

# Digestive-tract sarcoidosis

## French nationwide case–control study of 25 cases

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### Abstract

Digestive tract sarcoidosis (DTS) is rare and case-series are lacking. In this retrospective case–control study, we aimed to compare the characteristics, outcome, and treatment of patients with DTS, nondigestive tract sarcoidosis (NDTS), and Crohn disease.

We included cases of confirmed sarcoidosis, symptomatic digestive tract involvement, and noncaseating granuloma in any digestive tract. Each case was compared with 2 controls with sarcoidosis without digestive tract involvement and 4 with Crohn disease.

We compared 25 cases of DTS to 50 controls with NDTS and 100 controls with Crohn disease. The major digestive clinical features were abdominal pain (56%), weight loss (52%), nausea/vomiting (48%), diarrhea (32%), and digestive bleeding (28%). On endoscopy of DTS, macroscopic lesions were observed in the esophagus (9%), stomach (78%), duodenum (9%), colon, (25%) and rectum (19%). As compared with NDTS, DTS was associated with weight loss (odds ratio [OR] 5.8; 95% confidence interval [CI] 1.44–23.3) and the absence of thoracic adenopathy (OR 5.0; 95% CI 1.03–25). As compared with Crohn disease, DTS was associated with Afro-Caribbean origin (OR 27; 95% CI 3.6–204) and the absence of ileum or colon macroscopic lesions (OR 62.5; 95% CI 10.3–500). On the last follow-up, patients with DTS showed no need for surgery (versus 31% for patients with Crohn disease;  $P=0.0013$ ), and clinical digestive remission was frequent (76% vs. 35% for patients with Crohn disease;  $P=0.0002$ ).

The differential diagnosis with Crohn disease could be an issue with DTS. Nevertheless, the 2 diseases often have different clinical presentation and outcome.

**Abbreviations:** 95% CI = 95% confidence interval, ACE = angiotensin-converting enzyme, BMI = body mass index, BTNL2 = butyrophilin-like 2, CRP = C-reactive protein, CT = computed tomography, DTS = digestive tract sarcoidosis, GFR = glomerular filtration rate, Hg = Hemoglobulin, IBD = inflammatory bowel disease, NDTS = nondigestive tract sarcoidosis, NOD2 = nucleotide-binding oligomerization domain-containing protein 2, NYHA = New York Heart Association, OR = odds ratio.

**Keywords:** Crohn disease, digestive tract, outcome, sarcoidosis, treatment

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## 1. Introduction

Sarcoidosis is a rare systemic granulomatosis, with an estimated prevalence between 4.7 and 64/100000 habitants.<sup>[1]</sup> The disease mainly affects the lungs and chest lymph nodes, but can reach other organs in 30% to 50% of cases.<sup>[2]</sup> Some of affected sites, such as the heart and central nervous system, can result in poor prognosis.<sup>[3]</sup> Digestive tract involvement is extremely rare, described in 0.1% to 1.6% of cases.<sup>[4,5]</sup> Only a few case reports have described mainly gastric involvement, even if the whole digestive tract can be involved.<sup>[6,7]</sup> The symptoms related to digestive tract involvement are nonspecific and the diagnosis requires the presence of noncaseating granulomas in the digestive tract and the exclusion of other causes of granulomatous digestive disease. Thus, the main alternative diagnosis of granulomatous digestive disease is Crohn disease,<sup>[8]</sup> which can also be associated with extradigestive features such as arthritis, erythema nodosum, and uveitis.<sup>[9]</sup>

In this French nationwide study, we aimed to<sup>[1]</sup> describe the features, outcome, and treatment of symptomatic digestive tract sarcoidosis (DTS),<sup>[2]</sup> determine the factors associated with digestive tract involvement in sarcoidosis, and<sup>[3]</sup> compare the disease with Crohn disease to determine the characteristics that differentiate these 2 diseases involving the digestive tract.

## 2. Methods

### 2.1. Patient selection

We conducted a retrospective French nationwide study of patients with sarcoidosis and digestive tract impairment in 10 centers (internal medicine units=6, pulmonary unit=2, gastroenterology unit=2) between September 1988 and October 2012. Cases were collected through the “Groupe Sarcoidose Francophone.” The inclusion criteria were<sup>[1]</sup> diagnosis of sarcoidosis<sup>[10]</sup> based on clinical and radiological features associated with the presence of noncaseating granulomas in the absence of other granulomatous disorders; and<sup>[2]</sup> the presence of noncaseating granulomas in any digestive tract segment and digestive clinical symptoms. Ten cases were excluded because of no noncaseating granulomas on histology of digestive or extradigestive tissue. For each patient, data concerning the general characteristics, the clinical, radiological, biological features, and treatments were recorded considering each organ usually affected in sarcoidosis.<sup>[1]</sup>

### 2.2. Controls

To determine the characteristics of patients with DTS, we included patients with non-DTS (NDTS) (sarcoidosis without any digestive clinical symptoms at baseline and during the outcome and without digestive noncaseating granuloma) from the Avicenne Hospital pulmonary unit and Jean Verdier Hospital internal medicine unit. Each patient with DTS was paired to 2 patients with NDTS by age, time of diagnosis, and sex.

In the context of digestive tract granulomatosis, to determine the features consistent with sarcoidosis, we selected a control group of patients with Crohn disease selected from the Saint Antoine Hospital gastroenterology unit. We paired 4 patients with Crohn disease to each patient with DTS by age, time of diagnosis, and sex.

In accordance with the French law, a formal approval from an ethics committee was not required because of the retrospective design.

### 2.3. Statistical analysis

Continuous values are presented as median (range) and were compared by Mann–Whitney test. Categorical values are presented as number (%) and were compared by  $\chi^2$  test or Fisher exact test. Multivariate analyses were performed with stepwise logistic regression. Variables with  $P \leq 0.2$  on univariate analysis were included in the stepwise regression analysis to compare patients with DTS and NDTS, and to compare patients with DTS and Crohn disease.  $P < 0.05$  was considered statistically significant. Statview 5.0 was used for statistical analyses.

