Scholastic Case Reports (ISSN: 3108-1827) Research Article

Volume 2 Issue 2 February 2026

Epidemiological and Clinicobiological aspects of Sarcoidosis (Experience of the Internal Medicine Department/CAH)

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Received: January 29, 2026**; Published:** February 10, 2026

Abstract

Introduction: Sarcoidosis, or BBS (Besnier-Boeck-Schaumann disease), is a systemic granulomatous disease of unknown etiology. It is characterized by the formation of non-caseating epithelioid granulomas in the affected organs. A heterogeneous disease, its clinical manifestations are protean, with a predilection for the respiratory system. None of the clinical or paraclinical features of sarcoidosis is specific on its own. The diagnosis relies on a combination of positive findings: clinical manifestations and histopathological lesions after exclusion of other known causes of tuberculoid granuloma.

Objectives: Our main objective was to describe the epidemiological, clinical and biological characteristics of patients with sarcoidosis in an Algerian cohort.

Methods: This is a retrospective, single-center, descriptive study using electronic records of patients hospitalized in the internal medicine department of the central army hospital between January 2017 and December 2023, which included 29 adult patients with sarcoidosis.

Results: The mean age of our patients was 50.6 ± 13.47 years, with a female predominance (male-to-female ratio = 0.38). The majority of our patients (72%) had superficial and/or deep lymphadenopathy; hepatomegaly (31%); dyspnea (31%); and cough (27%). The chronic form was predominant (93%), with the mediastinal-pulmonary form being the most frequent (14%). There were 3 cases of severe localization (2/29 neurological and 1/29 cardiac). An inflammatory syndrome was present in 52% of cases, and biopsy with histopathological examination was performed and contributed to the diagnosis in 83% of cases.

Conclusion: A ubiquitous disease, characterized by geographic and ethnic epidemiological variability (in the absence of local data); of enigmatic etiopathogenesis. Its clinical polymorphism has earned it the name "The Great Mimicker," with limited biological contribution making the development of diagnostic criteria difficult; diagnosis is based on a suggestive clinical and radiological presentation, with, in most cases the demonstration of an epithelioid granuloma without caseous necrosis.

Key words: Sarcoidosis, granuloma, granulomatosis, epidemiology.

Introduction

Sarcoidosis, or BBS (Besnier-Boeck-Schaumann disease), is a systemic granulomatous disease of unknown etiology. (1)

It is characterized by non-caseating epithelioid granulomas in the affected organs.

This is a heterogeneous disease; its clinical manifestations are protean, with a predilection for the respiratory system. (1,2)

None of the clinical or paraclinical features is specific on its own.

The diagnosis is based on a combination of positive findings: clinical and histopathological lesions, after exclusion of other known causes of tuberculoid granuloma. (3)

History

It was initially described in 1877 by Jonathan Hutchinson.

The skin lesions were described by Ernest Henri Besnier in 1889 as "lupus pernio" and by Caesar Boeck in 1899 as "cutaneous sarcoid."

The multisystemic nature of the disease was described by Schumann in 1914.

Löfgren's syndrome: described by Löfgren and Lundback in 1953 (2)

Epidémiology

- Incidence: 3 to 10/100,000 inhabitants/year (4)
- Prevalence: varies by country:
- High prevalence: Scandinavian countries, Sweden: 160/100,000 (5,6)
- Intermediate prevalence: Italy, France (30.2/100,000) (7)
- Low prevalence: Far East; South Korea and Japan (3.7/100,000) (8)
- Age: rare before 15 years and after 75 years with two peaks in frequency; one peak: 25–45 years and a second peak: perimenopausal
- Sex: slight female predominance: female-to-male ratio: 1.2 to 1.7
- Familial sarcoidosis: described in 3.6–10%.

