Prevalence and clinical features of COVID-19 in a large cohort of 199 patients with sarcoidosis

Anne-Claire Desbois*[1,2,3], Cindy Marques*[1,2,3], Leila Lefèvre[2,3], Serge Barmo[2,3], Camille Lorenzo[2,3], Mathilde Leclercq[2,3], Gaëlle Leroux[2,3], Chloé Comarmond[1,2,3], Catherine Chapelon-Abric[2,3], Fanny Domont[2,3], Mathieu Vauthier[2,3], David Saadoun[1,2,3], Patrice Cacoub[1,2,3]

* equal contribution

1. Sorbonne Universités, UPMC Univ Paris 06, INSERM, UMR S 959, Immunology-Immunopathology- Immunotherapy (I3); F-75005, Paris, France;

2. Biotherapy (CIC-BTi) and Inflammation-Immunopathology-Biotherapy Department (DHU i2B), Hôpital Pitié-Salpêtrière, AP-HP, F-75651, Paris, France;

3. AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, F-75013, Paris, France, Centre national de référence des Maladies Autoimmunes et systémiques rares et Maladies Autoinflammatoires rares

Correspondence: Anne-Claire Desbois, MD, PhD, Department of Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpêtrière, 47-83 boulevard de l'Hôpital, 75013 Paris.
Phone: + (33)(1) 42 17 80 68. Fax: + (33)(1) 42 17 80 33.
E Mail:anneclaire.desbois@aphp.fr

Conflict of interest: The authors have declared that no conflict of interest exists.

Word Count: 1496 words, 10 217 characters (including spaces), 2 tables, 20 references.

Declarations

Ethics approval and consent to participate:

The study was approved by our institutional ethics review board "Ethics committee of research in Sorbonne University". All patients gave informed consent.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

The authors declare that they have no source of funding.

Authors' contributions:

ACD contributed to the conception and design of the work.
ACD and CM wrote the manuscript.
ACD, CM, LL, SB, CL, ML, GL, CC, CCA, FD, MV and DS collected the data.
CM have drafted the work
PC supervised the findings of this work.
All authors approved the final manuscript.

Acknowledgements:

We thank all patients and all physicians involved in the care of the patients.

Abstract

Objective: To investigate the prevalence, clinical features and outcomes of coronavirus disease 2019 (COVID-19) among sarcoidosis patients.

Methods: We retrospectively collected features of COVID-19 in a cohort of patients with sarcoidosis followed in a single tertiary university hospital.

Results: Among 199 sarcoidosis patients [mean age 58.8 (±14) years, 86 (43.2%) men], 26 (13%) were diagnosed with COVID-19 [definite (n=7), probable (n=12) and possible (n=7)]. Twenty-four out of 26 patients (92%) had at least one comorbidity, and 11/26 (42%) had two or more comorbidities. Demographic and clinical features of COVID-19 positive patients were similar to those of COVID-19 negative patients. The administration of hydroxychloroquine or immunosuppressant was not associated with the occurrence or the severity of COVID-19. Four out of 26 (15.4%) COVID-19 positive patients required admission to hospital and two of them died. Hospitalized patients [mean age of 61 (±11.5) years] were receiving higher doses of long term treatment with corticosteroids than non-hospitalized patients; 4/4 had pulmonary and 2/4 cardiac involvement of sarcoidosis, and all one or more comorbidity.

Conclusion: The prevalence of COVID-19 in sarcoidosis is slightly higher to that of the general population. Almost half of the COVID-19 positive patients have two or more comorbidities and about 15% present a severe course.

Word count: 200 words.

Keywords: sarcoidosis; COVID-19; SARS-CoV-2

List of abbreviations:

ACE: angiotensin-converting enzyme,

ARB: angiotensin II receptor blocker,

ARDS: severe acute respiratory syndrome,

COVID-19: coronavirus disease 2019,

ECMO: extracorporeal membrane oxygenation

IL6: interleukin 6,

NSAID: nonsteroidal anti-inflammatory drug,

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2,

SD: standard deviation,

TNF: tumor necrosis factor.

Key messages:

What is already known about this subject?

Since the outbreak of COVID-19, many data have been published in the general population and in some disease-specific groups, but data are lacking for patients with sarcoidosis.

What does this study add?