## 3. Results

### 3.1. General characteristics

Overall, 25 patients with median age 36 years (19–65 years) and female/male sex ratio 2:1 were included in the study. The diagnosis of sarcoidosis and digestive-tract involvement was concomitant in 48% cases; the diagnosis of sarcoidosis occurred before that of digestive tract involvement in 40% of cases (median time 37.5 months [range 6–332] and after in 12% (median time 66 months (range 29–264). Seven (28%) patients received antituberculosis therapy before the diagnosis of sarcoidosis because of suspected pulmonary tuberculosis. No mycobacterium was isolated in any of these cases, and the diagnosis of sarcoidosis was finally made after antituberculosis treatment failure.

At the time of digestive tract involvement, other sites were affected, for a median of 3 organs (range 0–7), concerning lungs ( $n=16$ ; 64%), lymph nodes ( $n=14$ ; 56%), liver ( $n=12$ ; 48%), joints ( $n=8$ ; 32%), skin ( $n=5$ ; 20%), central nervous system and cranial nerves ( $n=5$ ; 20%), spleen ( $n=4$ ; 16%), heart ( $n=4$ ; 16%), upper respiratory tract ( $n=3$ ; 12%), and kidneys ( $n=2$ ; 8%).

The most represented ethnicities in our study were African/Afro-Caribbean (56%) and white ethnicities (24%) (Northern African in 12% and Asian in 8%). There was no difference in the extradigestive features of sarcoidosis or in the type of digestive tract involvement between these ethnicities. Median age in African/Afro-Caribbean patients was 33.5 (19–65) versus 43 years (30–52] in whites ( $P=0.23$ ), and 79% of African/Afro-Caribbean patients were under steroids at diagnosis versus 33% of whites ( $P=0.12$ ).

### 3.2. Digestive tract characteristics

All cases showed clinical symptoms of digestive tract involvement, consisting of abdominal pain (56%), nausea/vomiting (48%), diarrhea (32%), rectal bleeding (24%), anorexia (12%), dysphagia (8%), dyspepsia (8%), hematemesis (4%), and constipation (4%). Weight loss  $>3$  kg was present in 52% of cases, with a median of 4 kg (0–21 kg) lost and body mass index (BMI) 21 kg/m<sup>2</sup> (11.5–48 kg/m<sup>2</sup>).

Abdominal/pelvic computed tomography (CT) was performed in 12 cases and results were normal in one-quarter. In the remaining cases, CT showed abdominal adenopathies in 42%, bowel wall thickening in 25%, fat infiltration in 17%, and ascites in 8%.

Anemia (hemoglobin [Hb] level  $<12$  g/L) was present in 56% cases, with median Hb 11.6 g/dL (range 5.8–14.7 g/dL). C-reactive protein level  $>10$  mg/L was noted in 40% of cases and hypoalbuminemia  $<35$  g/L in 44%. Liver cytolysis and/or cholestasis were noted in 40% of cases.

**Table 1****Frequencies and types of digestive lesions in patients with digestive tract sarcoidosis.**

No. (%)	Esophagus	Stomach	Duodenum	Ileum	Colon	Rectum
Inflammation	1 (4%)	13 (57%)	1 (4%)		4 (25%)	3 (18%)
Ulceration		6 (26%)	2 (9%)		3 (19%)	2 (12%)
Atrophy		4 (17%)	1 (4%)			
Polyp		4 (17%)			1 (6%)	
Bleeding		4 (17%)	1 (4%)			
Infiltration		3 (13%)				
Hypokinesia	2 (9%)	1 (4%)				
Telangiectasia		1 (4%)				
Stenosis		1 (4%)				
Edema			1 (4%)		2 (12.5%)	1 (6%)
Any macroscopic lesion	2 (9%)	18 (78%)	2 (9%)		4 (25%)	3 (19%)
Non-caseating granuloma on histology	1 (4%)	22 (96%)	3 (13%)	5 (31%)	6 (37.5%)	1 (6%)
Any macroscopic or histological lesion	3 (13%)	23 (100%)	4 (17%)	5 (31%)	6 (37.5%)	4 (25%)

**3.3. Endoscopic characteristics**

Upper gastrointestinal endoscopy was performed in 23 cases and ileocolonoscopy in 16, for digestive symptoms or unexplained weight loss. Macroscopic lesions were seen in esophagus (9%), stomach (78%), duodenum (9%), colon (25%) and rectum (19%), without any macroscopic lesions seen in the ileum (Table 1). The median number of segments with macroscopic lesions was 1 (range 0–5). We found only 1 stenosis (involving the pylorus) and no case of perforation or fistulae.

Noncaseating granulomas were seen in esophagus (4%), stomach (96%), duodenum (13%), ileum (31%), colon (37.5%), and rectum (6%). In the absence of any macroscopic lesions, systematic biopsies showed noncaseating granulomas in 33% of cases in the esophagus, 100% in the stomach, 18% in the duodenum, 62% in the ileum, 25% in the colon, and 25% in the rectum.

Defining an involved digestive segment in the presence of any macroscopic lesion and/or noncaseating granuloma, the esophagus was affected in 13% of cases, stomach in 100%, duodenum in 17%, ileum in 31%, colon in 37.5%, and rectum in 25% of cases. The median number of involved digestive segments was 1 (range 1–6).

