

Severe infections in sarcoidosis

Incidence, predictors and long-term outcome in a cohort of 585 patients

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Abstract

Sarcoidosis is associated with cell-mediated immunodeficiency and treatment of symptomatic sarcoidosis usually includes systemic immunosuppressants. Data relative to incidence, prognosis factors, and outcome of infections are scarce.

Retrospective cohort study of 585 patients with biopsy proven sarcoidosis in a tertiary referral specialist clinic, with a nested case-control analysis. Twenty nine patients (4.9%) with severe infections were compared to 116 controls subjects with sarcoidosis, matched according to their gender, ethnicity, age at diagnosis, and treatment with corticosteroids.

After a median follow-up of 8 years [range; 1–46], 38 severe infections [mycobacterial infections (n = 14), fungal infections (n = 10), bacterial (n = 8), viral (n = 3) and parasitic (n = 1)] were observed in 30 patients. The incidence of severe infections was 0.71% persons-year (CI 95% 0.5–0.98) and 0.43% persons-year (CI 95% 0.27–0.66). Patients with severe infection were more frequently of male gender (60% vs 46%) and were more likely treated by ≥ 3 immunosuppressive agents (OR = 3.8, IC 95% [1.5–9.64], $P = .005$) and by cyclophosphamide (OR = 5.55, IC 95% [1.9–16.1], $P = .002$), and with neurological (OR = 3.36 CI 95% [1.37–8.25], $P = .008$), or cardiac (OR = 2.65 CI 95% [1.09–6.43], $P = .031$) involvement of the sarcoidosis, compared to the controls. Two patients died within the 6 months following infection, due to progressive multifocal leucoencephalopathy (n = 1), and of peritonitis (n = 1).

Severe infections are observed in 5.1% of our patients with sarcoidosis after a median follow-up of 8 years. Risk factors for severe infections included neurological or cardiac involvement of sarcoidosis, the use of immunosuppressive agents and mainly cyclophosphamide.

Abbreviations: ATS = American Thoracic Society, BAL = bronchoalveolar lavage, CD4 = cluster of differentiation 4, CI = confidence interval, CSF = cerebrospinal fluid, ePOST = extrapulmonary physician organ severity tool, ERS = European Respiratory Society, HAART = highly active antiretroviral therapy, HIV = human immunodeficiency virus, IQR = interquartile range, JC virus = John Cunningham virus, OR = odds-ratios, PCR = polymerase chain reaction, PML = progressive multifocal leucoencephalopathy, TNF α = tumor necrosis factor alpha, WASOG = World Association of Sarcoidosis and Other Granulomatous disorder.

Keywords: immunodeficiency, immunosuppressants, infection, sarcoidosis, steroids

1. Introduction

Sarcoidosis is a multisystemic granulomatous disease of unknown etiology characterized by giant cell noncaseating

granuloma.^[1] It is an inflammatory disease whose pathophysiological mechanism is immunological but still misunderstood. It is an exaggerated immune response and granulomatous reaction to unidentified antigens (environmental or transmitting agents) in a context of genetic predisposition.^[2,3] Significant lymphopenia involving CD4 (cluster of differentiation 4), CD8, and CD19 T-cells is common in sarcoidosis patients and correlated with disease activity. Data suggests that lymphopenia relates more to disease pathology than medical treatment.^[4]

The treatment of symptomatic sarcoidosis usually includes glucocorticoids, and cytotoxic drugs like methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, and biologic agents like tumor necrosis factor alpha (TNF α) antagonist can be used in severe or refractory sarcoidosis. The use of immunosuppressive drugs is associated with an increased risk for infection.^[5]

In spite of CD4 + T-lymphocytopenia and treatment-induced immune suppression, the risk of severe or opportunistic infection is not usually considered to be higher in sarcoidosis, than in general population but this is still being debated.^[6] Some studies have described cases of opportunistic infections even in untreated patients, in particular cryptococcosis and progressive multifocal leucoencephalopathy (PML).^[7,8]

Few data are available with respect to the prevalence, risk factors, and outcome of severe infections in sarcoidosis. Some studies have specifically reported observations of opportunistic infections in patients with sarcoidosis. Baughman^[9] reported 7 (0.9%) fungal infections out of 753 patients with sarcoidosis seen

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at their institution over a 18 months period. Rubinstein et al^[10] followed up 197 patients for a mean duration of 7.2 years and reported no invasive opportunistic infection.

