven sarcoidosis, based on the American Thoracic Society (ATS)/European Respiratory Society (ERS)/World Association of Sarcoidosis

and Other Granulomatous Diseases (WASOG) criteria (2); iii) a biopsy-proven lymphoma classified as Hodgkin Lymphoma (HL) or non-HL (NHL) according to the World Health Organization (WHO) classification (7). The exclusion criteria were: i) diagnosis of other malignancies; ii) patients with Human Immunodeficiency Virus infection; iii) patients with a history of innate immune deficiency such as Common Variable Immunodeficiency (CVID) and constitutional hypogammaglobulinemias; iv) patients with a history of organ or hematopoietic cells transplantation; and v) isolated local granulomatous reactions inside or close to a resected tumour or its draining lymph nodes without any clinical or radiological manifestation. (8,9). Three groups were defined *a priori*: Group "Prior sarcoidosis" included patients with sarcoidosis diagnosis before lymphoma diagnosis, group "simultaneous diseases" included patients for whom both sarcoidosis diagnosis and lymphoma occurred simultaneously (within a year); and group "secondary sarcoidosis" included patients for whom lymphoma diagnosis was prior to sarcoidosis diagnosis. Patients with SA were identified from a cohort of 528 patients with sarcoidosis admitted at the Lyon University Hospitals between 2006 and 2018 (10). They were included according to the same inclusion and exclusion criteria; each patient with SLA was matched with two patients with SA based on age and sex.

Data collection

The clinical and laboratory data were collected and analysed by the same investigator (RC) using a standardised form. Data on age, sex, medical history, clinical examination, and sites of tissue biopsies sampling were collected at the time of sarcoidosis diagnosis. Chest radiographs were classified according to the Scadding's classification (11). Laboratory analyses, including blood cell count and haemoglobin, blood calcium, and serum angiotensin-converting enzyme level (ACE) were collected. Computed tomography (CT) and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) scan results, pulmonary function tests, bronchoscopies with bronchoalveolar lavage (BAL), cardiac investigations, and detailed medical treatments were also collected, when available. Other collected data included organ involvement, sarcoidosis relapses, and lymphoma status. A relapse was defined as the occurrence of new sarcoidosis symptoms during treatment or when it was stopped, requiring a modification of the treatment. The recovery was defined as the absence of sarcoidosis symptoms after 3 years without treatment (12).

Statistical analysis

Categorical variables were expressed as counts and percentages, and continuous variables were expressed as mean and standard deviation (SD) when the data were normally distributed and as median and interquartile range (IQR) otherwise. Normality was assessed using the Shapiro Wilk's test. According to the results of the Shapiro Wilk's test numerical variables were analysed using a Student's t-test or a Wilcoxon signed rank test, and for multiple group comparisons, an analysis of variance test was performed using either ANOVA or Kruskall-Wallis. All the tests were two-tailed, and a p-value < 0.05 was considered significant. When a multiple comparison test was performed, the p-value threshold was lowered to 0.01 to account for increase in type I error. All the analyses were conducted in an R environment v. 4.2.1, using the following packages: *tidyverse, compareGroups, matchit.*

Ethics

The study complies with the Declaration of Helsinki and was approved by the institutional review board of the *Hospices Civils de Lyon* (approval number 21_5333).

Results

Comparison between the SA and the SLA group (Table 1 and 2)

Among the 52 patients initially identified as having both sarcoidosis and lymphoma, four were excluded due to conditions suggesting immunodeficiency: three with hypogammaglobulinemia and one with HIV infection. A total of 48 patients who presented with SLA were identified. Among them, 2 were not included in the comparison with the SA group, since their age at sarcoidosis diagnosis was unknown and matching was therefore impossible; thus 46 patients with SLA were included (Figure 1). These patients were compared with a group of 92 patients with SA. The median (IQR) age was 48 (36.8-61.0)

Table 1. Epidemiolgic characteristics comparison between SA and SLA groups at Sarcoidosis diagnosis. (1) 2 Sjögren's syndrome, 1 systemic scleroderma, 2 systemic lupus erythematosus, and 2 hyperthyroidism in SLA group, and 2 hypothyroidism in SA group.

