Association of Sarcoidosis and Immune Thrombocytopenia

Presentation and Outcome in a Series of 20 Patients

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Abstract: The association of sarcoidosis and immune thrombocytopenia (ITP) has rarely been investigated. The aim of the current retrospective study was to investigate the clinical and biological phenotypes and outcome of this association in a large series of recent patients. Twenty patients (50% men) were included. Median age at sarcoidosis and ITP diagnosis was 36 (range, 10–83 yr) and 38 (range, 21–83 yr) years, respectively. In 11 of 20 (55%) patients, sarcoidosis onset preceded ITP (median interval, 48 mo; range, 6–216 mo). In 5 of 20 (25%) patients, the 2 conditions occurred concomitantly. In 4 of 20 (20%) patients, ITP onset preceded sarcoidosis (median interval, 68 mo; range, 15–153 mo). In 4 cases, sarcoidosis and ITP were not concomitant, since 1 condition was cured before the other was declared. In 12 of 20 (60%) patients there was a simultaneous onset or relapse of both ITP and sarcoidosis. Sarcoidosis phenotype was characterized by an acute onset in 40% of patients. The visceral involvement included thoracic sites in 19 of 20 (95%) patients and extrathoracic sites in 16 of 20 (80%) patients. At ITP onset, median platelet count was 11 $\times$ 10^9/L (range, 3–90); 17 (85%) patients had a platelet count <30 $\times$ 10^9/L. Seven (35%) patients had a bleeding score >8 without visceral bleeding.

Nineteen of the 20 (95%) patients were treated specifically for ITP. After the first-line therapy (prednisone at 1 mg/kg per day for at least 3 consecutive weeks in all patients; with IVIg in addition for 10 patients with severe bleeding score), 12 of 19 (63%) patients achieved a complete response, 6 (31.5%) had a partial response, and only 1 patient failed to respond. At the end of ITP follow-up (median, 70 mo; range, 12–142 mo), 18 (90%) patients achieved a complete response, 1 achieved a partial response, and 1 had no response. After a median follow-up of 105 months, 13 of 20 (65%) patients had persistent sarcoidosis requiring prolonged therapy, and thus sarcoidosis represented the main long-term concern. Main conclusions were 1) ITP presentation was usually severe, but response to treatment was favorable in almost all cases, with no death and no severe bleeding, in contrast with older reports, 2) sarcoidosis was remarkable for the high proportion of cases with an acute onset, a chronic course, and the need for prolonged prednisone therapy, 3) sarcoidosis and ITP onset and evolution were not always synchronous.

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Abbreviations: ALPS = autoimmune lymphoproliferative syndrome, CR = complete response to treatment, HCQ = hydroxychloroquine, ITP = immune thrombocytopenia, IVIg = intravenous immunoglobulin, NR = no response to treatment, PR = partial response to treatment.

INTRODUCTION

Sarcoidosis is a systemic disease of unknown cause characterized by the formation of granulomatous lesions in various organs with a predilection for the lower respiratory tract.[2] In 1938, Jersild et al[12] were first to report the occurrence of thrombocytopenia in sarcoidosis. However, to our knowledge no more than 65 cases have been reported. Thrombocytopenia can stem from 3 main mechanisms during sarcoidosis: hypersplenism, bone marrow infiltration, and immune thrombocytopenia (ITP), with this last mechanism accounting for more than 80% of cases.[16] In several papers, unlike lupus erythematosus or other autoimmune diseases associated with ITP, sarcoidosis-associated ITP has been reported as particularly severe at presentation and outcome, with a trend to unresponsiveness to available treatments and to death.[5] In the first review by Dickerman et al[5] in 1972, 5 deaths related to bleeding were reported among 33 patients (15%). In a more recent review since the development of immunoglobulin therapy, 2 deaths were found among 31 patients (6%).[16] However, most reported observations involved single cases or small series, leading to possible biases by selecting the most severe patients, as well as patients treated before the era of modern management of ITP.[14]

Since we had the opportunity to gather a series of 20 recent cases with both sarcoidosis and ITP through the networks of the Groupe sarcoidose francophone of the Société de Pneumologie de langue Française and the Centre de réference des cytopénies auto-immunes de l'adulte, we undertook a study to assess 1) the clinical and biological phenotypes of sarcoidosis and ITP, respectively, and 2) the response to therapy and prognosis of both conditions, with a particular interest in the context of "modern" management of ITP. Finally, we tried to clarify the relationship between the 2 conditions.

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PATIENTS AND METHODS

The study was conducted by the Groupe Sarcoidose Francophone (collaborative official work group of the Société de Pneumologie de langue Française) and by the Centre de référence des cytopénies auto-immunes de l'adulte. Participating physicians were asked to collect the medical records of their patients displaying both confirmed sarcoidosis and ITP. This retrospective and multicentric study was in agreement with French law and received institutional review board approval.

Patients

Patients were included if they fulfilled the following criteria: 1) confirmed sarcoidosis according to the statement of the ATS/ERS/WASOG;[27] 2) confirmed ITP according to the American Society of Hematology criteria[9] with platelet count $<100 \times 10^9$/L on at least 2 separate occasions; 3) absence of drug-induced thrombocytopenia; 4) absence of hypogammaglobulinemia suggesting underlying common variable immunodeficiency; 5) absence of large splenomegaly and/or portal hypertension and/or pancytopenia.