The clinical expression of sarcoidosis

Patients present with general signs (fever, weight loss, polyarthralgia and myalgia) with the most frequent respiratory manifestations (dry cough, dyspnea and chest pain), cutaneous manifestations (skin nodule, erythema nodosum), ocular (uveitis) and other manifestations (adenopathy, hepatosplenomegaly, renal interstitial nephropathy or related to hypercalcemia, and the two prognostic manifestations of neurosarcoidosis with neuromuscular deficit and cardiac sarcoidosis with potentially fatal ventricular conduction and excitability disorders

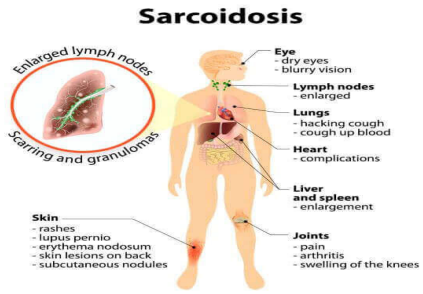

Figure 1: Clinical manifestations of Sarcoidosis (the great mimicker) (6)

There are two main clinical forms of sarcoidosis (6)

- **The acute form**: or Lofgren's syndrome (fever, lymphadenopathy, arthralgia, erythema nodosum, and tuberculin-like symptoms)

- **The variable chronic systemic form:** depending on the organs affected, with or without involvement of vital organs

Biological findings:

Limited contribution with no specific biological markers for sarcoidosis

Blood tests:

Angiotansin converting enzyme ACE level often elevated Calcium and phosphate levels: hypercalcemia with hypercalciuria Lymphopenia on the complete blood count, particularly CD4 T lymphocytes Hypergammaglobulinemia (5) Analysis of bronchoalveolar lavage (BAL) fluid (key for pulmonary sarcoidosis) typically shows lymphocytosis with a high CD4/CD8 ratio.

This is insufficient for diagnosis but allows for monitoring the progression of the disease under treatment.

Morphological examinations such as CT scans, MRIs, and PET scans are valuable for diagnosis.

Biopsy with histopathological examination reveals epithelioid tuberculoid granulomas with giant cells but without caseous necrosis.

Patients and methods

Study type: This is a retrospective, single-center descriptive study conducted in the internal medicine department of the central army hospital over a 7-year period between January 2017 and January 2023, including 29 adult patients with sarcoidosis confirmed by clinical, radiological and/or histopathological evidence**.**

Results

The average age of our patients was 42 years, with extremes between 23 and 63 years. Women were older than men at the time of diagnosis.

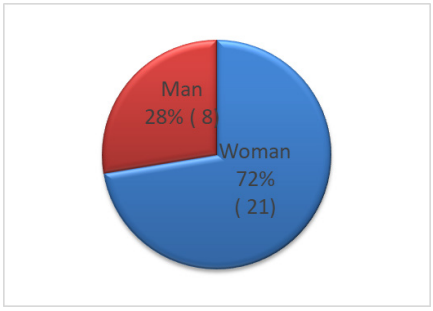

Figure 2: Distribution of patients by sex.

There was a clear female predominance with a male-to-female ratio of 0.38.

Familial cases: mediastinal-pulmonary sarcoidosis in the mother: 1 case (3.5%).

One-third of our patients had hypertension and 14% had diabetes, 2 cases of lymph node tuberculosis, 1 of deep vein thrombosis of the lower limbs, 1 of Hashimoto's thyroiditis, 1 of Behçet's disease, 1 of Ehlers-Danlos syndrome, and 1 case of psoriatic arthritis.

Personal medical history	Number	Percentage(%)
Hypertension	**10**	**34.5**
Diabetes mellitus	**4**	**14**
Lymph node tuberculosis	**2**	**7**
ST-segment elevation myocardial infarction (STEMI)	**1**	**3.5**
Atrial fibrillation	**1**	**3.5**
Transverse deep vein thrombosis (DVT)	**1**	**3.5**
Hashimoto's thyroiditis + pernicious anemia	**1**	**3.5**
Behçet's disease	**1**	**3.5**
Ehlers-Danlos syndrome	**1**	**3.5**
Psoriatic arthritis	**1**	**3.5**

Table 1: Distribution of patients by comorbidities

The four most common clinical manifestations observed in our population are

- Superficial lymphadenopathy

- Splenomegaly and dyspnea in approximately one-third of cases.

- Cough, present in one-quarter of cases.

