Current Rheumatology Reports (2019) 21: 7
https://doi.org/10.1007/s11926-019-0806-0

IMAGING (D MINTZ, SECTION EDITOR)

Radiologic Manifestations of Musculoskeletal Sarcoidosis

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Published online: 14 February 2019

Abstract

Purpose of Review The purpose of this review article is to present the spectrum of abnormalities and multi-modality imaging evaluations in patients with musculoskeletal sarcoidosis.

Recent Findings The articular manifestations of sarcoidosis are difficult to distinguish from those of the other inflammatory and degenerative arthropathies, and the muscular lesions in sarcoidosis are generally clinically silent and therefore often missed. Magnetic resonance imaging has shown these manifestations to be very common in active sarcoidosis, and should thus be included in the screening if musculoskeletal sarcoidosis is suspected.

Summary The clinician should consider magnetic resonance imaging for the evaluation of patients with sarcoidosis who have unexplained osteoarticular complaints if standard radiographs are negative. Furthermore, radiologists should include sarcoidosis in the differential diagnosis of musculoskeletal disease detected at magnetic resonance imaging in the appropriate clinical setting.

Keywords Sarcoidosis · Magnetic resonance imaging · Bony sarcoidosis · Sarcoidal arthropathy · Sarcoidal myopathy

Introduction

Sarcoidosis is a multisystemic inflammatory disorder of unknown etiology, characterized by T lymphocyte infiltration, granuloma formation, and impairment of normal tissue micro-architecture. It can affect all races and ethnic groups but occurs at different incidences in different countries [1, 2]. The age of presentation is most common between 20 to 40 years with a second peak occurring above 50 years [3, 4]. The lungs are the most frequently involved organ, followed by the skin, eyes, heart, liver, and the musculoskeletal system [5].

Musculoskeletal system findings are among the important features of extrapulmonary sarcoidosis involvement and may occur prior to or simultaneously with the pulmonary involvement [6].

Joint are the most common sites of involvement within the musculoskeletal system, with a prevalence of 10 to 35%. Bony sarcoidosis is rarer, although it is underestimated as it is often asymptomatic. It develops later in the course of the disease with prevalence in the literature of 1 to 15%. Phalangeal involvement is classic and best known among radiologists. Muscular features are often asymptomatic and almost always found on muscle biopsies [7, 8].

This article is part of the Topical Collection on *Imaging*

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Bone Sarcoidosis

Bone sarcoidosis is a relatively rare form of disease presentation, occurring in 0.5 to 34% patients with sarcoidosis [9, 10]. This wide variability is attributable to asymptomatic disease presentation [9, 11••, 12] and undetectable lesions on plain radiographs or even on computed tomography exams (CT) [10]. Typically, bone lesions develop later in the disease course [11••], although very rarely bone sarcoidosis may be the initial presentation of the disease, in which case its diagnosis can be very difficult [9]. In these rare cases, other sites of involvement need to be investigated, including the lungs and lymph nodes.

The classical aspect of bone sarcoidosis was first described by Kreibich in 1903 [13] and consists of a lacy lytic appearance [11••, 14, 15] in the phalanges of the hands. For several years, small bone sarcoidosis was considered the most common form of presentation associated with cutaneous involvement [13]; however, current cross-sectional imaging modalities, especially magnetic resonance imaging (MRI) and fluorine 18 fluorodeoxyglucose (FDG) PET/CT, have demonstrated that multifocal lesions in larger bones and in the axial skeleton are more common and often non-detectable on radiographs [9, 10, 15]. Moreover, a minority of these patients have skin lesions [9, 15].

Small Bone Sarcoidosis

Small bone sarcoidosis of the hands and feet occurs in approximately 5 to 7% of patients and is mainly unilateral or bilateral and asymmetric in the phalanges of the second and third fingers. Sarcoid dactylitis bone lesions are very characteristic and known as Perthes-Jüngling disease [11••].

