Rare disease

Primary Sjögren's syndrome with tuberculous arthritis of left knee

Ting Zhang,¹ Jia Cong,² Dong Xu,¹ Xiaomei Leng,¹ Fengchun Zhang¹¹Rheumatology Department, Peking Union Medical College Hospital, Beijing, China;²Medical Department, Peking Union Medical College Hospital, Beijing, China**Correspondence to** Dr Dong Xu, xudong741031@yahoo.com.cn**Summary**

A 56-year-old woman presented with recurrent pain and swelling of left knee, Raynaud's phenomenon and dry mouth. She was initially diagnosed with primary Sjögren's syndrome and was put on prednisone, which substantially relieved her complaints. But 8 months later, pain and swelling of left knee recurred with spiking fever, chills and shortness of breath. Escalation of prednisone did not improve the pain and swelling of left knee. CT of chest revealed pulmonary interstitial changes with coexisting infection. MRI of left knee was highly consistent with tuberculous arthritis, which was further confirmed by positive blood culture of *Mycobacterium tuberculosis* and acid-fast stain of synovial fluid.

BACKGROUND

Osteoarticular tuberculosis in patients with primary Sjögren's syndrome is relatively rare. Tuberculous arthritis could mimic pSS on articular manifestations, leading to confusion and delay in accurate diagnosis. Mismanagement can wreak havoc on involved joints.

CASE PRESENTATION

A 56-year-old woman was admitted to our hospital with recurrent pain and swelling of left knee for 17 months and intermittent fever for 5 months. Seventeen months before, she developed pain, swelling and warmth of left knee, with morning stiffness lasting for half an hour and limited range of motion. She denied trauma or fever. Other joints were spared. She also presented with Raynaud's phenomenon of both hands and dry mouth. Arthrocentesis was performed twice in local hospital, both suggesting no evidence for infection. The joint effusion was light yellow with white blood cells (WBCs) $3.1\text{--}4.0 \times 10^9/\text{l}$. Smear of synovial fluid, acid-fast stain and cultures were all negative. Four months later, she visited our hospital complaining aggravating pain of left knee despite non-steroidal anti-inflammatory drugs. Laboratory tests revealed pancytopenia with WBC $2.32 \times 10^9/\text{l}$, haemoglobin (HGB) 94 g/l and platelet (PLT) $96 \times 10^9/\text{l}$. Erythrocyte sedimentation rate was 87 mm/h. Antinuclear antibody (ANA) was positive with a speckled pattern. Anti-Ro (SS-A) was positive. CT of chest indicated pulmonary interstitial fibrosis, and x-ray of left knee suggested effusion in the joint cavity. Ocular and oral assessment suggested keratoconjunctivitis sicca and xerostomia. She was diagnosed with primary Sjögren's syndrome (pSS) and was administered with prednisone 30 mg per day. Her symptoms of left knee gradually subsided and prednisone was tapered following instructions. She was quite stable for a considerably long period of time. But 8 months after that, when she was on prednisone 12.5 mg per day, swelling and pain of left knee recurred, with intermittent spiking fever

of 39°C and chills, accompanied with shortness of breath. No night sweats or weight loss was noticed. Prednisone was increased to 30 mg per day, and hydroxychloroquine 200 mg twice daily was also administered. But it did not show any benefit in reference to fever or left knee symptoms. She visited our hospital again and was hospitalised for further investigation.

INVESTIGATIONS

On admission, WBC was $2.78 \times 10^9/\text{l}$, HGB 107 g/l and PLT $69 \times 10^9/\text{l}$. Liver and renal functions as well as uric acid were normal. CT of chest showed pulmonary interstitial changes with coexisting infection and high-intensity patches on upper lobe of left lung. MRI of left knee demonstrated synovial hyperplasia, bone erosions of distal femur, tibial plateau and patella, cracks of anterior and posterior horn of lateral meniscus, crippled anterior and posterior cruciate ligaments and lateral collateral ligament, cold abscess posterior to femoral intercondylar fossa, as well as oedema of subcutaneous soft tissue in front of patella.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included pSS with articular manifestations, tuberculous arthritis, Poncet's disease secondary to pulmonary tuberculosis and other autoimmune disorders with musculoskeletal involvement.

