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Vertebral sarcoidosis: diagnosis to management

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Sarcoidosis is a systemic inflammatory granulomatous disease that can develop in almost any organ system. Rheumatologists may encounter sarcoidosis in different situations varying from arthralgia to bone involvement. While the peripheral skeleton was a frequent location, data regarding axial involvement is scarce.

Most patients with vertebral involvement have a known diagnosis of intrathoracic sarcoidosis.

They tend to report mechanical pain or tenderness over the involved area.

Imaging modalities, particularly Magnetic Resonance Imaging (MRI), are a mainstay of axial screening. It helps exclude differential diagnoses and delineate the extent of bone involvement.

Histological confirmation combined with the appropriate clinical and radiological presentation is the key of diagnosis.

Corticosteroids remain the cornerstone of treatment. In refractory cases, methotrexate is the steroid-sparing agent of choice. Biologic therapies may be used, although the evidence base for their efficacy is bone sarcoidosis controversial.

Keywords: Sarcoidosis; spine; diagnosis; imaging; treatment.

INTRODUCTION

Sarcoidosis is a systemic disease of unknown etiology characterized by a noncaseating granulomatous reaction. It has a worldwide distribution with an ethnic bias toward African Americans and the Nordic population *(1,2)*. Usually, sarcoidosis affects the lungs; however, any organ system might be involved. Notably, musculoskeletal manifestations occur in over 25% of patients with joints, bones, and muscle involvement *(3)*.

While joint involvement is relatively common (10%-35%), osseous sarcoidosis is rare *(3)*. Its prevalence has been challenging to ascertain since

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the lesions are often asymptomatic. According to earlier studies, hands and feet are often affected by osseous sarcoidosis, while axial skeleton involvement is scarce. However, with the Magnetic Resonance Imaging (MRI) and positron emission tomography-computed tomography (PET-CT) scanning, axial involvement seems to be more detected.

There is no consensus on the treatment of osseous sarcoidosis. Corticosteroids are the first-line treatment for symptomatic patients. In refractory cases, immunosuppressive drugs are used.

This review aimed to present an overview of the clinical presentations of spinal sarcoidosis, imaging findings, and therapeutic options.

OSSEOUS SARCOIDOSIS

Since its first description by Besnier in 1889, the literature on osseous sarcoidosis has remained poorly represented, consisting mainly of case reports or small series. To date, its reported pre--valence is highly variable, reflecting differences in the populations studied and the diagnostic criteria employed. It has been estimated to occur in 3% to 13% of patients with sarcoidosis but may be underestimated *(4,5)*. The osseous location is frequent in back ethnicities suggesting a genetic predisposition *(5)*. Hence, Africans tend to have peripheral bone localization *(6)*.

In a cohort of 100 patients, osseous sarcoidosis was more common in females during the fifth decade of life *(7)*. Nevertheless, there have also been reports of early-onset juvenile sarcoidosis *(8)*. Bone involvement includes axial and appendicular skeleton. Axial bones are defined as the spine, pelvis, ribs, skull, scapula, sternum, and clavicular bone, whereas appendicular bones include the femur, tibia, fibula, feet, humerus, ulna, radius, and hands.

VERTEBRAL SARCOIDOSIS

Vertebral sarcoidosis is extremely rare, occurring in less than 1% of patients with sarcoidosis *(3)*. Since the first described case of antemortem vertebral sarcoidosis in 1957 in a 31year old man, many cases have been reported. A systemic review identified 50 cases of vertebral sarcoidosis, and half of them had a known history of sarcoidosis *(7)*. Primary isolated vertebral sarcoidosis is possible, but it is an infrequent occurrence. There is usually a long asymptomatic period between the initial diagnosis of sarcoidosis and the development of vertebral lesions. While most patients with spinal sarcoidosis often have sarcoid lesions in other bones, the primary axial site may occur in the absence of involvement of the peripheral skeleton.

In a cohort of 48 patients, osseous involvement was more common in female patients; however, vertebral sarcoidosis appeared to have a male preponderance *(9)*. The thoracic and the upper lumbar spine are more frequently affected, but multiple vertebral involvements are also possible. Any part of the vertebra can be affected, although the vertebral body involvement was found to be more common compared to pedicles and posterior arches involvement, as reported in previous studies *(10)*.

Patients with vertebral lesions usually report mechanical pain or tenderness in the involved area *(11)*. Clinical presentation is non-specific; backache or radicular pain can reveal the disease *(11,12)*. Moreover, vertebral sarcoidosis may be asymptomatic and remains, therefore, undiagnosed. Although complications of vertebral sarcoidosis are usually limited to pain, both neurologic impairment and fractures can occur *(13)*. Noncaseating granulomas can spread along with the bony intertrabecular space, destroying the bone and extending to the spinal canal. Spinal infiltration might also cause pathological fracture of vertebrae *(14)*.