	SA group	**SLA group**	**p-value**
	N=92	***N=46***	
Median age at sarcoidosis diagnosis, years, [IQR]	48.0 [36.8;61.0]	51.0 [41.2;59.0]	0.825
Median age at lymphoma diagnosis, years, [IQR]	-	53.3 [44;67.5]	-
Sex, n (%)			
Female	48 (52.2%)	24 (52.2%)	Ref.
Males	44 (47.8%)	22 (47.8%)	0.999
Median BMI [IQR]	24.8 [22.8;28.2]	25.0 [21.0;30.0]	0.977
Comorbidities, n (%)			
Hypertension	21 (22.8%)	9 (19.6%)	0.677
Diabetes mellitus	8 (8.7%)	6 (13.0%)	0.440
Dyslipidaemia	14 (15.2%)	10 (21.7%)	0.353
Heart failure	12 (13.0%)	5 (10.9%)	0.739
Asthma	4 (4.4%)	3 (6.5%)	0.597
Auto immune diseases ([1])	2 (2.17%)	7 (15.2%)	0.007

Abbreviations: **IQR:** interquartile range. BMI: Body mass index. SA: sarcoidosis alone. SLA: sarcoidosis-lymphoma association

Table 2. Clinical and radiological characteristics comparison between SA and SLA groups at Sarcoidosis diagnosis.

	SA group	**SLA group**	
	N=92	***N=46***	**p-value**
Clinical symptoms			
Fever	14 (15.2%)	7 (16.3%)	0.863
Night sweats	42 (45.7%)	5 (11.6%)	<0.001
Synovitis	17 (18.5%)	3 (6.5%)	0.059
Dry syndrome	4 (4.4%)	1 (2.2%)	0.585
Parotidomegalia	4 (4.4%)	3 (6.5%)	0.597
Cough	34 (37.0%)	11 (26.2%)	0.228
Central nervous system	3 (3.3%)	1 (2.2%)	0.786
Lymphadenopathy localisation			
Mediastinal	79 (85.9%)	37 (80.4%)	0.421
Axillary	3 (3.3%)	2 (4.4%)	0.748
Subclavicular	5 (5.4%)	4 (8.7%)	0.484
Cervical	3 (3.3%)	7 (15.2%)	0.018
Inguinal	3 (3.3%)	2 (4.4%)	0.748
Abdominal	7 (7.61%)	8 (17.4%)	0.100
Splenomegaly	4 (4.4%)	6 (13.0%)	0.085
Hepatomegaly	4 (4.4%)	5 (10.9%)	0.174
PET scan fixation			
Lungs	8 (8.7%)	11 (25.0%)	0.015
Mediastinal	79 (85.9%)	35 (79.5%)	0.362
Peripherical Lymphadenopathy	8 (8.70%)	11 (25.0%)	0.015
Relapses	33 (35.9%)	4 (8.9%)	0.001

Abbreviations: IQR: interquartile range. SA: sarcoidosis alone. SLA: sarcoidosis-lymphoma association

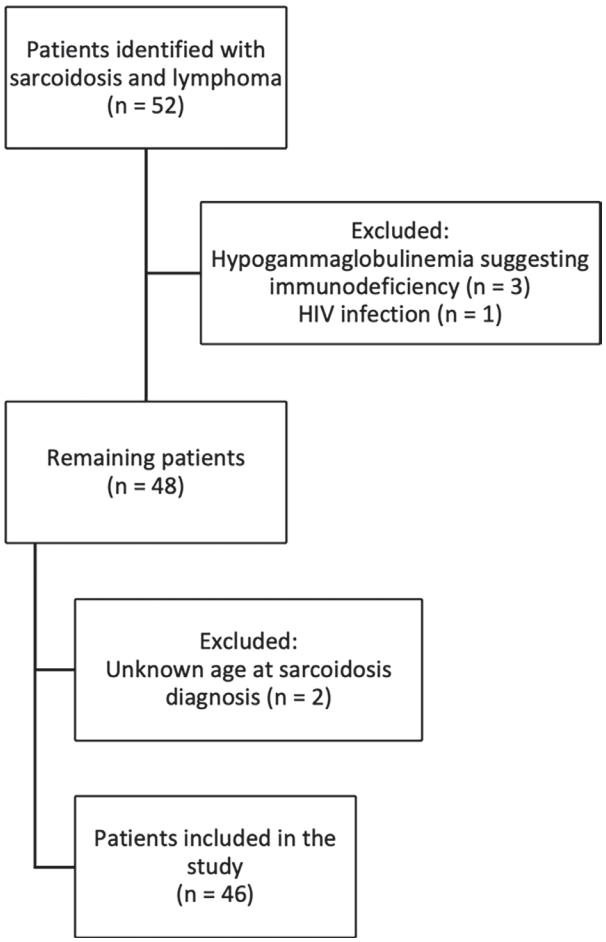

Figure 1. Flowchart – Patient Selection.

