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Case Report

Converging pathways of ankylosing spondylitis and rheumatic fever: A unique case ☆

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ABSTRACT

Ankylosing spondylitis is a chronic inflammatory disease that belongs to the group of seronegative spondyloarthropathies. Rheumatic fever is an abnormal immune response to group A Streptococcus infections. Severe or recurrent episodes of rheumatic fever can lead to significant morbidity and mortality, often resulting in the development of rheumatic heart disease. We present a unique case of a 50-year-old patient who suffered from rheumatic fever during childhood, which was complicated by mitral stenosis. He underwent surgical mitral valve replacement at the age of 35. At 47, he was diagnosed with ankylosing spondylitis following a 3-year history of worsening symptoms. This is the first case in the medical literature describing a patient with mitral stenosis postrheumatic fever coexisting with ankylosing spondylitis. A microbial infection triggering the autoimmune system in genetically susceptible individuals may be the underlying mechanism. However, further research is needed to fully understand the converging pathways of these 2 diseases.

Introduction

Ankylosing spondylitis is a chronic inflammatory disease that belongs to the group of seronegative spondyloarthropathies. Spondyloarthropathies can present with extra-axial manifestations, namely, enthesitic and peripheral articular manifestations, but also extra-articular manifestations, such as psoriasis, uveitis, and inflammatory bowel disease [1]. Osteoporosis has been reported to be the most prevalent comorbidity in spondyloarthropathies, followed by an increased cardiovascular risk [2]. Rheumatic fever is an abnormal immune re-

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sponse to group A Streptococcus infections, most commonly presenting as tonsillopharyngitis, generally during childhood. It affects multiple organ systems, including the heart, nervous system, musculoskeletal system, and skin. Severe or recurrent episodes of rheumatic fever can lead to significant morbidity and mortality, often resulting in the development of rheumatic heart disease [3].

We present a unique case of a patient who initially suffered from rheumatic fever complicated by mitral stenosis and later developed ankylosing spondylitis. This is the first reported case of the coexistence of these 2 diseases.

Case presentation

A 50-year-old man presented his rheumatologic complaints for the first time in 2021, reporting severe chronic pain in the lower back accompanied by stiffness of the spine, pain in the sacroiliac joints, and pain in the right talo-crural joint. The patient experienced episodes of pain during the night, which prevented sleep and rest. The patient described a history of intermittent neck pain, back pain, and rib pain over the past 3 years, treated symptomatically. In 2021 his symptoms worsened, with severe pain and stiffness, particularly in the lower back and sacroiliac joints, with significant restriction of movement. Regarding, childhood diseases: he reported frequent throat infections from ages 4-5, treated with penicillin. Patient was diagnosed with rheumatic mitral valve stenosis in 2008 and underwent mitral valve surgery in 2009. He was also diagnosed with type 2 diabetes mellitus in 2019, managed with oral antidiabetic therapy. Blood pressure was 110/70 mmHg and heart rate 100 per minute.

On, physical examination, skier's position, kyphosis, forward bent position of the neck, flexion deformity of both hip joints were inspected (Fig. 1). Examination of the spine demonstrated loss of lateral and anterior flexion of the lumbar spine, tenderness over the sacroiliac joints. Positive rib cage elasticity test, chest expansion of 3.4 cm and positive Schober's test were noted. On heart auscultation, irregular beats and metallic sound of the mechanical prosthesis was heard.

Pelvis X-ray (Figs. 2 and 3) depicted: complete ankylosis of the bilateral sacroiliac joints with full ossification of the articular spaces, sacralization of the L5, calcification of the interspinous and suprasinous ligaments in the lumbar region, lateral osteophytes on the lumbar vertebrae. Degenerative changes were seen in small joints from L3 to S1. Cervical Spine X-ray demonstrated some osteophytes and narrowing of intervertebral spaces. CT images demonstrated narrowing of bilateral sacroiliac joints, vertebral arthrosis, ossification of the supraspinous and interspinous ligaments from the ninth thoracic vertebrae to the fifth lumbar, as well as presence of sindesmophytes between lumbar intervertebral spaces (Fig. 4).

According to the widely used Modified New York Criteria, a diagnosis of ankylosing spondylitis is made when a patient meets the radiographic criterion of sacroiliitis grade 2 or higher bilaterally, along with at least 1 clinical criterion, such as low back pain and stiffness, limited lumbar spine movement, or restricted chest expansion. Based on these criteria, our patient meets the necessary requirements for a diagnosis of ankylosing spondylitis.

Fig. 1 – Typical kyphotic spine deformity in a patient with ankylosing spondylitis.