We conducted a single-center retrospective cohort study of 585 patients with biopsy proven sarcoidosis in order to assess the prevalence, main characteristics, and outcome of severe infections. We performed a nested case-control analysis in order to identify risk factors associated with severe infection in patients with sarcoidosis.

2. Materiel and methods

2.1. Patients

A single-center retrospective cohort analysis was conducted, including 585 consecutive patients with biopsy proven sarcoidosis followed at the hospital Pitié Salpêtrière in the internal medicine and clinical immunology department. One investigator (CCA) collected the data of the entire cohort. Patients presenting with a severe infection during their follow-up were identified and their data were collected (AD). To be included patients should have: (1) Clinical and paraclinical features consistent with the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders (ATS/ERS/WASOG) criteria for diagnosis of sarcoidosis and with histological evidence of sarcoidosis;^[11] (2) Serious infections were defined as those that led to hospitalization or death or required intravenous antibiotic treatment.^[12] They included bacterial, mycobacterial, viral, and fungal infections.

Age at diagnosis of sarcoidosis, the organs involved by sarcoidosis, stage of sarcoidosis, treatment history and at the time of infection was recorded. The standard dosing regimen of cyclophosphamide in our center was 700 mg/m² per month.

For severe nonmycobacterial infection, infection type, localization, treatment, and outcome were also reported. Laboratory parameters including blood lymphocytes count total and CD4, serum angiotensin-converting enzyme, gamma globulin level were noted at the time of diagnosis of sarcoidosis and at the time of severe infection.

The local ethics committee of La Pitié Salpêtrière hospital, Paris VI University, approved this study.

2.2. Statistical analysis

Characteristics of patients according to the occurrence of infections are reported as median (interquartile range [IQR]) for quantitative variables and counts (percent) for categorical variables.

The incidence of severe infections among patients with sarcoidosis was estimated with its 95% confidence interval (95% CI) from the cohort using a Poisson model.

A first analysis compared the characteristics of patients between the groups (infected or not) among the whole cohort: quantitative variables were compared using the Wilcoxon rank sum tests while categorical variables are compared using the Fisher exact tests.

A second part consisted in a nested case-control analysis: each case patient (with a severe infection) was matched with 4 control subjects (without severe infection) within the cohort, according to their sex, age at diagnosis of sarcoidosis, ethnicity, and treatment with corticosteroids. Matching was performed by minimizing the Mahalanobis distance between cases and controls without replacement of controls. Factors associated with severe or

opportunistic infection were identified in univariate analysis. Associations were estimated using Odds-Ratios (OR) and their 95% CIs in conditional logistic regression models to account for the matched design. All ORs estimated in this analysis should be interpreted as the estimated effect of variables, conditional on the matching factors (i.e., effect of variables while sex, ethnicity, age at diagnosis and corticosteroids use held constant).

Tests were two-sided and *P*-values lower than 5% were considered as indicating significant associations. Analyses were performed on R statistical platform, version 3.0.2.

3. Results

3.1. Characteristics of the cohort of sarcoidosis and according to the presence or not of severe infection

Main data are summarized in Tables 1–4 and Figure 1.

The cohort included 585 patients with biopsy proven sarcoidosis. A total of 22 episodes of severe nonmycobacterial infections were observed in 16 patients (median age: 38 years, IQR 29.5–63.2 and 75% of male) (Fig. 1 and Tables 1 and 2) and 14 episodes of mycobacterial infections were identified in 14 patients. Characteristics of the 585 patients included in this study are summarized in Table 3. There were 54% women (315 patients) and 46% men (270 patients), with median age of 38 years (29–49). The incidence of severe infections was 0.71% persons-year (CI 95% 0.50–0.98) and 0.43% persons-year (CI 95% 0.27–0.66) for nonmycobacterial severe infections. Patients originated from Europe (53%), Sub-Saharan Africa or Caribbean (23%), from Maghreb (18%) and other origin (6%). Main organ involvement of sarcoidosis included lung (60%), central nervous system (30%), cardiac (26%), skin (31%), eyes (26%), lymph nodes (24%), bones and joints (19%). About 27% of patients received at least 3 different immunosuppressive treatments including 82% of corticosteroids, 28% of hydroxychloroquine, 24% of methotrexate, and 22% of cyclophosphamide. Around 60% of patients with severe infection were male compared to 46% of patients without severe infection (*P* = .14). Patients with severe infection were more likely to be treated with ≥ 3 immunosuppressants (55% vs 26%, *P* = .0005) and were more frequently treated by thalidomide (10% vs 1%, *P* = .015), cyclophosphamide (52% vs 21%, *P* = .0003) and cyclosporine (10% vs < 1%, *P* = .002), respectively, as compared to those with no severe infection.

