CHAPTER 13

Sarcoidosis: joint, muscle and bone involvement

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Sarcoidosis is a multisystem granulomotous disease in which multiple organs, including the locomotor system, may be involved [1–5]. Osteoarticular manifestations of sarcoidosis may be specific or nonspecific. They may be the presenting feature or may occur late after onset, either isolated or combined with other clinical manifestations. Clinical features of joint involvement are found in 14% of cases at presentation, and up to 38% during follow-up [5]. The frequency of clinical muscle and bone involvement at presentation is low (<1%), and is found in 5–13% of patients during follow-up [5]. Locomotor involvement is often subclinical or not clinically recognised because of mild or unspecific symptoms in spite of a high prevalence on biopsy, as shown for muscle involvement [6]. Another systemic locomotor sequel is secondary osteoporosis, mostly due to glucocorticoid therapy [1].

Sarcoid joint involvement

Joint manifestations, including arthritis and periarthritis, occur in 14–38% of patients [1–5]. Arthralgias are even more common (70%) [5]. Sarcoid rheumatic involvement is generally divided into acute and chronic types [1–5]. There are so many differences between acute and chronic arthritis that is has been questioned whether they represent the same aspects of sarcoid joint disease [2].

Acute sarcoid arthritis

The most common form of joint involvement is an acute polyarthritis/periarthritis. The arthritis may be migratory, intermittent or additive in time, and can precede other manifestations of sarcoidosis by several months. These clinical presentations can, therefore, resemble reactive arthritis [7], rheumatoid arthritis or even spondylarthropathies [3]. More commonly, however, it is nonmigratory and accompanied by other signs of sarcoidosis [5], known as the Löfgren's syndrome [7–9].

Classically, Löfgren's syndrome consists of a triad with bilateral hilar lymphadenopathy, erythema nodosum and (peri)arthritis of large joints, particularly of the ankles and knees, although other peripheral large and small joints can be involved [7–9]. This presentation of acute sarcoidosis most frequently occurs in Caucasian females and is rare in Afro-Americans [2]. Fever and other constitutional symptoms commonly accompany

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acute sarcoid arthritis. Seasonal variation of acute sarcoid arthritis has been reported with clustering in the spring [7, 9].

In a series of 186 Spanish patients with Löfgren's syndrome, 93% had erythema nodosum and/or periarticular ankle inflammation at onset [9, 10]. At the time of diagnosis 81% had no respiratory symptoms. In contrast, 81% had stage I abnormalities on chest radiography, 16% stage II and 3% stage 0. Sonographic findings in 24 consecutive cases revealed joint effusion consistent with arthritis in 33%, periarthritis in 80% and a tenosynovitis in 33% patients [11].

Prognostically, Löfgren's syndrome is not recurrent in the majority of cases. In 17 cases followed prospectively over 2 yrs, the total duration of arthritis was 11 weeks (range 2–107 weeks) and erythema nodosum was mild and transient [7]. Of the 133 patients who were followed for a mean of almost 5 yrs, 8% continued to have active disease and 6% had several recurrences between 18 months and 20 yrs after complete resolution, although usually with mild organ dysfunction [9]. Thus, acute sarcoidosis classified as Löfgren's syndrome has a favourable prognosis, except in Afro-Americans and Asians [2]. Prolonged monitoring is necessary where prognosis is not so good.

Clinical features of acute or subacute monoarthritis, other than Löfgren's syndrome, are only rarely reported [2]. Synovial fluid is inflammatory, with predominance of lymphocytes [2]. Synovial or soft tissue biopsies can reveal granulomatous lesions [2]. There may be protracted courses and recurrences of arthritis [2].