We reported the prevalence, clinical features and outcomes of COVID-19 in a cohort of 199 patients with sarcoidosis followed in a single French tertiary university hospital. The rate of COVID-19 infections among patients with sarcoidosis appears to be very slightly higher to that of the general population. The rates of hospitalization and mortality appeared to be higher than in the general population.

How might this impact on clinical practice or future developments?

Cardiovascular comorbidities that are highly found in sarcoidosis patients probably make them more vulnerable to severe COVID-19. These findings should lead to be cautious for management of sarcoidosis patients during the pandemic.

Introduction

Coronavirus disease 2019 (COVID-19), mediated by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is responsible for a major health crisis worldwide. COVID-19 can be complicated with a severe acute respiratory syndrome (ARDS) and multi-organ failure. Sarcoidosis is a granulomatous disease of unknown origin affecting the lungs, the lymphatic nodes but also the nervous system, the eyes and the heart. The reported incidence among African and Americans in the United States is 35.5/100,000 compared with 10.9/100,000 in Caucasian patients (1). The incidence and the severity of COVID-19 in patients with sarcoidosis remains an unsolved issue. Sarcoidosis can be complicated by interstitial pneumonia leading to severe pulmonary illness. Immunosuppressive drugs are often used making sarcoidosis patients more vulnerable to infections. COVID-19 can be responsible for a cytokine storm syndrome for which immunosuppressive strategy could be beneficial (2, 3). To date, there is no data on clinical features of COVID-19 in sarcoidosis patients. A recent comparative cohort study showed that patients with rheumatic disease and COVID-19 infection were more likely to require mechanical ventilation but had similar mortality and hospitalization rates compared to patients without rheumatic disease (4).

Methods

This study was performed at the Department of Internal Medicine and Clinical Immunology in the tertiary university hospital Pitié-Salpêtrière (Paris, France). This study was approved by the local Ethic Committee. All patients with sarcoidosis, followed at the department were included. From May, 1st 2020 to 27Th May, six weeks after the pandemic peak in France, we systematically contacted by telephone patients followed in our center for sarcoidosis. We investigated their demographic characteristics, disease manifestations of sarcoidosis, the presence of symptoms suggesting SARS-CoV-2 infection, the results of nasopharyngeal PCR if available and their treatments. A definite COVID-19 was defined by the presence of symptoms suggesting SARS-CoV-2 infection with positive nasopharyngeal PCR or serology. A probable COVID-19 was defined by the presence of fever and/or three or more symptoms suggesting SARS-CoV-2 infection associated with a contact with a person infected by SARS-CoV-2 without available nasopharyngeal PCR. A possible COVID-19 was defined by the presence of three symptoms or more suggesting SARS-CoV-2 infection without available nasopharyngeal PCR and without history of contact with infected people.

Continuous variables are presented as mean (± SD) and categorical variables as number (%). Statistical comparisons were performed by using the Mann-Whitney test for quantitative

unpaired data, and the Chi-Square test for categorical variables. All statistical tests were two-tailed with a significance level of 0.05. Statistical significance was evaluated using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA).

Results

One hundred and nighty-nine patients diagnosed with sarcoidosis according to the criteria of the latest American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders statement on sarcoidosis (5) were included. The mean age of patients was 58.8 (± 14) years and 86 (43.2%) were male. Among the cohort, 26 (13%) patients were diagnosed with COVID-19 [definite (n=7), probable (n=12) and possible (n=7)].

COVID-19 positive sarcoidosis patients

Patients with COVID-19 consisted of 13 (50%) men with a mean age of 50.3 (±13.6) years. Main features of sarcoidosis included involvement of lungs (73%), lymph nodes (50%), heart (15.4%), central nervous system (23.1%) and eyes (46.2%). Twenty-four (92%) patients had at least one comorbidity [hypertension (26.9%), diabetes (23.1%), heart failure (7.7%), coronary artery disease (7.7%), chronic obstructive lung disease/asthma (19%), overweight (65.4%) or malignant tumors (3.8%)]. Eleven (42.3%) patients had two or more comorbidities. Six of them were ex-smokers and three were active smokers. Demographic and clinical features of patients COVID-19 positive were similar to those of sarcoidosis patients COVID-19 negative (**Table 1**). The administration of hydroxychloroquine was not associated with a decreased occurrence of symptomatic COVID-19 (given in 13.9% of patients COVID-19 negative vs 11.5% of infected patients, *p=1*). The use of immunosuppressant was not significantly associated with a higher risk of symptomatic COVID-19 (39.3% in patients COVID-19 negative vs 38.4% in COVID-19 positive patients, *p=0.96*).