3.2. Case-control study

Data are summarized in Table 4. Each sarcoidosis patient with a severe infection was matched with 4 control subjects who had a sarcoidosis but no actual or past severe infection (controls) according to their sex, ethnicity, age at diagnosis of sarcoidosis, and corticosteroids treatment. One case patient could not be matched leading to a sample size of *n* = 145 patients (29 cases matched to 116 controls) for this analysis. Conditionally on sex, age at diagnosis, ethnicity, and corticosteroids use, results were the following. Patients with severe infection presented more likely with neuro-sarcoidosis (OR = 3.36, CI 95% [1.37–8.25], *P* = .008) and cardiac sarcoidosis (OR = 2.65, CI 95% [1.09–6.43], *P* = .031). They were more likely to be treated by ≥ 3 immunosuppressants (OR = 3.8, IC 95% [1.5–9.64], *P* = .005) and by cyclophosphamide (OR = 5.55, CI 95% [1.9–16.1], *P* = .002) as compared to the controls.

Table 1**Main characteristics of the 16 patients with sarcoidosis and severe infection.**

Cases	Gender/ Age	Localization of sarcoidosis	Stage of pulmonary sarcoidosis	Prednisone daily dose at time of infection, mg	IS therapy at time of infection *	Time between sarcoidosis and infection (months)	Lymphocytes, cell/mm ³	CD4 T lymphocytes, cell/mm ³	Gamma- globulins, g/L
1	M/28	Mediastino-pulmonary + heart + CNS	II	50	No	120	445	96	ND
2	M/63	CNS (myelo-meningo- radiculitis)	—	10	Methotrexate	36	1250	612	> 12
3	M/77	Muscle + peripheral nervous system	—	5	Methotrexate	24	547	192	12
4	M/30	Mediastino-pulmonary + heart + CNS + eye	II	90	Cyclophosphamide	264	1500	ND	14
5	M/26	Mediastino-pulmonary + parotitis	II	60	No	0	ND	449	ND
6	F/64	CNS	—	10	MMF	24	1140	ND	3.2
7	M/41	Mediastino-pulmonary + heart + CNS + skin + adenopathy	II	20	Methotrexate, anti TNF α	72	1847	ND	ND
8	M/34	Mediastino-pulmonary + adenopathy	II	0	No	72	660	146	ND
9	M/38	Mediastino-pulmonary + liver + CNS	II	ND	Methotrexate	60	830	204	ND
10	F/58	Mediastinal + kidney + spleen + bone	I	80	No	0	1290	528	13.8
11	M/76	Mediastino-pulmonary + heart + skin + adenopathy	II	60	Cyclophosphamide	12	1870	900	2.8
12	M/37	Mediastino-pulmonary + ENT	II	37.5	Methotrexate	60	470	183	8.1
13	F/58	Mediastino-pulmonary + liver + heart + eye	II	35	Cyclophosphamide	12	1900	684	14.6
14	F/27	CNS + skin + arthralgy	—	9	Methotrexate	156	252	ND	18
15	M/22	Liver + kidney + heart + adenopathy	—	60	Anti TNF α	84	1000	ND	9.1
16	M/69	Gastric + bone marrow + liver + salivary glands	—	ND	No	3	< 200	34	ND

CNS=central nervous system, IS=immunosuppressant, MMF=mycophenolate mofetil, ND=not determined.

Table 2**Outcome of the 16 patients with sarcoidosis and severe nonmycobacterial infection.**