Like other inflammatory diseases, sarcoidosis is associated with bone mineral loss leading to an increased risk of fractures. The prevalence of vertebral deformities is also increased regardless of the bone mineral density status *(15)*. Nevertheless, a recent systemic review failed to show an in-creased risk of fracture or bone mineral loss in sarcoidosis *(16)*.

IMAGING FEATURES

Given the significant variability of radiological findings, the diagnosis of vertebral sarcoidosis can

be challenging. In conventional radiography, the pattern of axial involvement varies from purely lytic to mixed lytic-sclerotic and purely sclerotic lesions *(11)*. Although the sclerotic bone appears to be a rare pattern in appendicular localization, it is a common feature of spinal sarcoidosis *(17)*.

Vertebral involvement usually presents as mixed lytic-sclerotic lesions with a rim of sclerosis around the central osteolysis *(7)*. Osteosclerosis reflects the marrow infiltration and is usually seen in the late stages of the disease, often after long-term treatment *(18)*. Other imaging features include ivory vertebra and isolated lytic lesions, mimicking metastases *(19,20)*. Concomitant sacroiliitis was reported in 6% to 23.4% of cases in some series *(21)*. This finding might be a simple coincidence or a co-occurrence with another disease, such as spondyloarthritis *(21,22)*. However, this hypothesis was unsupported by Griep et al who reported the presence of noncaseating granuloma in the histological examination of the sacroiliac joint of a patient with sarcoidosis and sacroiliitis *(23)*.

Although it can be useful for screening spinal lesions, conventional radiography does not seem to be specific. Furthermore, in some cases, it fails to reveal these lesions. Conversely, CT is a more sensitive technique to assess vertebral involvement *(11)*. Besides sclerotic and lytic lesions, a wide variety of features may be shown, including pseudo-Pott appearance and grid appearance mimicking vertebral meningioma. Given the lack of a specific pattern, a bone biopsy is often mandatory, and a CT scan may help guide the biopsy *(24)*.

Despite its high cost, MRI remains the gold-standard test for axial sarcoidosis as it can provide additional information about soft tissue and bone marrow extension *(25)*. Classical features of lytic lesions present as low-signal intensity on T1-weighted images and high-signal intensity on T2-weighted images with variable enhancement following contrast medium administration depending on the nature of the tissue. In contrast, sclerotic lesions appear as low-signal intensity on both T1- and T2-weighted images.

MRI helps to monitor the progression of patients under treatment, as depicted in various reports, with MRI abnormalities resolving following successful therapy *(18,19)*. This outcome reflects the replacement of granulomas with a fibrous element, which is proof of recovery. However, the MRI appearance of vertebral sarcoidosis can be similar to that of myeloma or osteolytic bone metastases *(19)*.

In this regard, Moore et al proposed discriminating signs that may be useful to differentiate osseous sarcoidosis from metastases *(26)*. These signs include the perilesional or intralesional fat reflecting lesion involution and excluding malignancy. A brush-like border was also another feature of the benignity of the lesions. However, the authors agree that these signs remain non-specific, and the diagnosis was not based on MRI data alone *(26)*.

Bone scans with technetium-99 m methylene diphosphonate (Tc-99 m MDP), Gallium-67 (Ga-67) scan, and Fluorine-18 (F-18) fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) can be helpful when assessing the whole-body extent of sarcoidosis *(24,27,28)*. They have the advantage of evaluating the overall osseous sarcoid burden. Otherwise, they detect pulmonary and extrapulmonary involvement of sarcoidosis *(28,29)*. Technetium-99m pyrophosphate scintigraphy is used for bone screening, whereas 67Ga scans detect extraosseous sarcoidosis as well *(24,28)*.

Recently, 18FFDG PET emerged as a useful modality for the diagnosis and management of patients with sarcoidosis, offering multiple particular advantages (29). Compared to 67Ga scan, whole-body 18F-FDG PET is more sensitive for assessing the activity of sarcoidosis, monitoring treatment response, and detecting occult diagnostic biopsy sites *(30)*.

While it is commonly performed for a systematic evaluation of granulomatous disease, FDG PET/CT is not routinely performed in sarcoidosis to evaluate the osseous involvement *(5)*.

However, the role of FDG PET/CT in the detection of bone/ bone marrow involvement in sarcoidosis has been described in several studies as bone lesions commonly show increased FDG uptake *(31)*.

The prevalence of bone involvement assessed by PET/CT varies from 22 % to 30% *(32,33)*.

18 FDG PET/CT may be an excellent modality to detect bone involvement compared to more conventional modalities. In the study of Mostard

et al. the low-dose CT failed in detecting 97% of lesions demonstrated on PET/CT *(32)*. This finding suggests that physiological changes precede morphologic changes.

18F-FDG PET/CT can also be used to monitor the metabolic response of bone lesions under treatment *(33)*. Kaira et al. suggested that the combination of 18F-FMT PET with 18F-FDG PET may be useful to distinguish sarcoidosis from malignancy *(34)*.