The study was conducted between November 2007 and July 2009. We retrospectively collected medical records from patients who were investigated between 1998 and 2009 in respiratory (n = 2) or internal medicine departments (n = 6) from 5 French university hospitals (Assistance Publique Hôpitaux de Paris; Hospices civils de Lyon, Assistance Publique Hôpitaux de

TABLE 1. Characteristics of 20 Patients With Sarcoidosis and ITP

Patient	Sex/Race/Age at Onset of Sarcoidosis (yr)*	Extrathoracic Localization of Sarcoidosis	Therapy Before ITP	Steroid Therapy at Sarcoidosis Onset	Time With or Without Steroids/Last Steroid Dose per Day	Time Between ITP and Sarcoidosis (mo)
Sarcoidosis occurred before ITP						
1	F/B/43	SN, PLN	OP	No	Stopped 18 mo ago	24
2	F/B/43	SN, S, O, L	OP, HCQ, CYC, THA	Yes	156 mo/7 mg	156
3	M/W/33	L, O	OP, HCQ	Yes	90 mo/8 mg	90
4	M/W/30	—	OP	Yes	216 mo/15 mg	216
5	M/W/22	PLN	OP	No	Stopped 7 mo ago	17
6	F/W/53	S, O	OP, HCQ, AZA	Yes	34 mo/5 mg	34
7	M/B/37	O	OP	Yes	6 mo/30 mg	6
8	M/W/30	—	No	No	No	48
9	F/B/10	L, PLN	OP	Yes	156 mo/5 mg	156
10	F/B/27	—	No	No	No	24
11	M/W/45	S, SN	OP, HCQ	No	Stopped 24 mo ago	46
Concomitant ITP and sarcoidosis						
12	F/W/83	R	No	No	—	—
13	M/B/35	O	No	No	—	—
14	M/W/16	PLN	No	No	—	—
15	M/B/37	O	No	No	—	—
16	M/B/51	O	No	No	—	—
ITP occurred before sarcoidosis						
17	F/W/59	SG, S†	No	Yes	—	—
18	F/B/31	SN, L	No	No	—	—
19	F/B/22	L	No	No	—	—
20	F/W/46	—	No	No	—	—

Abbreviations: AZA = azathioprine, B = black, Ca = cardiac, CYC = cyclophosphamide, Dana = Danatrol, Disu = Disulone, F = female, HCQ = hydroxychloroquine, INF = infliximab, IVIg = intravenous immunoglobulin, L = liver, M = male, MTX = methotrexate, O = ocular, OP = oral prednisone, PLN = peripheral lymph node, Ritu = rituximab, S = skin, SG = salivary gland, SN = sinonasal, SPL = splenectomy, T = thorax, THA = thalidomide, VCR = vincristine, W = white.

*White group includes 1 Asian patient.

†No thoracic localization on chest X-ray.

Marseille, Centre Hospitalo-Universitaire de Clermont-Ferrand, Centre Hospitalo-Universitaire d'Amiens). For all patients, complete medical records were retrospectively collected by M. Mahévas, and reviewed by DV.

Clinical and Laboratory Data at Presentation of Sarcoidosis and ITP

For all patients, history, symptoms, medical examination, chest X-ray, and hematologic laboratory tests were compiled at first presentation of sarcoidosis and first presentation of ITP.

Staging of chest X-ray according to the ATS/ERS statement,[27] histology (n = 20), pulmonary function (n = 18), bronchoalveolar lavage (n = 10), and serum angiotensin-converting enzyme (n = 15) were collected at diagnosis of sarcoidosis. Airflow obstruction was defined by forced expiratory volume in 1 second/forced vital capacity <70%, and restrictive syndrome was defined by total lung capacity <80% predicted value.

Results of blood smear biopsy analyzed to assess morphology (n = 18), platelet count, and antiplatelet antibodies (n = 9) performed at diagnosis of ITP were also compiled. The degree of ITP severity was evaluated at onset and during evolution according to the previously reported bleeding score.[14] A serum protein electrophoresis was required for all patients.