Cases	Infectious agent	Site of infection	Treatment of infection	Outcome	Other infections	Duration of follow-up after infection, months
1	<i>Cryptococcus neoformans</i>	Meningoencephalitis	Fluconazole	Improve	No	84
2	<i>Escherichia coli</i>	Septicemia + osteo-arthrits	ND	Improve	No	48
3	<i>Haemophilus influenzae</i>	Meningitis	Amoxicillin	Improve	No	24
4	<i>Pseudomonas aeruginosa</i>	Pneumonia	Tazocillin + ciprofloxacin	Died	<i>E. coli</i> , <i>E. faecalis</i> , <i>Candida albicans</i> peritonitis	6
5	<i>Pneumocystis jirovecii</i>	Pneumonia	Cotrimoxazole	Improve	No	168
6	<i>Escherichia coli</i>	Septicemia+symphitis	Ceftriaxone + fosfomycine	Improve	No	48
7	<i>Cryptococcus neoformans</i>	Fungemia+arthrits	Flucytosine + amphotericin B	Improve	No	84
8	<i>Aspergillus fumigatus</i>	Pneumonia	Amphotericin B then itraconazole	Improve	No	6
9	CMV	Pneumonia	Ganciclovir	Improve	PCP, <i>E. faecalis</i> meningitis, malignant strongyloidiasis, occipital aspergillosis abscess, pulmonary actinomycosis	66
10	<i>Fonsecaea pedrosoi</i>	Cutaneous	Terbinafine	Improve	No	24
11	HHV-8	Cutaneous	Decrease IS	Stability	No	12
12	<i>Pseudomonas aeruginosa</i>	Pneumonia complicated by septic shock	Ceftazidime + Ciprofloxacin	Improve	No	6
13	<i>Fusarium</i>	Lung and brain abscess	ND	Improve	No	60
14	<i>Pseudomonas aeruginosa</i>	Pneumonia	Ticarillin	Improve	No	24
15	<i>Pneumocystis jirovecii</i>	Pneumonia	Cotrimoxazole	Improve	No	9
16	JC virus	Leuco-encephalopathy	Cidofovir	Died	No	3

CMV=cytomegalovirus, HHV=human herpesvirus, JC virus=John Cunningham virus, ND=not determined, PCP=pneumocystis pneumonia.

Table 3
Characteristics of sarcoidosis patients according to the presence or not of severe infection *

	All	Without severe infection	With severe infection
N, %	585	555 (94.9)	30 (5.1)
Age, years, median (IQR)	38 (29–49)	39 (29–49)	36 (29–50)
Gender			
Female	315 (54)	303 (54)	12 (40)
Male	270 (46)	252 (46)	18 (60)
Ethnic group			
White	311 (53)	298 (54)	13 (45)
North Africa	105 (18)	99 (18)	6 (20)
Black	134 (23)	124 (22)	10 (33)
Others	34 (6)	34 (6)	0
Location of sarcoidosis			
Pulmonary involvement	351 (60)	335 (60)	16 (53)
Cardiac involvement	154 (26)	142 (26)	12 (40)
Neurosarcoidosis	178 (30)	160 (29)	18 (60)
Lymph nodes	140 (24)	135 (24)	5 (17)
ENT	52 (9)	42 (8)	10 (33)
Skin	181 (31)	164 (32)	17 (23)
Kidney involvement	26 (4)	17 (3)	9 (12)
Bones/joints	114 (19)	110 (20)	4 (13)
Muscle	32 (5)	28 (5)	4 (13)
Eyes	153 (26)	149 (27)	4 (13)
Liver/Spleen	130 (22)	122 (22)	8 (27)
Treatment numbers of IS used			
1	249 (45)	243 (45)	6 (21)
2	163 (29)	156 (29)	7 (24)
3	97 (17)	86 (16)	11 (38)
4	37 (7)	34 (6)	3 (10)
5	15 (3)	14 (3)	1 (3)
6	2 (<1)	2 (<1)	0
7	2 (<1)	2 (<1)	1 (3)
ND	20	19	1
≥ 3 IS treatments	153 (27)	137 (26)	16 (55)
Corticosteroids	464 (82)	437 (82)	27 (90)
Thalidomide	11 (2)	8 (1)	3 (10)
Methotrexate	138 (24)	128 (24)	10 (34)
Cyclophosphamide	125 (22)	110 (21)	15 (52)
Cyclosporine	6 (1)	3 (1)	3 (10)
Mycophenolate mofetil	59 (10)	55 (10)	4 (14)
Anti-TNFα	25 (4)	22 (4)	3 (10)
Azathropine	25 (4)	25 (5)	0

* Data are expressed as N (%).
 ENT = ear, nose and throat, IS = immunosuppressant, ND = not determined, TNFα = tumor necrosis factor alpha.

