Chapter

# Skeletal Sarcoidosis

*Henco Nel and Eli Gabbay*

## Abstract

Osseous sarcoidosis is an uncommon manifestation, reported in 3–13% of patients with sarcoidosis. Although older literature suggested that hands and feet are most commonly affected, axial bone involvement may be more common than previously reported, since earlier studies relied mostly on plain X-rays, which may be less sensitive for axial bone lesions. Newer imaging modalities such as MRI and PET/CT scanning have demonstrated a larger incidence of vertebral involvement. Bone lesions are commonly asymptomatic and patients who have bone involvement may have higher incidences of multi-organ involvement. Osseous sarcoidosis appears to be mainly osteolytic in nature, but the radiographic appearance may be indistinguishable from other osteolytic lesions and therefore a biopsy is usually required to confirm the diagnosis. The histological findings of sarcoidosis in the bone are the same as in other tissues of the body. No general consensus exists for the treatment of bone sarcoidosis but corticosteroids are the most commonly prescribed first-line drugs. Methotrexate is the most widely studied steroid-sparing agent for sarcoidosis and it has been reported useful for a variety of organ symptoms, but especially where there is bone involvement.

**Keywords:** osteolytic lesions, vertebral involvement, PET/CT, corticosteroids, methotrexate

## 1. Introduction

Bone involvement is reported in approximately 3–13% of patients with sarcoidosis [1]. However, its frequency is likely underestimated as it is often asymptomatic [2–4]. The pathogenesis of sarcoidosis involving the skeletal system remains unknown. Patients with skeletal sarcoidosis usually have multiple bones involved and numerous other extra-osseous manifestations [3, 5]. Newer imaging modalities have demonstrated a relative increase in axial involvement [3, 4]. Treatment guidelines for skeletal sarcoidosis are lacking and evidence comes primarily from retrospective case series and individual case reports [3, 4]. Nonetheless, most patients with bone involvement respond well to corticosteroids in combination with methotrexate [5].

## 2. Pathophysiology

The pathogenesis of sarcoidosis specifically involving bone is unclear. Some authors have postulated that antigenic particles are spread hematogenously or through the lymphatic system, creating granulomas within the bone, bone marrow, and other organs [4]. This hypothesis may help to explain the greater frequency

of liver, spleen, and extrathoracic lymph node involvement in patients with bone sarcoidosis [4]. The mechanisms of osteolysis in sarcoidosis also remain unclear. Mechanisms that have been postulated include: high levels of 1,25 $(OH)_2$ D3 activity stimulating osteoclastic activity, local granuloma-induced osteoclastic reaction and the sarcoid granuloma being a source of an osteoclastic activating factor inducing bone resorption. However, none of these hypotheses have been shown to provide a satisfactory explanation related to the presence of bone lesions in sarcoidosis [1].

## 3. Epidemiology

Bone involvement is reported in 3–13% of patients with sarcoidosis, although its frequency is likely to be underestimated as it is often asymptomatic [1–3]. Imaging modalities such as magnetic resonance imaging (MRI) or positron emission tomography (PET)/computed tomography (CT) scans appear to identify more patients with bone involvement than historically appreciated using conventional radiography [6]. However, these imaging modalities are not routinely used for the diagnosis of skeletal sarcoidosis and are usually used to characterize organ involvement in systemic sarcoidosis or for the investigation of suspected cancer or fever of unknown origin [3, 4, 6]. Skeletal sarcoidosis appears to be more common in middle-aged and elderly white women [3, 4]. Zhou and colleagues demonstrated that white patients were three times more likely than blacks to have bone sarcoidosis while another study of 20 patients with bone sarcoidosis reported that 95% of these patients were white. Although this difference may reflect demographic characteristics at their institutions, it raises the possibility of a racial predilection [3, 4].

## 4. Clinical manifestations

Patients with bone sarcoidosis usually have numerous other extra-osseous manifestations and compared to matched cases, bone sarcoidosis patients have more multi-organ involvement than controls [3–5]. Patients with skeletal sarcoidosis also typically have more than one bone involved [3]. However, osseous involvement is frequently asymptomatic and can be incidentally detected in up to half of the patients [3, 5].

Skeletal sarcoidosis can involve focal areas of both the appendicular and axial skeleton. Pain and swelling are the most common symptoms [1, 3]. Older studies found that the hands and feet are most commonly affected, with axial bone involvement rarely reported [1]. However, axial bone involvement may be more common than previously reported, since earlier studies relied mostly on plain X-rays, which may be less sensitive for axial bone lesions [4]. Newer imaging modalities such as MRI and PET/CT scanning have demonstrated a larger incidence of vertebral involvement, and a recent retrospective study demonstrated that up to 70 percent of patients with skeletal sarcoidosis may have spinal disease [4].