Progressive Sarcoidosis at Onset of ITP	Evolution of ITP	Sarcoidosis Relapse After ITP/Type of treatment	Duration of Steroid Therapy (mo) Since ITP/Last Dosage OP (mg/d)	Sarcoidosis Follow-Up (mo)	Outcome at End of Follow-Up
No	Acute/CR	No	1/0	42	Free of treatment (12 mo)
Yes/SN, S	Acute/CR	Yes: SN, S/OP, INF	24/20	180	Still on treatment for sarcoidosis
Yes/Ca	No treatment for ITP	Yes: T/OP, MTX	72/8	162	Still on treatment for sarcoidosis
No	Chronic/Ritu: R	No	22/15	238	Still on treatment for ITP
No	Acute/CR	Yes: O/OP	24/0	140	Free of treatment (92 mo)
Yes/T	Chronic/SPL: CR	Yes: T/OP	72/10	142	Still on treatment for sarcoidosis
No	Relapse: OP, HCQ: CR	No	2/0	18	Free of treatment (10 mo)
No	Acute/CR	No	1/0	60	Free of treatment (12 mo)
Yes/T	Acute/CR	Yes: T, H/OP	72/5	228	Still on treatment for sarcoidosis
Yes/T	Relapse Evans, OP: CR	Yes: NS, S, T, H/OP	60/15	207	Still on treatment for sarcoidosis
Yes/S, N	SPL: CR	Yes: N, H/OP, MTX	108/6	156	Still on treatment for sarcoidosis
Yes	Chronic/Ritu: R	Yes: SN/OP, AZA	14/30	14	Still on treatment for sacroidosis and ITP
Yes	Acute/CR	No	108/5	132	Still on treatment for sarcoidosis
Yes	Relapse/OP: CR	No	21/5	21	Still on treatment for sarcoidosis
Yes	Acute/CR	Yes: T/OP	52/10	142	Still on treatment for sarcoiosis
Yes	Acute/CR	No	36/0	78	Free of treatment (41 mo)
No	Chronic/SPL: CR	24	8/5	8	Still on treatment for sarcoidosis and ITP
No	Free of treatment	12	36/0	36	Free of treatment (83 mo)
No	Relapse concomitant	12	59/0	59	Free of treatment (24 mo)
No	Free of treatment	156	67/30	67	Still on treatment for sarcoidosis

Outcome

Sarcoidosis Outcome

Chest X-ray, clinical evaluation, systemic treatments (steroid dosage or immunosuppressive therapy), recovery, or occurrence of relapses were systematically recorded. Sarcoidosis phenotypes were classified according to onset manifestations (acute or not), the need for systemic steroid treatment, and duration of treatment (either 12 mo or more).[21] Relapse of sarcoidosis was defined on the evidence of new localization or if a prior known localization worsened. Sarcoidosis was defined as chronic when the disease lasted more than 36 months. Sarcoidosis was classified as remitted if there was resolution of all manifestations linked to sarcoidosis spontaneously or when all therapies were withdrawn for more than 1 year with no relapse.

Hematologic Outcome

A platelet count remaining above 100×10^9/L for more than 3 months defined a complete response to treatment (CR). A partial response (PR) was defined as a platelet count $>30 \times 10^9$/L and at least doubling the baseline count. No response (NR) was defined as any platelet count $<30 \times 10^9$/L or less than doubling the baseline count.[9] Acute ITP was defined by a treatment-free complete remission of thrombocytopenia within 12 months after ITP onset. According to the working international group consensus, chronic ITP was defined as the persistence of thrombocytopenia for more than 12 months after the diagnosis.[25] At the end of the follow-up, it was noted for all patients whether they still required therapy for ITP or sarcoidosis or both.

Adverse Effects of Therapy

Adverse effects of therapy were systematically recorded.

Epidemiologic Characteristics of the Study Group and Control Populations

Patients' age, sex, and race in the study population were compared with those of control populations with either sarcoidosis alone or primary ITP. Control populations comprised patients with sarcoidosis recruited at a center particularly involved in sarcoidosis (Pulmonary Department of Avicenne Hospital, Assistance Publique Hôpitaux de Paris), and patients with primary ITP recruited in the Centre de référence des cytopénies auto-immunes de l'adulte.

RESULTS

Epidemiology

We identified 26 patients with sarcoidosis and ITP. Three were excluded because they had common variable immunodeficiency, and 3 were excluded for hypersplenism. Twenty adult patients were the subject of further analysis (10 women, 10 men) (Table 1). Ten patients were black African or native Caribbean, 9 patients were white, and 1 patient was Asian. One patient had a family history of sarcoidosis, but none had a family history of ITP. None had occupational or environmental exposure, or had taken medications known to induce granulomatous disease. Three were current smokers. Some of them had prior or concomitant associated diseases including high blood pressure (n = 3), gastrointestinal ulcer (n = 1), and neurologic stroke (n = 1). None had a history of recurrent infections, nor a prior history of autoimmune disease. The median age at sarcoidosis and at ITP presentation was 36 (range, 10–83 yr) and 38 (range, 21–83 yr) years, respectively. Analyzed by sex, mean age at sarcoidosis presentation was 41.7 years for females (range, 10–83 yr) and 33.6 years for males (range, 15–51 yr). Mean age at ITP onset was 43.3 years for females (range, 21–83 yr) and 36.2 years for males (range, 16–51 yr).

In the series of 237 patients with sarcoidosis alone consecutively recruited between 2007 and 2009 in the Pulmonary Department of Avicenne Hospital, Assistance Publique Hôpitaux de Paris, the sex ratio of sarcoidosis was 1.13 (F:M), the mean age at diagnosis was 41 years for women and 36 years for men, and the proportion of black patients was 30%.

In the 565 patients followed in the Centre de référence des cytopénies auto-immunes de l'adulte, the sex ratio in primary ITP was 2.32 (F:M), the mean age at diagnosis was 37 years for female patients and 49 years for males, and the proportion of black patients was 5%.

Chronologic Relationship Between Sarcoidosis and ITP

In 11 of 20 (55%) patients, sarcoidosis presentation preceded ITP onset with a median interval of 48 months (range, 6–216 mo) (Figure 1A). In 5 of 20 (25%) patients, both sarcoidosis and ITP were simultaneously discovered (Figure 1B). In 4 of 20 (20%) patients, ITP onset preceded sarcoidosis presentation with a median interval of 68 months (range, 15–153 mo) (Figure 1C).

