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Title: Spondyloarthritis and sarcoidosis: related or fake friends? A systematic literature review

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Abstract:

Background: Sarcoidosis and spondyloarthritis (SpA) have been regularly associated. Bone iliac granulomas have also been described. We propose herein a systematic review of rheumatologic axial manifestations of sarcoidosis.

Methods: PubMed and the Cochrane Library were used to conduct this systematic literature review. Case reports and cross-sectional studies were reviewed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Results: A total of 41 articles were eligible. Three cross-sectional studies on the association between SpA and sarcoidosis showed a prevalence of sacroiliitis and SpA ranging from 12.9 to 44.8% and 12.9 to 48.3% in inflammatory back pain (IBP) subgroups, respectively. However, the IBP definitions and sacroiliac joint (SIJ) imaging modalities (X-rays or magnetic resonance imaging) were heterogeneous, and X-ray was mainly used for sacroiliitis diagnosis (in 78% of cases). Thirty-one case-report articles of the sarcoidosis-sacroiliitis association were identified, representing 35 patients. ASAS criteria for SpA were met in half of cases (16/32) and 46% (12/26) had HLA B27 positivity. Sarcoidosis occurred after sacroiliac symptoms in 47% of cases. In the seven case-report articles with granulomatous sacroiliac bone involvement, unilateral involvement was significantly higher than in the sarcoidosis-sacroiliitis group ($p < 0.001$).

Conclusion: Literature analysis found a good evidence of the association between SpA and sarcoidosis, and special attention should be given to patients reporting IBP. Unilateral sacroiliitis may raise suspicion of granulomatous bone involvement, distinct from sacroiliitis. Imaging modalities used to study the SIJ in patients with sarcoidosis have been heterogeneous and further investigation is needed.

Keywords: sarcoidosis, sacroiliitis, sacroiliac joint, spondyloarthritis, bone, granulomatous

1. Introduction

Sarcoidosis is a granulomatous disease of unknown origin[1]. Lungs with mediastinal lymph nodes are frequently involved, but granulomas can affect all organs, among which the skin, lymphoid system, eyes, and liver are the most common[1]. The musculoskeletal system is involved in 4 to 38% of patients[2], consisting of acute forms, such as Löfgren's syndrome, or chronic presentation, such as sarcoid arthropathy, with synovial sarcoid granuloma. Bone sarcoidosis is rare, reported in 3 to 13% of sarcoidosis patients[3]. Sacroiliitis in sarcoidosis was initially described in 1951 by Verstraeten et al. in a case report[4]. It is characterized by sacroiliac joint (SIJ) inflammation and often inflammatory low back pain. Since the publication of this paper, links between sarcoidosis and sacroiliitis have been regularly reported in the literature. Most studies have reported radiographic sacroiliitis or bone iliac involvement but on a limited number of cases[5,6].

The aim of this systematic review was to identify the diagnostic characteristics, including radiological criteria, for sacroiliitis in patients with sarcoidosis and sacroiliac involvement. We included case reports and prospective and retrospective studies.

2. Methods

a. Publication search

This systemic review was performed in January 2020 using the Medline (using PubMed) and Cochrane databases. We identified articles in English and French using the Preferred Reporting Items for Systematic Reviews and MetaAnalysis (PRISMA) statement[7]. Keywords used in the search strategy were (*sarcoidosis OR sarcoid OR sarcoid**) AND (*sacroiliitis OR sacroiliac OR ankylosing spondylitis OR spondyloarthritis OR spondyloarthropathy*). Additional relevant papers were identified through other sources, mainly from the bibliographies of previous papers.

b. Inclusion criteria

All study designs (case report, retrospective or prospective, cross-sectional) were included. After the removal of duplicates, we selected papers evaluating the SIJ in patients with sarcoidosis. Sarcoidosis had to be confirmed through histological proof of non-caseating granulomas, with exclusion of other granulomatous diseases, especially mycobacterial infections[8]. We did not include cases of granulomatous reaction following anti-tumor necrosis factor alpha (TNF α) therapy for spondyloarthritis (SpA) or other autoimmune diseases because the immunopathogenesis of sarcoidosis is not well known and because of the iatrogenic link of drug-induced sarcoidosis-like reactions (DISRs)[9] following anti-TNF α therapy. DISR due to anti-TNF α therapy is considered to be a differential diagnosis, according to the granulomatous "drug reaction" mentioned in the ATS/ERS/WASOG statement on sarcoidosis[8].