The classic cystic, lacy, and honeycomb-like pattern of osteolysis appearance (Fig. 1), which is virtually pathognomonic in patients with a sarcoidosis diagnosis in other systems [15], may be associated with areas of cortical rupture and extracortical expansion, resulting in soft tissue edema and sausage finger. Although no additional MRI investigation is required, sarcoid lesions have low signal intensity on T1-weighted imaging (T1WI), intermediate to high signal intensity on T2-weighted imaging (T2WI), and variable enhancement after gadolinium-based contrast administration. Extracortical involvement is best demonstrated by MRI, which enables visualization of the fine perpendicular lines parallel to the cortex resembling periosteal reaction, while extracortical involvement is traditionally not seen on radiographs [14].

Deformities in the hands and feet are related to pathological fractures or bone remodeling rather than joint involvement [11••, 14, 15].

In addition, nail involvement with thickening and irregularity may be seen on radiographs, and is associated with bone lesions in the phalanges, but the inverse is not true as nail involvement is not seen without bone involvemnt [16, 17].

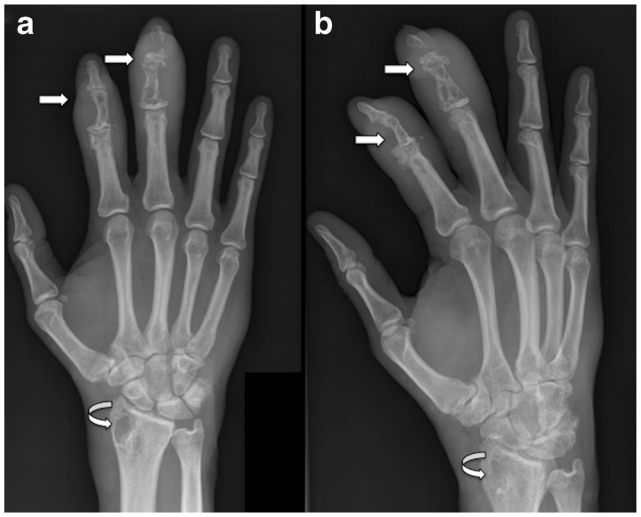

Fig. 1 Sarcoid dactylitis bone lesions (Perthes-Jüngling disease/small bone sarcoidosis). A 42-year-old female with right hand and wrist pain for 1 year. Radiographs (**a**, **b**) of the right hand and wrist shows 2nd and 3rd digit dactylitis with multiple pseudocystic lacunae within the bone that are clearly demarcated, confluent, and with acro-osteolysis (arrows), a very characteristic pattern of sarcoid dactylitis bone lesion. Additionally, a larger sarcoid lytic bone lesion in the distal radius is identified (curved arrows). Add lace-like pattern in third proximal phalanx in B

Large Bone Sarcoidosis

Multifocal axial skeleton involvement, mainly in the pelvis and spine, may be the most common presentation of bone disease [9, 15–17]. Fifty percent of these lesions are asymptomatic [9]. Mostard et al. [10] performed PET/CT on 122 patients with severe sarcoidosis, and more than one-third were found to have bone involvement. Most of these lesions were multifocal and without underlying bone osteolysis at a low-dose CT.

On radiographs, large bone sarcoidosis (Fig. 2) is more often occult or is a focal lytic appearance. Sclerotic or mixed lesions are rarer [14, 15]. Unlike lesions in small bones, there is usually no cortical rupture or extracortical expansion, which may explain the low sensitivity on plain radiography.

MR imaging reveals indistinct or well-margined lesions of varying sizes with a variety of appearance, including round, confluent irregular marrow infiltration, less well-defined discrete lesions with a "starry sky" appearance, and patchy, diffuse intramedullary lesions, sometimes with foci of preserved fat marrow inside or around of the lesion (Fig. 3) [14–16]. Usually, there is low signal intensity on T1WI, intermediate, or high signal intensity on T2WI/STIR (short tau inversion recovery) and variable enhancement after gadolinium-based contrast injection. Lesions may show spontaneous regression on follow-up images without specific treatment [14–16].

