Osteoarticular Involvement in a Series of 100 Patients with Sarcoidosis Referred to Rheumatology Departments

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ABSTRACT. ***Objective.*** To analyze the pattern of osteoarticular lesions in patients with sarcoidosis hospitalized in 4 rheumatology departments.

Methods. We carried out a systematic retrospective analysis of cases with sarcoidosis admitted in the last 10 years, using hospital databases. Two distinct groups were defined from the outset: patients with Löfgren's syndrome (LS) or sarcoid rheumatism (SR). We assessed the following items: distribution of arthritis, chronicity, systemic manifestations, biochemical and immunological measures.

Results. We included 100 patients (75% women); 43% had LS and 57% SR. Osteoarticular symptoms revealed the disease in 85% of patients. The patients in the LS group were younger than those in the SR group (41 ± 9 vs 48 ± 13 yrs; $p < 0.006$) and were more likely to have oligoarthritis involving ankles (58% vs 32%; $p = 0.04$) and high C-reactive protein concentrations (63% vs 33%; $p < 0.005$). Patients with SR presented osteoarticular symptoms in the form of oligoarthritis (32%), polyarthritis (32%), bony erosion in 8/57 (14%), and osteitis in 9/57 (16%). Lung interstitial involvement was more frequent in the SR group than in the LS group (38% vs 18%; $p = 0.03$). Chronic polyarthritis was associated with the detection of rheumatoid factor ($p = 0.004$). Osteitis occurred in older patients ($p = 0.02$).

Conclusion. SR was the most frequent manifestation leading to hospitalization; it was characterized by oligoarthritis and polyarthritis and associated with interstitial lung involvement. Osseous involvement occurred in a quarter of SR patients with similar frequency of erosions targeting the distal small bones and osteitis. These latter occurred at a later age. (First Release July 15 2008; J Rheumatol 2008;35:1622–8)

Key Indexing Terms:
SARCOIDOSIS ARTHRITIS ARTHRALGIA BONE LOFGREN'S SYNDROME

Sarcoidosis is an inflammatory disorder of unknown cause, first described in 1877 and characterized by the presence of noncaseating granulomas in tissues. It occurs worldwide, but is most frequent in northern Europe and the United States[1]. It involves multiple organs, most commonly the lungs, lymph nodes, skin, and eyes, but may be clinically evident in any organ system, including the musculoskeletal system[2]. It is diagnosed on the basis of clinical symptoms, chest radiographic findings, histological evidence of disease, and the exclusion of other causes of granulomatous disease, such as tuberculosis.

Rheumatic manifestations have been reported to occur in 4% to 38% of patients and may manifest clinically as inflammatory arthritis, periarticular soft tissue swelling, tenosynovitis, dactylitis, bone involvement, or myopathy. The high level of variability in the cumulative frequencies of musculoskeletal findings in published series reflects discrepancies in the studied populations and classification criteria used for the various rheumatic syndromes[3]. Further, some bony and muscular lesions may be asymptomatic and may therefore be missed if imaging is not carried out systematically.

Our aim was to investigate musculoskeletal involvement in a series of patients with sarcoidosis hospitalized in several French rheumatology units.

MATERIALS AND METHODS

We carried out a systematic retrospective analysis of all cases of sarcoidosis admitted to 4 rheumatology departments between 1996 and 2006, based on information present in hospital databases. Sarcoidosis was diagnosed on

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the basis of classical criteria, and all medical records were reviewed to confirm the diagnosis. We validated and included 100 patients in whom sarcoidosis was diagnosed on the basis of suggestive clinical involvement, radiological findings, histological lesion (biopsy evidence of noncaseating epithelioid granuloma with giant cells), or Löfgren's syndrome (LS).

LS was generally defined as the presence of lung adenopathy, arthralgia, or arthritis in addition to erythema nodosum[4]. All patients had at least 1 osteoarticular symptom justifying their treatment in a rheumatology unit. LS is considered as an acute, frequent, and usually self-limited form of sarcoidosis[4]. Articular symptoms are very prevalent in this subset and they are taken into account for its classification. Thus we arbitrarily decided to consider LS as a distinct entity for the purpose of our study although different pathophysiology is not established.