At the onset of COVID-19, patients infected were receiving ARBs/ACE inhibitors (23.1%), HMGCoa reductase inhibitors (15.4%), corticosteroids [84.6%, mean dose of 8.6(6) mg/day], hydroxychloroquine (11.5%), immunosuppressant (38.4%), IL-6 inhibitors (7.7%), and TNF inhibitors (3.8%). Main symptoms of COVID-19 in this cohort of sarcoidosis patients are listed in **Table 2**. Specific treatments for COVID-19 consisted in lopinavir/ritonavir and pristinamycin (n=1), hydroxychloroquine (n=2), azithromycin (n=1) and withdrawal of immunosuppressant (n=2).

COVID-19 positive sarcoidosis patients requiring hospitalization

Among the 26 patients with COVID-19, four (15.4%) required admission to hospital [medicine ward (n=2) and intensive care unit (n=2)], one required mechanical ventilation, one high flow nasal cannula and two died. One woman (73 years) with sarcoidosis associated with Takayasu arteritis died at the emergency room because of acute respiratory insufficiency. One man (49 years) with stage 4 pulmonary sarcoidosis, diabetes and history of pulmonary embolism, was admitted to hospital 10 days after COVID-19 onset. He did not receive specific treatments for COVID-19. He required mechanical ventilation and died 20 days after hospital admission.

All patients requiring admission to hospital [50% of male gender, mean age of 61(11.5) years] presented pulmonary sarcoidosis (stage II/III for two and stage IV for one), two of them had cardiac sarcoidosis and none had neurological sarcoidosis. All of them had at least one comorbidity [hypertension (n=1), diabetes (n=2), coronary artery disease (n=1), Takayasu (n=1), heart failure (n=1), and overweight (n=4)]. Three (75%) of them had two or more comorbidities. None of them was an active smoker. At the onset of COVID-19, three patients were receiving corticosteroids [mean dose of 12.3 (7-20) mg/day], one mycophenolate mofetil and one leflunomide. None was receiving hydroxychloroquine.

Discussion

To our knowledge, this study is the first report on the prevalence, clinical presentation and outcome of COVID-19 in patients with sarcoidosis. The prevalence of infected patients (13%) in our cohort of sarcoidosis patients does seem significantly different to that estimated COVID-19 prevalence in Ile de France (9.9%) and Grand-Est (9.3%), both regions being the most affected by the pandemic in France (6). Our results are consistent with previous data on cohort of patients with other inflammatory and autoimmune disorders (4).

The rate of infected patients with severe symptoms requiring hospitalization reached 15%, which is about four times higher than the rate of hospitalizations in the general population in France, estimated at respectively 3.6% and 3.5% (2.1 - 5.4) for all the French population and patients aged 50 to 59 years-old, the age group corresponding to the median age of sarcoidosis patients in our cohort (6). In the same line, the rate of death is 7.7% in our cohort. However, this should be considered with caution given the small number of patients concerned although this mortality rate seems to be higher than that estimated in the population aged from 50 to 59 years old in France (than 1%) (6). This mortality rate may be explained by the high prevalence of comorbidities in sarcoidosis patients, as 92% COVID-19 positive sarcoidosis patients in our cohort had one or more comorbidities. The rate of diabetes in our cohort is two

to three times higher than that of the general population (<10% before 60 years in France) (8). The prevalence of diabetic patients in our sarcoidosis cohort reached 23% for patients with COVID-19 and 50% for hospitalized patients, compared to 6% and 14% respectively in a New York series reporting patients with an immune-mediated inflammatory disease COVID-19 positive (9). The body mass index of sarcoidosis patients is also particularly high (10). Indeed, diabetes, hypertension and obesity are risk factors known to be associated with poor prognosis in COVID-19 positive patients, increasing the rate of hospitalizations and mortality (11 – 15). The mortality rate in diabetic COVID-19 positive patients was reported to reach 7.8% (16) and 30% in hospitalized patients, which is quite similar to the mortality rate found in our cohort. Consistently, all hospitalized patients in the present study have at least one comorbidity. It should be noted that one of the two dead patients had severe cardiovascular comorbidities, and that the second had stage four sarcoidosis pulmonary involvement (17).