Chronic sarcoid arthritis

Chronic sarcoid articular involvement is rare and appears to affect only 0.2% of sarcoid patients [12, 13], usually together with other complications of sarcoidosis, particularly chronic cutaneous sarcoidosis [3] and in Black patients [2, 3]. Medium-sized and large joints are often affected symmetrically and a simulataneous tenosynovitis may occur. Some cases have been described with severe destructive arthropathy requiring total arthroplasty [14]. Synovial biopsy shows noncaseating granulomas. In some cases, rheumatoid arthritis may be suspected, particularly when there is a coincident rheumatoid factor, occurring in ~30%. The course of chronic sarcoid arthritis is characterised by periodic exacerbation and improvement with a good functional outcome [2]. However, joint destruction or deformities may be seen, including Jaccoud's type arthropathy [2].

In children, a chronic juvenile arthritis may be mimicked by combination of polyarthritis, uveitis and skin lesions [15]. A positive synovial biopsy may help establish the diagnosis.

Sarcoid synovial and tendinous involvement

Periarticular manifestations appear much more commonly than previously thought, in some reports in >60% of patients [2, 16, 17]. Tenosynovitis, articular cysts or infiltration of subcutaneous tissue causing elephant foot-like thickening have been reported [17]. Tenosynovitis usually affects extensor tendons of the fingers more often than flexor tendons, but carpal tunnel syndrome may also manifest itself [2]. Biopsy of synovium, tendon sheaths or subcutaneous tissue may reveal noncaseating granulomas.

Some bone locations, such as dactylitis and sacroiliac location, are associated with clinical and/or radiographic signs of joint involvement. These are further described in the section on sarcoid bone involvement (see later).

Treatment of sarcoid joint involvement

In cases of acute sarcoid arthritis, most frequently it is sufficient to give cold packs *t.i.d.* with a training programme combined with nonsteroidal anti-inflammatory drugs (NSAIDs) (table 1) [2]. The outcome of articular involvement is generally favourable as recovery is uneventful, generally within 1–6 months [2]. According to open label studies, sarcoid arthritis has also been treated efficaciously by systemic glucocorticoids and colchicine (oral or *i.v.*) [12]. Periarthritis is often responsive to rest, cold application and NSAIDs, whereas glucocorticoids are generally not needed nor recommended.

A chronic destructive synovitis may need treatment with glucocorticoids intra-articularly or systemically, and, in the latter case, is probably best combined with methotrexate or azathioprine, though firm evidence from randomised controlled trials is lacking [1–5]. Possibly, there is an indication for an anti-tumour necrosis factor (TNF)-α strategy in selective cases with chronic destructive arthritis in the near future.

In children, a much more aggressive treatment is needed, often comprising of a combination of glucocorticoids with immunosuppressants [15].

Sarcoid muscular involvement

There are several reasons why some patients with sarcoidosis develop muscle problems, including involvement of the skeletal muscle by sarcoidosis, steroid-induced myopathy, small fibre neuropathy and reduced physical activity.

Sarcoid muscle involvement is usually asymptomatic and resolves spontaneously, although granulomas are commonly demonstrated by biopsy in 50–80% of sarcoid cases [6]. In a group of 29 sarcoid patients who spontaneously complained of fatigue, skeletal muscle weakness was found that was associated with reduced health status and exercise intolerance [18]. Gallium scintigraphy is considered the main method that can demonstrate muscular involvement [19]. In some cases magnetic resonance imaging (MRI) can be helpful for diagnosis, but small lesions can be overlooked [2].

Rarely, acute inflammatory myopathy resembling polymyositis, as well as palpable myopathic nodules and a chronic progressive myopathy, have been described [6, 20–23]. The latter myopathic type occurs predominantly in elderly females with a painful bilateral involvement and often results in muscle weakness, atrophy and even muscle contracture [23].

The rarest type is the acute sarcoid myositis, as is reported in 18 cases [20, 22]. This is usually found in younger patients with proximal muscle weakness mimicking acute polymyositis.