### 4.1 Axial involvement

Axial sarcoidosis most commonly affects the spine followed by the pelvis [3–5]. Vertebral involvement is mostly asymptomatic and underdiagnosed [3]. The disease frequently affects the lower thoracic and upper lumbar vertebrae, but the cervical spine including the atlantoaxial (C1-C2) joint may also be involved [7, 8]. In symptomatic patients, pain is a prominent feature, especially at the thoracolumbar region [4]. With the more frequent use of advanced imaging (MRI, PET/CT) to evaluate

sarcoidosis, there has been increasing recognition of the greater relative frequency of axial involvement. In one series of 20 patients with osseous sarcoid, involvement of the axial skeleton, especially the pelvis and lumbar spine, was seen in 90 percent of patients but was often asymptomatic [3]. In another study, 3.5 percent of patients (64 out of 1802) with sarcoidosis had bone involvement and axial involvement was more common than appendicular involvement [4]. Skull sarcoidosis is uncommon and a recent systematic review yielded only 22 known cases, all of which were case reports [9]. In 35% of these cases, skull sarcoidosis was detected incidentally in asymptomatic patients [9].

### 4.2 Appendicular involvement

The most commonly affected appendicular skeletal sites are the proximal and middle phalanges of the hands [1]. With phalangeal involvement, patients can experience local pain and tenderness in the affected region, which can exhibit swelling, reduced function, distortion of fingers, and overlying erythema [3, 5]. The findings are often bilateral but asymmetric [1, 3]. There is also frequent involvement of the feet [3, 4]. Hand lesions were more common in African Americans in one study, but bone involvement overall was more frequent in whites [4].

## 5. Laboratory findings

Laboratory findings in bone sarcoidosis are generally nonspecific and similar to those seen in other forms of systemic sarcoidosis without bone disease [4, 10]. However, bone marrow involvement may cause leukopenia [11] and one study showed a significantly lower white blood cell (WBC) count in patients with skeletal sarcoidosis, compared to sarcoidosis patients without bone involvement [4].

Erythrocyte sedimentation rate (ESR), alkaline phosphatase (ALP), and serum calcium are normal in the majority of patients with skeletal sarcoidosis and this may reflect a distinct pathophysiology compared to other diseases that affect bones, such as Paget's disease, malignancy, osteoporosis, or osteomalacia [3]. Therefore, skeletal sarcoidosis should be considered in sarcoidosis patients who present with spinal and pelvic bone lesions, especially among asymptomatic patients with normal serum calcium and (ALP) [3].

## 6. Imaging

A number of changes can be seen using conventional radiographs, MRI, and PET/CT in patients with osseous sarcoidosis [4]. Conventional radiographs are usually sufficient for evaluation of the hands and feet, but MRI and PET/CT are more sensitive for the detection of changes in other parts of the skeleton [4].

### 6.1 Conventional (plain) radiography

A plain radiograph cannot reliably reflect early bone lesions, only the gross changes are clear [12]. Nonetheless, conventional radiography can be used to reveal the location of sarcoid bone lesions in the small bones of the hands and feet [10]. Classic sarcoid lesions in the small bones of the hands and feet are well characterized and diagnosed with conventional radiographs, on which they demonstrate the familiar "lacy" lytic appearance. The resulting alignment deformities in the hands and feet are often due to pathologic fractures with bone collapse rather than joint

abnormalities [13]. Although osseous sarcoidosis appears to be mainly osteolytic in nature, osteoblastic lesions have also been reported [12]. Sclerotic changes may represent the result of a secondary reaction related to treatment and they are not necessarily lesions that have been osteoblastic from the beginning [12].

Other radiographic bone lesions that have been described include diffuse marrow infiltration, punched-out lesions, permeative lesions and destructive lesions (dactylitis). Diffuse marrow infiltration with absorption and disruption of bone trabeculae is more frequently, earlier and accurately identified by bone scan than plain radiography. Punched-out lesions are small cortical defects surrounded by normal bone, usually seen in relatively unaggressive sarcoidosis, and persist indefinitely. Permeative lesions start with tunneling in the cortex of the shafts of small bones, followed by remodeling of the cortical and trabecular architecture to give a reticular pattern. Destructive lesions include rapidly advancing bone involvement with multiple fractures, devitalized cortex, considerable soft tissue swelling, but no periosteal reaction such as new bone formation. Destructive lesions are rare and seen in <0.2% of cases. More than seventy percent of patients can have a combination of lesions [12].