3.3. Characteristics of the 16 patients with severe nonmycobacterial infections

The 22 severe infections included 14 patients with 1 infection, 1 patient with 2 infections and the remaining one with 6 infections (in 3 different time periods with a 1 year interval between periods 1 and 2 and a 4-year interval between periods 2 and 3). Nine (60%) patients were of Caucasian origin, 4 (26%) originated from Sub-Saharan Africa or West Indies and 2 (13%) originated from Maghreb. The average time between the diagnosis of sarcoidosis and the episode of infection was 5.2 years. No patient underwent pneumocystis prophylaxis by cotrimoxazole-thrime-toprim.

Fungal infections were the most frequent infections with 10 episodes. The most frequent pathogen (n=3) was *Pneumocystis jirovecii*. Three patients developed a pneumocystis pneumonia with initial clinical presentation of febrile dyspnea, successfully

Table 4
Case-control study of factors associated with severe infection *

Parameters	Total	Severe infection, n (%)	OR (CI 95%)	P
	N = 145	29 (20)		
Location of sarcoidosis				
Pulmonary involvement				
No	48	13 (27)	1	
Yes	97	16 (16)	0.55 (0.25–1.24)	.15
Heart				
No	108	17 (16)	1	
Yes	37	12 (32)	2.65 (1.09–6.43)	.031
Neurosarcoidosis				
No	86	11 (13)	1	
Yes	59	18 (31)	3.36 (1.37–8.25)	.008
Lymph nodes				
No	106	24 (23)	1	
Yes	39	5 (13)	0.49 (0.17–1.41)	.18
ENT				
No	128	26 (20)	1	
Yes	17	3 (18)	0.83 (0.21–3.24)	.79
Skin				
No	101	24 (24)	1	
Yes	44	5 (11)	0.41 (0.14–1.16)	.093
Kidney				
No	134	25 (19)	1	
Yes	11	4 (36)	2.57 (0.67–9.93)	.17
Bones/joints				
No	117	25 (21)	1	
Yes	28	4 (14)	0.61 (0.19–1.93)	.4
Muscle				
No	3134	25 (19)	1	
Yes	11	4 (36)	0.41 (0.12–1.49)	.18
Eye				
No	113	25 (22)	1	
Yes	32	4 (12)	0.49 (0.15–1.55)	.22
Liver/spleen				
No	110	22 (20)	1	
Yes	35	7 (20)	1 (0.36–2.75)	1
Treatment of sarcoidosis ≥ 3 IS treatments				
No	98	13 (13)	1	
Yes	47	16 (34)	3.8 (1.5–9.64)	.005
Methotrexate				
No	102	19 (19)	1	
Yes	43	10 (23)	1.34 (0.55–3.28)	.52
Cyclophosphamide				
No	105	14 (13)	1	
Yes	40	15 (38)	5.55 (1.9–16.1)	.002
Mycophenolate mofetil				
No	131	25 (19)	1	
Yes	14	5 (29)	1.67 (0.49–5.66)	.41
Anti-TNFα				
No	137	26 (19)	1	
Yes	8	3 (38)	2.6 (0.57–11.89)	.22
Thalidomide†				
No	141	26 (18)		
Yes	4	3 (75)	–	–
Cyclosporine†				
No	142	26 (18)		
Yes	3	3 (100)	–	–
Azathropine†				
No	144	29 (20)		
Yes	1	0 (0)	–	–

* Cases patients (severe infection) were matched (1:4 ratio) to controls (no severe infection) according to age, sex, ethnicity, and previous therapy with glucocorticosteroids; 145 were included in the analysis (29 cases, 116 controls), 1 case patient could not be matched.

† OR (95%CI) was not estimated due to the small count and/or separation of data.
 CI = confidence interval ENT = ear, nose and throat, IS = immunosuppressant, OR = odds-ratio, TNFα = tumor necrosis factor alpha.