The diaphragm and intercostal muscles may also be impaired. It has been demonstrated that patients with sarcoid granulomas infiltrating skeletal muscle had

Table 1. – Treatment options in sarcoidosis with locomotor complaints

	Analgesics	Nonsteroidals	Corticoid local	Corticoid *p.o.*
Arthralgia	+++	+	-	-
Myalgia	+++	+	-	-
Arthritis	+	+++	++	+[#]
Enthesitis	+++	++	+	+/-
Myositis	+	++	-	+++[#]
Periostalgia	+++	+++	-	-
Osseous involvement	++	++	-	-[#]

+++: highly indicated; ++: indicated; +: may be tried; -: not indicated. [#]: disease modifier should be considered.

impaired respiratory muscle function [18, 24]. With a lack of a correlation between subjective symptoms, *i.e.* exertional dyspnoea and/or fatigue, and chest radiograph abnormalities, lung function may be explained by respiratory muscle impairment. The relevance of inspiratory muscle impairment in sarcoid patients is underscored by significant correlations found between dyspnoea scores and health status and quality of life [25–27]. In addition, it has been shown that small fibre neuropathy is a frequent finding of sarcoid patients with fatigue [28].

Treatment of sarcoid muscle involvement

There are currently no studies available on the treatment of sarcoid muscle involvement. In severe cases, glucocorticoids and immunosuppressive drugs are given (table 1). For patients with muscle weakness, controlled physical training programmes are advocated, as shown in other conditions [17, 29].

Sarcoid bone involvement

In 1928, Jungling described osteitis tuberculosa multiplex cystica with an estimated incidence of 1–13%, the variation depending on radiological or clinical criteria [30]. Bone involvement occurs between the ages of 30–50 yrs and is more frequent in Blacks. It is rarely a presenting feature (in <1% of patients) [5] and usually occurs in patients known to have sarcoidosis with multisystemic involvement, in chronic pulmonary or multivisceral sarcoidosis and in patients with chronic skin lesions, especially lupus pernio [1]. Bone lesions are mainly seen in the bones of hands and feet, but other locations, such as the skull, nasal bones and vertebrae, have been described. They are usually asymptomatic, but may be painful, and, in case of severe lesions, adjacent joints can be involved [3]. Radiological findings most frequently show cystic lesions, punched-out lesions, osteolysis, reticularisation of cortical bone or cortical defects and, rarely, sclerotic, periostitis or destructive lesions [4, 31–33].

Biopsy reveals granulomas in the medullary cavity and destruction of the adjacent bone tissue [31–33]. Thereby confluent lacunae and cavities of varying sizes surrounded by normal bone may occur. Margins may reveal subsequent sclerosis. Granulomatous tissue may affect the periosteum and may invade neightbouring soft tissue. Histomorphometry has shown increased bone resorption in the vicinity of intramedullary sarcoid nodules, probably due to local mediators [4].

On technetium bone scanning an increased uptake is seen, suggesting, or sometimes mimicking, neoplastic lesions [2]. To differentiate these from sarcoid lesions additional imaging may be needed. Computed tomography (CT) scanning shows bone destruction or sclerosis, particularly marginally, without extra-osseous mass or extension to soft tissues. MRI scanning shows nonspecific lesions with a reduced signal on T1, and increased signal on T2-weighted sequences, enhanced by Gadolinium. The combination of these features does not preclude a neoplastic or infectious condition [2]. There is no indication for routine radioisotope bone scanning in patients with sarcoidosis, and this examination should be restricted to patients with clinical suspicion of osseous sarcoidosis [34].

Dactylitis

Involvement of fingers, particularly 2nd and 3rd digits, and less frequently of toes, is the most frequent bone manifestation [4]. Dactylitis may be asymptomatic but may also

cause moderate pain and stiffness. Distal phalangeal swellings are associated with purple-violet, cyanotic discolouration, and splitting of nails or nail dystrophy. Acro-osteolysis may give the appearance of pseudo-clubbing or sausage-like fingers [33].

Pelvic pathology

Involvement of the pelvis is featured by bony sclerosis, sometimes with lytic lesions and surrounding condensation. In the majority of patients it is symptomatic, *i.e.* painful [4]. A genuine sacroiliitis is rare, and in the literature this is reported only once [4]. Sacroiliac pathology is considered to be secondary to confluencing bone lesions of sacrum and ilium. Such localisation cannot be established without a biopsy to rule out tuberculosis or other infectious processes of that joint [4].