### 6.2 Radionuclide bone scan

Radionuclide scans appear to pick up the infiltration of sarcoidosis earlier and more accurately than radiographs and they successfully demonstrate up to 30% more osseous lesions than conventional radiography [12]. However, sarcoidosis bone lesions show variable uptake on bone scintigraphy and lesions that are occult on technetium-99 m (Tc99m) can demonstrate mild to marked fluorodeoxyglucose (FDG) avidity on PET/CT throughout the axial and appendicular skeleton [3].

### 6.3 PET/CT

A systematic review of the utility of PET imaging to monitor sarcoidosis disease activity noted that PET may often detect incidental lesions [14]. However, it is currently unclear how often asymptomatic osseous lesions might be incidentally detected with PET imaging in sarcoidosis [3]. PET scans in patients with skeletal sarcoidosis typically show active metabolism in bone, but no feature can reliably distinguish sarcoidosis from malignant lesions, particularly in the spine and pelvis and bone biopsies may be required to exclude malignancy [5]. A study from the Netherlands of 122 patients with biopsy-proven severe sarcoidosis (defined as persistent, unexplained disease-related disabling symptoms) revealed focal bone uptake and/or more diffuse bone marrow involvement in more than one-third of patients by use of PET/CT scanning, although 94 percent of the lesions were not evident on low-dose bone CT [6]. This was much higher than expected according to most previous published studies. Moreover, it showed that PET/CT may be an excellent modality to detect bone involvement compared with more conventional modalities [2, 15]. Also of great interest was the low rate of abnormalities on low-dose CT. Clear bone lesions on CT were identified in only 2 of the 32 patients with PET-detected bone abnormalities. This finding suggests that physiological changes may precede morphologic changes [6].

The use of PET to assess the extent of disease can also uncover a suitable location for biopsy to obtain histological evidence for the diagnosis [6]. Furthermore, assessment of inflammatory activity is helpful to monitor the course of the disease and guide therapeutic strategies, but establishing the presence of inflammatory activity can be a challenge for clinicians. In recent years, PET has been shown to be a very sensitive technique to assess the inflammatory activity in sarcoidosis by detecting

and quantifying the level of inflammatory and granulomatous reactions that occur in the lungs and elsewhere in the body [16, 17]. Several reports have demonstrated a significant reduction of FDG uptake after the initiation of treatment in bone sarcoidosis patients [3, 6, 18]. An example of a pretreatment and posttreatment PET scan of a patient with widespread bone sarcoidosis is shown in **Figure 1**.

### 6.4 MRI

MRI may be the most sensitive modality in the detection of axial skeleton, large tubular bones and bone marrow involvement in sarcoidosis. Long bone and axial skeletal involvement may be occult at conventional radiography but depicted at MR imaging, with an appearance that resembles that of osseous metastases [13]. With the majority of large tubular bone lesions, there is no MRI evidence of periosteal involvement or cortical destruction, although cortical disruption and extraosseous extension are usually seen when small bones are involved. The lack of cortical destruction with large-bone lesions might explain why the majority of these lesions are radiographically occult and clinically silent. On MRI, granulomatous infiltration