years in the SA group and 51 (41.2- 59.0) years in the SLA group (p=0.825). In the SLA group, there were significantly more autoimmune diseases (15.2% vs 2.2%, p= 0.007) comprising Sjögren's syndrome (n=2), systemic scleroderma (n=1), systemic lupus erythematosus (n=2), and hyperthyroidism (Graves' disease (n=2); Table 1).

Regarding the clinical symptoms at sarcoidosis diagnosis, patients with SA experienced more frequently night sweats than those with SLA (45.7% vs 11.6%, p< 0.001). No significant difference was found between groups for laboratory results and pulmonary function tests (data not shown). Regarding the imaging findings and the radiological location of lymphadenopathies, there were significantly more cervical locations in the SLA group (15.2% vs 3.3%, p=0.018). Similarly, the proportion of peripheral lymphadenopathies and lungs hypermetabolism on the ^{18}F-FDG PET images were higher in the SLA group (25.0% vs 8.7% p=0.015). There was no significant difference regarding the initial systemic therapy (data not shown). A significantly higher proportion of sarcoidosis relapses was found in the SA group compared with the SLA group (35.9% vs 8.9% p=0.001; Table 2).

Comparison of the SA group versus Group "prior sarcoidosis" (Table 3 and 4)

Compared with patients with SA, there were significantly more autoimmune diseases (17.6% vs. 2.2%, p=0.028) in Group "prior sarcoidosis". The patients with SA experienced night sweats more frequently (45.7% vs. 6.7%, p=0.003), as well as sarcoidosis relapses (35.9% vs. 11.8%, p=0.049). There was no significant difference in the other variables analysed.

Characteristics of the lymphomas

The median (IQR) age at lymphoma diagnosis was 53.3 (44-67.5) years. The group "prior sarcoidosis" was composed of 17/46 (37%) patients, the group "simultaneous diseases" was composed of 10/46 (21.7%) patients, and the group "secondary sarcoidosis" of 19/46 (41.3%) patients. The median (IQR) follow-up was 11 (1-53) years. A HL was diagnosed in 12 patients and non-HL in 34 comprising Diffuse Large B-Cell Lymphoma (DLBCL, [n=20]), marginal zone lymphoma (n=4), follicular lymphoma (n=3), Mucosa-Associated Lymphoid Tissue (MALT) lymphoma (n=2), Burkitt lymphoma (n=1), and T-cell lymphoma (n=4; Table 5).

Comparison between SLA groups (Table 5 and 6)

The mean (SD) age at sarcoidosis diagnosis was not significantly different between the three groups; it was 51.9 (±14) years in group "prior sarcoidosis", 48.6 (±17.1) years in group "simultaneous diseases", and 50.4 (±15.5) years in group "secondary sarcoidosis". The mean age at lymphoma diagnosis was significantly higher in group "prior sarcoidosis" compared with the two other groups (65.9 vs 48.3 vs 44.5, p< 0.001). The median (IQR) time between sarcoidosis and lymphoma diagnosis was 132 (60-216) months in group "prior sarcoidosis", 6 (3-6.75) months in group "simultaneous diseases" and 60 (28-84) in

Table 3. Epidemiologic characteristics comparison between SA and group with sarcoidosis preceding lymphoma.at Sarcoidosis diagnosis. (*) 2 gougerot sjogren's disease, 1 systemic scleroderma, 2 systemic lupus erythematous, 2 hyperthyroidisms, in SLA group.