Skull

Lesions of the vault of the skull are rare. Less than 30 cases have been reported [35]. The incidence may be underestimated, as symptoms generally are absent or only minor, such as headache or local swelling. Bony lacunae vary in size and localisation. Radiographs show osteolysis of full thickness of the skull without peri-lesional condensation. Cases of partial or complete regression, both spontaneous or with treatment, have been described. Involvement of the base and of other cranial bones, *i.e.* sinus, petrous bones, orbits, mandible, and nasal bone, seems to be found more frequently with the widespread use of facial CT scans [4].

Vertebrae

Involvement of the spine is rare [4]. Complaints are manifested by a mechanical spinal pain associated with stiffness, affecting the lumbar and lower dorsal spine in the majority of patients. Neurological compression is rare, but may be the consequence of cervical lesions. Radiographs generally reveal osteolytic features of vertebral body or pedicle but occur with peripheral condensation, vertebral compression and lesions of the laminae reminiscent of spondylodiscitis, particularly as there is sometimes a false paravertebral spindle image associated with lesions of the ganglia [4]. Generally, there is no disc space narrowing. Some cases of ivory or pseudo-pagetic vertebrae have been reported [4].

Treatment of sarcoid bone involvement

Sarcoid bone involvement responds poorly to glucocorticoids as well to other drugs (table 1) [4]. Symptomatic relief may be obtained by NSAIDs, colchicine and chloroquine [4].

Calcium metabolism and osteoporosis in sarcoidosis

Hypercalcaemia and hypercalciuria. Hypercalcaemia affects 10% of sarcoid patients. Hypercalciuria is reported in $\leq 50\%$ of cases and is associated with nefrolithiasis, occurring in $\sim 1\%$ of sarcoid cases. Hypercalcaemia is caused by increased extra-renal production of 1,25 dihydroxyvitamin D_3 by activated macrophages in the sarcoid granuloma's. Whether hypercalcaemia and hypercalciuria in sarcoidosis are risk factors for osteoporosis is unknown. The aetiology, symptoms and treatment of hypercalcaemia and hypercalciuria are described in Chapter 14.

Osteoporosis

In addition to localised bone lesions due to sarcoid granulomas, generalised bone loss has been described in sarcoid patients [36–40]. The aetiology of osteoporosis is multifactorial. In sarcoid patients, specific risk factors for osteoporosis include the frequent use of glucocorticoids, hypercalcemia and hypercalciuria and their treatment modalities (low calcium intake), and decreased physical activity. However, the relative importance of these risk factors in relation to osteoporosis has not been evaluated specifically in sarcoidosis. No data are available on fracture risk in sarcoidosis. However, chronic use of glucocorticoids is associated with an increased fracture risk.

Only two studies reported bone mineral density (BMD) in untreated sarcoidosis [36, 37]. In 18 untreated pre-menopausal females, BMD was normal in the spine and in the femoral neck, but in five post-menopausal females, BMD was lower in the spine and marginally lower in the femoral neck [36]. In another study, 36 patients with untreated sarcoidosis had a normal mean BMD, as measured by quantitative CT scanning (qCT), and BMD was lowest in long-standing disease [37].

Many patients with sarcoidosis are treated with glucocorticoids. Long-term treatment with glucocorticoids results in suppression of bone formation, accelerated bone loss and an increased risk of fractures [38]. Studies specifically studying the effects of glucocorticoids in sarcoidosis are also scarce. In a study of African-Americans with sarcoidosis, low BMD was common, comparable to chronic obstructive pulmonary disease and was associated with low body mass index (BMI) [39]. Using qCT, bone loss of 15% was found after 2 yrs, and was even greater in post-menopausal females (-26% after 2 yrs) [40].