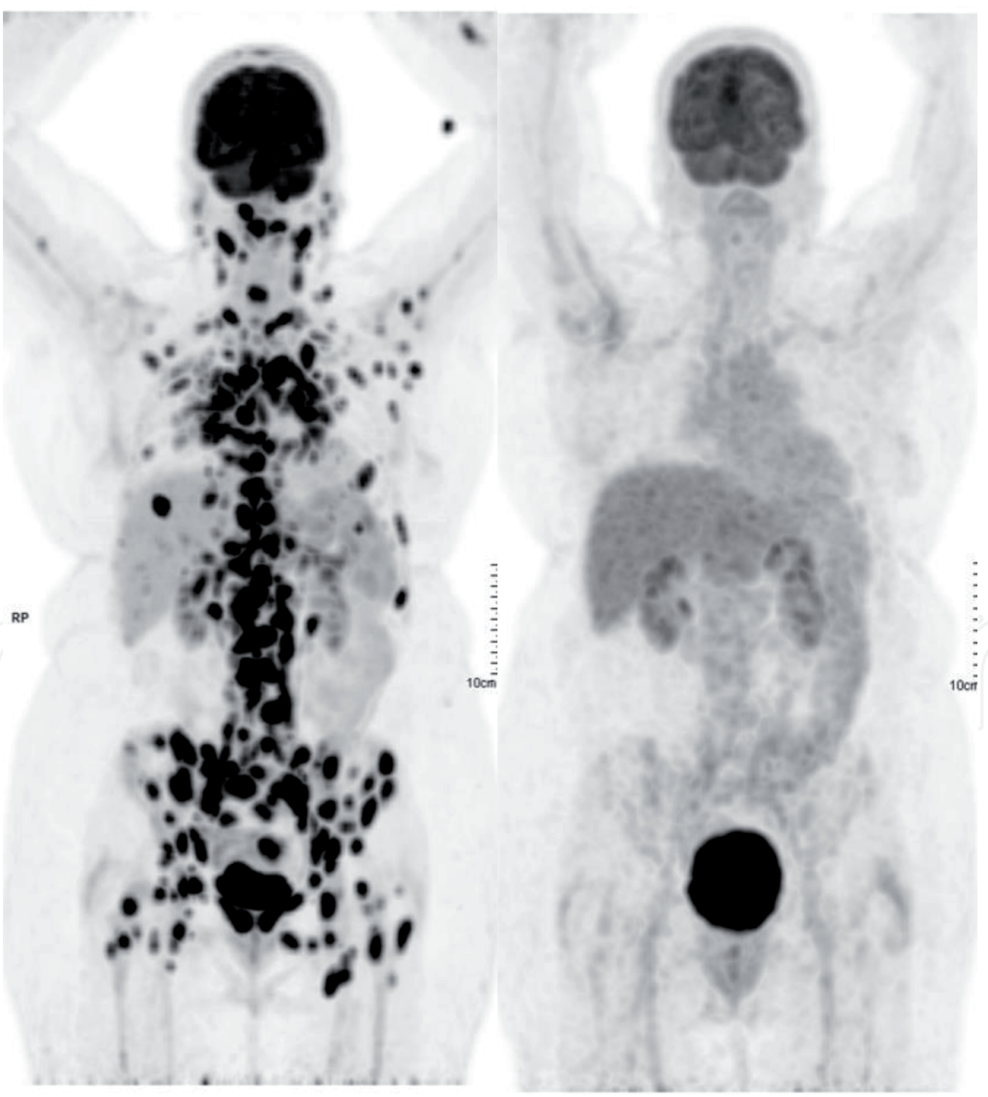


**Figure 1.**
*PET/CT scan showing marked improvement after initiation of immunosuppressive therapy with no definitive evidence for residual FDG-avid disease (Right), compared to previously demonstrated intense FDG-uptake within the lymph nodes above and below the diaphragm, within multiple skeletal lesions and within lesions involving the lungs, liver and spleen (Left).*

of the bone marrow results in an abnormal signal. The lesions are most often hypointense on T1-weighted imaging, hyperintense on T2-weighted and Short Tau Inversion Recovery (STIR) imaging and show enhancement after contrast administration [13]. **Figure 2** demonstrates contrast enhancing lesions of the skull and C2 vertebra.

Despite the sensitivity of MRI compared with conventional radiography, osseous sarcoidosis lesions cannot be reliably distinguished from metastatic lesions on routine MRI [19]. In a comparison of osseous sarcoidosis with osseous metastatic lesions, the presence of intra- or perilesional fat, lesional border characteristics (i.e., sharply defined, brush-like, or poorly defined), and the presence of an extraosseous soft tissue mass, as well as posterior element involvement of spinal changes, were indicative of osseous sarcoidosis, but overall had only moderate sensitivity for the diagnosis, despite relatively high specificity [19].

MR imaging of sarcoidosis lesions of the small bones also provides information not available at radiography, demonstrating marrow lesions that are radiographically occult, extension of granulomas beyond the cortex, and periosseous soft-tissue involvement [13]. Large bone lesions can have a variety of appearances,