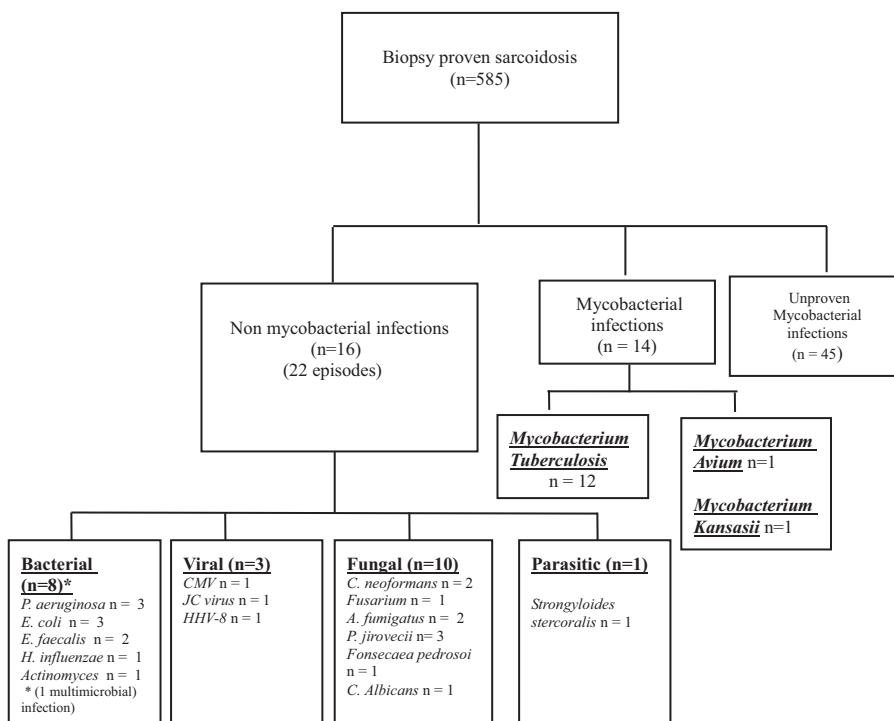


Figure 1. Flowchart of the cohort of patients with biopsy proven sarcoidosis.

treated by trimethoprim-sulfamethoxazole. There were 2 cryptococcosis including a *Cryptococcus neoformans* meningoencephalitis (acute history of headache with fever associated with positive CSF [cerebrospinal fluid] culture and CSF antigen for *C neoformans*) successfully treated by antifungal therapy (induction treatment by Amphotericin B–flucytosine for 2 weeks then fluconazole 600 mg/day for 3 months) and a *C neoformans* arthritis and septicemia (positive culture) treated by Amphotericin B–Flucytosine in induction phase followed by oral voriconazole with good outcome. Two *Aspergillus* related infections were noted, including one pulmonary aspergillosis treated by Amphotericin B then itraconazole and one patient presented a brain abscess with positive culture for *Aspergillus fumigatus*.

One infection was due to *Fusarium* (PCR [polymerase chain reaction] 16 S) with brain and lung abscess and one patient had a chromomycosis with skin localisation (right arm) with good outcome after treatment by terbinafine and lowering immunosuppressive therapy. The last one was a multimicrobial peritonitis due to fungal and bacterial pathogens (*Candida albicans*, *Escherichia coli*, and *Enterococcus faecalis*).

We reported 8 severe bacterial infections. The most common type was severe pneumonia due to *Pseudomonas aeruginosa* (n = 3). Six (67%) required intensive care unit, of whom one had a septic shock. The evolution was favorable in all cases with appropriate antibiotic therapy.

There were 2 bacterial meningitis, (one due to *Haemophilus influenzae*, and the other to *E faecalis* complicated by hydrocephalus requiring ventricular shunt), 2 osteoarticular infections (both due to *E coli*) and one multimicrobial peritonitis (*E coli*, *E faecalis*, *C albicans*). We found one episode of pulmonary actinomycosis, with positive bronchoalveolar lavage culture (nonacid fast, gram positive, identified as actinomycetes) treated by amoxicillin and with successful response.

There were 3 viral infections including one probable cytomegalovirus pneumonia (positive PCR in BAL [bronchoalveolar lavage]

with new infiltrates on imaging and dyspnea)^[13] treated by ganciclovir, one Kaposi’s sarcoma who required significant decreased of immunosuppressive treatment and one progressive multifocal leukoencephalopathy (PML) with identification of JC (John Cunningham) virus by PCR in cerebrospinal fluid.

One patient, who originated from an endemic area (Central Africa), presented a disseminated strongyloidiasis. No information was available about antiparasitic treatment before corticosteroids.

One patient was not receiving corticosteroids and/or immunosuppressive treatment at the time of infection. CD4 T cell lymphopenia was often present at the time of infection (median level of 204/mm³, IQR[146–612]). We observed that the median adjusted ePOST (extrapulmonary physician organ severity tool), an activity score of sarcoidosis^[14] was higher at the time of diagnostic of sarcoidosis (8, range 5.75–9.25) compared with the time of severe infection (6, range 3.75–7.25). At the end of follow-up the median adjusted ePOST was lower (2.5, range 1–4).