Prevention and treatment of glucocorticoid-induced osteoporosis in sarcoidosis

As always, the patient's individual risk factors should be carefully reviewed when initiating glucocorticoid therapy [41]. Factors that influence bone loss and fracture risk include the dose of glucocorticoids, the underlying condition and the presence of other risk factors, such as increasing age, sex, low BMI, previous personal and familial fracture, low calcium intake, vitamin D deficiency (low sun exposition and/or low intake), low physical activity, smoking, excessive alcohol consumption, menopausal status, hypogonadism in males, decreased general health status and low BMD. These factors should be considered in all patients that are anticipated to have treatment with glucocorticoids. An example of risk calculation in glucocorticoid-treated patients is available and was based on age, sex, BMI, dose of glucocorticoids, smoking, past fracture, past fall and underlying disease [42]. These risk factors allowed calculation of the individual fracture risk. A female aged 65 yrs, with low BMI, a previous history of fracture and falls, treated with 15 mg glucocorticoids *q.d.* (total risk score 54) had a 5-yr fracture risk of 45%. A male with a similar history would have a comparable fracture risk of 29% [42].

Many guidelines are available on the prevention and treatment of glucocorticoid osteoporosis in patients that are expected to be, or already are, on long-term (>3 months) glucocorticoid treatment [43]. As an example, an algorithm of the Dutch guidelines is shown in figure 1 [44]. Bone measurement is not considered necessary in high-risk patients (taking >15mg·day^{-1} of glucocoricoids, having a prevalent vertebral fracture, taking intermediate doses of glucocorticoids (7.5–15 mg·day^{-1}) together with having other major risk factors (post-menopausal females, elderly males)). In such patients, treatment with bisphosphonates is indicated, irrespective of BMD values. In other cases, bone measurement in the hip and/or spine using dual X-ray absorptiometry is recommended in all patients who are expected to take glucocorticoids for >3 months and in patients who are on long-term glucocorticoid treatment. If BMD is then found to be

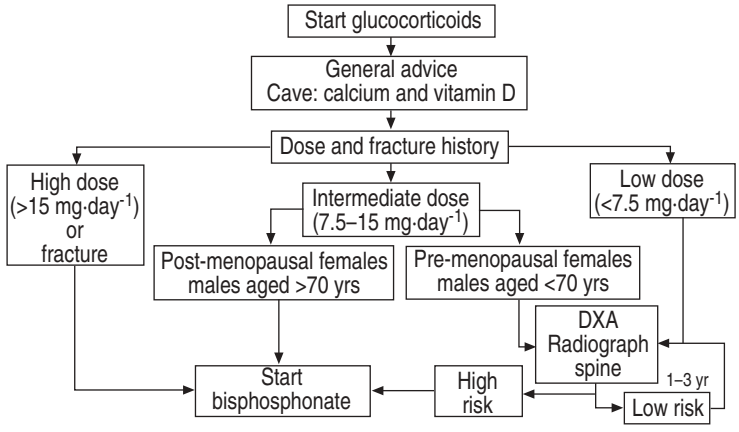

Fig. 1. – Prevention of glucocorticoid osteoporosis in sarcoidsis. DXA: dual X-ray absorptiometry. Adapted from [43].

low (*e.g.* a T-score of <-1.0), treatment with bisphosphonates should be considered. If BMD is normal (T-score >-1.0), measurements should be repeated after 6–12 months and then at yearly intervals [44].

In addition, a radiograph of the spine is advocated when vertebral fractures are suspected (in the presence of thoracic hyperkyphosis, height loss of >2 cm, an occiput-wall distance of >0 cm or a rib-pelvis distance of <2 finger breadths) [45].

Proposed general measures in chronic glucocorticoid users include lifestyle changes, such as good nutrition, cessation of smoking, moderate alcohol intake, appropriate physical activity, exercise, maximal reduction of glucocorticoid dose, consideration of alternative formulations or routes of administration, and prescription of alternative immunosuppressive agents [41].

The use of calcium and vitamin D supplements, as advocated in all guidelines [43], should in the case of sarcoidosis only be considered when calcium homeostasis is normal (normal serum calcium and normal calciuria).