	SA group	**Group Prior Sarcoidosis**	**p-value**
	N=92	***N=17***	
Age at sarcoidosis diagnosis, years, (IQR)	48.0 [36.8;61.0]	51.9 [37.2; 66]	0.642
Age at lymphoma diagnosis, years, (IQR)	-	66.1 [57.3: 74]	-
Sex			
Female	48 (52.2%)	10 (58.8%)	Ref.
Males	44 (47.8%)	7 (41.2%)	0.629
BMI	24.8 [22.8;28.2]	25.0 [21.0;30.0]	0.977
Comorbidities Hypertension	21 (22.8%)	4 (23.5%)	0.924
Diabetes mellitus	8 (8.7%)	2 (11.8%)	0.672
Dyslipidemia	14 (15.2%)	3 (17.6%)	0.777
Heart failure	12 (13.0%)	3 (17.6%)	0.608
Asthma	4 (4.35%)	1 (5.9%)	0.752
Auto immune diseases (*)	2 (2.2%)	3 (17.6%)	0.028

Abbreviations: **IQR:** interquartile range. BMI: Body mass index. SA: sarcoidosis alone

Table 4. Clinical and radiological characteristics comparison between and group with sarcoidosis preceding lymphoma at Sarcoidosis diagnosis.

	SA group	**Group Prior Sarcoidosis**	**p-value**
	N=92	***N=17***	
Clinical symptoms			
Fever	14 (15.2%)	2 (13.3%)	0.904
Night sweats	42 (45.7%)	1 (6.7%)	0.003
Synovitis	17 (18.5%)	0 (0.0%)	.
Dry syndrome	4 (4.4%)	1 (5.9%)	0.752
Parotidomegalia	4 (4.4%)	2 (11.8%)	0.282
Cough	34 (37.0%)	2 (13.3%)	0.074
Centra lnervous system	3 (3.3%)	1 (2.2%)	0.786
Lymphadenopathy localisation			
Mediastinal	79 (85.9%)	13 (76.5%)	0.351
Axillary	3 (3.3%)	1 (5.9%)	0.612
Subclavicular	5 (5.4%)	2 (11.8%)	0.374
Cervical	3 (3.3%)	3 (17.6%)	0.053
Inguinal	3 (3.3%)	0 (0.0%)	.
Abdominal	7 (7.61%)	3 (17.6%)	0.235
Splenomegaly	4 (4.35%)	2 (11.8%)	0.282
Hepatomegaly	4 (4.4%)	1 (5.9%)	0.752
Pet scan Fixation			
Lungs	8 (8.7%)	4 (28.6%)	0.060
Mediastinal	79 (85.9%)	12 (80.0%)	0.557
Peripherical Lymphadenopathy	8 (8.7%)	4 (26.7%)	0.076
Relapses	33 (35.9%)	2 (11.8%)	0.049

Abbreviations: IQR: interquartile range. SA: sarcoidosis alone

Table 5. Epidemiologic characteristics comparison between subgroups of patients with sarcoidosis lymphoma association.

	Group Prior Sarcoidosis	Group Simultaneous diseases	Group Secondary sarcoidosis	p-overall
	N=17	*N=10*	*N=19*	
Mean age at sarcoidosis diagnosis, years, (SD)	51.9 (14.0)	48.6 (17.1)	50.4 (15.5)	0.860
Mean age at Lymphoma diagnosis, years, (SD)	65.9 (9.03)	48.3 (17.3)	44.5 (14.9)	<0.001
Median time between sarcoidosis and lymphoma diagnosis (month)	132 [60.0;216]	6.00 [3.00;6.75]	60.0 [24.0;84.0]	<0.001
Sex				0.815
Female	10 (58.8%)	5 (50.0%)	9 (47.4%)	
Male	7 (41.2%)	5 (50.0%)	10 (52.6%)	
BMI	25.6 (5.06)	26.8 (4.21)	25.2 (5.98)	0.730
Comorbidities				
Hypertension	4 (23.5%)	1 (10.0%)	4 (21.1%)	0.798
Diabetes mellitus	2 (11.8%)	2 (20.0%)	2 (10.5%)	0.735
Dyslipidemia	3 (17.6%)	3 (30.0%)	4 (21.1%)	0.811
Heart failure	3 (17.6%)	0 (0.0%)	2 (10.5%)	0.424
Asthma	1 (5.9%)	1 (10.0%)	1 (5.3%)	1.000
Auto immune disease	3 (17.6%)	1 (10.0%)	3 (15.8%)	1.000
Lymphoma characteristics				
Hodgkin's lymphoma	2 (11.8%)	8 (80.0%)	2 (11.1%)	<0.001
DLBCL	8 (47.1%)	1 (10.0%)	11 (61.1%)	0.028
Marginal zone lymphoma	0 (0.0%)	1 (10.0%)	3 (16.7%)	0.192
Follicular lymphoma	3 (17.6%)	0 (0.0%)	0 (0.0%)	0.220
Burkitt lymphoma	0 (0.0%)	0 (0.0%)	1 (5.56%)	0.596
Malt lymphoma	2 (11.8%)	0 (0.0%)	0 (0.0%)	0.343
T-cell lymphoma	2 (11.8%)	0 (0.0%)	2 (10.5%)	1.000