Two patients (12.5%) died within the 6 months following infection.

3.4. Characteristics of the 14 patients with mycobacterial infections

A total of 14 episodes of mycobacterial infections were identified in 14 patients [12 *Mycobacterium tuberculosis* (n = 12), *Mycobacterium avium* (n = 1), and *Mycobacterium kansasii* (n = 1)].

4. Discussion

We examined the incidence, prognosis factors, and outcome of severe infections in a large cohort of patients with biopsy proven sarcoidosis.

The most striking conclusions drawn by this study are: (1) Severe infections, including mycobacterial ones, occurred in 5.1% of our patients; (2) Severe infections occurred predominantly in patients with neurological or cardiac sarcoidosis and in patients treated by immunosuppressants and mainly cyclophosphamide, conditionally on basic characteristics and known factors (sex, age at diagnosis, ethnicity, and corticosteroids use).^[15,16]

Few data are available with respect to incidence of infections during sarcoidosis, but the risk is considered to be low. In the present study, the incidence of severe infections was of 0.71% persons-year and occurred in 5.1% of our cohort of patients with proven sarcoidosis. Mycobacterial infections occurred in 2.4% of our cohort.

Winterbauer and Kraemer^[16] reported 5 (4.1%) opportunistic infections [3 cases of pulmonary aspergilloma, one case of pulmonary tuberculosis and one patient with disseminated herpes zoster infection] in a cohort of 122 patients over 7.2 years. Rubinstein et al^[10] did not report any infection in 197 sarcoidosis patients followed 18 months in the 1980s. Baughman^[9] reported 7 (0.9%) fungal infections in 753 patients over a 18 month period and with an incidence rate 0.6 per persons per year.

A systematic literature review conducted between 1966 and 2004 documented 65 cases reports of sarcoidosis complicated by opportunistic infection.^[17] *Cryptococcus* was the most reported infection with 41 cases (59%) followed by mycobacterial infections (13%), nocardiosis (11%), histoplasmosis and pneumocystosis (9%), and aspergillosis (7%). Before the diagnosis of infection, patients were taking corticosteroids and immunosuppressant in 50% and 3%, respectively. There were no data relative to CD4 T cell lymphocytopenia and the outcome was good as all patients improved under anti-infectious treatment. A retrospective study has reported 18 cases of cryptococcosis complicating sarcoidosis and reviewed 72 cases of the literature. They occurred in treatment naïve sarcoidosis patients in one-third of the cases. The mean CD4 lymphocyte count was 145/mm³ (range 55–1300). Risk factors for infection included extra-thoracic sarcoidosis and treatment with corticosteroids.^[16] More recently, Lefaucheur et al^[18] reported 10 cases of progressive multifocal encephalopathy associated with sarcoidosis and 20 observations from literature. The mean CD4 lymphocyte cell count was 235 ± 142 mm³, 10 patients were naïve of treatment, and 17 (57%) patients died.

In the present study, we describe 39% mycobacterial infections (14/36), 28% fungal infections (10/36), 22% bacterial infection (8/36), 8% viral infection (8/36), and 3% parasitic infection (1/36). Fungal complications were the most frequent nonmycobacterial infections in our experience. This is consistent with previous report in the literature.^[19] However, the type of pathogens found was different; *Pneumocystis jirovecii* was the main fungal complication in our cohort. This was likely due to our recruitment of severe extra-pulmonary sarcoidosis patients frequently treated by glucocorticosteroids. In contrast, *Cryptococcus* and *Aspergillus* pathogens have been largely described to be associated with sarcoidosis in the literature. In France, sarcoidosis represents 2.9% of HIV negative cryptococcosis.^[6] A recent French series reported 18 cases of cryptococcosis and 72 additional cases from the literature.^[7] Two-third of patients were treated by corticosteroids at the time of infection. Bacterial infections were evidenced in 22% of cases. They included mainly severe gram-negative infections (i.e., *P aeruginosa*, or *E coli*). Bacterial complications associated with sarcoidosis reported in the literature included mainly nocardiosis and *M tuberculosis* or

atypical mycobacterial infections. In our series, mycobacterial infection was noted in 2.4% (14/585) of our patient with biopsy proven sarcoidosis. Viral infection was the fourth cause of infection and accounted for 1 of the 2 deaths due to PML. PML has been previously reported during sarcoidosis and also in treatment-naïve patients. Sarcoidosis was found to account for 8–9% of the causes of PML.^[20–22] Jamilloux et al^[8] have reported that the mortality rate of PML was higher in sarcoidosis than in human immunodeficiency virus (HIV) infected patients treated by HAART (highly active antiretroviral therapy). We described one Kaposi disease that required a decrease in corticosteroids and immunosuppressant therapies to be controlled. This may represent a serious therapeutic issue especially in severe and difficult to treat patients with sarcoidosis.