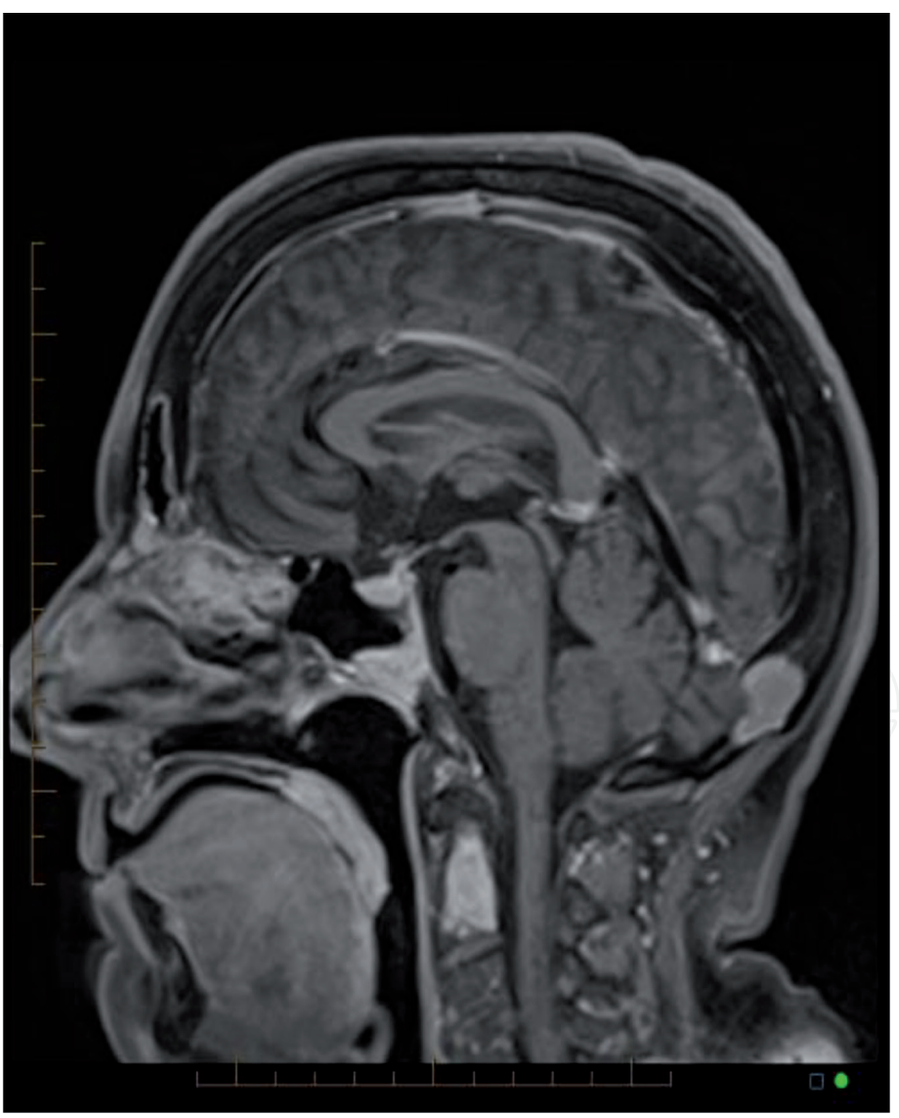

**Figure 2.**
*Post-contrast T1 weighted SPACE sequence with fat saturation demonstrates contrast enhancement of osseous lesions of the clivus, occipital bone, and C2 vertebra. MRI demonstrates the C2 lesion involves the vertebral body and odontoid process.*

including round, cannonball-like intramedullary lesions, confluent irregular marrow infiltration, less well-defined discrete lesions with a "starry sky" appearance, and patchy, diffuse intramedullary lesions [13].

### 6.5 CT scan

Computed tomography (CT) scanning is often used to evaluate pulmonary or lymph node involvement in sarcoidosis, and bony lesions can be detected on these scans. However, CT scan is nonspecific, as is conventional radiography, and the sensitivity of CT for osseous sarcoid is lower than MRI or PET/CT [4]. On radiography and CT, sarcoidosis bone lesions can be mixed, lytic, or sclerotic but may also be undetectable, particularly in the axial skeleton and long bones [19].

## 7. Pathology

The histological findings of sarcoidosis in the bone are the same as in other tissues of the body [12]. The lesion of sarcoidosis is a focal, well-defined granuloma formed by the accumulation of epithelial cells, multinucleated giant cells, lymphocytes, macrophages and fibroblasts. The centre of the granuloma is composed of macrophage-derived cells and CD4+ T cells, whereas the periphery of the granuloma is composed of a large number of antigen-presenting interdigitating macrophages, CD4+ and CD8+ T cells [20, 21]. **Figure 3** demonstrates a cluster of well-formed, non-necrotising granulomas.