The use of long-term hormonal therapy in post-menopausal females is currently controversial, since the results of the Women's Health Initiative Study indicated that the advantages of hormonal therapy in post-menopausal females are less than the disadvantages (risk for cardiovascular events and breast cancer) [46].

In sarcoid patients treated with glucocorticoids, salmon calcitonin (by nasal spray in 11 patients or intramuscular injection in 18 patients) over 2 yrs stabilised BMD in the spine (measured by qCT) [47]. However, calcitonin is not recommended in most guidelines or is only proposed as an alternative in case of contraindications or intolerance for bisphosphonates [43].

Alendronate was studied over 1 yr in 15 sarcoid patients treated with glucocorticoids. Alendronate stabilised BMD in the ultradistal radius (measured by dual photon absorptiometry) [48]. Potent bisphosphonates (alendronate and risedronate) are recommended for the prevention of glucocorticoid osteoporosis (fig. 1) [41, 44]. Fracture reduction in glucocorticoid-induced osteoporosis (GIOP) has been shown (as a secondary endpoint) in studies with alendronate and risedronate [49, 50]. It is advocated that therapy with bisphosphonates to prevent or treat GIOP should last as long as glucocorticoids are used [41, 44]. After stopping glucocorticoids, further treatment is only indicated if the risk for osteoporotic fractures remains high, based on clinical risk factors and BMD [43]. Many patients with sarcoidosis are of a young age. The use of

bisphosphonates should be limited in pre-menopausal females of childbearing age, as bisphosphonates have a long half-life and as the effects of bisphosphonates on foetal bone growth are unknown.

Coexistent sarcoid involvement mimicking autoimmune disease

If salivary and/or lacrimal glands are affected by sarcoidosis, the clinical picture of Sjogren's syndrome, an autoimmune disorder resulting in dryness of primarily the eyes and mouth, is mimicked [51]. About a dozen of cases with sarcoidosis and Sjogren's syndrome have been reported. In a series of 464 primary Sjogren's patients, only five met criteria of coexistent sarcoidosis (1%). During long-term follow-up, five patients had extra-glandular manifestations: four had a nonerosive polyarthritis and one a vasculitis [51]. As the frequency of sarcoidosis in the population is in the range of 10–80 per 100,000, the frequency of sarcoidosis in Sjögren's patients is ~500-times higher than in the normal population. In patients with sarcoid gland involvement, low-dose corticosteroids induced regression of lymphadenopathy, but the sicca symptoms remained together with anti-SSA and/or anti-SSB auto-antibodies [51].

Conclusions

Sarcoidosis is a multisystemic disease, with a wide spectrum of clinical presentation. It can present with locomotor signs and symptoms, ranging from asymptomatic organ involvement to overt clinical presentation in joints, muscles and bones, and from an acute to a chronic condition. There are indications that symptomatic and immunosuppressive therapies can be effective for some of the locomotor involvements, but clearly more data are needed, especially with the availability of biologicals such as anti-TNF medications.

As many patients are treated with glucocorticoids, special attention is required for prevention of glucocorticoid-induced osteoporosis, with general measures and potent bisphosphonates necessary for patients at risk.

Summary

Sarcoidosis is a granulomatous systemic disease potentially involving the locomotor system. The most common presentation is acute sarcoidosis in Löfgren's syndrome. Alternative manifestations include chronic articular involvement, synovial and tendinous involvement, muscular complications, and bone involvement, such as dactylitis, pelvic pathology, skull abnormalities and spinal problems. Systemic involvements may reflect coexistent autoimmune disease and disturbed calcium metabolism resulting in osteopenia or osteoporosis.

Corticosteroids are commonly used to treat more serious cases, but may result in additional risks of osteoporosis, which may currently be counteracted by bisphosphonates. Modern treatment options seem to be efficacious in chronic sarcoid inflammation due to the ability to block tumour necrosis factor. However, further studies are needed, specifically in the field of locomotor presentations of sarcoidosis.

Keywords: Arthritis, bone metabolism, dactylitis, glucocorticoids, myositis, osteoporosis, sarcoidosis, tendonitis.

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