Sarcoidosis and ITP ran their courses separated by various lapses of time in 4 of 20 (20%) patients, with the first condition being cured before the onset of the second. Both sarcoidosis and ITP occurred first in 2 patients, respectively. In 12 of 20 (60%) patients there was a simultaneous occurrence of both ITP and sarcoidosis onset or relapse. This included the following 3 possibilities: 1) both ITP and sarcoidosis presentations were concomitant (n = 5) (see above); 2) there was a relapse of previously diagnosed sarcoidosis at ITP onset (n = 6) and this occurred during the tapering of the treatment for sarcoidosis; and 3) there was a simultaneous relapse of both sarcoidosis and ITP (n = 1). Finally, in 4 (20%) patients, it was not possible to assess the relationship between the 2 diseases: 2 patients were still on steroid therapy for sarcoidosis at ITP onset with no new manifestations (for 2 yr and 6 mo, respectively), 1 patient presented a relapse of sarcoidosis several months after cured acute ITP, and in 1 patient, the discovery of noncaseating granulomas in the spleen removed for refractory ITP led to the diagnosis of sarcoidosis.

Sarcoidosis

Sarcoidosis Presentation

At sarcoidosis presentation, thoracic involvement was demonstrated on chest radiography for 19 of 20 (95%) patients, and most of them had stage I (n = 8) or stage II (n = 9) disease (Table 2). Eight of 18 (44%) patients had abnormal pulmonary function tests (restrictive syndrome: n = 7, and airflow obstruction: n = 1). Bronchoalveolar lavage cell count showed a percentage of lymphocytes >20% in 10 patients (100%), and the lymphocyte T CD4/CD8 ratio was >3.5 in 5 of 10 (50%) patients. Extrathoracic disease was found in 16 of 20 (80%) patients, in particular ocular (n = 7), liver (n = 5), peripheral lymph nodes and sinonasal (n = 4 each). In 8 of 20 (40%) patients, the onset of sarcoidosis was acute, with occurrence of acute anterior uveitis (n = 7) associated in 2 patients with erythema nodosum, or of symptomatic hypercalcemia (n = 1). The patient with hypercalcemia also had confirmed renal disease. Serum angiotensin-converting enzyme was increased in 5 of 15 (33%) patients.

Sarcoidosis at ITP Presentation

Among the 11 patients in whom sarcoidosis preceded ITP, 9 patients needed treatment for sarcoidosis before ITP onset, with