Therefore, we predefined 2 groups of patients at the outset: one group fulfilling the criteria for LS, and all the remaining non-LS patients defined as having sarcoid rheumatism (SR). The following variables were analyzed in the 2 groups: demographic data (age at diagnosis, sex); clinical information relevant to sarcoidosis (clinical history and examination), and more detail concerning any arthritis [distribution and chronicity of the symptoms (> 6 months)]; imaging findings [radiographic or thoracic computerized tomography (CT) scan; stage I defined by hilar lymphadenopathy, stage III by interstitial lung involvement, and stage II by mixed lesions]; histological evidence; laboratory values: plasma angiotensin-converting enzyme (ACE), C-reactive protein (CRP), and creatine kinase (CK) levels, calcemia, presence of rheumatoid factor (RF, ELISA method); duration of followup; and treatments administered. We assessed the frequency of patients fulfilling the criteria for rheumatoid arthritis (RA)[5]. We analyzed tenosynovitis and dactylitis in the SR group, as all patients underwent radiographic examinations of at least the chest, hands, and feet, and evaluated erosions and osteitic lesions (i.e., Perthes-Jüngling disease was considered in the case of particular osteitic manifestations with a progressive form of polycystic osteitis, which also involved the surrounding soft tissue). Other skeletal regions and axial or long bones were assessed by radiograph only in the case of clinical symptoms. Scintigraphy, magnetic resonance imaging (MRI), or articular echography was performed in a very few specific cases, providing insufficient data to be analyzed in our study.

Descriptive data are presented as means ± standard deviation (SD) or numbers (%). Data were analyzed using chi-squared tests, with Yates' correction when appropriate, and nonparametric tests (Mann-Whitney U-test).

RESULTS

Demography. We included 100 patients with definite sarcoidosis, and no patients were excluded because of uncertain diagnosis. LS was found in 43% of patients, and the remaining 57% classified as having SR. A tissue biopsy had been performed in 17 of the 43 (39.5%) patients in the LS group and in 42 of the 57 (74%) in the SR group. All these biopsies revealed noncaseating epithelioid granuloma with giant cells. Mean age at admission was 45 ± 12 years, and 75/100 of the patients were women [35 of 43 in the LS group vs 40 of 57 in the SR group; not significant (NS)]. The patients in the LS group were younger than those in the SR group (41 ± 9 vs 48 ± 13 yrs; $p < 0.006$). The mean duration of followup was 53 ± 5 months and the duration of followup was significantly different between the 2 groups (18 ± 31 mo in the LS group vs 85 ± 101 mo in the SR group; $p < 0.0001$).

Musculoskeletal involvement was the initial manifestation of the disease in 85/100 of the whole population: 42 of the 43 (98%) patients in the LS group versus 43 of the 57 (75%) in the SR group ($p = 0.002$). Neither group showed a significant difference in terms of the months in which the disease first appeared. In particular, there was no higher prevalence in spring for the patients with LS. Patient characteristics did not differ significantly between centers.

Articular manifestations. The articular manifestations of the 2 groups of patients with sarcoidosis are shown in Table 1. The prevalence of oligoarthritis was high in both groups, with lower-limb joints most frequently involved (88/100), especially ankles (77/100). Oligoarthritis and polyarthritis were frequently symmetric (79/100).

The frequencies of oligoarthritis [58% (22/43) vs 32% (18/57); $p = 0.04$], arthritis involving ankles [91% (39/43) vs 67% (38/57); $p = 0.02$], and monoarthritis [21% (9/43) vs 5% (3/57); $p = 0.01$] were higher in the LS group than in the SR group. No chronic polyarthritis was observed in the LS group. After ankles, the joints most frequently involved in the LS were, in descending order of importance: knees, wrists, elbows, interphalangeal joints, metacarpophalangeal (MCP) joints, and shoulders (Table 2), with arthritis and arthralgia observed.

The frequency of polyarthritis was similar to that of oligoarthritis in the SR group [18 patients for each (32%)]. Ankles were most frequently affected, followed by wrists, knees, MCP joints, interphalangeal joints, elbows, and shoulders (Table 2), with arthritis and arthralgia observed. Chronic polyarthritis was found in 12 of the 57 (21%) patients in the SR group. Eight of the 12 cases of chronic polyarthritis included tenosynovitis that most often targeted fingers and wrist flexors and tendons in the ankles.

Two cases of polyarthritis (2/57; 3%) could be classified as overlapping with RA and fulfilled the American College of Rheumatology criteria for RA[5]. The first case was a 47-year-old woman with myalgia, uveitis, lung polyadenopathy, leg erythema nodosum, and distal chronic polyarthri-

Table 1. Musculoskeletal involvement in sarcoidosis.

Involvement	Löfgren Syndrome, n = 43	Sarcoid Rheumatism, n = 57	p
Arthritis (%)			
Monoarthritis	9 (21)	3 (5)	0.01
Oligoarthritis	22 (58)	18 (32)	0.04
Polyarthritis	8 (19)	18 (32)	NS
Arthritis involving ankles	39 (91)	38 (67)	0.02
Chronic (> 6 mo)	0	12 (21)	0.001
Erosive	0	8 (14)	0.002
Tenosynovitis	1 (2)	8 (14)	NS
Osseous (%)	0	15 (26)	0.0005
Osteitis	0	9 (16)	0.005
(cystic/sclerotic)		8 (14)/1 (2)	
Muscle (%)			
Myalgia	5 (12)	6 (10)	NS
Polymyositis-like syndrome	0	1 (2)	NA

NS: not significant; NA: not applicable.