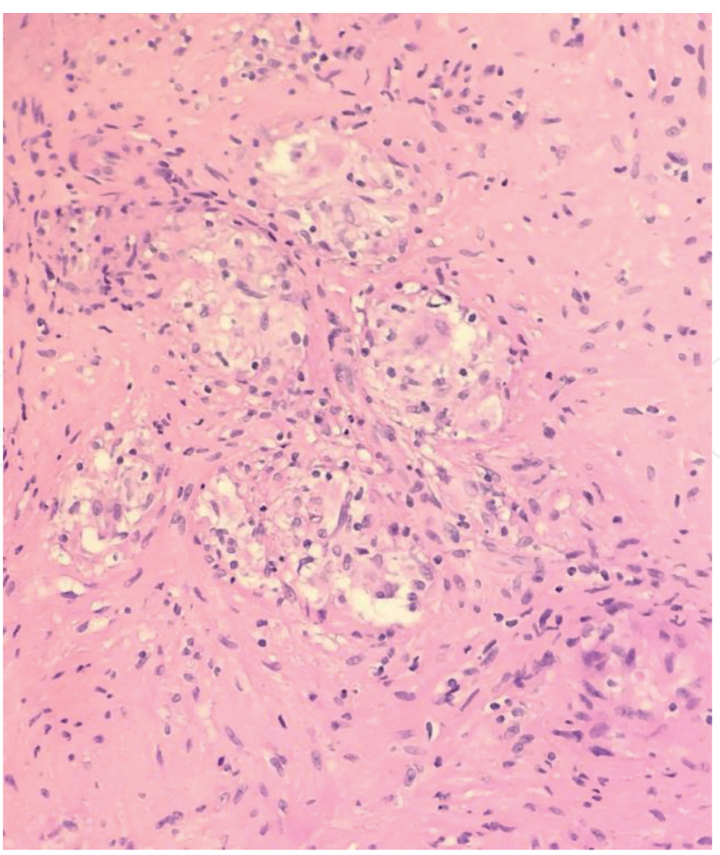

**Figure 3.**
*Microscopic examination of clivus bone tissue demonstrating a cluster of well-formed, non-necrotising granulomas.*

## 8. Diagnosis

In patients with classic skeletal lesions, either on conventional hand radiographs or with characteristic lesions detected on MRI or PET/CT, and biopsy-proven sarcoidosis in another organ, a biopsy may not be necessary, depending upon the clinical context [1, 13]. In one study, non-caseating granulomas were identified in all thirty-five patients with a positive MRI or PET/CT who underwent bone biopsy [3]. This observation might suggest that pathological confirmation may not be required for patients with typical imaging patterns [5].

However, because it is not possible to reliably distinguish granulomatous bone involvement of sarcoidosis from other causes by MRI or other imaging modalities, a biopsy is often required [4, 19]. A site appropriate for biopsy should be readily identified and this should be guided by imaging and symptoms [4]. In those without a prior diagnosis of sarcoidosis, radiologists should include sarcoidosis in the differential diagnosis of musculoskeletal disease detected on MRI in the appropriate clinical setting and should be alerted that large bone and axial skeleton sarcoidosis lesions encountered on MRI might resemble metastatic lesions [22, 23].

## 9. Differential diagnosis

Despite the increased sensitivity of MRI and PET/CT scans compared to conventional radiography, no imaging modality can reliably distinguish the features of osseous sarcoidosis and other skeletal pathologies [5, 6, 19].

Major conditions that should be considered in the differential diagnosis of bone sarcoidosis include:

Metastatic cancer or hematopoietic malignancy – The bone lesions in sarcoidosis can mimic those of metastatic cancer (eg, of the breast or prostate), lymphoma, multiple myeloma, or osseous hemangioma [19, 24, 25]. In patients with sarcoidosis documented in other organs and tissues and without any evidence of malignancy, it may be possible to infer that bone lesions, particularly with characteristic imaging changes, are due to sarcoidosis rather than malignancy. However, malignancy and sarcoidosis cannot be reliably distinguished on plain radiographs, by MRI [19], or on PET/CT. Therefore, a biopsy is often required to make this distinction if there is any clinical uncertainty [6].

Infection – Disseminated granulomatous infections like tuberculosis can result in focal or multifocal bone lesions. Fungal infections including disseminated cryptococcosis can also cause widespread osteolytic lesions and should be considered, particularly in immunosuppressed patients [26]. Serologic testing and/or biopsy and culture of the affected area can be performed to exclude infection [27].

Paget's disease of bone – Sarcoidosis of the long bones may resemble Paget's disease since both disorders are associated with increased uptake on bone scans and with lytic and sclerotic lesions on radiography. Unlike Paget's disease, however, the serum alkaline phosphatase (ALP) concentration is usually normal in patients with sarcoidosis [3].