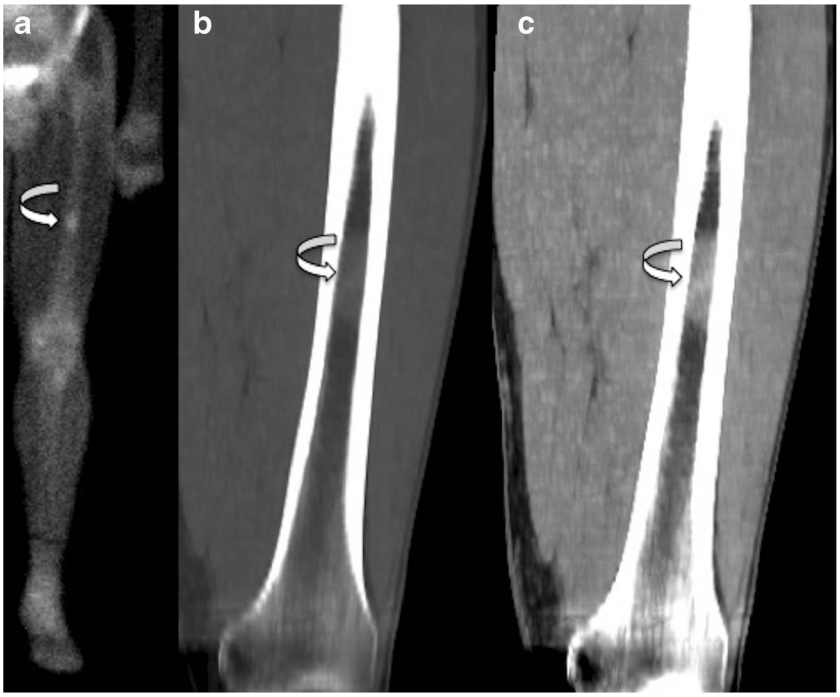

Fig. 2 Large bone sarcoidosis. A 59-year-old male patient with femoral pain. A bone lesion suspected for bone metastasis was detected in (**a**) late phase bone scintigraphy as a nodular region of increased uptake centered on the femoral diaphysis (curved arrow). CT scanning (**b**, **c**) used to guide the biopsy shows a solid nodular intra-medullary mass in the femoral diaphysis, without cortical disruption or soft tissue expansion (curved arrow). The final anatomopathology diagnosis was bone sarcoidosis (large bone sarcoidosis)