Table 2. Distribution of arthritis and arthralgia. All figures are n (%).

Joints Involved	Löfgren Syndrome, n = 43		Sarcoid Rheumatism, n = 57	
	Arthralgia	Arthritis	Arthralgia	Arthritis
Ankle	33 (77)	39 (91)	18 (32)	21 (37)
Knee	14 (33)	10 (23)	21 (37)	13 (23)
Wrist	15 (35)	6 (14)	18 (32)	15 (26)
Metacarpophalangeal	6 (14)	2 (5)	12 (21)	9 (16)
Interphalangeal	7 (16)	3 (7)	12 (21)	11 (19)
Shoulder	5 (12)	0	6 (11)	3 (5)
Elbow	10 (23)	0	15 (26)	6 (11)
Spine	3 (7)	0	8 (14)	0
Hip	3 (7)	0	7 (12)	0

tis without erosion. She tested positive for RF, but anticyclic citrullinated peptide antibody levels had not yet been tested. Skin biopsy led to the diagnosis of sarcoidosis. The second case was a 74-year-old woman first diagnosed with RA in 1983 on the basis of erosive chronic polyarthritis and the presence of RF. In 2004, a noncaseating granuloma was identified on salivary gland biopsy performed because of sicca syndrome. She was initially treated with parenteral gold salts and then with corticosteroids alone.

In one patient, the disease presented in a form resembling Sjögren's syndrome, with polyarthralgia and sicca syndrome as first symptoms. Labial biopsy revealed Chisolm grade II without granuloma, and antinuclear antibodies were negative. This patient later developed chronic polysynovitis with skin nodules. Plasma ACE concentration was not abnormally high, and all other biological test results remained normal. No lung involvement was observed. The diagnosis of sarcoidosis was confirmed by the presence of noncaseating granuloma on synovial biopsy performed because of recurrent synovitis.

Bone involvement. Osseous involvement was reported in 15/57 (26%) patients with SR, presenting erosions of small bones of the hands (Figure 1) and feet in 8/57 patients (14%) and cystic osteitic lesions in 9/57 (16%) patients (Figure 1). Cystic lesions were found in the right shoulder in 1 female patient and in the lumbar spine or sacroiliac in 2 male patients. Three patients presented a cystic lesion at the end of the ulna and 2 in association with finger erosions. Among these patients, 2 cases of dactylitis were described. One male patient presented a sclerotic lesion of the left hip. Osteitic lesions occurred in older patients (53 ± 12 yrs vs 46 ± 14; p = 0.02), but no other phenotypic association was found for erosion or osteitic lesions. No osseous involvement was observed in the LS group.

Biological results. The main laboratory results are shown in Table 3. CRP concentration was high at the time of diagnosis in 45% of all patients. ACE levels were high in 40% of patients. None of the patients had high CK levels, whereas 5% of the patients tested positive for RF. Calcemia was determined in 95 patients and exceeded 2.6 mmol/l in 2 patients from the SR group.

A CRP concentration exceeding 10 mg/l at the time of hospitalization was more frequent in the LS group than in the SR group [63% (n = 27/43) vs 33% (n = 18/57); p < 0.005]. No significant difference in ACE concentration was found between the 2 groups of patients with sarcoidosis, nor among the SR group when patients with articular lesions were compared to those with bony lesions. RF was more frequently detected in the SR group than in the LS group [7% (n = 4/57) vs 2% (n = 1/43); p = 0.03]. The detection of RF was found to be associated with chronic polyarthritis in the SR group (p = 0.004).

Association of osteoarticular involvement with systemic manifestations. Extraarticular manifestations are listed in Table 3. Mediastinal adenopathy and skin lesions were the most frequently observed manifestations in both groups. In the LS group, we found lung involvement [adenopathy in 39/43 (91%) and interstitial lung disease in 8/43 (18%)], uveitis [4/43 (9%)], and myalgia [5/43 (12%)].

The frequency of lung interstitial involvement was higher in the SR group than in the LS group [39% (22/57) vs 18% (8/43); p = 0.03]. In this group, a stage II was found in 18/57 patients (32%) and a stage III in 4/57 patients (7%). We observed myalgia in 6/57 (10%) of SR cases, with 1 case of polymyositis-like syndrome. Three cases of cardiac involvement, presenting as myocarditis, were observed. No significant association was found between chronic polyarthritis and extraarticular manifestations.