Abbreviations: IQR: interquartile range. BMI: Body mass index. DLBCL: Extranodal diffuse large B-cell lymphoma

group "secondary sarcoidosis". There was no difference between the groups regarding the sex ratio, body mass index, or comorbidities. In addition, there was no significant difference between the groups regarding the clinical symptoms, the laboratory results (Table 6), nor the imaging data (chest X-ray Scadding's stage and ^{18}F-FDG PET uptake; data not shown). In the group "simultaneous diseases" , there was significantly more HL (8/10 patients, 80.0%) than in the other groups (p<0.001). In the group "prior sarcoidosis", 12/17 patients (70.6%) recovered from sarcoidosis at the time of lymphoma diagnosis (Table 6). In group "secondary sarcoidosis", 12/19 patients (63.2%) were asymptomatic at the time of sarcoidosis diagnosis. Among the 17 patients in Group Prior Sarcoidosis, 11 (61 %) had received systemic corticosteroids prior to the diagnosis of lymphoma. Additional immunosuppressive agents had been used in a minority of patients: methotrexate in 2 cases and azathioprine in 1 case. Notably, none of the patients in this group had been exposed to anti-TNF therapy. Among the 17 patients in Group Prior

Table 6. Clinical, biological and radiological characteristics between subgroups of patients with sarcoidosis lymphoma association.

	Group Prior Sarcoidosis	Group Simultaneous Diseases	Group Secondary sarcoidosis	
	N=17	*N=10*	*N=19*	p.overall
Clinical symptoms				
Fever	2 (13.3%)	2 (20.0%)	3 (16.7%)	0.881
Night sweats	1 (5.9%)	3 (30.0%)	1 (5.6%)	0.176
Synovitiss	0 (0.0%)	1 (10.0%)	2 (10.5%)	0.416
Dry syndrome	1 (5.3%)	0 (0.0%)	0 (0.0%)	1.000
Parotidomegalia	2 (10.5%)	0 (0.0%)	1 (5.3%)	0.791
Cough	2 (11.8%)	4 (40.0%)	5 (29.4%)	0.240
Lymphadenopathy localization				
Mediastinal	14 (77.8%)	7 (70.0%)	17 (89.5%)	0.351
Axillary	1 (5.6%)	0 (0.0%)	1 (5.3%)	1.000
Subclavicular	2 (11.1%)	2 (20.0%)	0 (0.0%)	0.104
Cervical	3 (16.7%)	2 (20.0%)	2 (10.5%)	0.768
Inguinal	0 (0.0%)	1 (10.0%)	1 (5.3%)	0.684
Abdominal	3 (16.7%)	3 (30.0%)	2 (10.5%)	0.419
Splenomegaly	2 (11.1%)	2 (20.0%)	2 (10.5%)	0.732
Hepatomegaly	1 (5.3%)	2 (20.0%)	2 (10.5%)	0.427
Pet scan Fixation				
Lungs	4 (28.6%)	4 (40.0%)	3 (15.8%)	0.296
Mediastinal	12 (75.0%)	7 (70.0%)	16 (84.2%)	0.727
Peripherical Lymphadenopathy	4 (25.0%)	2 (20.0%)	5 (26.3%)	1.000
Laboratoy results				
Hypercalcemia >2.6 mmol/l	1 (16.7%)	0 (0.0%)	1 (8.3%)	0.866
Anemia < 120 g/l	1 (14.3%)	3 (42.9%)	3 (25.0%)	0.631
Elevated serum ACE> 70 U/l	2 (40.0%)	3 (50.0%)	2 (16.7%)	0.406
Initial systemic therapy at SD				
Corticotherapy	11 (61.1%)	4 (44.4%)	10 (52.6%)	0.746
Methotrexate	2 (10.5%)	0 (0.0%)	2 (10.5%)	1.000
Azathioprine	1 (5.3%)	0 (0.0%)	0 (0.0%)	1.000
Sarcoidosis Relapses	2 (10.5%)	0 (0.0%)	2 (10.5%)	1.000
Lymphoma Relapses	2 (10.5%)	1 (11.1%)	4 (23.5%)	0.568
Symptoms at Lymphoma Relapses				
B symptoms (fever, night sweats, weight loss)	6 (35 %)			
Peripheral lymphadenopathy	4 (23,5 %)			
Mediastinal lymphadenopathy	3 (17.6 %)			
Splenomegaly	2 (10.5%)			
Asthenia	2 (10.5%)			
Digestive symptoms	1 (5.3 %)			
Bone pain	1 (5.3 %)			

