CASE REPORT

Co-occurrence of rheumatoid arthritis and sarcoidosis

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SUMMARY

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by erosive arthritis. Sarcoidosis is a chronic disease characterised by formation of non-calcified granulomas. Our case, a 35-year-old woman, presented with metacarpophalangeal, proximal interphalangeal (PIP) joints and arthritis of both ankles, of 6-month duration. She had morning stiffness lasting 1 h, restriction of range of motion and erythema nodosum. Laboratory tests showed elevated acute phase responses and serum ACE levels, and anti-cyclic citrullinated peptide antibody positivity. There was periarticular osteoporosis on her hand and wrist on direct X-rays and hilar lymphadenopathy on her thorax CT. The pathological result of endobronchial ultrasound biopsy showed non-calcified granuloma congruent with sarcoidosis. According to clinical, laboratory and histopathological evaluation, the patient was diagnosed with RA and sarcoidosis. Corticosteroids and methotrexate were started, and on her sixth month of follow-up, her clinical and laboratory findings and lymphadenopathies on CT had regressed. The clinical follow-up continues; the patient appears to be in clinical remission.

BACKGROUND

Sarcoidosis is a systemic disease characterised by the involvement of multiple tissues and organs with a non-calcified granuloma reaction, which is not yet well understood.¹ Although the exact pathogenesis of sarcoidosis is not known, it is currently accepted that, in genetically susceptible individuals, it is caused through alteration of the cellular immune response after exposure to an environmental, occupational or infectious agent.² The proinflammatory cytokines originating from Th1 cells and macrophages trigger the inflammatory cascade, and granuloma forms by the increase of tissue permeability, cell influx and local cell proliferation.³ Appearance of non-calcified epithelioid cell granulomas is the irrevocable pathological finding for sarcoidosis.⁴ The fact that the disease has varied clinical findings, and different degrees of prevalence and progress in different race and ethnic groups, indicates that sarcoidosis is a heterogeneous disease.^{5 6} It is frequent in females and arises around the fourth decade. Sarcoidosis is a chronic granulomatous disease presenting with various clinical symptoms. The most frequent presentation of the disease is bilateral hilar lymphadenopathies, pulmonary infiltrations, and skin and eye lesions. Sarcoidosis may imitate various primary rheumatological diseases (connective tissue diseases, spondyloarthritis, vasculitis) and may be seen coincidentally with them.⁷ Rheumatoid arthritis (RA) is a chronic

inflammatory disease that may be cause erosive synovitis and extra-articular involvement. Overlap syndromes with the other rheumatological diseases (systemic lupus erythematosus (SLE), SjS) has been reported previously,⁸ but co-occurrence with sarcoidosis is rarely seen.

In this report, we present a woman with RA and sarcoidosis diagnosed according to clinical, laboratory and histopathological findings.

CASE PRESENTATION

A 35-year-old woman presented to our rheumatology clinic with ankle, wrist, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints pain, swelling and morning stiffness, of 6-month duration. Locomotor system examination revealed arthritis of ankles, wrists, and bilateral second and third MCP joints, and tenderness and range of motion restriction on PIP joints and on both shoulders.

INVESTIGATIONS

Laboratory investigations showed erythrocyte sedimentation rate 47 mm/h (normal <20 mm/h) and C reactive protein 20 mg/dL (normal 0–5 mg/dL). Serological tests were analysed, showing antinuclear antibody 1/80 granular positive, anti-cyclic citrullinated peptide (CCP) antibodies 200 IU/mL (normal <5 IU/mL) and rheumatoid factor 104 IU/mL (normal <14 IU/mL). Serum ACE was 102 (normal <52); serum calcium and 25-hydroxy D3 were normal. While hand and wrist X-ray showed periarticular osteoporosis, abdominal ultrasonography was normal. Thorax CT scan was performed, and bilateral hilar lymphadenopathies, the biggest of which was 26×15 mm, and one lymphadenopathy on the subcarinal zone, were reported (figure 1). Tuberculin skin test was negative. A chest disease specialist was consulted, and bronchoscopy and endobronchial ultrasonography-guided biopsy were performed. On histological examination, non-calcified granulomas were supportive for the diagnosis of sarcoidosis.

DIFFERENTIAL DIAGNOSIS

According to clinical, laboratory and pathological findings, co-occurrent RA and sarcoidosis was diagnosed. Tuberculosis and other granulomatous diseases were excluded according to tuberculin skin test and laboratory investigations.

TREATMENT

Low-dose corticosteroid, hydroxychloroquine 200 mg/day, methotrexate 15 mg/week and folic acid 5 mg/week were started.