Treatment. Nonsteroidal antiinflammatory drugs (NSAID) were prescribed to 72/100 patients, and systemic corticosteroids to 47/100 patients. Among patients treated by corticosteroids, 31/47 (66%) had skeletal involvement that did not respond to NSAID (persistence of arthritis), and the others had extraskeletal manifestations.

During their stay in hospital, 4 patients received intraarticular injections of corticosteroids. The treatment for chronic involvement was methotrexate (MTX) in 14/100, hydroxychloroquine in 13/100, and azathioprine in 3/100 of all patients included in our survey.

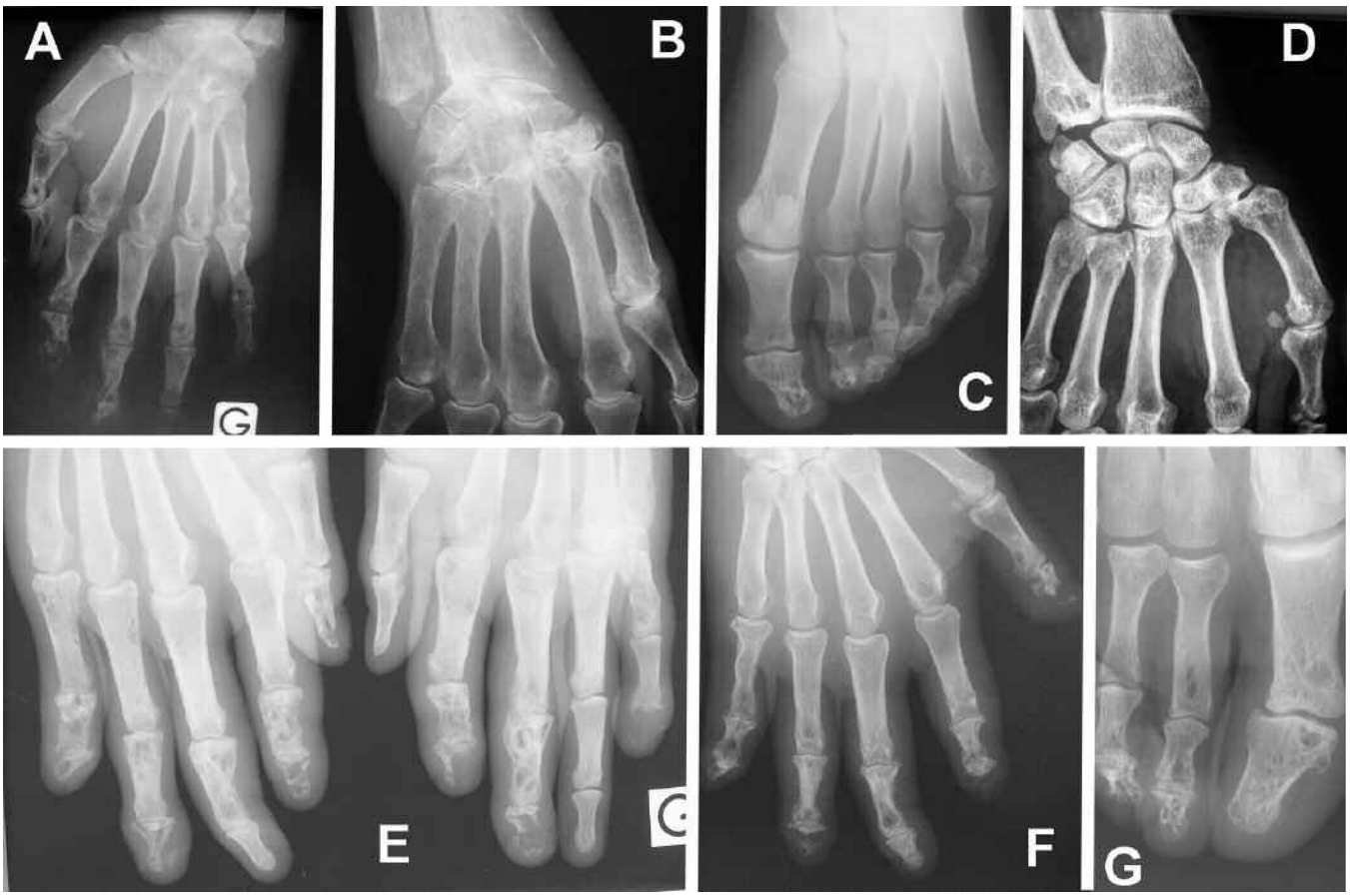

Figure 1. Pattern of osteoarticular involvement found on radiographs in the patients with erosions of the wrist (A, B), metacarpal (B) and metatarsal bones (C), osteitic lesions (A, C, D, E, F, G), and typical Perthes-Jüngling osteitis (A, E, F, G).