Table 6 (*Continued*)

	Group Prior Sarcoidosis	Group Simultaneous Diseases	Group Secondary sarcoidosis	
	N=17	*N=10*	*N=19*	p.overall
Cough	1 (5.3 %)			
Recovery from sarcoidosis when lymphoma is diagno	12/17	-	-	
Deaths	4 (21.1%)	0 (0.0%)	1 (5.3%)	0.244

Abbreviations: IQR: interquartile range. ACE: angiotensin-converting enzyme

Sarcoidosis, the most frequent clinical features at the time of lymphoma diagnosis were B symptoms (n=6), peripheral lymphadenopathy (n=4), and mediastinal lymphadenopathy (n=3). Other reported symptoms included splenomegaly (n=2), asthenia (n=2), digestive symptoms (n=1), bone pain (n=1), and cough (n=1) (Table 6).

Discussion

The present study reported that within the SLA clinical entity, it seemed that the three clinical situations, depending on when lymphoma is diagnosed, were quite distinct with very different diagnostic issues. Moreover, the features of SLA patients did not differ significantly from those of SA patients. The first clinical situation is group "prior sarcoidosis", in which the median time between sarcoidosis and lymphoma diagnosis found was consistent with the initial description of SLS by Brincker (5); the onset of sarcoidosis precedes the diagnosis of the associated lymphoma by several years. In the initial description of SLS, the median age at sarcoidosis onset was > 40 years, approximately 10 years older than the cancer-free patients with sarcoidosis (13), and Hodgkin's disease was the predominant lymphoma subtype. The difference in age at sarcoidosis diagnosis was not investigated herein since the SA group was matched to the SLA group based on the age at sarcoidosis diagnosis. However, a greater proportion of DLBCL was found in the present study, which is consistent with several other published studies (14–16). Conversely, an increased risk of lymphoma among sarcoidosis patients was not found in a pooled analysis of individual data from 12 case-control studies and one retrospective case-control study (17,18). However, in these studies the sample size of the sarcoidosis group was small, likely resulting in insufficient statistical power to find the association. Furthermore, a large-scale Danish study supports the hypothesis of an increased risk of lymphoma in these patients(19,20). Lymphoma could arise as a consequence of the prolonged immune response in the disease (3). It has been observed that some patients with sarcoidosis exhibited elevated levels of B-cell activating factor (BAFF) (21), what may favour the development of lymphoma (22). In Sjogren's syndrome a similar mechanism of prolonged immune response was observed to favour the development of lymphoma(23). Herein, a few patients of the SLA group had a history of Sjogren's syndrome, however, the predominant lymphoma in Sjogren's syndrome is marginal zone lymphoma, which was not the case in the present study. Among patients from group "prior sarcoidosis", the majority were considered to have recovered from sarcoidosis, which leads to suspect subclinical residual disease activity with persistent B lymphocyte stimulation. In our cohort, 11 out of 17 patients with prior sarcoidosis had received corticosteroids, and only a few had been exposed to other immunosuppressive agents. These findings suggest that while immunosuppressive therapy was present, it was unlikely the predominant driver of lymphoma development in this population. The clinical presentation of lymphoma in patients with prior sarcoidosis was variable, with B symptoms and lymphadenopathy being the most common features. These findings highlight the importance of considering lymphoma in the differential diagnosis when new or atypical symptoms arise in patients with a history of sarcoidosis. It would be interesting to know whether hypermetabolic adenopathies would be visible on PET scan, but this information was lacking. Taking these findings into account, clinicians should be vigilant about the potential lymphoma in patients with sarcoidosis onset after the age of 40 and prolonged follow-up could be judicious even when sarcoidosis is considered cured. The