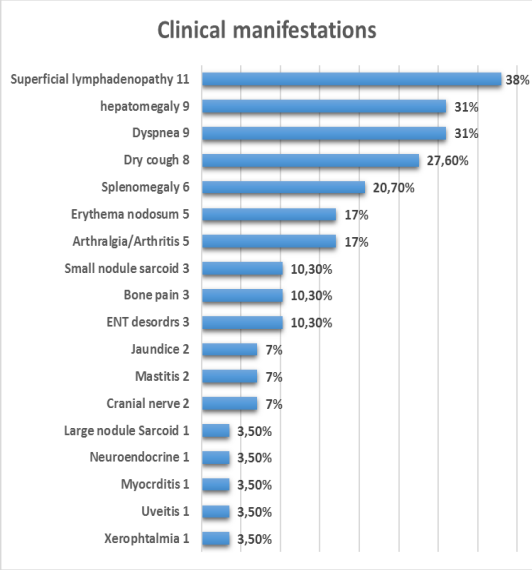

Figure 3 : Distribution of patients according to clinical manifestations.

The chronic systemic form was the most frequently observed.

Paraclinical findings:

Cellular Immunity (Tuberculin Skin Test)

The tuberculin skin test was anergic in slightly more than two-thirds of cases.

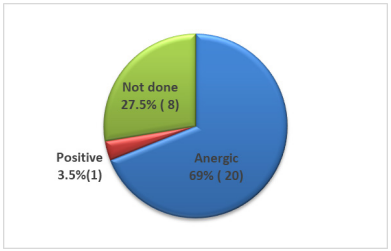

Figure 4: Distribution of patients according to Tuberculin Skin Test.

Biology

Inflammatory markers: Biological inflammation was present in half of our population

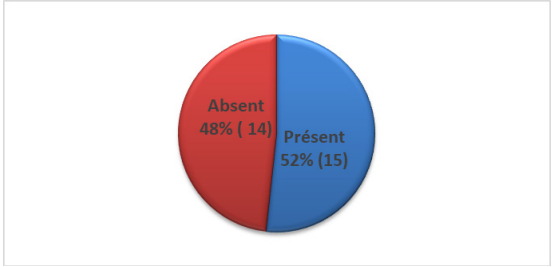

Figure 5: Distribution of patients according to biological inflammation.

The blood count was normal in two-thirds of cases.

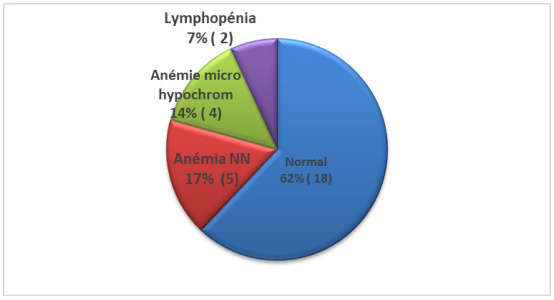

Figure 6: Distribution of patients according to the blood count

Angiotensin-converting enzyme (ACE) was elevated more than half of the cases

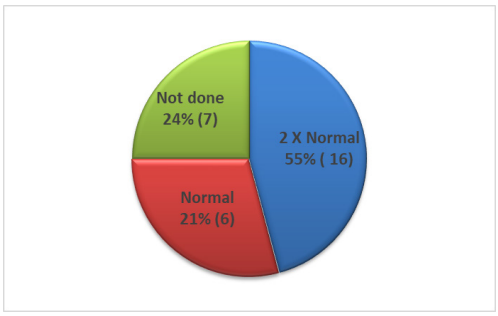

Figure 7: Distribution of patients according to angiotensin converting enzyme (ACE).

Hypercalcemia was present in only 14% of cases (4 patients), lead to renal failure in 2 cases: 1 case with acute or functional renal failure due to severe hypercalcemia (3.8 mmol/L) and 1 case of obstructive renal failure due to bilateral kidney stones.

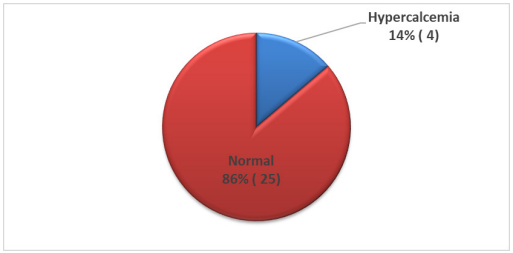

Figure 8: Distribution of patients according to the serum calcium Morphological Exploration

1- Chest X-ray: Performed on all patients; Chest CT scan: Performed on 86 (25) Radiological stage 2 mediastinal-pulmonary sarcoidosis was the most frequently observed.