Table 3. Extraarticular manifestations of sarcoidosis.

Manifestation	Löfgren Syndrome, n = 43	Sarcoid Rheumatism, n = 57	p
Lung interstitial involvement (CT scan), n (%)	8 (18)	22 (39)	0.03
Lung adenopathy (CT scan), n (%)	39 (90)	36 (63)	0.001
Cutaneous involvement, n (%)	39 (91)	27 (47)	< 0.0001
Ocular involvement, n (%)	4 (9)	8 (14)	NS
Myocarditis, n (%)	0	3 (5)	NS
C-reactive protein (mg/l), mean ± SD, n > 10 mg/l (%)	36.4 ± 42.4 (63)	25.2 ± 43.2 (33)	0.005
Plasma angiotensin-converting enzyme, mean ± SD, n > 52 IU (%)	61.3 ± 32.4 (40)	68.9 ± 60.4 (40)	NS
CK, mean ± SD, n > 200 IU (%)	59.8 ± 36.8 (0)	53.3 ± 36.3 (0)	NS
Rheumatoid factor-positive (> 10 IU, ELISA) (%)	1 (2)	4 (7)	0.03

CT: computerized tomography; CK: creatine kinase; SD: standard deviation; NS: not significant.

In the LS group, 38/43 (88%) patients were treated with NSAID and 7 (16%) with corticosteroids. Colchicine was used for skin and articular involvement in 8 (19%) patients, and 2 (5%) were treated with hydroxychloroquine.

In the SR group, NSAID [34/57 patients (60%)] or corticosteroids [40/57 (70%) patients] were used for first-line treatment. Regarding corticosteroids, 17/40 (30%) were given these drugs for nonskeletal manifestations. MTX was the second-line therapy used in 14 of the 57 patients with SR (25%). Patients treated with MTX presented acute or chronic polyarthritis (10/14) with osseous involvement (8/14), or muscular or multivisceral syndrome. Hydroxychloroquine was used in 11/57 patients (19%) with isolated skeletal manifestations. The patients treated with azathioprine [3/57

patients (5%)] comprised 1 patient with multivisceral disease and 2 with chronic erosive polyarthritis. Two patients (2/57;3.5%) were treated with gold drugs for erosive chronic polyarthritis. No patient was treated with anti-tumor necrosis factor-α (TNF-α) in our series.

DISCUSSION

A majority of the patients with sarcoidosis referred to rheumatology units in this series had SR rather than LS. SR was associated with interstitial lung involvement, and oligoarthritis, including ankle involvement, was the most frequent presentation. Chronic polyarthritis was associated with the presence of RF. Erosions affected the small bones of the hands and feet, and osteitic lesions occurred in older patients.

A comparative analysis of the main clinical features of patients with sarcoidosis and osteoarticular involvement from 4 studies in different parts of the world is summarized in Table 4[4,6-8]. In these studies, mean age at diagnosis ranged from 36 to 47 years and, in 2 of these studies, there were more female than male patients. Sarcoidosis generally affects young adults of both sexes, but most studies have reported a slightly higher frequency in women, taking into account all the lesions observed. Our results are consistent with these previous studies and confirm the higher prevalence in women, but data from Norway and India have suggested that osteoarticular involvement may be more common in men. This finding requires further evaluation.

LS accounted for 43% of osteoarticular manifestations; we were unable to identify a period in the year when the incidence of this syndrome was higher than at other times. In other reports, most patients developed this syndrome in the first 6 months of the year, particularly during the spring[1,4,9,10]. In our study, LS onset occurred throughout the year, with no difference in seasonal variation between our 4 centers.

About two-thirds of the patients in the LS group had oligoarthritis. Articular manifestations mostly involved the lower limbs and, more rarely, the upper limbs. Consistent with published results, arthritis in the LS group was transient and self-limited, but caution is required in the interpretation of our results, due to the retrospective design of the study[3,9,11,12]. More than half the patients with LS had high CRP concentrations, and fewer than half had high ACE levels. This suggests, as in other reports, that ACE was not a reliable indicator of disease activity in patients with LS; nor did it help to confirm or exclude the disease[4].

We classified patients without LS but with musculoskeletal symptoms as having SR, and tried to describe the characteristics of this condition. Oligoarthritis and polyarthritis were the main symptoms requiring hospitalization in the patients of the SR group. Arthritis was present at the onset of the disease in patients with LS, and osteoarticular symptoms revealed the disease in most of the patients with SR. Arthritis was mostly symmetric and affected the ankles in two-thirds of the whole group of patients. These results are consistent with a previous study carried out in India, in which 47% of oligoarthritis, 47% of polyarthritis, and 60% of arthritis cases involved the ankles[6]. Thus, oligo- or polyarthritis involving the ankles may be considered suggestive of sarcoidosis[1,13].