## 10. Treatment

Treatment guidelines for extrapulmonary sarcoidosis are lacking and evidence for benefit in patients with osseous sarcoidosis comes primarily from retrospective case series and individual case reports [3, 4]. Most patients with osseous sarcoidosis

will already be receiving treatment for other disease manifestations when bone disease is identified or will require therapy for these manifestations if they are newly diagnosed [3, 4]. Isolated, asymptomatic bone disease may not require systemic immunosuppressive treatment and some cases of spontaneous remission have been reported [28, 29]. Nevertheless, corticosteroids remain the most commonly prescribed first-line therapy for bone sarcoidosis. Corticosteroids have been shown to be very effective in providing symptomatic relief and treatment with these agents may also result in radiological improvement [5, 30]. However, some patients may have persistent radiological abnormalities despite clinical resolution [30].

Prolonged corticosteroid therapy is associated with long-term complications and methotrexate or hydroxychloroquine have often been used, usually in combination with corticosteroids, in order to allow lower corticosteroid dose [4]. Methotrexate is the most widely studied steroid-sparing agent for sarcoidosis and it has been reported useful for a variety of organ symptoms but especially where there is bone involvement [4, 28]. Most patients with bone sarcoidosis respond well to corticosteroids in combination with methotrexate [5]. **Figure 1** demonstrates the radiological improvement in a patient that received prednisolone and methotrexate. Other second line-agents including azathioprine and third-line treatments such as anti-TNF inhibitors are often prescribed for patients with severe sarcoidosis, whose disease cannot be controlled by low-dose corticosteroids and may represent alternative options, although these are not well studied in bone sarcoidosis [4]. However, there is evidence that tumor necrosis factor (TNF) is involved in the pathogenesis of sarcoidosis, and there have been reports of successful treatment of refractory bone sarcoidosis with anti-TNF agents [3, 4]. In rare cases with irreversible bone pain, neurological involvement, or pathological fractures, surgery can be considered [30].

## 11. Prognosis

The presence of bone lesions generally implies a more advanced, chronic, and severe disorder overall, with more organs and tissues affected by sarcoidosis [2, 15]. Nevertheless, most patients with bone sarcoidosis respond well to corticosteroids in combination with methotrexate and this usually results in symptomatic improvement [4, 5]. Infrequently, spontaneous remission of skeletal sarcoidosis may also occur [29].

## 12. Conclusion

The incidence of skeletal sarcoidosis is probably underestimated as it is often asymptomatic. However, bone involvement in patients with sarcoidosis generally implies multi-organ and chronic disease. Skeletal sarcoidosis appears to be more common in middle-aged and elderly white women and frequently involves the spine. Laboratory findings are generally nonspecific and similar to those seen in other forms of systemic sarcoidosis without bone involvement. Conventional radiographs are usually sufficient for evaluation of the hands and feet, but MRI and PET/CT are more sensitive for the detection of changes in other parts of the skeleton. Newer imaging modalities are increasingly being used to evaluate skeletal involvement in sarcoidosis but most patients still require a biopsy to confirm the diagnosis. Although no general consensus exists for the management of bone sarcoidosis, the majority of patients respond well to corticosteroids in combination with methotrexate.

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## Author details

Henco Nel[1*] and Eli Gabbay[2]

1 Sir Charles Gairdner Hospital, Nedlands, Australia

2 School of Medicine, University of Notre Dame, Fremantle, Australia

*Address all correspondence to: henco.nel@health.wa.gov.au

## References

[1] Wilcox A, Bharadwaj P, Sharma OP. Bone sarcoidosis. Curr Opin Rheumatol 2000; 12:321.

[2] James DG, Neville E, Carstairs LS. Bone and joint sarcoidosis. Semin Arthritis Rheum 1976; 6:53.

[3] Sparks JA, McSparron JI, Shah N, et al. Osseous sarcoidosis: clinical characteristics, treatment, and outcomes--experience from a large, academic hospital. Semin Arthritis Rheum 2014; 44:371.

[4] Zhou Y, Lower EE, Li H, et al. Clinical characteristics of patients with bone sarcoidosis. Semin Arthritis Rheum 2017; 47:143.

[5] Ben Hassine I, Rein C, Comarmond C, et al. Osseous sarcoidosis: A multicenter retrospective case-control study of 48 patients. Joint Bone Spine 2019; 86(6):789-793.

[6] Mostard RL, Prompers L, Weijers RE, et al. F-18 FDG PET/CT for detecting bone and bone marrow involvement in sarcoidosis patients. Clin Nucl Med 2012; 37:21.