In our cohort, the high rate of patients with metabolic syndrome can partly be explained by a high rate of systemic corticosteroid therapy, i.e. 85% of COVID-19 patients and 75% of hospitalized patients compared to 9% and 29% respectively in the study by Haberman et al (18). Our results are consistent with those of previous studies showing that the use of systemic corticosteroids is a risk factor for a severe course of COVID-19, particularly in inflammatory bowel diseases (19). None of the hospitalized patients was a daily smoker or ex-smoker, which is consistent with several studies finding a low proportion of smokers among patients with a moderate to severe outcome. However, the relationship between smoking and COVID-19 outcome is controversial, with multiple conflicting reports in the current literature (15, 20).

Conclusion

In conclusion, the rate of COVID-19 infections among patients with sarcoidosis appears to be very slightly higher to that of the general population. The rates of hospitalization and mortality appeared to be higher than in the general population.

References

1. Llanos O, Hamzeh N. Sarcoidosis. Med Clin North Am. 2019 May;103(3):527–34.

2. Alijotas-Reig J, Esteve-Valverde E, Belizna C, Selva-O'Callaghan A, Pardos-Gea J, Quintana A, et al. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review. Autoimmun Rev. 2020 Jul;19(7):102569.

3. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmun Rev. 2020 Jul;19(7):102568.

4. D'Silva KM, Serling-Boyd N, Wallwork R, Hsu T, Fu X, Gravallese EM, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US "hot spot." Ann Rheum Dis. 2020 May 26

5. Hunninghake GW, Costabel U, Ando M, Baughman R, Cordier JF, du Bois R, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffuse Lung Dis. 1999 Sep;16(2):149–73.

6. Salje H, Tran Kiem C, Lefrancq N, Courtejoie N, Bosetti P, Paireau J, et al. Estimating the burden of SARS-CoV-2 in France. Science. 2020 May 13.

7. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med. 2020 Jun 3.

8. Santé Publique France : Diabète : https://www.santepubliquefrance.fr/maladies-et-traumatismes/diabete.

9. Haberman R, Axelrad J, Chen A, Castillo R, Yan D, Izmirly P, et al. Covid-19 in Immune-Mediated Inflammatory Diseases - Case Series from New York. N Engl J Med. 2020 Apr 29.

10. Organisation de coopération et de développement économiques (OCDE) : Population en surpoids ou obèse : https://www.oecd-ilibrary.org/social-issues-migration-health/overweight-or-obese-population/indicator/french_debbeb4b-fr

11. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7.

12. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 28;395(10229):1054–62.
13. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020 06.
14. Buckner FS, McCulloch DJ, Atluri V, Blain M, McGuffin SA, Nalla AK, et al. Clinical Features and Outcomes of 105 Hospitalized patients with COVID-19 in Seattle, Washington. Clin Infect Dis. 2020 May 22.
15. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020 Apr 22.
16. Zhu L, She Z-G, Cheng X, Qin J-J, Zhang X-J, Cai J, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab. 2020 02;31(6):1068-1077.e3.
17. Song JW, Hong S-B, Lim C-M, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J. 2011 Feb;37(2):356–63.
18. Haberman R, Axelrad J, Chen A, Castillo R, Yan D, Izmirly P, et al. Covid-19 in Immune-Mediated Inflammatory Diseases - Case Series from New York. N Engl J Med. 2020 Apr 29.
19. Brenner EJ, Ungaro RC, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD, et al. Corticosteroids, but not TNF Antagonists, are Associated with Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results from an International Registry. Gastroenterology. 2020 May 18.
20. Chakladar J, Shende N, Li WT, Rajasekaran M, Chang EY, Ongkeko WM. Smoking-Mediated Upregulation of the Androgen Pathway Leads to Increased SARS-CoV-2 Susceptibility. Int J Mol Sci. 2020 May 21;21(10).