TREATMENT

Arthrocentesis was performed with positive acid-fast stain of synovial fluid. The diagnosis of tuberculous arthritis of left knee was further confirmed by positive blood culture of *Mycobacterium tuberculosis*. She was managed with quadruple antituberculosis regimen of isoniazid, rifampin, pyrazinamide and ethambutol, as well as prednisone 40 mg per day. She rejected arthroscopy and was transferred to a special tuberculosis hospital.

OUTCOME AND FOLLOW-UP

On follow-up, she was still on antituberculosis regimen, and prednisone had been tapered to 10 mg. She complained no fever or shortness of breath, no pain or swelling of left knee.

DISCUSSION

Sjögren's syndrome (SS) is a slowly progressive, autoimmune disorder, typically affects exocrine glands including the salivary and lacrimal glands. Autoreactive lymphocytic infiltration damages exocrine glands and results in keratoconjunctivitis sicca and xerostomia. In addition to glandular impairment, extraglandular manifestations include involvement of the skin, musculoskeletal system, lungs, kidneys, liver, peripheral nerves and so forth. Most patients with SS develop increased circulating polyclonal immunoglobulins and autoantibodies, including two fairly specific antibodies directed against the Ro (SS-A) and La (SS-B) antigens. ANA and rheumatoid factor can also be commonly detected. This disease can occur alone as pSS, or be associated with other autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis and polymyositis as secondary SS (sSS).¹

This patient met the classification criteria of SS,² with oral symptoms, ocular signs, confirmed salivary gland involvement and positive anti-Ro. Since there was no other accompanying autoimmune disease, she was diagnosed as pSS.

The presenting symptom of this patient is monoarthritis of left knee. Arthralgias or signs of arthritis have been noted in 25% to 85% of pSS patients, usually in the form of tenderness or swelling in multiple peripheral joints.¹ In contrast to RA, they are usually non-erosive.³ In our patient, the initial investigation of synovial fluid indicated inflammatory arthritis with negative evidence of pathogens, and initial chest CT was not suggestive for potential tuberculosis infection. Besides, the dramatical improvements of articular symptoms after administration of prednisone, as well as the long stable period after tapering prednisone, were all supportive for articular manifestations with pSS initially other than infectious arthritis. But the symptoms of left knee recurred with spiking fever and shortness of breath. Fever not associated with infectious process can also be present in SS as a constitutional symptom.³ And shortness of breath could be contributed to pulmonary involvement with interstitial changes secondary to pSS, which was verified in this patient at the first time of her chest CT checkup. But the articular symptoms reemerged 8 months after the initiation of prednisone, and aggravated despite reincreasing the dosage, which was inconsistent with mere articular involvement of SS.

So aside from pSS with osteoarticular symptoms, the differential diagnosis of the monoarthritis of left knee in this patient should include inflammatory and non-inflammatory causes.⁴ Non-inflammatory causes like osteoarthritis, fracture, haemarthrosis, osteonecrosis and benign or malignant tumours could be easily excluded in our patient according to the articular symptoms and history. For inflammatory causes, crystal-induced arthritis, infectious arthritis due to bacteria, fungi, mycobacteria, virus or spirochetes and systemic diseases with monoarticular involvement including psoriatic arthritis, reactive arthritis, RA and SLE, should all be taken into consideration.