Laboratory findings showed erythrocyte sedimentation rate of 10 mm/hr, white blood cell count of 9.18 × 10^9/L, red blood cell count of 5.16 × 10^12/L, hemoglobin level of 16.1 g/dL, hematocrit of 47.3%, and C-reactive protein of 4.4 mg/L. Additional findings included a positive HLA-B27, low Vitamin D3 (11.3 ng/mL), and low total calcium (1.83 mmol/L). Other markers such as anti-citrulline peptide antibodies, anti-Scl 70, ANA, Anti-U1RNP, antiphospholipid antibodies, rheumatoid factor, antinuclear antibodies, Anti-Ds DNA, C3, C4 complement, Anti-RoSSA, Anti-LaSSB, P-ANCA, and C-ANCA were

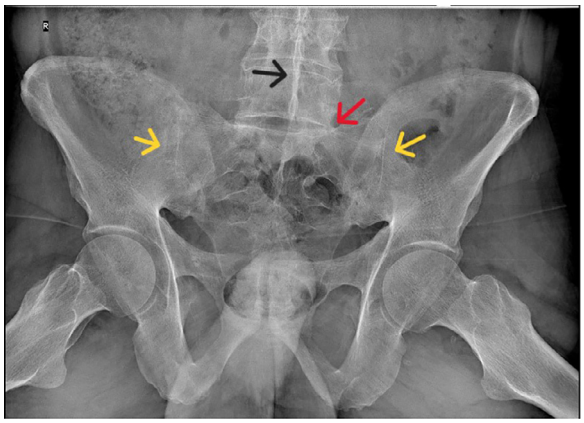

Fig. 2 – X-ray of the sacroiliac joint showing bilateral sacroiliac ankylosis (yellow arrow), left sacralization of L5 (red arrow), calcification of the supraspinous and interspinous ligament, the dagger sign (black arrow).

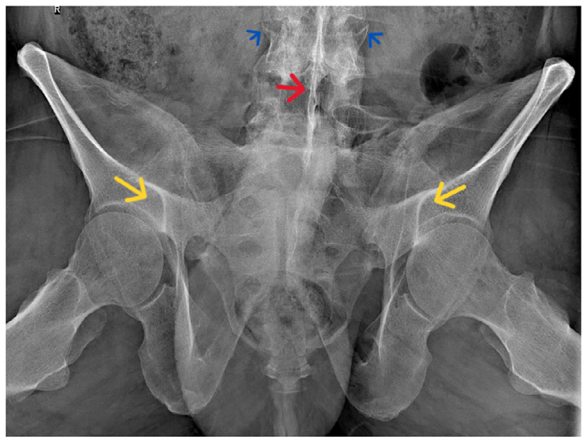

Fig. 3 – Posterior X-ray of the sacroiliac joint showing bilateral sacroiliac ankylosis (yellow arrow), the dagger sign (red arrow) and lumbar vertebrae osteophytes (blue arrow).