Table 1: Clinical characteristics of sarcoidosis patients without and with COVID-19

	Patients without COVID-19 (n=173)	**Patients with COVID-19 (n=26)**	***p***
Clinical features			
Age (mean, SD)	53.2(14.1)	50.3(13.6)	0.32
Male gender, n(%)	73(42.2)	13(50)	0.64
Involvements of sarcoidosis			
Lung involvement, n(%)	124(71.7)	19(73)	0.95
Stage of pulmonary involvement II/III, n(%)	73(42.2)	14(60.8)	0.5
Stage of pulmonary involvement IV, n(%)	5(2.9)	1(3.8)	0.58
Vital capacity (%), mean (SD)	79.2(38)	80.9(37)	
Total lung capacity (%), mean (SD)	77.3(33.4)	76.8(33.2)	
Diffusing capacity for carbon monoxide (%), mean (SD)	64.5(31.2)	69.3(29.3)	
Lymph nodes, n(%)	80(46.2)	13(50)	0.83
Cardiac, n(%)	30(17.3)	4(15.4)	1
Neurological, n(%)	63(36.4)	6(23.1)	0.39
Ophthalmological, n(%)	67(38.7)	12(46.2)	0.61
Other comorbidities			
One or more other comorbidity, n(%)	136(78.6)	24(92)	0.6
Hypertension, n(%)	53(30.6)	7(26.9)	0.8
Diabetes, n(%)	36(20.8)	6(23.1)	0.83
Cardiac failure, n(%)	8(4.6)	2(7.7)	0.63
Chronic respiratory disease (chronic obstructive lung disease or asthma) , n(%)	22(12.7)	5(19)	0.39
Malignant tumor, n(%)	27(15.6)	1(3.8)	0.21
Body Mass Index (mean, SD), n(%)	27.6(7)	27.1(4.8)	0.85
Smoking habits			
Ex-Smoker, n(%)	40(23.1)	6(23.1)	0.99
Daily smoker, n(%)	19(11)	3(11.5)	1
Treatments			
NSAID, n(%)	10(5.8)	2(7.7)	0.66
ACE inhibitors or ARBs, n(%)	39(22.5)	6(23.1)	0.96
HMGCoa reductase inhibitors, n(%)	29(16.8)	4(15.4)	1
Hydroxychloroquine, n(%)	24(13.9)	3(11.5)	1
Corticosteroids, n(%)	117(67.6)	22(84.6)	0.47
Corticosteroids dosage, mg/day mean(SD)	6.7(3.4)	8.6(6)	0.29
Immunosuppressants, n(%)	68(39.3)	10(38.4)	0.96
Methotrexate, n(%)	38(22)	4(15.4)	0.62
Mycophenolate mofetil, n(%)	23(13.3)	3(11.5)	1
Azathioprin, n(%)	2(1.2)	1(3.8)	0.35
TNF inhibitors, n(%)	11(6.4)	1(3.8)	1
IL-6 inhibitors, n(%)	2(1.2)	2(7.7)	0.09

ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker, COVID-19: Coronavirus disease 2019, IL6: interleukin 6, NSAID: nonsteroidal anti-inflammatory drug, SD: standard deviation, TNF: tumor necrosis factor

Table 2: Clinical characteristics and outcome of COVID-19 in sarcoidosis patients

	Patients with COVID-19 (n=27)
Symptoms of COVID-19	
Asthenia, n(%)	16(61.6)
Fever, n(%)	18(69.3)
Cough, n(%)	19(73.1)
Rhinorrhea, n(%)	10(38.5)
Anosmia, n(%)	5(19.2)
Dysgeusia, n(%)	7(26.9)
Headaches, n(%)	17(65.4)
Myalgia, n(%)	14(53.8)
Shortness of breath, n(%)	12(46.2)
Chest pain, n(%)	8(30.8)
Diarrhea, n(%)	6(23.1)
Cutaneous lesions, n(%)	4(15.4)
Duration of symptoms, mean (SD) days	16.6(13.8)
Chest findings: extension of ground-glass opacities and/or consolidation	
<10%	1(25%)
10-25%	1(25%)
25-50%	2(50%)
Treatments	
Hydroxychloroquine, n(%)	2(7.7)
Antibiotic therapy, n(%)	2(7.7)
Antiviral therapy, n(%)	1(3.8)
Tocilizumab, n(%)	0(0)
Increase or initiation of corticosteroids, n(%)	0(0)
Withdrawal or decrease of immunosuppressants, n(%)	2(7.7)
Outcomes	
Admission to hospital, n(%)	4(15.4)
Admission to Intensive care, n(%)	2(7.7)
Invasive ventilation, n(%)	1(3.8)
Oxygen therapy, n(%)	2(7.7)
High flow nasal cannula, n(%)	1(3.8)
ECMO, n(%)	0(0)
Death, n(%)	2(7.7)
Discharged, n(%)	2(7.7)

COVID-19: Coronavirus disease 2019, ECMO: extracorporeal membrane oxygenation, SD: standard deviation.