**3.4. Treatment of DTS**

At the time of diagnosis of DTS, 20% of patients were receiving steroids (median prednisone amount 19 mg [5–30 mg]) and 8% of patients were receiving another immunosuppressive drug for treatment of sarcoidosis. After the diagnosis of digestive tract involvement, the immunosuppressive treatment consisted of steroids for 64% of cases (median prednisone amount 40 mg [10–60 mg]) and another drug in 32%: azathioprine (n=2; 8%), sulfasalazine (n=2; 8%), hydroxychloroquine (n=2; 8%), methotrexate (n=1; 4%), and cyclophosphamide (n=1; 4%). The treatment was initiated because of digestive symptoms in 24% of patients. A proton pump inhibitor was used in 94% of cases, red cell transfusions in 12%, and endoscopic treatment in 8% (n=2): 1 pyloric stenosis dilatation and 1 haemostatic treatment for gastric bleeding linked to telangiectasias.

**3.5. Outcome of DTS**

After a median of 67 months (range 3–262 months) of follow-up, 24% of cases had persistent digestive tract symptoms consisting

of diarrhea, abdominal pain, vomiting, and weight loss. At the last follow-up, BMI increased from a median of 21 kg/m<sup>2</sup> at baseline (range 11.5–46) to 25.4 kg/m<sup>2</sup> (range 16.8–46.4) ( $P=0.03$ ). Persistent extradigestive lesions were noted in 44% of cases (20% lungs, 16% liver, 8% lymph nodes, 8% heart), with a median number of affected organs of 0 (range 0–3) versus 3 (0–7) at baseline ( $P<0.0001$ ). In 64% of cases, steroids were still used and were combined with another immunosuppressive drug in 28% of cases (12% methotrexate, 8% hydroxychloroquine, 4% azathioprine, 4% mycophenolate mofetil). The prednisone amount was tapered from a median of 40 mg/day (range 10–60 mg) at baseline to 10 mg/day (5–40 mg). Only 1 patient died from postoperative sepsis following ablation of a hepatic tumor (histology revealed a granulomatous pseudotumor).

**3.6. Comparison between patients with DTS and with NDTs**

We included 50 patients with NDTs as controls (median age at 39 years [range 15–62] and sex ratio 2:1) (Table 2).

As compared with patients with NDTs, those with DTS showed more African/Afro-Caribbean origin (56% vs. 32%;  $P=0.03$ ), less Northern Africa origin (12% vs. 37%;  $P=0.03$ ), more weight loss >3 kg (52% vs. 14%;  $P=0.0003$ ), less thoracic adenopathies (60% vs. 92%;  $P=0.0014$ ), more liver involvement (44% vs. 22%;  $P=0.048$ ), more kidney involvement (12% vs. 0%;  $P=0.03$ ), and more anemia (28% vs. 8%;  $P=0.04$ ) (Table 2). On multivariate analyses, DTS was associated with northern Africa origin (odds ratio [OR] 5; 95% CI 1.01–25), weight loss >3 kg (5.81; 1.44–23.3), and absence of thoracic adenopathies (5; 1.03–25). At diagnosis, the 2 groups did not differ in use of steroids (48% vs. 52%;  $P=0.74$ ) or other immunosuppressive drugs (16% vs. 14%;  $P=0.99$ ).

At the last follow-up, the number of affected organs was greater for patients with NDTs than with DTS, with a median of 2 (0–5) versus 0 (0–3) organs ( $P=0.0017$ ) (Table 3). In particular, pulmonary involvement was more frequent (54% vs. 28%;  $P=0.033$ ), with higher New York Heart Association dyspnea score (2 [1–3] vs. 1 [1–2];  $P=0.002$ ). The 2 groups did not differ in use of steroids (56% vs. 64%;  $P=0.52$ ) and daily amount of prednisone (median 5 mg for both;  $P=0.38$ ). Nonetheless, patients with NDTs more frequently received another associated immunosuppressive drug (54% vs. 28%;  $P=0.03$ ).

**Table 2****Characteristics of patients with DTS and with NDTS.**

	DTS (n=25)	NDTS (n=50)	P
Age, y	36 (19–65)	39 (15–62)	0.46
Sex, female (%)	17 (68)	34 (68)	0.99
Smoking (%)	7 (33)	12 (34)	0.94
Ethnicity			
White (%)	6 (24)	12 (29)	0.64
African/Afro-Caribbean (%)	14 (56)	12 (32)	0.03*
Asian (%)	2 (8)	0 (0)	0.14
Northern Africa (%)	3 (12)	15 (37)	0.03*
Familial history of sarcoidosis	1 (4)	3 (6)	0.99
Time between onset of symptoms and diagnosis, mo	9.7 (0–67)	5 (0–62)	0.1
Löfgren syndrome	0 (0)	7 (14)	0.09
BMI, kg/m <sup>2</sup>	23.3 (11.5–46.1)	25.9 (18.8–36.4)	0.02*
Weight loss >3 kg (%)	13 (52)	7 (14)	0.0003*
Weight loss, kg	4 (0–21)	0 (0–15)	0.0006*
Extradigestive lesions			
Lung (%)	22 (88)	35 (70)	0.09
Skin (%)	7 (28)	18 (36)	0.49
Specific lesions (%)	6 (24)	11 (22)	0.84
Erythema nodosum (%)	1 (4)	6 (12)	0.41
Thoracic lymph nodes (%)	15 (60)	37 (92)	0.001*
Spleen (%)	5 (20)	6 (12)	0.49
Anemia (%)	7 (28)	4 (8)	0.037*
Nervous system (%)	6 (24)	8 (16)	0.42
Cranial nerves (%)	2 (8)	4 (8)	0.99
Central nervous system (%)	5 (20)	3 (6)	0.108
Uveitis (%)	0 (0)	5 (10)	0.162
Ocular sicca (%)	6 (24)	10 (20)	0.69
Heart (%)	2 (8)	2 (4)	0.597
Hypercalcemia (%)	0 (0)	1 (2)	0.99
Kidneys (%)	3 (12)	0 (0)	0.03*
Granulomatous interstitial nephritis (%)	2 (8)	0 (0)	0.11
GFR <60 mL/min	3 (12)	0 (0)	0.03*
Diabetes insipidus (%)	1 (4)	0 (0)	0.3
Parotid (%)	5 (20)	3 (6)	0.11
Upper respiratory tract (%)	2 (8)	3 (6)	0.99
Mouth sicca (%)	6 (24)	7 (14)	0.28
Joints (%)	8 (32)	14 (28)	0.72
Liver (%)	11 (44)	11 (22)	0.048*
No. of injured organs	4 (2–8)	3 (1–6)	0.15
ACE elevation	12 (57)	22 (69)	0.39
Steroids treatment (%)	12 (48)	26 (52)	0.74
Dose, mg/day	0 (0–100)	0 (0–80)	0.89
Immunosuppressor (%)	4 (16)	7 (14)	0.99
Methotrexate	1 (4)	2 (4)	0.99
Hydroxychloroquine	2 (8)	5 (10)	0.99
Azathioprine	1 (4)	0 (0)	0.33
Cyclophosphamid	1 (4)	0 (0)	0.33
Mycophenolate mofetil	1 (4)	0 (0)	0.33