second clinical situation is group "simultaneous diseases" where lymphoma and sarcoidosis are diagnosed within the same year. In this situation, a majority of Hodgkin's disease was found, which presents a major diagnostic challenge since these two diseases often share a similar clinical presentation; thus, the histopathological analysis is crucial. Furthermore, it is well documented that Hodgkin's disease is often associated with a granulomatous reaction (24–26) that can embed lymphomatous cells, making the diagnosis complex (25,27). Taking these findings into account, clinicians must be aware of the frequent association between these two diseases in order to avoid premature and erroneous conclusions about the absence of a lymphoma. The third clinical situation corresponds to group "secondary sarcoidosis", in which a majority of DLBCL was found, and where the time between lymphoma and sarcoidosis diagnosis was much shorter than in group "prior sarcoidosis". In this group, two-thirds of patients were asymptomatic at the time of diagnosis. Moreover, the clinical presentation was dominated by the presence of mediastinal adenopathies and few general symptoms. Furthermore, the prognosis of sarcoidosis was good and there were few relapses. A previous study described a series of patients where sarcoidosis appeared after lymphoma diagnosis (17); the onset of sarcoidosis was found to occur at a median time of 18 months after lymphoma, which is consistent with the present findings. Conversely, unlike the present study, in this study an equal proportion of Hodgkin's and non-Hodgkin's lymphomas was found. It is noteworthy that half of sarcoidosis cases in this study were asymptomatic, as reported herein, and there was a high frequency of mediastinal lymphadenopathy. Furthermore, the prognosis for these sarcoidosis cases was excellent, since less than half of the patients received a treatment and the vast majority achieved complete remission of the disease. In cases where lymphoma precedes sarcoidosis, it is crucial to distinguish true sarcoidosis from relapsing lymphoma reactive granulomatosis. In the present study, the features of patients with SA were also compared with those of patients with SLA Two previous studies have addressed this issue. Cerri *et al*. first reported a series of 10 patients with SLA (28) and observed a higher proportion of radiological stage I on radiography in the SLA group and no relapse in this group. These two features were also found herein. However, they reported a significantly higher serum ACE level in the SLA group. *Alzghoul et al*. compared the clinical presentation of sarcoidosis with and without lymphoma using a national US registry that included 43 patients with SLA among 3560 patients with sarcoidosis (29). They found that skin and salivary gland involvement were significantly more common in SLA. These findings were not replicated herein. However, we noted a higher proportion of pulmonary parenchymal involvement on PET scan. In these previous studies, the types of lymphoma as well as the time between diagnoses were not detailed, which limits comparability of results. Herein, the SA group was also compared to the Group "prior sarcoidosis", which was never investigated in previous studies and showed results similar to the comparison between SLA and SA. However, a more frequent history of autoimmune diseases was noted in the group "prior sarcoidosis". The hypothesis of authentic CVID could be considered, but no hypogammaglobulinemia or history of recurrent infections in these patients were found. This could be explained by the presence of unknown immune disorders in these patients that facilitate the development of these diseases (30); there could be numerous genomic similarities between the development of lymphoma and sarcoidosis (31). The present study has several limitations. First, its retrospective design led to incomplete or missing data, and the involvement of specialists from various departments and centres may have introduced heterogeneity. Additionally, recruitment from tertiary care centres may have favoured the inclusion of more atypical cases of sarcoidosis, potentially limiting generalisability. As in most retrospective studies, the univariate nature of the analyses increases the risk of type I error. Furthermore, follow-up duration could not be determined for all patients due to insufficient documentation, introducing potential exposure bias. We acknowledge that matching on date of diagnosis or admission could have improved temporal comparability, but this was limited by incomplete retrospective data, especially for earlier cases. Due to the retrospective design, we cannot entirely exclude that some granulomatous lesions were tumor-associated rather than true systemic sarcoidosis, although clinical and radiological features supported a systemic diagnosis. Finally, although this is the largest series reported to date on this topic, the overall sample size remains limited, resulting in reduced statistical power.

Conclusion

The present study did not identify any robust predictive factor of lymphoma development in patients with sarcoidosis. However, it highlighted distinct clinical scenarios according to when lymphoma is diagnosed that must be taken into account by clinicians for disease management.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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