This patient did not fulfil criteria for other autoimmune disease. And the pattern of left knee attacks, response to prednisone as well as normal uric acid did not approve the diagnosis of gout or pseudogout, leaving infectious arthritis the biggest concern. The second CT scan of chest revealed interstitial lung disease, and signs indicating infections located at the upper lobe of left lung, which was a predilection of tuberculosis infection.⁵ If confirmed pulmonary tuberculosis, the recurred arthritis could be Poncet's disease, which was aseptic reactive arthritis developing in the presence of tuberculosis elsewhere.⁶ But MRI of left knee was consistent with tuberculous arthritis,^{7,8} demonstrating synovial hyperplasia, cortical erosions, cold abscesses and meniscal tears. Arthrocentesis revealed synovial fluid with positive acid-fast stain, and blood culture was positive for *Mycobacterium tuberculosis*, which led to the final diagnosis of pulmonary tuberculosis and tuberculous arthritis of left knee on the basis of pSS.

It should also be queried that whether the initial symptoms of left knee was actually caused by tuberculosis. It was reported that approximately 10% to 11% of extrapulmonary tuberculosis involved joints and bones, accounting for 1% to 3% of all tuberculous cases.⁹ Peripheral tuberculous arthritis most commonly manifested as monoarthritis of weight-bearing joints, the knee as the most frequently involved site, ranging from 26.7% to 31% in different studies. Approximately 51.0% of these patients had radiographic evidence of pulmonary tuberculosis.¹⁰ The average interval from onset of symptoms to consultation (patients' delay) ranged from 20.4 weeks to 25.4 months in different ethnic populations with disparity in prevalence of tuberculosis,¹⁰⁻¹⁵ while in pulmonary tuberculosis, the reported range of average patients' delay was 4.9-162 days for both low and high income countries.¹⁶ In general, patients with osteoarticular tuberculosis had a longer duration of symptoms of the disease prior to the diagnosis when compared with patients with pulmonary tuberculosis, suggesting the difficulty of early diagnosis of tuberculous arthritis or the lack of sufficient clinical awareness. However, all these data were based on immunocompetent population, and no counterpart data were available for immunocompromised patients with autoimmune diseases. In our case, the initial results of arthrocentesis, chest CT and the response to treatment were not supportive for infectious arthritis. The long-term application of prednisone sustainably relieved the presenting symptoms for 8 months before the recurrence, further reduced the probability of initial tuberculous arthritis at onset. Since the patient was immunocompromised, she was vulnerable to tuberculosis in our country which has a high prevalence of tuberculosis.¹⁷ We suppose the initial inflammation in the left knee resulting from pSS may lead to increased permeability of local vessels, which may explain the later involvement of tuberculosis infection in exactly the same joint. Nevertheless, it was always important to reevaluate patients timely to avert a stereotype of diagnosis when property of their symptoms changed. The recognition of this rare complication should be promoted and always be included in the differential diagnosis of chronic monoarthritis in patients with connective tissue disease.

The predisposing factors of tuberculosis infection in this patient include immunopathological disturbance secondary to pSS per se and the administration of immunosuppressants

including corticosteroid. But pSS alone does not seem to be a susceptible factor for tuberculosis infection. We searched Pubmed for SS and osteoarticular tuberculosis or tuberculous arthritis in English literature, which only yielded two case reports, one in symphysis pubis and the other in left ankle.^{18 19} Even reactive arthritis seemed to be rare in association with pSS, with only one report on chlamydia-induced reactive arthritis.²⁰ But when it comes to SLE patients, it was suggested that they were at a particular risk of developing osteoarticular tuberculosis.²¹ The discrepant pathological processes involved in these two distinguished disease profiles could be an explanation for different susceptibility of tuberculosis, which may also be contributed by the disparity in frequency and dosage of corticosteroid administration in the two disease settings. Further investigations are needed to address these issues.

Learning points

- ▶ Sjögren's syndrome can present with monoarthritis.
- ▶ Compared with lupus, accompanied tuberculosis infection is relatively rare in pSS.
- ▶ The awareness of tuberculous arthritis should be promoted in case of 'refractory arthritis' in connective tissue disease.

Competing interests None.

Patient consent Obtained.

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