Data are median (range) unless indicated. ACE=angiotensin-converting enzyme, DTS=digestive tract sarcoidosis, GFR=glomerular filtration rate, NDTS=nondigestive tract sarcoidosis.  
\*  $p < 0.05$ .

### 3.7. Comparison with Crohn disease controls

We included 100 patients with Crohn disease as controls (median age 35.5 years [range 15–62] and sex ratio 2.1) (Table 4).

As compared with Crohn disease patients, those with DTS showed less history of inflammatory bowel disease (0% vs. 17%;  $P=0.022$ ), less smoking (33% vs. 63%;  $P=0.01$ ), less white origin (24% vs. 73%;  $P=0.0001$ ), less ileal or colonic involvement (25% vs. 95%;  $P=0.0001$ ), anal or perianal lesions

**Table 3****Outcome of patients with DTS and with NDTS at last follow-up.**

Evolution	DTS (n=25)	NDTS (n=50)	P
Follow-up, mo	67 (3–262)	88 (3–334)	0.16
BMI	25.4 (16.8–46.5)	26.5 (18–55)	0.45
Lungs involvement (%)	7 (28)	26 (54)	0.033*
NYHA score	1 (1–2)	2 (1–3)	0.002*
Hypoxemia <60 mmHg (%)	0 (0)	0 (0)	1
Pulmonary hypertension (%)	0 (0)	0 (0)	1
Long-term oxygen therapy (%)	0 (0)	0 (0)	1
New organ involvement (%)	8 (32)	26 (54)	0.07
No. of new organ involvement	0 (0–2)	1 (0–6)	0.038*
Persistent organ involvement (%)	11 (44)	44 (92)	<0.0001*
No. of persistent organ involvement	0 (0–3)	2 (0–5)	0.0017*
ACE elevation (%)	8 (47)	24 (58)	0.42
Hypergammaglobulinemia (%)	5 (62)	9 (45)	0.68
CRP >10 mg/L (%)	4 (27)	2 (14)	0.65
Steroids (%)	16 (64)	27 (56)	0.52
Dose	5 (0–40)	5 (0–50)	0.38
Other immunosuppressor on last follow-up (%)	7 (28)	26 (54)	0.03*
No. of immunosuppressors lines during follow-up	1 (0–6)	1 (0–5)	0.92
Methotrexate (%)	8 (32)	19 (40)	0.52
Hydroxychloroquine (%)	6 (24)	17 (35)	0.32
Azathioprine (%)	2 (8)	7 (15)	0.71
Cyclophosphamide (%)	6 (24)	1 (2)	0.0055*
Mycophenolate mofetil (%)	4 (16)	2 (4)	0.17
Sulfasalazine (%)	2 (8)	0 (0)	0.11
Cyclosporin A (%)	1 (4)	0 (0)	0.34
Leflunomide (%)	0 (0)	5 (10)	0.16
TNF- $\alpha$ antagonist (%)	0 (0)	3 (6)	0.55
Rituximab (%)	0 (0)	1 (2)	1
Thalidomide (%)	1 (4)	1 (2)	1
Death (%)	1 (4)	0 (0)	0.34

Data are median (range) unless indicated. ACE=angiotensin-converting enzyme, BMI=body mass index, CRP=C-reactive protein, DTS=digestive tract sarcoidosis, NDTS=nondigestive tract sarcoidosis, NYHA=New York Heart Association, TNF=tumor necrosis factor.  
\*  $p < 0.05$ .

(0% vs. 17%;  $P=0.023$ ), but more often were of African/Afro-Caribbean origin (56% vs. 4%;  $P=0.0001$ ) and Asian origin (8% vs. 0%;  $P=0.04$ ) and had more upper digestive tract involvement (78% vs. 6%;  $P=0.0001$ ). On multivariate analyses, DTS was associated with African/Afro-Caribbean origin (OR 27.2; 95% CI 3.6–203.9) and absence of ileal or colonic involvement (OR 62.5; 95% CI 10.3–500).

At the last follow-up (Table 5), persistent clinical digestive involvement was more frequent in patients with Crohn disease than DTS (65% vs. 24%;  $P=0.0002$ ), as was stenosis (26% vs. 4%;  $P=0.015$ ), perforations (17% vs. 0%;  $P=0.02$ ), and surgical interventions (31% vs. 0%;  $P=0.0013$ ). BMI was higher in DTS group (25.4 [16.8–46.5]) versus 21.9 [16.6–39.2];  $P=0.032$ ). Patients with DTS more frequently used steroids at the last visit (64% vs. 23%;  $P < 0.0001$ ), but other immunosuppressive drugs were more frequent for patients with Crohn disease (55% vs. 28%;  $P=0.02$ ).