Sodium fluoride labeled with fluorine 18 (sodium fluoride F 18 [18F-NaF]) is another radiotracer for skeletal imaging. Growing evidence suggests that 18F-NaF PET/CT provides increased sensitivity and specificity in bone metastases detection. However, in a previous report, 18F-NaF PET/CT failed to discern metastatic disease from osseous sarcoidosis *(35)*.

However, like the other imaging techniques, PET/CT lacks specificity and fails to distinguish sarcoidosis from other bone lesions. Thus, the biopsy remains a crucial diagnostic step to confirm the diagnosis of vertebral sarcoidosis *(5)*.

DIFFERENTIAL DIAGNOSES

Given the variable manifestations of vertebral sarcoidosis, other diagnoses should be considered. The metastatic skeletal disease is the primary differential diagnosis of vertebral sarcoidosis *(36)*. However, metastatic lesions may coexist with osseous sarcoidosis *(26)*. Even after the biopsy, other causes of noncaseating epithelioid granuloma must be excluded. Granulomas occur in mycobacterial disorders, including tuberculosis, histoplasmosis, and fungal and parasitic infections.

The same histopathological findings exist in Wegener's granulomatosis and Langerhans cell histiocytosis.

MANAGEMENT

Vertebral sarcoidosis is so rare that there are no guidelines for its treatment, and optimal treatment remains controversial in the absence of clinical trials. Thus, symptoms guided the therapeutic strategy, and asymptomatic lesions may not require treatment. Even without specific treatment, lesions may show spontaneous regression on follow-up images *(19)*.

Since osseous sarcoidosis often occurs in patients with a systemic disease, many patients will receive treatment for other non-osseous manifestations. However, patients presenting with back pain, stiffness, or vertebrae fracture should receive care. Corticosteroids are often used as first-line treatment and can achieve a clinical and radiological response *(5,37)*. However, radiographic abnormalities may persist despite a clinical resolution *(9)*.

The prednisolone dose is usually 15-40 mg/day, tapered according to the clinical response *(4,5)*.

An intrathecal pain pump relieved the pain in some refractory cases *(38)*. Calcitonin has also been used as an adjuvant to corticosteroids to control the pain *(11)*. In nonresponsive patients, the use of conventional immunosuppressive drugs is more anecdotal.

Methotrexate (7.5 to 15 mg per week) is the most used in musculoskeletal sarcoidosis as a GC-saving agent *(39)*. Other conventional synthetic disease modifying antirheumatic drugs (**csDMARDs**) such as hydroxychloroquine showed to be effective for the management of vertebral sarcoidosis Studies based on single cases or small series revealed encouraging results. However, since the development of biologic therapies, they are less and less used in extra-pulmonary sarcoidosis. In fact, anti-TNF therapy could be an alternative for refractory patients with spinal sarcoidosis considering its well-proven efficacy in rheumatic diseases *(36)*.

According to previous reports, anti-TNF agents improve spinal mobility, physical function, and quality of life. Biologic agents used in the literature are Infliximab and Adalimumab *(36,40)*. However, this therapy may have a suspensive effect after discontinuation of treatment. In one report, four months after a 6-month treatment course of Infliximab, the patient experienced relapse of symptoms *(41)*. Interestingly, a growing number of observations have reported the development of sarcoidosis in patients treated with TNF-inhibitors (paradoxical side effect) *(42)*. But, there have been no reports of osseous sarcoidosis occurring during anti-TNF therapy.

Bisphosphonates, an anti-osteoclastic inhibiting bone turnover, have been approved as a part of the therapeutic arsenal in osseous sarcoidosis. However, there has yet to be evidence of its effects on spinal manifestations *(11,18)*. Notably, one report described a stabilization of vertebral destruction, but this result was biased by the concomitant steroid therapy *(38)*.

Regarding the management of the spinal complication, surgical stabilization, decompression, and radiotherapy were effective.

Indeed, one report suggested the effectiveness of this radiotherapy in the local control of bone sarcoidosis *(13)*. It was successful in reducing the symptoms and resolving the lesions on MRI.

Properly designed longitudinal studies are warranted to codify the therapeutic strategy for this unusual location of sarcoidosis.

CONCLUSION

Vertebral sarcoidosis is scarce. Often underdiagnosed, it may be the cause of back pain, disability, and even neurological complications. The spinal lesions are frequently non-detectable on radiographs. Notably, MRI is gaining increasing interest and represents a fundamental tool for the assessment of vertebral sarcoidosis.

Lesions may resolve spontaneously without treatment. Otherwise, oral corticosteroids can be effective. Corticosteroids are the cornerstone of the management of osseous sarcoidosis, including axial localization. They have a favorable effect on clinical, radiological, and histological features of sarcoidosis. Other agents are also successfully used, although the level of evidence supporting their usage is still low.

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