Stage of the sarcoïdosis	Number	Percentage
Stage 0	**5**	**17%**
Stage 1	**4**	**14%**
Stage 2	**11**	**38%**
Stage 3	**8**	**27.5%**
Stage 4	**1**	**3.5%**

Table 2: Distribution of patients according to radiological stage

Abdominal and pelvic ultrasound and/or CT scan performed in 80% (23)

In addition to confirming hepatomegaly and splenomegaly (31% and 20.7% respectively), abdominal lymphadenopathy was present in 27.5%, resulting in a total of deep lymphadenopathy (abdominal and mediastinal) in 72.4% (21), the most frequent finding in our population

Brain MRI performed in 2 patients (7%):

Patient 1: cerebral thrombosis of the sigmoid sinus, granulomatous involvement of cranial nerves III, IV, VI with hypophysitis and leptomeningeal involvement

Patient 2: Granulomatous pachymeningeal localization, involvement of V, VII.

Cardiac exploration

Cardiac MRI and myocardial scintigraphy: one (1) case of sarcoid myocarditis

Endoscopic exploration

Bronchoscopy: 27.5% (8) allowed for BAL (4) and bronchial biopsies (8), and suggested the diagnosis based on macroscopic appearance in 7% (2)

Nasofibroscopy: 14% (4) allowed for suggested diagnosis and nasal biopsy (4) and nasopharyngeal biopsy (2).

Biopsy site	Number
Superficial lymphadenopathy	8 cervical lymph nodes (5), axillary lymph nodes(3)
Deep lymphadenopathy	3 abdominal lymph nodes (2), médiastinal lymph nodes (1)
Nasal	4
Accessory salivary gland	2
Bronchial	2
Bone	2
Mammary	2
Cutaneous	1
Rate (splenectomy)	1

Table 3: Anatomopathological study.

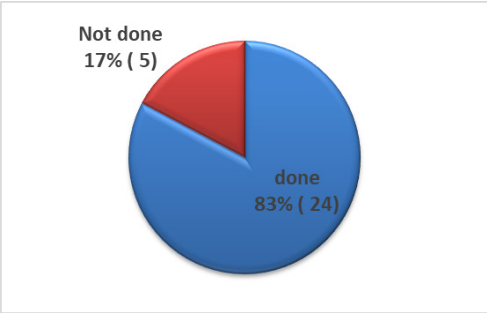

Figure 9: distribution of patients according to whether the biopsy was performed Biopsy was performed in 5 patients at 2 sites and in 19 patients at a single site.

Biopsy was not performed in 5 patients due to:

Lack of indication, as in Löfgren's syndrome (2 cases)

A highly suggestive clinical and radiological presentation, as in neurosarcoidosis (brain MRI) (1 case) Contributing cytology of the bronchoalveolar lavage (BAL) (2 cases)

Clinical Forms

Following this investigation, the following clinical forms were identified:

- Mediastinal-pulmonary form: 14% (4)

- Löfgren's syndrome: 7% (2)

- Hepatosplenic form: 3.5% (1)

- Form with tumor syndrome (Lymphadenopathy + Hepatosplenomegaly + Pulmonary sclerosis): 3.5% (1)

- Lymph node form: 3.5% (1)

- ENT form: 3.5% (1)

- Systemic forms: 65% (19)

- Predominant neurological involvement: 7% (2)

- Predominant renal involvement: 7% (2)

- Predominant breast involvement: 7% (2)

- Predominant cardiac involvement: 3.5% (1)

A depressive syndrome within the framework of the parasarcoid syndrome was present in 1 patient (3.5%).

Discussion

Study	Country	Incidence /100000/an	Age (year)
Swedish National Patient Regisrer (2003- 2012) (8)	Suede	11.5	56.2+/- 14.4
Danish national patient register (2001- 2015) (7)	Denmark	14.5	46.0+/- 15.0
National Health Insurance (NHI) service Data (2003 – 2015) (13)	South Korea	1.3	48.8+/-14.2
Hospital histopathogy and electronic Discharge summaries (1981-2016)(12)	Island	4.15	50.8+/- 14
Seine-Saint-Denis conty , France (2012) (9)	France	4.9	44.6+/- 0.7
University Hospital of Parma, Province of Parma (2000-2013) (10, 11)	Italy	_	50.6 +/- 15.4
I. Gorsane Hôpital Charles- Nicolle (1976 – 2017) (14)	Tunisia	_	47.1 +/- 13.5
Our study (CAH) (2017-2023)	Algeria	_	50.6 +/- 13.47

Table 4: Demographic data on sarcoidosis in the literature.