## 4. Discussion

We describe the largest series of digestive tract involvement in sarcoidosis. This rare manifestation of sarcoidosis must be sought in the presence of weight loss and especially with digestive symptoms. Sarcoidosis may affect every segment of the digestive tract, but the stomach is the preferred disease location. Although

**Table 4****Characteristics of patients with DTS and Crohn disease.**

	DTS (n=25)	Crohn disease (n=100)	P
Age, y	36 (19–65)	35.5 (15–62)	0.5
Sex, female (%)	17 (68)	68 (68)	0.99
Familial history of IBD (%)	0 (0)	17 (17)	0.02*
Smoking (%)	7 (33)	63 (63)	0.01*
Ethnicity			
White (%)	6 (24)	69 (73)	0.0001*
African/Afro-Caribbean (%)	14 (56)	4 (4)	0.0001*
Asian (%)	2 (8)	0 (0)	0.04*
Northern Africa (%)	3 (12)	14 (15)	0.52
Time between onset of symptoms and diagnosis, mo	8 (0–266)	3 (0–250)	0.21
Extradigestive involvements			
Skin (%)	5 (20)	10 (10)	0.18
Oral ulcers (%)	1 (4)	5 (5)	0.99
Joints (%)	7 (28)	20 (20)	0.38
Uveitis/scleritis (%)	0 (0)	3 (3)	0.99
Digestive tract macroscopic lesions			
Upper digestive tract (%)	18 (78)	6 (6)	0.0001*
Ileum (%)	0 (0)	67 (67)	0.0001*
Colon (%)	4 (25)	55 (55)	0.03*
Ileum or colon (%)	4 (25)	95 (95)	0.0001*
Rectum (%)	3 (19)	32 (32)	0.38
Anus (%)	0 (0)	17 (17)	0.02*
Treatment			
Endoscopic treatment (%)	2 (8)	Not determined	
Surgery (%)	0 (0)	4 (4)	0.58
Steroids (%)	16 (64)	49 (49)	0.21

Data are median (range) unless indicated. DTS = digestive tract sarcoidosis, IBD = inflammatory bowel disease.

\* $p < 0.05$ .

Crohn disease is the major differential diagnosis, the 2 diseases have important differences. Indeed, patients with sarcoidosis often have multivisceral granulomatous involvement. Moreover, sarcoidosis is associated with a low prevalence of ileal or colonic macroscopic involvement, with no anal lesions, and better digestive outcome than Crohn disease.

Digestive tract involvement is rare in sarcoidosis, and only case reports and 2 series of 5<sup>[5]</sup> and 4<sup>[11]</sup> patients have been described. Considering the cases with our inclusion criteria, 43 cases were reported since 1972.<sup>[5,11–43]</sup> This low prevalence may be underestimated because retrospective reports concerned only symptomatic patients, and only systematic endoscopy could reveal the prevalence of DTS. Furthermore, the issue of the differential diagnosis of sarcoidosis is particularly important with digestive tract involvement, especially when this is the first manifestation of the disease, as for 12% of our patients. Tuberculosis and Crohn disease are usually the main alternative diagnoses. The digestive tract is a rare localization of tuberculosis,<sup>[44]</sup> which may be fatal if the diagnosis is missed and immunosuppressive drugs are introduced.<sup>[45]</sup>

Even African/Afro-Caribbean patients seem to have more severe disease, we did not find any significant differences concerning digestive tract involvement according to the ethnicity in our study.<sup>[46,10]</sup> On the contrary, when comparing with Crohn disease patients, patients with digestive sarcoidosis were more frequently African/Afro-caribbeans, with significant association of this involvement with this ethnicity (OR 27.2; 95% CI 3.6–203.9).

In our patients, the 5 more frequent digestive symptoms were abdominal pain (56%), weight loss (52%), nausea/vomiting (48%), diarrhea (32%), and digestive bleeding (28%). These data

**Table 5****Outcome of DTS and Crohn disease at last follow-up.**

Evolution	DTS (n=25)	Crohn disease (n=100)	P
Follow-up in months, median (range)	67 (3–262)	92.5 (0–366)	0.23
BMI, median (range)	25.4 (16.8–46.5)	21.9 (16.6–39.2)	0.032*
Persistent clinical digestive activity (%)	6 (24)	65 (65)	0.0002*
Stenosis	1 (4)	26 (26)	0.015*
Perforation	0 (0)	17 (17)	0.02*
Digestive cancer	0 (0)	0 (0)	0.99
Endoscopic treatment during follow-up (%)	3 (12)	2 (2)	0.054
Surgery during follow-up (%)	0 (0)	31 (31)	0.0013*
No. of surgeries	0 (0–0)	0 (0–3)	0.0015*
Steroids at last follow-up (%)	16 (64)	23 (23)	<0.0001*
Other immunosuppressor at last follow-up (%)	7 (28)	55 (55)	0.02*
No. of immunosuppressor lines during follow-up, median (range)	1 (0–6)	1 (0–2)	0.15
Methotrexate (%)	8 (32)	9 (9)	0.003*
Hydroxychloroquine (%)	6 (24)	0 (0)	<0.0001*
Cyclophosphamide (%)	6 (24)	0 (0)	<0.0001*
Mycophenolate Mofetil (%)	4 (16)	0 (0)	0.001*
Sulfasalazine (%)	2 (8)	0 (0)	0.039*
Cyclosporine A (%)	1 (4)	0 (0)	0.2
Thalidomide (%)	1 (4)	0 (0)	0.2
Azathioprine (%)	2 (8)	50 (50)	<0.0001*
TNF- $\alpha$ antagonist (%)	0 (0)	30 (30)	0.0005*
Deaths (%)	1 (4)	0 (0)	0.2

BMI = body mass index, DTS = digestive tract sarcoidosis, TNF = tumor necrosis factor.