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Figure 1 Multiple bilateral hilar lymphadenopathies on thorax CT scan.

OUTCOME AND FOLLOW-UP

The patient's symptoms regressed significantly during the follow-up. On the sixth month of treatment, laboratory values of acute phase reactants were within normal limits. Comparing the control CT with the previous one, lymphadenopathies had regressed significantly (figure 2). The patient, whose general condition is well, is still followed up by our outpatient clinic.

DISCUSSION

Sarcoidosis is a Th1-related multisystemic granulomatous disease characterised by bilateral hilar lymphadenopathies, pulmonary infiltrations, and skin and eye lesions. Sarcoidosis can imitate many rheumatological diseases and can develop co-occurently with them. It may present clinical findings similar to connective tissue diseases such as Sjögren's syndrome (SS), SLE and scleroderma, as well as vasculitis or spondyloarthropathies. Enzenauer and Xest⁹ showed that sarcoidosis developed in 6 of 569 patients with connective tissue diseases. Sarcoidosis and SS co-occurrence is the most reported and was explained by a common aetiopathogenesis or simply by coincidence.¹⁰ De Bandt *et al*¹¹ reported sarcoidosis and scleroderma co-occurrence in five patients. They reported that the prognoses of the diseases are worse when they are co-occurent, but they could not generalise this because of the low number of patients in their study. In another study, a female patient presenting with granulomatous dermatitis and interstitial pulmonary disease was

Figure 2 Control thorax CT scan: lymphadenopathies had regressed significantly after therapy.

diagnosed as scleroderma and sarcoidosis co-occurrence after radiological and histopathological evaluation.¹² Sarcoidosis and RA co-occurrence is rarely reported. Menard *et al*¹³ reported both diseases with histological proof. Kucera¹⁴ remarked on the positivity of HLA-DR4 as a risk factor for this co-occurrence in their study. Locomotor system involvement is important when consider the co-occurrence of these two diseases. RA is a chronic erosive disease that may involve wrist, MCP and PIP joints. Whereas, two different types of joint involvement in patients with sarcoidosis are seen. Acute arthritis is more frequent with the involvement of unilateral or bilateral ankle, knee and wrist joints. Chronic sarcoid arthritis, which is rarely seen, is more common in black race, and involves the knee, ankle, wrist, and MCP and PIP joints. It may cause Jaccoud's-type arthropathy or/and joint destruction. Other than erosive destructive changes on direct X-ray, it causes soft tissue swelling, periarticular osteoporosis and joint space narrowing.¹⁵ In our case, presence of bilateral ankle arthritis and erythema nodosum raises the possibility of sarcoidosis, but involvement of wrist, MCP and PIP joints, with positive anti-CCP antibodies, supports the diagnosis of RA. The diagnosis of sarcoidosis must be supported by a biopsy, with the presence of hilar lymphadenopathies and/or respiratory symptoms. Also, the other pathologies that cause granulomatous diseases must be excluded. In our patient, the sarcoidosis diagnosis was made according to erythema nodosum, bilateral ankle arthritis, elevated serum ACE levels, and presence of non-calcified granulomas in the biopsy.

However, there have also been RA cases reported of sarcoidosis developing after anti-tumour necrosis factor- α (TNF- α) administration.¹⁶ It was thought that when TNF- α , which has a major role in the formation of non-calcified granulomas, is suppressed, sarcoidosis is triggered with the help of different infectious agents. Further, infliximab may be an effective and reliable treatment agent in a patient diagnosed with RA and sarcoidosis.¹⁷ These results may suggest that these two diseases have similar aetiopathogenesis. However, when we consider that both diseases have a high prevalence (1/100 for RA, 0.4–64/1000 for sarcoidosis), a sporadic co-occurrence is a higher probability. RA and sarcoidosis are two different diseases and it is obvious that they do not have a common genetic base. Both are related with alleles that code major histocompatibility complex (MHC) class-II. The relation between RA and HLA-DR4 is well known. While HLA-DR5 is found to be significantly high in German patients with sarcoidosis, HLA-B8 is found to be related with acute sarcoidosis arthritis and spontaneous remission of the disease. The presence of typical HLA alleles for both diseases suggests coexistence of the two diseases rather than similar pathogenesis.

Learning points

- ▶ Co-occurrence of rheumatoid arthritis and sarcoidosis is very rare.
- ▶ Both diseases have similar clinical manifestations and overlap diagnosis is important for prognosis and treatment.
- ▶ Factors such as prevalence data, absence of genetic relationship and response to treatment support the theory of co-occurrence rather than of common pathogenesis.
- ▶ Multicentric studies that may shed light on this subject are needed.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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