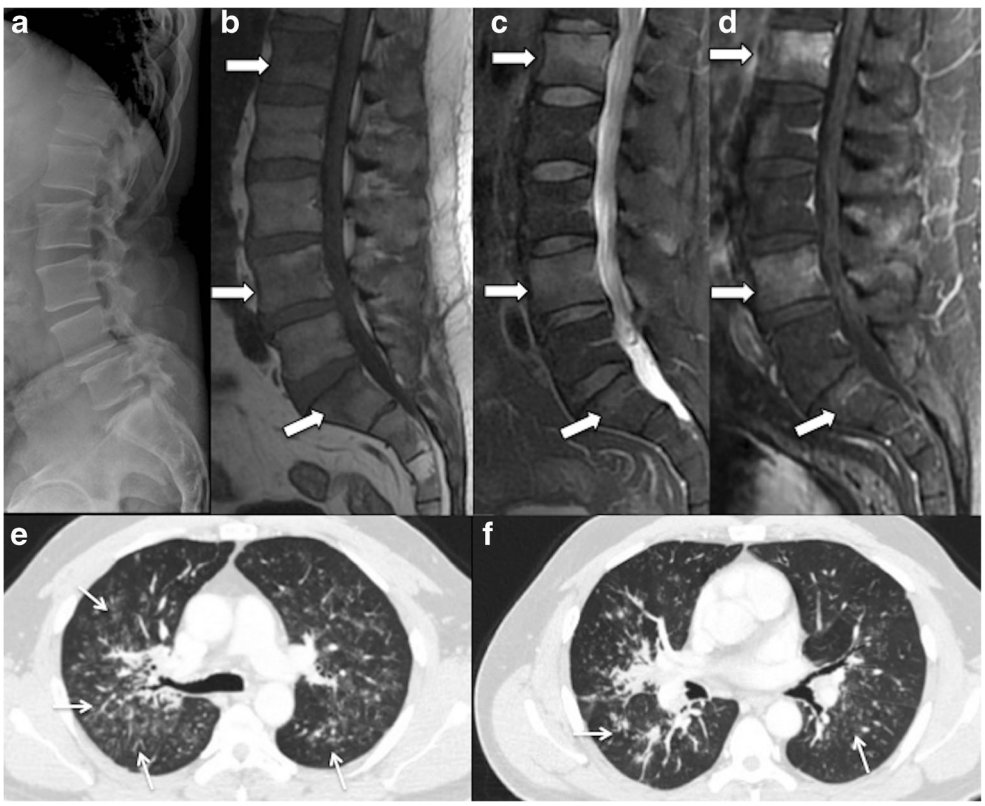

Fig. 3 Vertebral sarcoidosis. A 57-year-old male patient with chronic back pain. Radiographs (**a**) show degenerative disease without any significant bone lesions. FSE sagittal MR imaging T1 (**b**), STIR (**d**), and T1 fat-sat after contrast injection (**e**) shows multiple vertebral bone lesions (arrows) with hyperintensity on STIR, hypointense on T1-weighted imaging and enhancement after contrast injection. Axial high-resolution CT scan of the lungs shows the typical perilymphatic distribution of micronodular pulmonary sarcoidosis (thin arrows), highly suggestive of pulmonary sarcoidosis. A rare case of vertebral involvement followed up for multi-organ sarcoidosis

Although some authors believe that border characteristics and focal areas of fat preservation may be useful in distinguishing sarcoidosis and metastases, Moore et al. [16] found that osseous sarcoidosis lesions cannot be reliably distinguished from metastatic lesions on routine MRI, even by experienced musculoskeletal radiologists.

Sarcoidal Arthropathy

Sarcoidal arthropathy is the most common rheumatologic manifestation of sarcoidosis, affecting approximately 10–38% of patients [18]. This manifestation can be divided into two groups differing in their clinical course and prognosis. The first is acute transient arthropathy, which frequently resolves without permanent sequelae, and the second is persistent or chronic arthropathy, which, although less common, can progress to joint deformity.

Acute Transient Arthropathy

The most common form of the acute transient arthropathy in sarcoidosis is Lofgreen syndrome (Fig. 4), typically characterized by the triad of arthralgia, bilateral hilar adenopathy, and erythema nodosum [19]. Arthralgia is thought to be due to circulating inflammatory cytokines on the joints [20, 21]. The early pattern, usually seen during the first 6 months of symptoms, consists of symmetrical (76%), oligoarticular (87%), or polyarticular (11%) involvement of the large lower limb joints (96%). The majority of patients (95%) present with swelling in both ankles [3]. Monoarthritis is unusual. Some patients (10%) present with arthritis of the small hand joints. Other symptons and signs are fever (50%), erythema nodosum (40%), and a red-bluish discoloration around the ankles.

Clinical criteria were proposed to enable the diagnosis of articular sarcoidosis [21]. Patients who have three of the following four characteristics are 99% sensitive and 93% specific: (1) erythema nodosum, (2) symptom duration less than 2 months, (3) age less than 40, and (4) symmetrical ankle arthritis (Fig. 5).

A raised erythrocyte sedimentation is found in the majority of patients (84%).

In the majority of cases of acute joint involvement, chest imaging shows the presence of pulmonary disease. Symmetrical inflammatory arthritis of the ankles present for less than 60 days in subjects under 40 years old combined with erythema nodosum is almost specific for sarcoidosis. In this presentation, particularly if symptoms, appropriate chest investigations are required.

On imaging, often only soft tissue swelling, epiphyseal demineralization, and/or a fluid joint effusion are seen. The main differential diagnosis is rheumatoid arthritis. It is the