\* $p < 0.05$ .

are similar to features reported in the literature<sup>[5,11–43]</sup>: abdominal pain (70%), weight loss (39%), nausea/vomiting (23%), diarrhea (16%), and digestive bleeding (12%). In our case series, endoscopy usually revealed macroscopic lesions, most often in the stomach (78% cases), but 16% of our cases had no macroscopic lesions, and systematic biopsies revealed granulomas in 100% for the stomach to 18% for the duodenum and 31% for the ileum. In the literature, the stomach is the most-often involved segment (58% cases reported), but any segment may be affected, from the esophagus to rectum.<sup>[5,11–43]</sup> In our series, every patient had stomach involvement, and each segment could be affected with a frequency similar to previous reports.<sup>[5,11–43]</sup>

As compared with patients with NDTs, those with DTS less often had thoracic adenopathies (60% vs. 92%;  $P = 0.0014$ ), but more often liver involvement (44% vs. 22%;  $P = 0.048$ ). Anemia was more frequent in DTS cases (28% vs. 8%;  $P = 0.04$ ) and may be caused by iron deficiency linked to chronic digestive bleeding, malabsorption of iron, folates or cobalamin,<sup>[37,47]</sup> but in this retrospective study, the precise mechanism of anemia was not examined. Patients with than without DTS more often had significant weight loss (52% vs. 14%;  $P = 0.0003$ ). Weight loss, reported in 28% of patients with sarcoidosis,<sup>[48]</sup> was independently associated with DTS in our case series (OR 5.8, 95% CI 1.44–23.3). During follow-up, BMI normalized and became similar to that for patients with NDTs (median 25.4 vs. 26.5 kg/m<sup>2</sup>;  $P = 0.45$ ).

Despite similarities between Crohn disease and sarcoidosis, many differences are noted. Indeed, both diseases do not affect the same population because we found African and Afro-Caribbean ethnicity independently associated with sarcoidosis

(OR 27.2; 95% CI 3.6–203.9). Moreover, our patients with DTS often had multivisceral lesions not usually seen in Crohn disease (interstitial lung disease, adenopathy, granulomatous hepatitis, hypercalcemia, central nervous system or heart involvement). The digestive manifestations also clearly differ. Sarcoidosis more often involved the superior digestive tract (78% vs. 6%;  $P=0.0001$ ), especially the stomach. Patients with Crohn disease more often had macroscopic ileal or colonic involvement (95% vs. 25%;  $P=0.0001$ ), whereas the ileum or colon were involved in 30% of sarcoidosis cases in previous reports.<sup>[5,11–43]</sup> We found the absence of ileal or colonic involvement independently associated with DTS in our study (OR 62.5, 95% CI 10.3–500). Thus, the absence of ileal or colonic involvement in a patient with a granulomatous digestive tract disease, especially with an African or Afro-Caribbean origin, must encourage considering the diagnosis of sarcoidosis.

The outcomes of Crohn disease and DTS also differ because Crohn disease patients have more severe digestive outcomes. Indeed, in our series, less DTS than Crohn disease patients had persistent digestive clinical activity at last follow-up (24% vs. 65%;  $P=0.0002$ ). Only a few surgical digestive complications were noted in sarcoidosis, both in our series (4% of stenosis, no perforation, fistulae, occlusion or surgery) and in the literature (7% stenosis, 2% perforation, 5% occlusion),<sup>[5,11–43]</sup> whereas 31% of patients with Crohn disease had surgical complications in our series.

Crohn disease and sarcoidosis have different susceptibility factors, as reflected in our study by the differences in frequency of smoking, familial history of inflammatory bowel disease and ethnic origin. Very few similarities exist between these 2 chronic granulomatosis. Both have a common North-South epidemiologic gradient.<sup>[49,50]</sup> Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) polymorphisms in leucine-rich repeat domains are associated with Crohn disease,<sup>[51]</sup> and NOD2 mutations are present in Blau disease, a juvenile form of sarcoidosis.<sup>[52,53,54]</sup> Similar single-nucleotide polymorphisms in several genes were identified in sarcoidosis and Crohn disease<sup>[55,56,57,58,59,60,61]</sup>: butyrophilin-like 2 (BTNL2), rs1398024, interleukin-23 receptor, and HERC2. No other association was found between the diseases, which seem to have a different pathophysiology, which agrees with the differences in clinical presentation. The association between Crohn disease and sarcoidosis in the same patient is exceptional,<sup>[62]</sup> but cannot be excluded in our patients. Nonetheless, the evolution of disease in our patients does not advocate for an association with Crohn disease.

The diagnosis of DTS required endoscopic evaluation in all patients in our study. In the absence of digestive symptoms or middle complaints, the value of imaging methods could be discussed. Entero-CT and entero-MRI are used in Crohn disease, but few data about the value of these imagings are available in DTS.<sup>[63,64]</sup> PET/CT is often used in sarcoidosis, with few cases reported for DTS, but the value of PET/CT for digestive involvement could be limited because of frequent digestive uptakes.<sup>[65]</sup> Considering the treatment of digestive tract involvement, recent studies demonstrated the value of tumor necrosis factor (TNF)- $\alpha$  antagonists in pulmonary and neurological involvements.<sup>[66,67]</sup> TNF- $\alpha$  antagonists could be interesting to consider for DTS, especially they are widely used and effective in Crohn disease.

Some limitations exist in this retrospective study. Since the patient selection was from the “Groupe Sarcoidose Franco-phonie,” only noticeable cases were probably proposed, by

secondary or tertiary centers. Therefore, the described manifestations of sarcoidosis could be less important in the general population. This bias was partially corrected by the selection of controls from the same secondary centers. Furthermore, we could not precisely evaluate the efficiency of treatment on digestive tract involvement because the treatment was sometimes initiated for other organ involvement. Moreover, because symptomatic patients were selected, we cannot extrapolate our results to asymptomatic forms, which frequency could not be evaluated from this article.

In conclusion, DTS, a rare manifestation of sarcoidosis, must be sought in the presence of weight loss and digestive symptoms. Sarcoidosis must be considered in every patient with digestive granulomatosis, especially in the absence of macroscopic ileal or colonic lesions. The digestive tract outcome seems to be less severe with sarcoidosis than Crohn disease.