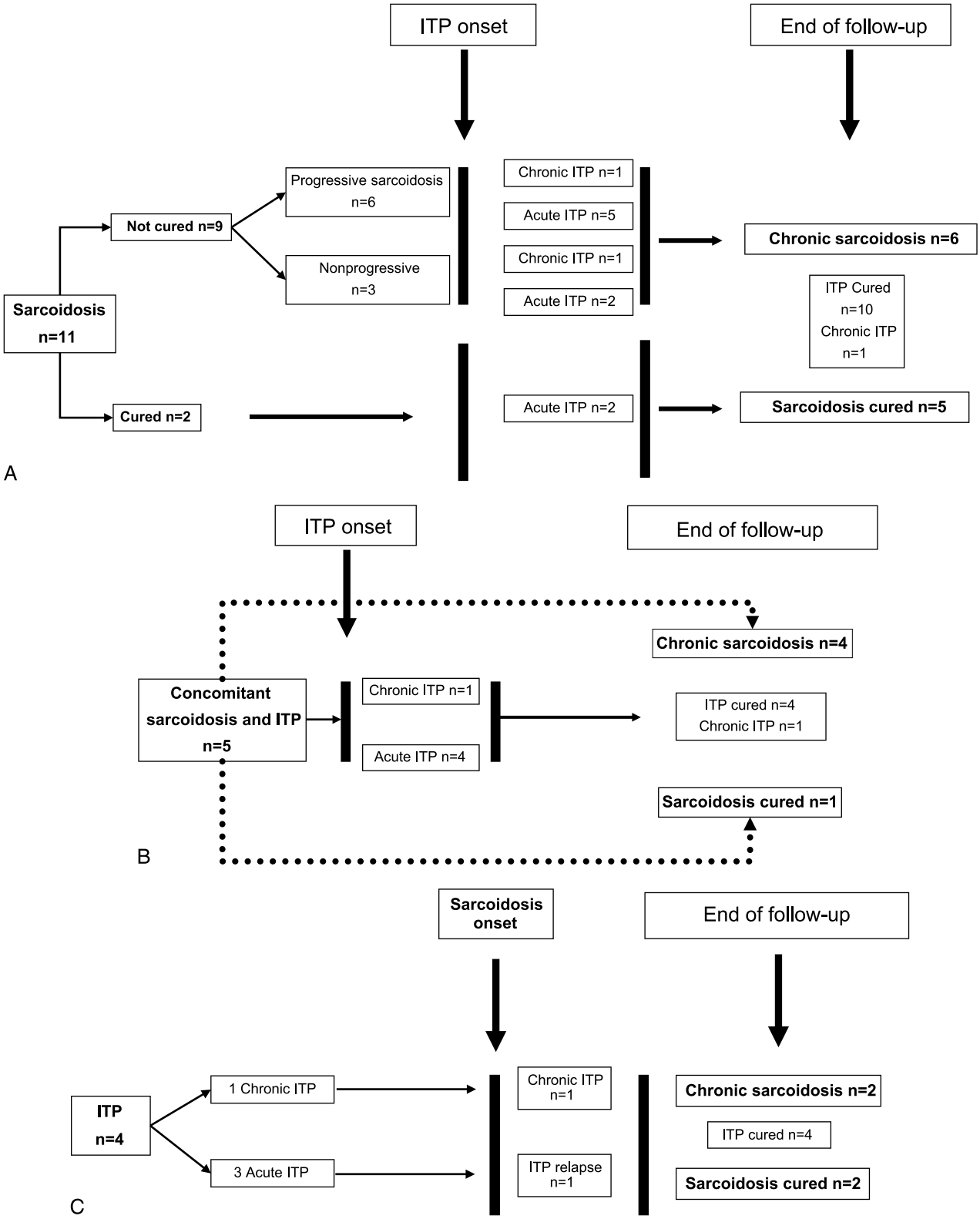

FIGURE 1. Flowcharts for 20 patients included in the study. A, Patients with sarcoidosis preceding ITP (n = 11); B, patients with concomitant sarcoidosis and ITP (n = 5); C, patients with ITP preceding sarcoidosis (n = 4).

TABLE 2. Characteristics of Patients at Presentation of Sarcoidosis

	No. of Patients	%
Men/women	10/10	50
White*/black	10/10	50
Intrathoracic lesions	19	95
Initial chest radiographic stage, n (%)		
Stage 0	1	5
Stage I	8	40
Stage II	9	45
Stage III	1	5
Stage IV	1	5
Extrathoracic localization of sarcoidosis	16	80
Ocular	7	35
Liver	5	25
Peripheral lymph node	4	20
Sinonasal	4	20
Skin	3	15
Salivary gland	2	10
Renal	1	5
Hypercalcemia	1	5
Spleen	1	5

*White group includes 1 Asian patient.

steroid therapy in all 9 (median, 48 mo; range, 6–216 mo), and with additional immunosuppressive therapy in 2 patients (thalidomide, cyclophosphamide, azathioprine) and additional hydroxychloroquine (HCQ) in 3 patients. Two patients were free of any manifestations and were considered cured of sarcoidosis at the onset of ITP. One who had not required any treatment had a spontaneous resolution of sarcoidosis, while in the other case steroids had been discontinued for 18 months. Seven patients were still being treated for sarcoidosis at ITP onset (steroid therapy: n = 6 patients; median dosage, 10 mg; range, 5–40 mg; HCQ: n = 2 patients; azathioprine: n = 1), and 6 patients had a relapse of sarcoidosis. Among patients with concomitant ITP and sarcoidosis presentations, 12 of 20 (60%) patients had either an onset or a relapse of sarcoidosis at ITP onset with thoracic disease in 7 of 12 (58%) patients and/or extrathoracic disease in 8 of 12 (66%) patients. There was no difference in clinical phenotype of sarcoidosis between patients in whom sarcoidosis preceded, was concomitant with, or occurred after ITP.

Treatment and Outcome of Sarcoidosis After ITP Onset

The median follow-up of sarcoidosis was 105 months (range, 3–230 mo). No patient died. At the end of follow-up, 8 of 20 (40%) patients were free of any manifestation of sarcoidosis, and could be considered in remission from sarcoidosis. Seven of them had no treatment for sarcoidosis for at least 12 months (median, 41 mo; range, 12–83 mo). In the eighth patient, steroids were reintroduced for ITP, but sarcoidosis had been cured before ITP onset. Two of these patients had been treated for more than 36 months for sarcoidosis. Thirteen of 20 (65%) had chronic disease, and 12 were still on oral steroids specifically for sarcoidosis (n = 11) or for both diseases (n = 1) at the end of follow-up, with a median dose of 10 mg/d (range, 5–30 mg/d). Among them, 4 patients had persistent manifestations of sarcoidosis at the end of follow-up. During the follow-up, 10 (50%) patients experienced a relapse of sarcoidosis affecting thoracic (5 patients) and extrathoracic sites (5 patients). The median delay between ITP and relapse of sarcoidosis was 30 months (range, 3–96 mo). Sarcoidosis relapse was associated with ITP relapse in 2 cases and with chronic ITP in 2 other cases. All were treated with prednisone, and with immunosuppressive therapy in 5 cases.

Clinical Phenotype of Sarcoidosis

Clinical phenotype was evaluated according to the criteria of Prasse et al.[21] In 8 of 20 (40%) patients, the onset of sarcoidosis was acute. Assessing the sarcoidosis treatment time accurately was sometimes blurred because of the treatment needed for ITP. Thirteen of 20 (65%) patients had to be treated for more than 12 months with oral corticosteroids, 2 patients had to be treated for 12 months, and 5 did not need any treatment.