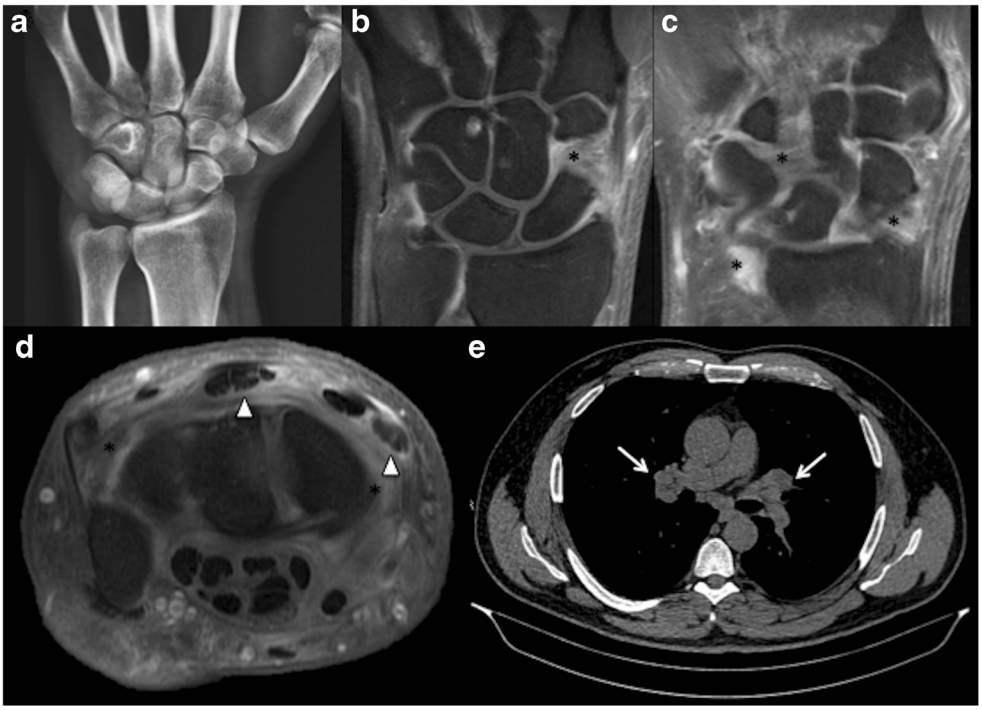

Fig. 4 Lofgren syndrome. A 52-year-old male with arthralgia, bilateral hilar adenopathy, fever, and erythema nodosum. Radiographs (**a**) of the left wrist show no significant findings. FSE coronal and axial MR imaging with T2 fat-sat (**b**) and T1 fat-sat after contrast (**c**, **d**) shows extensive infiltration of the soft tissues with wrist joint effusion and synovitis (stars). We also identified extensor tenosynovitis (arrow head). These findings suggest inflammatory disease. Non-enhanced chest CT scan with mediastinal window (**e**) shows bilateral, non-compressive hilar enlarged lymph nodes (arrows) suggestive of pulmonary sarcoidosis