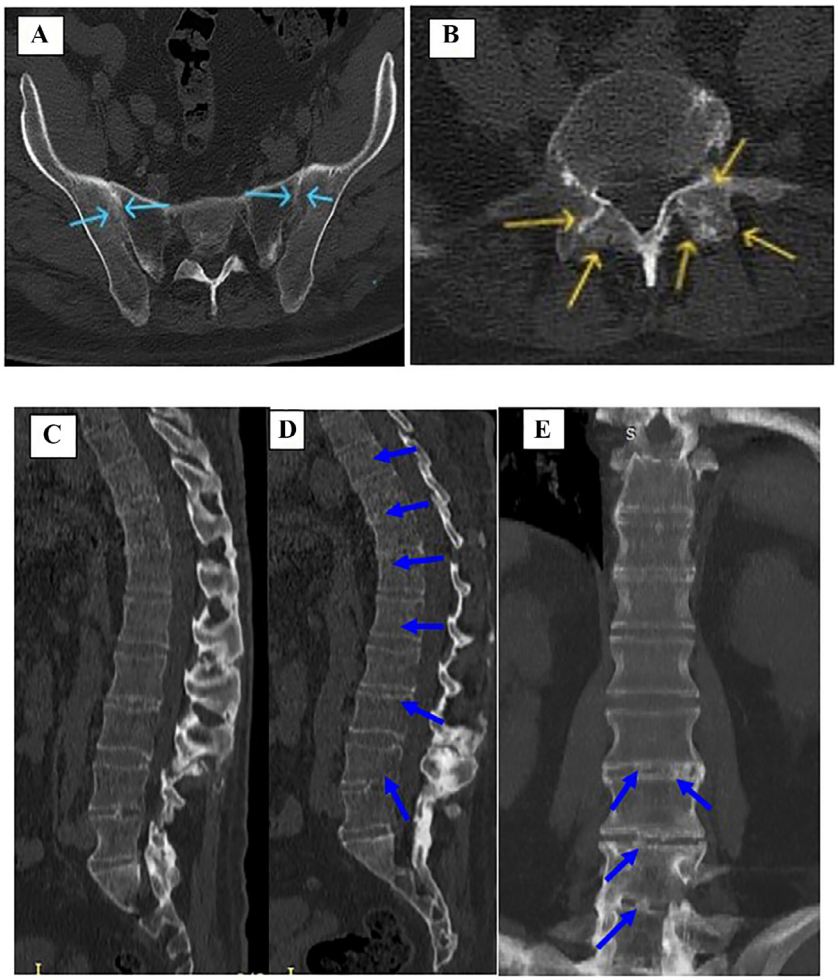

Fig. 4 – CT images: (A) CT of the pelvis in the axial projection of the sacroiliac joint, blue arrows show subchondral sclerosis and narrowing of the bilateral joint spaces, particularly on the right side. (B) CT of L5 vertebra in axial projection, yellow arrows indicate bilateral arthrosis. (C and D) CT in the sagittal projection of the thoraco-lumbar spine, blue arrows indicate calcifications (ossifications) of the supra and intrespinous ligaments from Th9 to L5. (E) CT in the coronal section of the thoraco-lumbar spine shows the intervertebral spaces L2-L3, L3-L4 and L4-L5 with content of syndesmophytes.

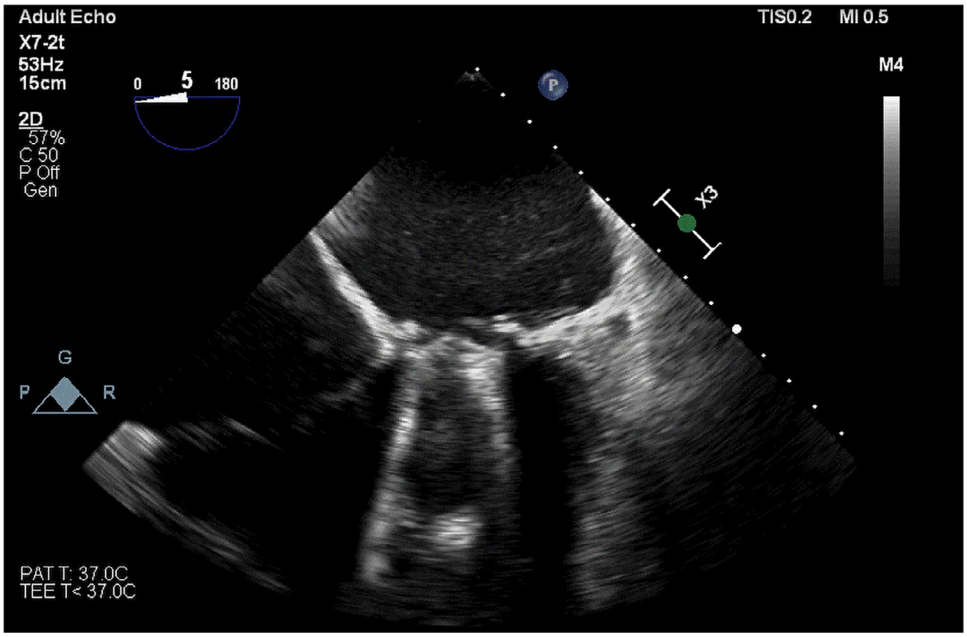

Fig. 5 – Transesophageal echocardiography (Phillips EPIQ 7C) in mid-esophageal 4 chamber view depicting prosthetic mechanical mitral valve.

negative. DEXA-Osteodensitometry T score at L3 was -1.7 and -1.8, indicating osteopenia. Although a positive HLA-B27 test is not required for diagnosis, it can support the diagnosis of ankylosing spondylitis. However, not all patients with the condition are HLA-B27 positive. Elevated CRP or erythrocyte sedimentation rate may indicate systemic inflammation, but these markers are not specific to ankylosing spondylitis.

Echocardiography and transesophageal echocardiography showed a normal functioning prosthetic mechanical mitral valve (Fig. 5). Both atria were severely enlarged, left atrium 78 mm and right atrium 72 mm, with presence of spontaneous echo contrast of 3+. Left and right ventricular size were within normal reference range. A moderate tricuspid regurgitation was noted. Pulmonary artery systolic pressure was 40 mmHg.

Treatment regarding rheumatologic condition included initial treatment with nonsteroidal anti-inflammatory drugs (diclofenac sodium injection 75 mg/3 mL), infusion therapy of corticosteroids (methylprednisolone 20 mg), proton pump inhibitors (pantoprazole 40 mg), Vitamin D3 (300,000 IU monthly for 3 months), and Osteopan Plus (food supplement with calcium, vitamin D, vitamin K, zinc, copper and lysine). After 1 week, the patient's spine showed reduced swelling, pain, and stiffness. The patient was subsequently started on biological therapy with a TNF antagonist (infliximab 3 mg/kg) according to the Euro protocol for ankylosing spondylitis (0, 2, 6, and every 8 weeks for 7 doses). Additional tablet therapy included sulfasalazine 500 mg twice daily, Prednisone 10 mg daily for 1 month (then maintenance dose of 5 mg), Osteopan Plus, CH-Alpha Osteo (bioactive collagen peptides), and pantoprazole 20 mg twice daily (30 minutes before meal).