ITP

ITP Onset

Median platelet count at onset was 11×10^9/L (range, 3–90 $\times$ 10^9/L). Nadir platelet count was 10×10^9/L (range, 1–60 $\times$ 10^9/L). Seventeen (85%) patients had a platelet count $<30 \times 10^9$/L. Seven (35%) patients had a bleeding score >8, without visceral bleeding. Five patients were asymptomatic. Bone marrow smear examination performed in 18 patients showed an increase of megakaryocytes in all, with no evidence of cytologic abnormalities. Bone marrow biopsy performed in 2 patients was normal, with no evidence of granuloma or lymphoma. One had anticardiolipin antibodies (>40 IgG) with no incidence of arterial, venous, or obstetrical thrombosis. Antinuclear antibodies were negative in all. Red blood cell antibodies detected by direct antiglobulin testing were present in 2 patients. One had autoimmune hemolytic anemia, and the other presented with ITP-associated autoimmune neutropenia. There was no evidence of double-negative (CD4−/CD8−) T cells in the peripheral blood of these 2 patients. Monoclonal antibody immobilization of platelet antigen (MAIPA) was performed in 3 patients; it was positive in 2 patients with chronic ITP and negative in 1 with acute ITP; enzyme-linked immunosorbent assay (ELISA) was performed in 5 (all with acute ITP) and was positive in only 2 cases.

ITP Treatment and Evolution

The median time of follow-up was 70 months (range, 12–142 mo) (Table 3). ITP did not require any specific therapy in 1 patient (Table 1, Patient 3), in whom platelet count increased spontaneously to $>50 \times 10^9$/L with no bleeding. This patient was still on oral corticosteroid therapy (prednisone 10 mg/d) at time of ITP diagnosis, and needed to increase oral steroid therapy to 40 mg/d associated with methotrexate 6 months later for a relapse of sarcoidosis with cardiac disease. Then the platelet count rose, and remained above 100×10^9/L during the following 72 months.

Nineteen of the 20 (95%) patients were treated specifically for ITP (Figure 2). After the first-line therapy (prednisone 1 mg/kg per d for at least 3 consecutive wk in all patients, associated with intravenous immunoglobulin [IVIg] in 10 patients), 12 of 19 (63%) patients achieved CR, 6 had PR (31.5%), and only 1 patient failed to respond. Among the 12 patients with CR, 3 experienced a relapse of ITP (including 1 with Evans syndrome) and were treated successfully with steroids and achieved CR (1 received additional treatment with HCQ). Seven of 19 patients needed a second- or third-line therapy (prednisone n = 2; IVIg n = 2; vincristine n = 1; Disulone n = 1; Danatrol n = 2; HCQ n = 1; splenectomy n = 3; rituximab n = 2). A splenectomy was performed as second-line therapy at 3 months in 1 patient who achieved CR. The course of ITP was chronic in 4 patients,

TABLE 3. Characteristics of Patients With ITP During Follow-Up

Patient	Sex/Race/Age at Onset of ITP (yr)*	Nadir Platelet Count (10^9/L)	Initial Bleeding Score	Bone Marrow Aspirate	First-Line Therapy: Short-Term Response	Second-/Third-Line Therapy: Response	Response at End of Follow-Up	Follow-Up After ITP Onset Platelet Count and Treatment at Last Evaluation	Duration of Steroid Therapy (mo) Since ITP/Last Dosage OP (mg/d)
1	F/B/45	1	15	MK+++	OP/IVIg: CR		CR	13/294	1/0
2	F/B/56	7	4	MK+++	OP/IVIg: CR		CR	24/259	24/20
3	M/W/40	60	0	—	—		CR	74/120	72/8
4	M/W/38	9	9	MK+++	OP/IVIg: R	Chronic: VCR-Dana-HCQ-Ritu: R	NR	22/25	22/15
5	M/W/24	1	7	MK+++	OP/IVIg: CR		CR	116/237	24/0
6	F/W/56	9,5	8	MK+++	OP: NR	Splenectomy: CR	CR	108/460	72/10
7	M/B/38	3	8	MK+++	OP/IVIg: CR	Relapse: OP, HCQ: CR	CR	13/460	2/0
8	M/W/34	30	0	MK+++	OP: CR		CR	12/230	1/0
9	F/B/22	17	6	MK+++	OP: CR		CR	72/166	72/5
10	F/B/29	5	4	MK+++	OP/IVIg: CR	Relapse Evans, OP: CR	CR	60/234	60/15
11	M/W/49	10	5	MK+++	OP: R	Chronic: IVIg, Disu, AZA, splenectomy: CR	CR	156/265	108/6
12	F/W/83	12	10	MK+++	OP/IVIg: R	Chronic: Dana-Ritu: R	R	14/66	14/30
13	M/B/35	5	10	MK+++	OP/IVIg: CR		CR	108/190	108/5
14	M/W/16	19	0	MK+++	OP: R	OP: CR	CR	21/100	21/5
15	M/B/37	40	0	MK+++	OP/IVIg: CR		CR	142/175	52/10
16	M/B/51	50	0	—	OP: CR		CR	78/222	36/0
17	F/W/59	11	4	MK+++	OP: R	Chronic: IVIg, splenectomy: CR	CR	60/226	60/5
18	F/B/30	4	10	MK+++	OP/IVIg: CR		CR	84/308	1/0
19	F/B/21	4	2	MK+++	OP: CR	Relapse: OP: CR	CR	68/100	48/0
20	F/W/33	20	0	MK+++	OP: R	OP: CR	CR	99/100	72/30

Abbreviations: See Table 1. MK = megakaryocytes.