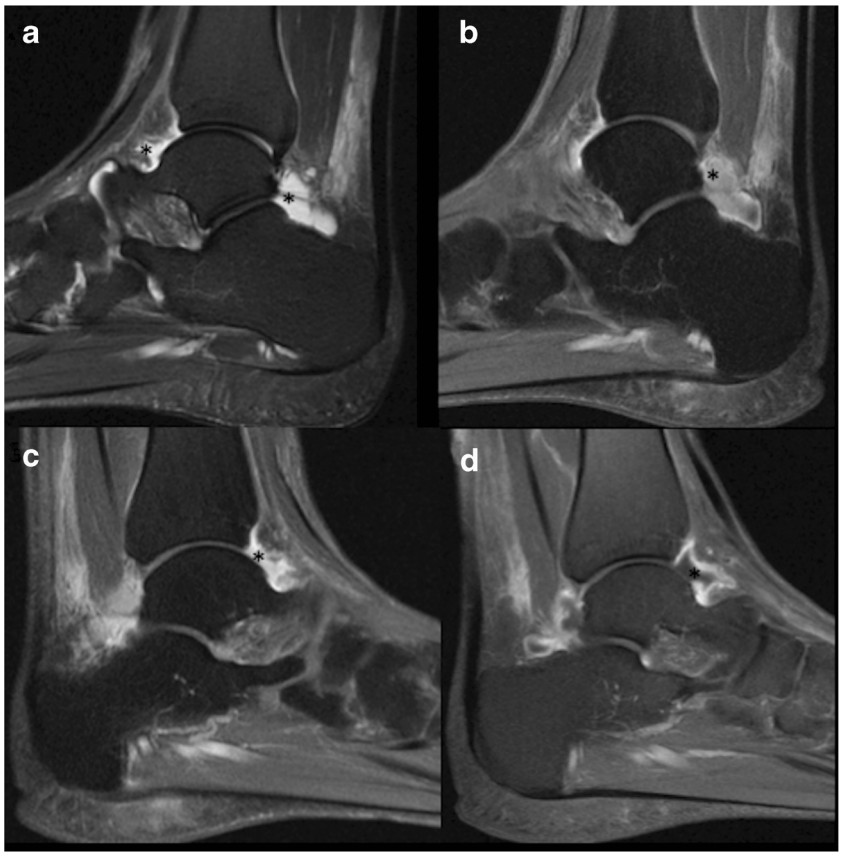

Fig. 5 Acute transient arthropathy. A 38-year-old male patient with erythema nodosum and symmetrical ankle arthritis for 1 month. Bilateral ankle FSE sagittal MR imaging with T2 fat-sat (**a**, **c**) and T1 fat-sat after contrast (**b**, **d**) shows moderate intra-articular effusion with synovitis in the tibiotalar joints bilaterally

clinical presentation rather than the imaging appearance that makes one consider the diagnosis of sarcoidosis.

The average duration of symptoms is approximately 2 to 3 months, and most patients go into remission within 6 months of receiving nonsteroidal anti-inflammatory drugs or steroids [22–24].

Chronic Arthropathy

The chronic type of articular sarcoidosis is rare, occurring in only 0.2% of cases at least 6 months after disease onset and most often affects Black males with advanced multi-organ sarcoidosis. This type of sarcoidosis may have polyarthritis or less commonly oligoarthritis and presents as a granulomatous synovitis with joint destruction or Jaccoud's deformity (without joint destruction) [24]. Concomitant findings are tenosynovitis, lupus pernio, and bilateral hilar lymphadenopathy (80–90%). The ankles, knees, and hands are preferentially affected in that order, and the shoulders and wrists more rarely. The differential diagnosis with rheumatoid arthritis may be difficult because among such sarcoid patients, the arthritis is rheumatoid factor-positive in 10–47% of cases. Diagnosis is based on clinical criteria, including negative serology for anti-cyclic citrullinated peptide antibodies and antinuclear antibodies, as well as the absence of the specific erosive joint deformity which is seen in rheumatoid arthritis [25]. Synovial biopsy showing a non-caseating granuloma establishes the diagnosis of sarcoidosis.

Radiography is frequently normal but may show signs of demineralization associated with soft tissue infiltration. Some more destructive forms may be accompanied by narrowing of the joint space and demineralization of the subchondral bone.

MRI findings are not specific, but MRI can depict lesions that cannot be visualized on x-rays, such as tenosynovitis—particularly involvement of the extensor tendons of the fingers or more rarely the flexor tendons, tendinitis, bursitis, and synovitis [14].

Sarcoidal Myopathy

Asymptomatic muscle involvement in sarcoidosis occurs in up to 80% of patients diagnosed with sarcoidosis [26], and muscle non-caseating granulomas can be detected with biopsy.

Symptomatic muscle involvement in sarcoidosis is classified into three types [27•]: nodular, chronic myopathy, and acute myositis. Symptomatic muscle involvement in sarcoidosis usually occurs in the chronic multi-systemic form of the disease. It is rarely an initial or isolated presentation [26]. Also, more than one type of presentation can coexist in the same patient [28•].