c. Collection data

We collected the following data from the case reports: sex, age at diagnosis, imaging used for the author's diagnosis of sacroiliitis, sacroiliitis according to the ASAS 2009 criteria[10], SIJ score on radiography based on the modified New York (mNY) criteria, ankylosis, HLA B27 status, presence of back pain (mechanical or inflammatory), back pain \geq 3 months, age at onset < 45 years old, features of SpA (inflammatory back pain (IBP), arthritis, enthesitis, dactylitis, uveitis, psoriasis, inflammatory bowel disease, good response to NSAIDs, family history of SpA, elevated CRP), diagnosis of sarcoidosis (granuloma on biopsy and/or Löfgren syndrome), grading of sarcoidosis on thoracic radiography,

granuloma-affected organs, and temporal relationship of sarcoidosis with SIJ symptoms (before, after, or concurrent diagnosis).

3. Results

In total, we identified 317 articles in PubMed, and 37 articles in the Cochrane Library. After removing duplicates and adding five articles identified in the bibliography of previously selected papers, 335 articles were screened. Based on the title and abstract, 265 articles were excluded and 70 were assessed for full-text eligibility. Twenty-nine full-text articles were excluded, mainly due to DISRs following anti-TNF α treatment. Finally, 41 papers were considered for the study. The PRISMA®-flow diagram is shown in **Figure 1**. Three of the 41 papers were cross-sectional studies[5,11,12] (summarized in **Table 1**). Among the remaining 38 case reports, two groups were identified: a sacroiliitis-sarcoidosis group[4,13–42] and a group with granulomatous bone sacroiliac involvement mimicking sacroiliitis[6,43–48]. The main characteristics of the sacroiliitis-sarcoidosis group are summarized in **Tables 2 and 3** and those of the group with sacroiliac bone involvement in **Table 4**.

a. Cross-sectional studies

In 2005, Erb et al.[11] published the first monocentric cross-sectional cohort study of back pain in a sarcoidosis population, in which 61 patients were analyzed. Almost all patients were Caucasian, with a sex-ratio close to one. Five patients did not meet the ATS/ERS/WASOG criteria for sarcoidosis due to the absence of compatible histology and Lofgren's syndrome, but were nevertheless considered to have sarcoidosis and included in the study. Radiographic evaluation of the SIJ was performed by double reading, but the criteria for a diagnosis of sacroiliitis was not mentioned. The authors considered four patients to have sacroiliitis with only one patient with bilateral involvement. Radiological sacroiliitis was considered independently of a SpA diagnosis in this study, but one patient had HLA B27 antigen. There was no difference between patients with or without sacroiliitis in this study. The prevalence of sacroiliitis was estimated to be 6.6% (4/61) in the sarcoidosis population, 8.2% (4/49) in the back-pain sub-group, and 12.9% (4/31) in the IBP subgroup.

Kobak et al.[5] reported six cases of bilateral sacroiliitis scored according to mNY criteria based on standard pelvic radiography in a monocentric cohort of 42 patients with biopsy-proven sarcoidosis. All patients in the X-ray sacroiliitis group had IBP according to Calin criteria. The authors thus diagnosed six cases of SpA according to ASAS 2009 criteria[10]. SpA-sarcoidosis patients were more likely to be female and lacking HLA B27. Eight patients without sacroiliitis also had IBP. The prevalence of sacroiliitis and SpA in the sarcoidosis population was estimated to be 14.3% (6/42) and 43% (6/14) in the IBP subgroup.

Sigaux et al.[12] recently published a prospective study of back pain with MRI exploration in a biopsy-proven sarcoidosis cohort of 337 patients. Among 64 back-pain patients, 29 had IBP. The diagnosis of sacroiliitis was defined as bone-marrow edema in a compartment of the SIJ on one slice for bilateral lesions or on two consecutive slices for unilateral localization. Two blinded readers (one rheumatologist and one radiologist) analyzed MRI, and a consensus was reached in case of disagreement. Sacroiliitis was diagnosed in 13 patients with IBP (5 also had radiographic sacroiliitis according to the mNY criteria). The patient characteristics in the sacroiliitis subgroup were not reported. SpA was diagnosed in all patients with sacroiliitis; one patient with mechanical pain was diagnosed with SpA due to the association of HLA B27 positivity, psoriasis, and enthesitis and one patient had a vertebral inflammatory