*White group includes 1 Asian patient.

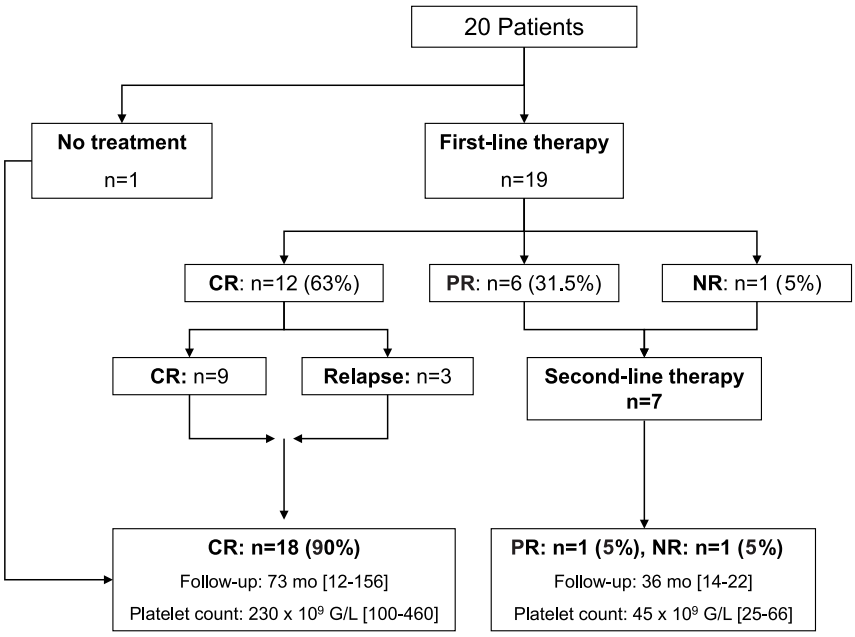

FIGURE 2. Hematologic outcome of patients.

among them 2 underwent splenectomy and achieved CR, and 2 were treated with rituximab (375 mg/m^2, 4 infusions), 1 of whom achieved PR at 1 year. However, 1 of them experienced a relapse at 18 months. At the end of follow-up, 18 (90%) patients had CR, 2 (10%) had chronic ITP, 1 had PR, and 1 had NR. Eight (40%) patients were cured, whereas 12 patients (60%) were still on oral steroids for sarcoidosis at the time of analysis, with a median dose of 10 mg/d (range, 5–30 mg).

Safety of Treatments

Four patients developed steroid-induced type 2 diabetes mellitus, and 3 had steroid-induced osteoporosis. One had peripheral neuropathy secondary to thalidomide. One had a pulmonary embolism post-splenectomy.

DISCUSSION

In the current retrospective study we analyzed data from a large series of patients with both sarcoidosis and ITP followed in the framework of 2 networks, 1 focused on sarcoidosis and the other on ITP. All medical records were reviewed by 2 investigators experienced in ITP and in sarcoidosis, respectively. The main conclusions of the study concerning ITP are that ITP 1) is severe and symptomatic at presentation, 2) usually follows a favorable course without death or severe bleeding as a result of modern therapeutic management,[24,25] and 3) altogether follows a far less severe course than previously reported in the literature. On the other hand, sarcoidosis was remarkable for the frequency of acute onset, a chronic course, and a prolonged need for oral steroid therapy for most patients. Finally, in some patients, the courses of sarcoidosis and ITP were separated by time, suggesting that ITP may sometimes be a primary problem rather than an intrinsic manifestation of sarcoidosis.

Several mechanisms can be involved in the occurrence of thrombocytopenia in sarcoidosis, and careful attention was devoted to exclude alternative diagnoses. Splenomegaly, which has been reported to occur in 10% of sarcoidosis patients,[8] can induce hypersplenism with a sequestration in the spleen leading to platelet destruction.[8,15] We did not include in the study 3 patients with hypersplenism. None of these 3 patients had a platelet count $<100 \times 10^9$/L. Common variable immunodeficiency can cause autoimmune cytopenia and granulomatous disease and can mimic sarcoidosis with thrombocytopenia. In this setting, contrary to sarcoidosis, there is often a history of recurrent infections and hypogammaglobulinemia.[20] Thus, we investigated the history of infections and of gammaglobulin levels in the current study to rule out any possibility of common variable immunodeficiency. Finally, we also considered the autoimmune lymphoproliferative syndrome (ALPS), since it can cause splenomegaly and autoimmune cytopenia.[19] This diagnosis was discussed in particular in 1 patient who had a history of familial sarcoidosis and in 1 patient with autoimmune neutropenia. ALPS was ruled out by the absence of double-negative T cells in peripheral blood.