## References

- Valeyre D, Prasse A, Nunes H, et al. Sarcoidosis. *Lancet* 2014;383:1155–67.
- Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001;164:1885–9.
- Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med* 2007;357:2153–65.
- Morimoto T, Azuma A, Abe S, et al. Epidemiology of sarcoidosis in Japan. *Eur Respir J* 2008;31:372–9.
- Farman J, Ramirez G, Rybak B, et al. Gastric sarcoidosis. *Abdom Imaging* 1997;22:248–52.
- Ebert EC, Kierson M, Hagspiel KD. Gastrointestinal and hepatic manifestations of sarcoidosis. *Am J Gastroenterol* 2008;103:3184–92. quiz 3193.
- Vahid B, Spodik M, Braun KN, et al. Sarcoidosis of gastrointestinal tract: a rare disease. *Dig Dis Sci* 2007;52:3316–20.
- Shapiro JL, Goldblum JR, Petras RE. A clinicopathologic study of 42 patients with granulomatous gastritis. Is there really an « idiopathic » granulomatous gastritis? *Am J Surg Pathol* 1996;20:462–70.
- Bernstein CN, Blanchard JF, Rawsthorne P, et al. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2001;96:1116–22.
- Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med* 1999;160:736–55.
- Maàmour N, Guellou S, Ben Hariz F, et al. Gastrointestinal sarcoidosis. *Rev Médecine Interne Fondée Par Société Natl Française Médecine Interne* 2010;31:262–7.
- Holman GA, Kolendich KM. Gastric sarcoidosis in the setting of chronic lymphocytic leukemia. *Dig Dis Sci* 2014;59:35–8.
- Pearce J, Ehrlich A. Gastric sarcoidosis. *Ann Surg* 1955;141:115–9.
- Bat T, Morgan CM, Marx R, et al. Colon sarcoidosis presenting with abdominal pain. *Endoscopy* 2014;46(Suppl 1 UCTN):E121.
- Shkolnik LE, Shin RD, Brabeck DM, et al. Symptomatic gastric sarcoidosis in a patient with pulmonary sarcoidosis in remission. *BMJ Case Rep* 2012;2012.
- Samarasena JB, Chu E, Muthusamy VR. An African American man with dysphagia: a unique initial presentation of sarcoidosis. *Endoscopy* 2012;44(Suppl 2 UCTN):E63–64.
- Inomata M, Ikushima S, Awano N, et al. Upper gastrointestinal sarcoidosis: report of three cases. *Intern Med Tokyo Jpn* 2012;51:1689–94.
- Hunjan T, Chaudery M, Zaidi A, et al. Appendicular sarcoidosis mimicking acute appendicitis. *BMJ Case Rep* 2012;2012.
- Esmadi M, Ahmad DS, Odum B, et al. Sarcoidosis: an extremely rare cause of granulomatous enterocolitis. *J Gastrointest Liver Dis JGLD* 2012;21:423–5.
- Tsujino T, Ito Y, Yoshida H, et al. Duodenal mass in a patient with weight loss and liver dysfunction. Duodenal and liver sarcoidosis. *Gut* 2011;60:1659–60. 1677.