Table 4. Musculoskeletal involvement in 4 series of patients with sarcoidosis hospitalized in rheumatology departments.

Characteristic	Spain, 1999[4]	Norway, 1996[6]	India, 2001[7]	Morocco, 2005[8]	France, 2007
No. of patients	186	49	29	18	100
Sex, male/female (% female)	157/29 (85)	30/19 (39)	15/14 (48)	2/16 (88)	25/75 (75)
Mean age, yrs	37	36	44	47	45
Arthritis, %	NA	3.2 joints	AA: OA 43, PA 36 CA: OA 47, PA 47	NA	LS: OA 58, PA 19 SR: OA 32, PA 32
Arthritis involving ankles (n of patients)	NA	49	AA: 11, CA: 9	5	LS 39, SR 21
Month at onset	Spring: 49%	First 4 months of the year: 51% January to June: 63%	NA	NA	No difference
Löfgren, %	100	88	7	11	43
Erosions/cystic or sclerotic bone lesions	0/0	0/0	0/0	0/5 (28%)	LS 0/0, SR 8/9 (14%/16%)
Chronic arthritis, %	NA	0	51	28	LS 0, SR 21%
Recurrence, %	NA	4	AA: CR = 71% PR = 14% CA: CR = 33% PR = 60%	NA	NA
Increased ACE, %	50	NA	NA	NA	LS 40, SR 40
RF+, %	NA	4	NA	NA	LS 2, SR 7

AA: acute arthritis; CA: chronic arthritis; CR: complete remission; PR: partial remission; RF: rheumatoid factor; NA: not available; LS: Löfgren syndrome; SR: sarcoid rheumatism.

In previous studies, chronic arthritis was found to be a rare complication of sarcoidosis and was frequently found together with other complications of the disease[1,3,13,14]. In our series, 21% of the patients hospitalized suffered from chronic arthritis. RF was detected more frequently in these patients than in those without chronic arthritis and may be a risk factor for chronicity, but this hypothesis will require confirmation with prospective data, due to the small number of patients testing positive for RF.

Bone involvement in sarcoidosis has been reported to occur in 1% to 15% of patients[1,13]. Variability in the cumulative frequency of bone lesions may be accounted for in part by the absence of pain in most patients and by normal radiographs in some cases[15] but also not excluding the possibility that more sensitive examinations could reveal abnormalities. Our data show that osseous involvement is not rare, occurring in a quarter of patients with SR, and erosions involved predominantly the hands and feet. One patient in our series had bone cysts and a reticular pattern in the metacarpals and phalanges on radiograph. The axial skeleton and long bones are involved in rare cases, but such osseous involvement was found in 7 patients in our survey, all symptomatic. Bone lesions generally occur in patients who also have chronic skin lesions, but none of our patients with bone lesions had skin lesions[1,13]. The patients with osteitic lesions were older in our series. Dactylitis has been reported to occur in 0.2% of all patients with sarcoidosis[3,16–18]. In our series, we found 2 patients with dactylitis and active multivisceral sarcoidosis. By contrast, in a large US series of dactylitis, sarcoidosis was recognized as the first cause (17%) before spondyloarthropathies, mainly psoriatic arthritis[19].

One patient in our series had a polymyositis-like syndrome and 11 had myalgia. Symptomatic muscular involvement is known to be rare (0.5% to 2.3% of patients with sarcoidosis), but such involvement can be found on biopsy in up to 50%–80% of patients with sarcoidosis[2].

Not all patients with sarcoidosis need therapy. Several specific conditions require therapy, including hypercalcemia, cardiac, neurological, and ocular involvement. Pulmonary involvement is treated when it is symptomatic or in case of deterioration. Regarding patients with sarcoidosis, 30% to 70% need corticosteroids[20,21]. NSAID or corticosteroids are the mainstay of therapy for skeletal sarcoidosis[13,14,18]. LS and arthralgia are generally relieved with NSAID or hydroxychloroquine[22]. The use of other immunosuppressive agents in sarcoidosis should be reserved for patients displaying disease progression despite the use of systemic corticosteroids or who require systemic therapy but cannot tolerate the side effects of steroids. In such a situation, alternative treatments exist, including immunosuppressive drugs (MTX, azathioprine) and noncytotoxic anti-inflammatory agents (hydroxychloroquine). MTX has emerged as the second-line treatment of choice[13,23-25]. Kaye, *et al* showed that, in 5 patients with musculoskeletal sarcoidosis treated with oral prednisone that failed to control the disease, low-dose oral MTX had beneficial effects in all patients[23]. Moreover, MTX permitted a reduction of the corticosteroid posology. They concluded that MTX was an efficient, safe, and corticosteroid-sparing therapeutic agent for the treatment of recalcitrant musculoskeletal manifestations of sarcoidosis[23]. But many patients with sarcoidosis are unable to tolerate corticosteroids or alternative therapeutic agents due to side effects, or have disease refractory to these agents, which highlights the need for other treatments.