[7] Cutler SS, Sankaranarayanan G. Vertebral sarcoidosis. JAMA 1978; 240:557.

[8] Sundaram M, Place H, Shaffer WO, Martin DS. Progressive destructive vertebral sarcoid leading to surgical fusion. Skeletal Radiol 1999; 28:717.

[9] Robles LA, Matilla AF, Covarrubias MP. Sarcoidosis of the Skull: A Systematic Review. World neurosurgery 2020; 139:387-394.

[10] Kuzyshyn, H, Feinstein, D, Kolasinski, SL, et al. Osseous sarcoidosis: a case series. Rheumatol Int. 2015; 35: 925-933.

[11] Yanardağ H, Pamuk GE, Karayel T, Demirci S. Bone marrow involvement in sarcoidosis: an analysis of 50 bone marrow samples. Haematologia (Budap). 2002;32(4):419-425.

[12] Yaghmai I. Radiographic, angiographic and radionuclide manifestations of osseous sarcoidosis. Radiographics 1983;3(3):375-396.

[13] Moore SL, Teirstein AE. Musculoskeletal sarcoidosis: spectrum of appearances at MR imaging. Radiographics 2003;23(6):1389-1399.

[14] Treglia G, Taralli S, Giordano A. Emerging role of whole-body 18F-fluorodeoxyglucose positron emission tomography as a marker of disease activity in patients with sarcoidosis: a systematic review. Sarcoidosis Vasc Diffuse Lung Dis 2011; 28:87-94.

[15] Neville E, Carstairs LS, James DG. Sarcoidosis of bone. Q J Med 1977; 46:215.

[16] Teirstein AS, Machac J, Almeida O, et al. Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. Chest 2007; 132:1949 – 1953.

[17] Braun JJ, Kessler R, Constantinesco A, Imperiale A. 18F-FDG PET/CT in sarcoidosis management: review and report of 20 cases. Eur J Nucl Med Mol Imaging 2008; 35:1537 – 1543.

[18] Nel H, Davis B, Adler B, Gabbay E. Case report of osteolytic lesions in a patient with multisystem granulomatous disease. BMJ Case Rep. 2021;14(6):e242685.

[19] Moore SL, Kransdorf MJ, Schweitzer ME, et al. Can sarcoidosis and metastatic bone lesions be reliably

differentiated on routine MRI? AJR Am J Roentgenol 2012; 198:1387.

[20] Semenzato G, Pezzutto A, Chilosi M, Pizzolo G.Redistribution of T lymphocytes in the lymph nodes of patients with sarcoidosis. N Engl J Med 1982; 306(1):48-49.

[21] Kasahara K, Kobayashi K, Shikama Y, et al. The role of monokines in granuloma formation in mice: the ability of interleukin 1 and tumor necrosis factor-alpha to induce lung granulomas. Clin Immunol Immunopathol 1989; 51(3):419-425.

[22] Talmi D, Smith S, Mulligan ME. Central skeletal sarcoidosis mimicking metastatic disease. Skeletal Radiol 2008; 37(8):757-761.

[23] Waanders F, van Hengel P, Krikke A, et al. Sarcoidosis mimicking metastatic disease: a case report and review of the literature. Neth J Med 2006; 64(9):342-345.

[24] Vinnicombe S, Heron C, Wansbrough-Jones M. Dense bones. Br J Radiol 1992; 65:1049.

[25] Sun SS, Tsai SC, Hung CJ, et al. Tc-99m MDP and Ga-67 citrate scintigraphic findings in sarcoidosis with osseous involvement. Clin Nucl Med 2001; 26:472.

[26] Yang CJ, Hwang JJ, Wang TH, et al. Clinical and radiographic presentations of pulmonary cryptococcosis in immunocompetent patients. Scand J Infect Dis 2006; 38:788.

[27] Kenney CM 3rd, Goldstein SJ. MRI of sarcoid spondylodiskitis. J Comput Assist Tomogr 1992; 16:660.

[28] Sweiss NJ, Lower EE, Korsten P, et al. Bone Health Issues in Sarcoidosis. Current Rheumatology Reports 2011;13(3):265-272.

[29] Salmon JH, Perotin JM, Direz G, et al. Vertebral sarcoidosis. Spontaneous favorable outcome: A case report and literature review. Rev Med Interne 2013; 34:42.

[30] Gowani ZS, Sathiyakumar V, Holt GE. Osseous Sarcoidosis. JBJS Rev. 2015;3(4):1.