Cardiologic therapy included acenocoumarol 4 mg according to the INR level, bisoprolol 5mg/day, digoxin 0.125 mg/day.

The patient demonstrated significant improvement in rheumatologic symptoms, with decreased pain and stiffness. Regular follow-up appointments were planned to monitor and adjust the treatment regimen as necessary. As for the cardiologic status, the patient is stable and is recommended to have regular follow-ups.

Discussion

Ankylosing spondylitis can coexist with other rheumatologic disorders. There are reports about coexisting of ankylosing spondylitis and rheumatoid arthritis [4]. Psoriatric arthritis can present with axial involvement similar to ankylosing spondylitis and patients with ankylosing spondylitis can also exhibit symptoms of psoriatric arthritis. However, it remains a matter of ongoing debate whether axial-dominant psoriatric arthritis and ankylosing spondylitis are separate entities with overlapping characteristics, or whether they represent different clinical presentations of the same disease [5]. The coexistence of ankylosing spondylitis and systemic lupus erythematosus is extremely rare, with fewer than a dozen reported cases. Most of these cases occur in females, with systemic lupus erythematosus generally preceding the onset of ankylosing spondylitis [6].

The most common etiology of mitral stenosis worldwide is a rheumatic fever sequel [7,8]. Currently, rheumatic fever complicated with rheumatic valve disease mainly affects the population in low- and middle-income nations, as well as in indigenous populations in wealthy nations where initial Streptococcus pyogenes infections may not be treated [9]. In our country, although the incidence of rheumatic valve disease

has declined substantially over the last 2 decades, it remains the highest in Europe. [10,11].

It is very rare that patients that experience post rheumatic fever consequences have a coexisting rheumatologic disorder. There are a few cases that report a coexistence of systemic lupus erythematosis and history of rheumatic fever [12–14]. Authors suggest that both diseases exhibit a decrease in regulatory T-cells, suggesting the possibility of overlapping immunological pathways that lead to common manifestations in these conditions [14].

The connection between ankylosing spondylitis and rheumatic fever could be their infectious etiology, as reactive arthritis, ankylosing spondylitis, and rheumatic fever are all said to be associated with infections [15]. While the infectious etiology involving a specific agent is well-established for rheumatic fever, there are hypotheses suggesting an association between ankylosing spondylitis and previous infections. A recent meta-analysis showed that infections are associated with an increased risk of ankylosing spondylitis in both the case-control and cohort studies [16]. Ankylosing spondylitis might be triggered by respiratory tract infections and genitourinary system infections. It is suggested that infectious agents may impact on immune cells and the immune system of the host, including polyclonal activation of T and B cells and the secretion of related cytokines, leading to a breakdown of immune-tolerance [17]. There is a general consensus that both genetic and environmental factors, primarily microbial, play fundamental roles in the development of autoimmune diseases. A previous history of clinical pharyngitis, gastroenteritis/urethritis can be implied from patients with rheumatic fever or reactive arthritis, whilst, other rheumatic diseases like rheumatoid arthritis and ankylosing spondylitis are usually lacking such an association with a noticeable microbial infection. Ankylosing spondylitis is believed to be caused by subclinical infections with Klebsiella microbes [18,19]. Microbes play an important role in the disease causations in most immune-mediated rheumatic diseases, including rheumatic fever and ankylosing spondylitis. Molecular mimicry is considered the fundamental mechanism leading to the development of these diseases in genetically susceptible individuals. In this process, the causative microbe triggers the formation of antimicrobial antibodies that can bind to cross-reactive self-antigens, causing tissue damage through the activation of the complement system and the cytotoxic effects of recruited inflammatory cells [20]. However, although both diseases involve inflammation and immune system dysfunction, they do not share the same known pathway. Ankylosing spondylitis is mostly driven by a chronic autoimmune process related to genetic factors, while rheumatic fever is a postinfectious autoimmune disease caused by molecular mimicry following a streptococcal infection.

Conclusions

Mitral stenosis resulting from rheumatic fever can coexist with ankylosing spondylitis. This is the first case in the medical literature to describe a patient with both of these rheumatologic diseases. A microbial infection triggering the autoimmune system in genetically susceptible individuals may be the underlying mechanism. However, further research is needed to fully understand the converging pathways of these 2 diseases.

Patient consent

The patient provided written informed consent for the publication of this case report and its accompanying images. A copy of the written consent can be made available for review upon request by the Editor-in-Chief of this journal.

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