Many studies have shown the importance of TNF-α in sarcoid granuloma development[26] and so TNF-α could be a potential target in the treatment of sarcoidosis. Numerous reports have suggested some efficacy of TNF-α antagonists (infliximab, etanercept, and adalimumab) in refractory sarcoidosis with musculoskeletal involvements[27-34]. A study in 2005 including 10 patients reported some beneficial effects of infliximab therapy on cutaneous, ocular, hepatic, or neurologic lesions of sarcoidosis. In this latter report, a patient with bone involvement detected by MRI, localized on T9 and T12 vertebrae, showed some improvement following infliximab therapy[35]. Saleh, *et al* also reported some improvements with infliximab in 12 patients with multiorgan refractory sarcoidosis including one patient with bone lesions[36]. Unexpectedly, the development of pulmonary sarcoidosis was also reported in one patient treated with infliximab for psoriatic arthritis and in another patient with RA treated with etanercept. Another patient treated with etanercept for RA developed pulmonary and skin sarcoidosis. In all patients, the diagnosis is proven by biopsy and a sarcoidosis remission is observed when the TNF-α antagonists are stopped[37,38]. Clinicians will need to assess the potential benefits of TNF-α antagonists in each individual patient and weigh the importance of a therapeutic response against the adverse effects. Prospective, randomized, controlled trials assessing anti-TNF treatments are required to evaluate the efficacy of this treatment in cases of complicated and/or refractory sarcoidosis. It remains unclear whether this treatment is likely to be specifically useful against osteoarticular sarcoidosis.

Our study has several limitations: It is a retrospective study, and sensitive techniques assessing asymptomatic lesions (i.e., scintigraphy or MRI) were not performed. However, we have included quite a large number of patients considering the rarity of the disease, which may contribute to a better definition of the underestimated clinical aspect of this systemic disease. We focused on patients with sarcoidosis hospitalized in rheumatology units; thus, our results do not reflect the osteoarticular symptoms of the whole population of patients with sarcoidosis, but only provide description of musculoskeletal involvement in patients referred to rheumatology with at least one osteoarticular symptom.

Sarcoidosis may lead to several musculoskeletal mani-

festations. In our series of 100 patients, SR, as defined here, was the main cause of hospitalization. The patients of the LS group were younger than those of the SR group, and were more likely to present oligoarthritis involving ankles and high CRP concentrations. The osteoarticular symptoms observed in the SR group were oligoarthritis, polyarthritis, erosions, and osteitis. Lung interstitial involvement was more frequent in the SR group than in the LS group. Chronic polyarthritis was associated with the detection of RF. Bony lesions occurred in a quarter of patients with SR; patients with osteitic involvement were older and erosions affected the small bones of the hands and feet.