- [21] Bredenoord AJ, Jafari J, Kadri S, et al. Case report: achalasia-like dysmotility secondary to oesophageal involvement of sarcoidosis. *Gut* 2011;60:153–5.
- [22] Ziora D, Trzepióra B, Kozielski J. Gastric sarcoidosis – a case report. *Pneumonol Alergol Pol* 2010;78:374–8.
- [23] Ushiki A, Koizumi T, Kubo K, et al. Colonic sarcoidosis presenting multiple submucosal tumor-like lesions. *Intern Med Tokyo Jpn* 2009;48:1813–6.
- [24] Marie I, Sauvetre G, Levesque H. Small intestinal involvement revealing sarcoidosis. *QJM Mon J Assoc Physicians* 2010;103:60–2.
- [25] Friedman M, Ali MA, Borum ML. Gastric sarcoidosis: a case report and review of the literature. *South Med J* 2007;100:301–3.
- [26] Boyum RD, Yeung KJA, Kaplan KJ, et al. Pediatric gastrointestinal sarcoidosis presenting with protein-losing enteropathy. *J Pediatr Gastroenterol Nutr* 2007;44:152–6.
- [27] Brunner J, Sergi C, Müller T, et al. Juvenile sarcoidosis presenting as Crohn's disease. *Eur J Pediatr* 2006;165:398–401.
- [28] Doudier B, Schleinitz N, Hardwiggen J, et al. Digestive sarcoidosis: an unusual case revealed by acute ileocecal invagination. *Rev Médecine Interne Fondée Par Société Natl Française Médecine Interne* 2003;24:700–2.
- [29] Beniwal RS, Cummings OW, Cho WK. Symptomatic gastrointestinal sarcoidosis: case report and review of the literature. *Dig Dis Sci* 2003;48:174–8.
- [30] Lukens FJ, Machicao VI, Woodward TA, et al. Esophageal sarcoidosis: an unusual diagnosis. *J Clin Gastroenterol* 2002;34:54–6.
- [31] Marcato N, Abergel A, Froment S, et al. Sarcoidosis gastropathy: diagnosis and contribution of echo-endoscopy. *Gastroentérologie Clin Biol* 1999;23:394–7.
- [32] Takashima M, Hanai H, Sato Y, et al. Association of Crohn's ileitis with pulmonary and cutaneous sarcoidosis in a Japanese patient. *Gastrointest Endosc* 1998;48:637–9.
- [33] Dumot JA, Adal K, Petras RE, et al. Sarcoidosis presenting as granulomatous colitis. *Am J Gastroenterol* 1998;93:1949–51.
- [34] Fireman Z, Sternberg A, Yarchovsky Y, et al. Multiple antral ulcers in gastric sarcoid. *J Clin Gastroenterol* 1997;24:97–9.
- [35] Hilzenrat N, Spanier A, Lamoureux E, et al. Colonic obstruction secondary to sarcoidosis: nonsurgical diagnosis and management. *Gastroenterology* 1995;108:1556–9.
- [36] Parlier G, Josset P, Charritat JL, et al. Sarcoidosis in children with digestive manifestations. *Arch Pédiatrie Organe Off Société Fr Pédiatrie* 1996;3:141–3.
- [37] MacRury SM, McQuaker G, Morton R, et al. Sarcoidosis: association with small bowel disease and folate deficiency. *J Clin Pathol* 1992;45:823–5.
- [38] Levine MS, Ekberg O, Rubesin SE, et al. Gastrointestinal sarcoidosis: radiographic findings. *AJR Am J Roentgenol* 1989;153:293–5.
- [39] Panella VS, Katz S, Kahn E, et al. Isolated gastric sarcoidosis. Unique remnant of disseminated disease. *J Clin Gastroenterol* 1988;10:327–31.
- [40] Gallagher P, Harris M, Turnbull FW, et al. Gastric sarcoidosis. *J R Soc Med* 1984;77:837–9.
- [41] Munt PW. Sarcoidosis of the appendix presenting as appendiceal perforation and abscess. *Chest* 1974;66:295–7.
- [42] Gould SR, Handley AJ, Barnardo DE. Rectal and gastric involvement in a case of sarcoidosis. *Gut* 1973;14:971–3.
- [43] Davies RJ. Dysphagia, abdominal pain, and sarcoid granulomata. *Br Med J* 1972;3:564–5.
- [44] Donoghue HD, Holton J. Intestinal tuberculosis. *Curr Opin Infect Dis* 2009;22:490–6.
- [45] Sorrentino D, Avellini C, Zearo E. Colonic sarcoidosis, infliximab, and tuberculosis: a cautionary tale. *Inflamm Bowel Dis* 2004;10:438–40.
- [46] Judson MA, Boan AD, Lackland DT. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. *Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG World Assoc Sarcoidosis Granulomatous Disord* 2012;29:119–27.
- [47] Tinker MA, Viswanathan B, Laufer H, et al. Acute appendicitis and pernicious anemia as complications of gastrointestinal sarcoidosis. *Am J Gastroenterol* 1984;79:868–72.
- [48] Nunes H, Bouvry D, Soler P, et al. Sarcoidosis. *Orphanet J Rare Dis* 2007;2:46.
- [49] Little BP. Sarcoidosis: overview of pulmonary manifestations and imaging. *Semin Roentgenol* 2015;50:52–64.
- [50] Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut* 1996;39:690–7.
- [51] Hugot JP, Chamaillard M, Zouali H, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature* 2001;411:599–603.
- [52] Miceli-Richard C, Lesage S, Rybojad M, et al. CARD15 mutations in Blau syndrome. *Nat Genet* 2001;29:19–20.
- [53] Rosé CD, Pans S, Casteels I, et al. Blau syndrome: cross-sectional data from a multicentre study of clinical, radiological and functional outcomes. *Rheumatol Oxf Engl* 2015;54:1008–16.
- [54] Kanazawa N, Okafuji I, Kambe N, et al. Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor-kappaB activation: common genetic etiology with Blau syndrome. *Blood* 2005;105:1195–7.
- [55] Franke A, Fischer A, Nothnagel M, et al. Genome-wide association analysis in sarcoidosis and Crohn's disease unravels a common susceptibility locus on 10p12.2. *Gastroenterology* 2008;135:1207–15.
- [56] Fischer A, Nothnagel M, Franke A, et al. Association of inflammatory bowel disease risk loci with sarcoidosis, and its acute and chronic subphenotypes. *Eur Respir J* 2011;37:610–6.
- [57] Rybicki BA, Walewski JL, Maliarik MJ, et al. ACCESS Research GroupThe BTNL2 gene and sarcoidosis susceptibility in African Americans and Whites. *Am J Hum Genet* 2005;77:491–9.
- [58] Li Y, Wollnik B, Pabst S, et al. BTNL2 gene variant and sarcoidosis. *Thorax* 2006;61:273–4.
- [59] Adrianto I, Lin CP, Hale JJ, et al. Genome-wide association study of African and European Americans implicates multiple shared and ethnic specific loci in sarcoidosis susceptibility. *PLoS One* 2012;7:e43907.
- [60] Prescott NJ, Lehne B, Stone K, et al. Pooled sequencing of 531 genes in inflammatory bowel disease identifies an associated rare variant in BTNL2 and implicates other immune related genes. *PLoS Genet* 2015;11:e1004955.
- [61] Hong SN, Park C, Park SJ, et al. Deep resequencing of 131 Crohn's disease associated genes in pooled DNA confirmed three reported variants and identified eight novel variants. *Gut* 2015.
- [62] Kallel L, Fekih M, Ben Ghorbel I, et al. A rare case of systemic sarcoidosis followed by Crohn's disease: a fortuitous association or etiopathogenic link? *Presse Médicale Paris Fr* 1983 2010;39:148–50.
- [63] Fiorino G, Bonifacio C, Peyrin-Biroulet L, et al. Prospective comparison of computed tomography enterography and magnetic resonance enterography for assessment of disease activity and complications in ileocolonic Crohn's disease. *Inflamm Bowel Dis* 2011;17:1073–80.
- [64] Siddiki HA, Fidler JL, Fletcher JG, et al. Prospective comparison of state-of-the-art MR enterography and CT enterography in small-bowel Crohn's disease. *AJR Am J Roentgenol* 2009;193:113–21.
- [65] Leroy C, Girard C, Girard-Madoux M-H, et al. An unusual case of duodenal sarcoidosis. *Rev Med Interne Fondée Par Soc Natl Française Med Interne* 2015.
- [66] Baughman RP, Drent M, Kavuru M, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med* 2006;174:795–802.
- [67] Judson MA, Baughman RP, Costabel U, et al. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. *Eur Respir J* 2008;31:1189–96.