Female predominance: a female/male sex ratio of 1.55 is found in the different series (ACCESS - A Case Control Etiology Study of Sarcoidosis (multicenter study, 14 centers in 10 countries, N: 720) - the role of estrogen??), which could also explain the average age in our series (2nd peak of perimenopausal frequency). (7, 8, 9).

The familial form is present in 1 case 3.5%, the familial form is described in literature: 3.6 - 10% depending on the series.

Table 5 comparison of clinical findings with those in the literature (8, 9, 11, 12)

Clinical manifestations	Our study % /N	Literature data
Superficial lymphadenopathy	38% (11)	30 % (1/3 of cases)
Hepatomegaly	31% (9)	5 – 30%
Splenomegaly	20.7% (6)	10%
Erythema nodosum	17%(5)	5 – 25%
Sarcoid (small nodule and large nodule)	%14 (4)	24%
Arthralgia/arthritis	17 %(5)	10 – 35%
Bone pain	10.3% (3)	3 – 13%
ENT involvement	10.3% (3)	2% (1 – 3%)
Mastitis	7 % (2)	< 1%.
Cranial nerve (VII and V) and III, IV, VI	7 % (2)	5 – 15 %
Neuroendocrine (hypophysitis)	3.5 % (1)	9 – 15%
Myocarditis	3.5 % (1)	2 – 5% (japanese registry)
Uvéitis	3.5 % (1)	10 – 25 %
Xerophtalmia	3.5% (1)	< 4 %

Several points should be noted:

- Neuroendocrinology: one case (1) of a 51-year-old woman with hypophysitis: she presented with corticotropic and thyrotropic insufficiency. Hypothalamic-pituitary involvement in sarcoidosis represents less than 1% of cases of sella turcica.

Nonspecific cutaneous involvement (erythema nodosum) was present in 5 cases, and specific cutaneous involvement (sarcoid) in 4 cases, representing 31.3% of cases, which is close to the data in the literature where cutaneous involvement is present in one-third of sarcoid patients.

Jaundice is rare in sarcoidosis, as seen in a 20-year-old cirrhotic patient (who underwent a liver transplant), and one case of subicterus in sarcoid liver disease.

Mastitis is rare (less than 1% in the literature, 7% (2 cases) in our series).

According to the literature: the tuberculin skin test (TST) is anergic in 70% of cases. In our series, it was positive in one patient with a history of lymph node tuberculosis, but not performed in 27% of cases, either because the clinical and histological presentation was immediately suggestive of the diagnosis or due to a national tuberculin shortage at some point.

Anemia was present in 31% of cases, either normocytic normochromic or microcytic hypochromic, of inflammatory origin, without autoimmune hemolytic characteristics. Peripheral lymphopenia was also observed in 2 cases. This is frequently reported in the literature (due to the influx of T lymphocytes to the granuloma).

In the literature, angiotensin-converting enzyme (ACE) level was elevated (2 x ULN) in 60% of cases.

Study	Effectif	Percentage/ N
Zammouri (Tunisia 2019) (15)	24	38% (9)
Rastelli (Italy 2021) (16)	39	28% (11)
Kamata (Japan 2018) (17)	16	31% (5)
Loffler (Germany 2015) (18)	27	19% (5)
Our study	29	14% (4)

Table 6: Hypercalcemia (comparaison with literature)

Compared to data from the literature, our result is close to that of the German study by Loffler.

Morphological exploration

Table 7: Chest X-ray (100%), Chest CT scan: 86% (25) (comparison with literature) (8, 9)

Radiological Stage	Our study % (N)	Literature *
Stage 0	17 % (5)	5-10 %
Stage I	14% (4)	50%
Stage II	38 % (11)	25%
Stage III	27.5 % (8)	15%
Stage IV	3.5% (1)	5-10%

Study Limitations

Information bias: data collection via electronic patient records usable from 2017.

Recruitment bias: limited hospitalizations during the COVID-19 pandemic.

Conclusion

A ubiquitous disease, characterized by:

Epidemiological variability: depending on geography, race, and ethnicity (in the absence of local data).

An enigmatic etiopathogenesis that remains unknown to this day; several hypotheses exist, likely a multifactorial origin.

Its clinical polymorphism has earned it the nickname “The Great Mimicker,” making the development of diagnostic criteria difficult.

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