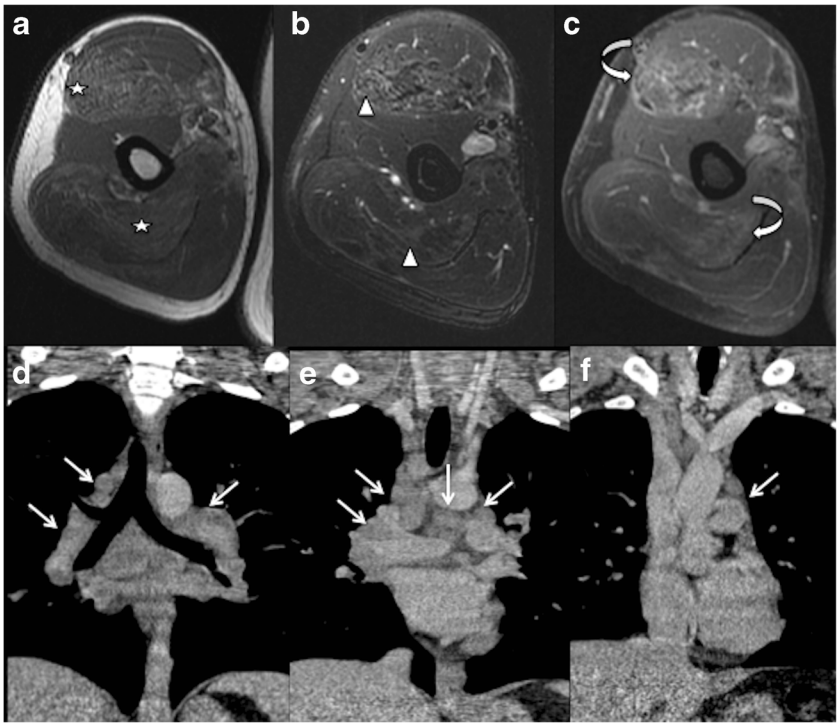

Fig. 6 Sarcoidal myopathy. A 29-year-old male with progressive weakness and atrophy of the right arm. FSE axial MR imaging with T1 (**a**), T2 fat-sat (**b**), and T1 fat-sat after contrast shows edema (arrow head) and focal areas of fat-infiltration (star) with gadolinium enhancement (curved arrows) at the biceps and triceps muscles. The biceps biopsy showed the diagnosis of muscle sarcoidosis. A non-enhanced chest CT scan with mediastinal windows (**d**–**f**) shows bilateral hilar enlarged lymph nodes (arrows) highly suggestive of pulmonary sarcoidosis

In cases of muscular sarcoidosis, MRI is useful for localizing disease and assessing disease extension when the patient has localized disease (Fig. 6). PET/CT is useful for examining patients with diffuse disease [27•]. Active muscular sarcoidosis usually demonstrates avid FDG activity, which can be used to detect other sites of disease and localize the most suitable biopsy site [27•].

The chronic myopathy type occurs mainly in women aged between 50 and 60 years and is characterized by a slow progressive symmetrical weakness and atrophy of the proximal muscle groups [26]. MRI can show atrophy or fatty infiltration of the muscles as a result of sarcoid muscle involvement [29]. It is useful in demonstrating the extent of edema and fatty replacement and determining optimal sites for muscle biopsy [14].

The acute myositis type is characterized by muscle swelling and pain and is usually accompanied by elevated serum muscle enzymes (creatine kinase). In this setting, MRI can be negative because of the small size of the granulomata [30].

The nodular presentation usually manifests in a rather younger population (less than 40 years of age) and affects mostly the lower limbs (90%) [29]. The importance of this type of muscle involvement is that it can be mistaken for a soft tissue tumor. The nodules tends to occur at the myotendinous junction and are frequently bilateral and multifocal. The classic sarcoid nodule at MRI shows a star-shaped central structure of low signal which does not enhanced with intravenous contrast and is found in the chronic stage of muscular sarcoidosis. Histologically, the low signal corresponds to fibrous tissue. The peripheral region tends to show slightly high signal intensity and enhancement after gadolinium injection, related to the high cellularity of granulomas and frequently associated surrounding edema [30].

Respiratory muscle involvement is an underdiagnosed condition and can promote exertional dyspnea in conjunction with many other factors such as lung parenchymal involvement, cardiac involvement, pulmonary hypertension, anemia, and fatigue [29].

MRI improves the detection of musculoskeletal disease in patients with sarcoidosis, and correlation with clinical and laboratory findings is essential because the MRI findings are not specific in most cases [14].

Summary

Imaging features of thoracic manifestations of sarcoidosis are clearly defined and commonly know; unfortunately, the same does not apply to the rheumatological features of the disease. This fact may raise significant diagnostic problems. The classical bony lesions of sarcoid dactylitis are very characteristic and well known, but the other presentations of bone and bone marrow sarcoidosis are not. The articular manifestations of sarcoidosis are difficult to distinguish from those of the other inflammatory and degenerative arthropathies. The muscular lesions in sarcoidosis are generally clinically silent and therefore often

missed. MRI has shown these manifestations to be very common in active sarcoidosis, thus MRI should be included in the screening if initial musculoskeletal sarcoidosis is suspected.

The clinician should consider MRI for the evaluation of patients with sarcoidosis who have unexplained osteoarticular complaints if standard radiographs are negative. Radiologists should include sarcoidosis in the differential diagnosis of musculoskeletal disease detected at MRI in the appropriate clinical setting.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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