According to the literature, ITP in sarcoidosis is particularly severe, often complicated by severe bleeding, unresponsiveness to therapy, and death in up to 15% of patients.[3,4,14] However, the severity of ITP as reported could have been skewed by an ascertainment bias. Moreover, many cases were reported before currently available first-line (IVIg) and second-line (including rituximab) therapy was available.[16] In the current report we confirm that ITP in sarcoidosis is a severe condition at presentation with a platelet count $<30 \times 10^9$/L in 85% of cases and with a high bleeding score in one-third of cases. The bleeding score justified treatment with high doses of steroids in all but 1 patient and with IVIg in half the patients. Such a therapeutic regimen was given according to recommendations established in primary ITP.[24] In our experience, the first-line therapy must be guided by the bleeding score.[13] In the current series, the final response to treatments could be considered generally good, in contrast to previous data in the literature concerning sarcoidosis-associated ITP, since we did not observe any deaths or severe bleeding episodes despite reviewing the medical records of 20 patients. Among them, 4 had relapses, but dramatically responded to steroid therapy. Only 4 had truly chronic ITP lasting more than 12 months. This is in contrast to sarcoidosis, in which the

relapses were frequent and justified the prolonged use of steroids. Altogether, these data suggest that recommendations concerning therapeutic management of primary ITP can also be considered appropriate in sarcoidosis-associated ITP.

Splenectomy was effective for controlling the disease in the 3 patients who had it performed. Splenectomy must be, however, reserved for patients whose thrombocytopenia is not controlled by first-line and second-line therapy, and lasts for more than 6–12 months. In the literature, splenectomy was performed in 7 patients with sarcoidosis.[1,4,6,23,28] It was effective in 6 patients, and complicated by death related to thrombocytopenia and severe bleeding in the seventh. Rituximab, the chimeric monoclonal antibody, was used in 2 patients, and was effective for treating the thrombocytopenia in the 2 patients with a PR at 1 year, although 1 patient relapsed at 18 months. The combination of ITP and sarcoidosis provided the unique opportunity to study the effect of B-cell depletion in sarcoidosis. In 1 patient with prior thoracic and renal sarcoidosis, the absence of rituximab efficacy on sarcoidosis should be noted, since the occurrence of a relapse with new sinonasal involvement was evidenced some months after the rituximab course. No firm conclusion could be drawn concerning the impact of rituximab on the sarcoidosis component in the other patient, since sarcoidosis was quiescent before and after the introduction of this drug.

The second major point of the current study concerned the assessment of the clinical phenotype and prognosis of sarcoidosis in patients with associated ITP. Sarcoidosis usualy occurred before the onset of ITP. Black patients were overrepresented among patients with sarcoidosis and ITP. The acute onset and the frequency of presentation with acute anterior uveitis have to be underscored. Most patients experienced visceral involvement at multiple thoracic and extrathoracic sites. A high frequency of patients had a chronic course: 60% in the current series had a disease duration >36 months, and a great proportion of them had disease for far longer. According to Prasse et al,[21] three-quarters of patients at least needed prednisone therapy for sarcoidosis per se, and almost all of them (13 of 15) had to be treated for more than 12 months in 1 or iterative courses. As a matter of fact, 50% of patients experienced a relapse of sarcoidosis either at the thoracic or extrathoracic level.

In the current study there was no particularly severe involvement of the lung, with no cases having advanced respiratory insufficiency or pulmonary hypertension, and most not evolving to radiographic stages III or IV. Some severe extrathoracic manifestations were observed, in particular cardiac, renal, and sinonasal localizations, but they could be controlled with steroids and immunosuppressive drugs. There were no deaths, and no evidence of severe organ damage at the end of follow-up. Thus, sarcoidosis was remarkable for its multiple organ involvement, some severe localizations, a long duration in most cases, the frequency of relapses, and the frequent need for prolonged therapy. Most sequelae were the result of adverse effects of steroid therapy, even though the use of additional immunosuppressive drugs made it possible to lower prednisone doses.

The relationship between sarcoidosis and autoimmunity is not clear. Autoantibodies such as rheumatoid factor, antineutrophil or antimonocyte cytoplasmic antibodies, antiphospholipid antibodies, and others can be detected in patients with sarcoidosis.[7,10,11,30] However, clinically overt autoimmune manifestations are rare in sarcoidosis, and then are usually linked to comorbidities such as common variable immunodeficiency,[18,22] lupus erythematosus, rheumatoid arthritis, scleroderma, or thyroiditis.[29] Other cytopenias associated with sarcoidosis are very rare, for example, we found fewer than 10 cases of autoimmune hemolytic anemia and sarcoidosis in the literature.[3] Thus, we found it interesting to look for a chronologic relationship between sarcoidosis and ITP. In 60% of cases there was a concomitant onset or relapse of both conditions, suggesting that ITP could be considered as a secondary manifestation of sarcoidosis. Furthermore, chronic evolution of ITP was associated in all but 1 patient with chronic sarcoidosis, emphasizing that the course of both diseases could be linked. In 4 patients (20% of cases), the course of both conditions occurred at 2 clearly differentiated periods with a clear free time interval between them, a finding compatible with the chance association of 2 independent diseases. However, we acknowledge that considering comparative chronologic relationships between the onset and course of sarcoidosis and ITP does not definitively clarify the nature of the link between them.

The main limitations of the study are its retrospective nature and the fact that it was conducted in highly specialized centers with biases in the selection of patients. Moreover, the control populations used to compare epidemiology of sarcoidosis and primary ITP, respectively, were recruited in only 2 centers.

In conclusion, there is a good long-term prognosis with a favorable response to modern management of ITP in patients with sarcoidosis. The cause for the association of these 2 diseases remains unknown.

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