REFERENCES

1. Pettersson T. Rheumatic features of sarcoidosis. Curr Opin Rheumatol 1997;9:62-7.
2. Fayad F, Liote F, Berenbaum F, Orcel P, Bardin T. Muscle involvement in sarcoidosis: a retrospective and followup studies. J Rheumatol 2006;33:98-103.
3. Torralba KD, Quismorio FP Jr. Sarcoid arthritis: a review of clinical features, pathology and therapy. Sarcoidosis Vasc Diffuse Lung Dis 2003;20:95-103.
4. Mana JC, Gomez-Vaquero C, Montero A, et al. Lofgren's syndrome revisited: a study of 186 patients. Am J Med 1999;107:240-5.
5. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
6. Gran JT, Bohmer E. Acute sarcoid arthritis: a favourable outcome? A retrospective survey of 49 patients with review of the literature. Scand J Rheumatol 1996;25:70-3.
7. Govindarajan V, Agarwal V, Aggarwal A, Misra R. Arthritis in sarcoidosis. J Assoc Physicians India 2001;49:1145-7.
8. Alaoui FZ, Talaoui M, Benamour S. Osteo-articular manifestations of sarcoidosis [French]. Presse Med 2005;34:19-24.
9. Glennas A, Kvien TK, Melby K, et al. Acute sarcoid arthritis: occurrence, seasonal onset, clinical features and outcome. Br J Rheumatol 1995;34:45-50.
10. Fite E, Alsina M, Mana J, Pujol R, Ruiz J, Morera J. Epidemiology of sarcoidosis in Catalonia: 1979-1989. Sarcoidosis Vasc Diffuse Lung Dis 1996;13:153-8.
11. Perruquet JL, Harrington TM, Davis DE, Viozzi FJ. Sarcoid arthritis in a North American Caucasian population. J Rheumatol 1984;11:521-5.
12. Milman N, Selroos O. Pulmonary sarcoidosis in the Nordic countries 1950-1982. II. Course and prognosis. Sarcoidosis 1990;7:113-8.
13. Barnard J, Newman LS. Sarcoidosis: immunology, rheumatic involvement, and therapeutics. Curr Opin Rheumatol 2001;13:84-91.
14. Tozman EC. Sarcoidosis: clinical manifestations, epidemiology, therapy, and pathophysiology. Curr Opin Rheumatol 1991;3:155-9.
15. Wilcox A, Bharadwaj P, Sharma OP. Bone sarcoidosis. Curr Opin Rheumatol 2000;12:321-30.
16. Eschard JP, Etienne JC. Osteoarticular manifestations of sarcoidosis [French]. Rev Med Interne 1994;15 Suppl:305S-7S.
17. Allanore Y, Perrot S, Menkes CJ, Kahan A. Management of a patient with sarcoid calcaneitis and dactylitis. Joint Bone Spine 2001;68:175-7.
18. Ugwonali OF, Parisien M, Nickerson KG, Scully B, Ristic S, Strauch RJ. Osseous sarcoidosis of the hand: pathologic analysis and review of the literature. J Hand Surg (Am) 2005;30:854-8.
19. Rothschild BM, Pingitore C, Eaton M. Dactylitis: implications for clinical practice. Semin Arthritis Rheum 1998;28:41-7.
20. Baughman RP, Lynch JP. Difficult treatment issues in sarcoidosis. J Intern Med 2003;253:41-5.
21. Baughman RP, Lower EE, du Bois RM. Sarcoidosis. Lancet 2003;361:1111-8.
22. Nunes H, Soler P, Valeyre D. Pulmonary sarcoidosis. Allergy 2005;60:565-82.
23. Kaye O, Palazzo E, Grossin M, Bourgeois P, Kahn MF, Malaise MG. Low-dose methotrexate: an effective corticosteroid-sparing agent in the musculoskeletal manifestations of sarcoidosis. Br J Rheumatol 1995;34:642-4.
24. Baughman RP, Lower EE. A clinical approach to the use of methotrexate for sarcoidosis. Thorax 1999;54:742-6.
25. Baughman RP. Therapeutic options for sarcoidosis: new and old. Curr Opin Pulm Med 2002;8:464-9.
26. White ES. Infliximab in sarcoidosis: more answers or more questions? Am J Respir Crit Care Med 2006;174:732-3.
27. Yee AM, Pochapin MB. Treatment of complicated sarcoidosis with infliximab anti-tumor necrosis factor-alpha therapy. Ann Intern Med 2001;135:27-31.
28. Roberts SD, Wilkes DS, Burgett RA, Knox KS. Refractory sarcoidosis responding to infliximab. Chest 2003;124:2028-31.
29. Ulbricht KU, Stoll M, Bierwirth J, Witte T, Schmidt RE. Successful tumor necrosis factor alpha blockade treatment in therapy-resistant sarcoidosis. Arthritis Rheum 2003;48:3542-3.
30. Khanna D, Liebling MR, Louie JS. Etanercept ameliorates sarcoidosis arthritis and skin disease. J Rheumatol 2003;30:1864-7.
31. Callejas-Rubio JL, Ortego-Centeno N, Lopez-Perez L, Benticuaga MN. Treatment of therapy-resistant sarcoidosis with adalimumab. Clin Rheumatol 2006;25:596-7.
32. Hobbs K. Chronic sarcoid arthritis treated with intraarticular etanercept. Arthritis Rheum 2005;52:987-8.
33. Pritchard C, Nadarajah K. Tumour necrosis factor alpha inhibitor treatment for sarcoidosis refractory to conventional treatments: a report of five patients. Ann Rheum Dis 2004;63:318-20.
34. Sweiss NJ, Curran J, Baughman RP. Sarcoidosis, role of tumor necrosis factor inhibitors and other biologic agents, past, present, and future concepts. Clin Dermatol 2007;25:341-6.
35. Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. Chest 2005;127:1064-71.
36. Saleh S, Ghodsian S, Yakimova V, Henderson J, Sharma OP. Effectiveness of infliximab in treating selected patients with sarcoidosis. Respir Med 2006;100:2053-9.
37. O'Shea FD, Marras TK, Inman RD. Pulmonary sarcoidosis developing during infliximab therapy. Arthritis Rheum 2006;55:978-81.
38. Verschueren K, Van Essche E, Verschueren P, Taelman V, Westhovens R. Development of sarcoidosis in etanercept-treated rheumatoid arthritis patients. Clin Rheumatol 2007;26:1969-71.