Parasitic infections in sarcoidosis are anecdotal with only 2 reports of strongyloides infection in the literature. In our study, one case of disseminated strongyloidiasis was observed in a patient treated by corticosteroids and who was coming from an endemic area. It is important to consider and treat occult infection before initiating immunosuppressive treatments in these high risk patients.

Almost all severe nonmycobacterial infections occurred in patients treated with corticosteroids and/or immunosuppressive therapies, contrasting with previous reports who described opportunistic infections in treatment-naïve patients with sarcoidosis.^[7,8] This discrepancy might be due to the specific recruitment in our internal medicine department including high proportion of severe extra-pulmonary forms needing immunosuppressive therapies and steroids in most cases.

Conditionally on sex, age at diagnosis, ethnicity and corticosteroids use, we identified 2 types of risk factors associated with severe infection: treatment and localization of sarcoidosis. Treatment with ≥ 3 immunosuppressants or cyclophosphamide was significantly associated with severe infections (OR = 3.8 and 5.6, respectively). In addition, neurosarcoidosis, and cardiac sarcoidosis were associated with severe infection (OR = 3.4, and 2.7, respectively).

In rheumatoid arthritis, TNFα inhibitors have been associated with a 2- to 4-fold increased risk of serious bacterial infections and also with an increased risk of opportunistic infection.^[12] In our study, the number of patients treated by TNFα inhibitors (4% of the cohort) was too low to draw any conclusion. Patients with severe sarcoidosis have been associated with increased risk for infections. Bernard et al have reported that cryptococcosis was more frequent in patients with neuro-sarcoidosis (28 vs. 8%), and cardiac involvement (17 vs. 0%).^[7] In the present study, these 2 localizations were clearly associated with higher risk of severe infection.

The median level of CD4 lymphocytes was of 204/mm³ at the time of severe infection. Peripheral CD4 lymphocytopenia has been reported in up to 40% of sarcoidosis patients and significant peripheral lymphopenia is correlated with severe disease manifestations of sarcoidosis.^[4,6] The 2.7% rate of severe nonmycobacterial infections reported here over 8 years of follow-up seems rather low considering this deficient immune status. However, lymphopenia is more severe during flare-ups of sarcoidosis but corrects with corticosteroids and the sequestration of lymphocytes in the granuloma is associated with the peripheral CD4 lymphocytopenia. It is still unclear if low CD4 count can be considered as a risk factor for opportunistic infections like pneumocystosis in non-HIV patients.^[23] Indeed, peripheral CD4 lymphopenia is correlated to the severity of sarcoidosis.^[4] However, the use of immunosuppressants is also

associated with severity of disease and with a higher likelihood of infections.

Our study has some limitations. The number of cases of severe infections associated with sarcoidosis was small and precluded any complex multivariate model selection procedure to identify multiple risk factors. We therefore relied on a nested case-control design to identify factors associated with severe infection, while benefiting from the advantages of the cohort in terms of biases limitation.^[24] This precluded the adjusted estimation of the association of the matching variables (sex, age at diagnosis, ethnicity, and corticosteroids use) with severe infections, which remains to be addressed in a larger cohort with a greater number of events, allowing complex multivariate modelling. The number of patients treated by TNF α inhibitors was too low to draw any definite conclusion about its possible association with the occurrence of infections in sarcoidosis.

In conclusion, severe nonmycobacterial infections are observed in 3% and mycobacterial infection in 2% of our patients with sarcoidosis. Severe nonmycobacterial were mostly fungal and bacterial infections who represent half of all infections episodes. Although outcomes are regularly good, 2 patients (7%, 2/30) died within the 6 months following infection. Infections are likely associated with severe CD4 lymphopenia. Risk factors for severe infections included the use of ≥ 3 immunosuppressants, mainly cyclophosphamide and the neurological and cardiac localizations of sarcoidosis.

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