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Case Report Open Access

Thromboangiitis obliterans manifests as rheumatic symptoms

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Thromboangiitis obliterans (TAO) is a non-atherosclerotic inflammatory arthritis mainly involving small arteries and veins. Although it is closely related to the tobacco exposure, the general pathophysiology of the disease remains unclear. TAO mainly affects young male patients with ischemic ulcer, pain during rest, limping, chills in limbs, and migratory thrombophlebitis. However, some patients present joints swelling and pain as the first manifestations before the clinical manifestations above. They are easy to be misdiagnosed as rheumatic diseases, which is a challenge to the diagnosis and treatment of rheumatologists. Here we report a case in which TAO was misdiagnosed as Seronegative Spondyloarthritis (SpA) and eventually amputated.

Keywords: Thromboangiitis obliterans; Rheumatism; Seronegative Spondyloarthritis; Vasculitis

Introduction

Thromboangiitis obliterans (TAO) is a non-atherosclerotic inflammatory arthritis mainly involving small arteries and veins. Although it is closely related to the tobacco exposure, the general pathophysiology of the disease remains unclear. TAO mainly affects young male patients with ischemic ulcer, pain during rest, limping, chills in limbs, and migratory thrombophlebitis. However, some patients present joints swelling and pain as the first manifestations before the clinical manifestations above. They are easy to be misdiagnosed as rheumatic diseases, which is a challenge to the diagnosis and treatment of rheumatologists. Here we report a case in which TAO was misdiagnosed as Seronegative Spondyloarthritis (SpA) and eventually amputated.

Case-report

A 36-year-old man was admitted to hospital with gangrene of his right foot and ulcer of left leg with infection in March, 2019. His medical history began in 2008 and was characterized by repeated swelling and pain in the right ankle. He had gone to many hospitals and found that antinuclear antibody spectrum (ANAs), rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (A-CCP), human leukocyte antigen-B27 (HLA-B27) were all negative, blood uric acid level were normal. The erythrocyte sedimentation rate (ESR) and C - reactive protein (CRP) were in high level. Ultrasound showed synovitis of the right ankle joint, no abnormality was found in the MRI of the sacroiliac jointmus culoskeletal. He was diagnosed as SpA and then non-steroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, methotrexate, leflunomide, Adamamab were given successively for his treatment. His joint symptoms were intermittently relieved and then his left ankle began to swell and pain in 2009. Although the anti-rheumatic treatment continued, the ankle pain

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was not completely relieved, the calf muscles gradually became stiff and swollen, the pain after exercise increased and the symptoms resolved after rest in 2012. He was still treated as SpA by rheumatologists. For economic reasons, he had to stop to use biologics and be given prednisone 30 mg/d with disease-modifying anti-rheumatic drugs (DMARDs), and then prednisone was gradually reduced to 10 mg/d and maintained for 2 years. Then the leg swelling and stiffness symptoms were more serious than before, and the pain in the knee joint resulted in difficult to walk. The skin on the outer side of the left leg was pigmented with itching, and skin ulcers appear after scratching. He went to many hospitals for relevant examination. The X-ray showed that, 1. There was no obvious abnorma-lity in the vertebral body; 2. Knees, ankles and feet are osteoporosis. No abnormality was found in pelvic X-ray and MRI. The ultrasounds showed that 1.the bone surface of both ankles were rough; 2. The blood flow of intramuscular veins in both legs was slow, which could not exclude the possibility of thrombosis. In June 2018, he stopped to use prednisone and DMARDs himself, and then received acupuncture and traditional Chinese medicine treatment for 3 months. The skin of his right toe began to turn black, and then gradually appeared the whole skin of his right foot. He began to be admitted to our hospital for further treatment. We conducted a detailed medical history, physical examination and relevant tests. The patient's knees were swollen, tender, deformed and the local skin temperature did not increase. 1/3 of the lower leg soft tissue had become swollen and stiff. An ulcer of about 4 * 6 cm2 can be seen on the outer skin of the left (Figure 1). The skin below the right ankle joint was blackened with dry gangrene. A crack about 10 cm can be seen on the heel (Figure 2).We found that he had no history of inflam-matory back pain, uveitis, psoriasis and other SpA Clinical features during the course of the disease. No obvious abnormalities were found in the cardiopulmonary, abdomen and nervous system. No abnormalities were found in the joints and soft tissues of both upper limbs, either. ESR and CRP were all increased, the autoantibody profile, including ANAs、antiphospholipid antibody (APLA)、anti-neutrophil cytoplasmic antibody (ANCA)、RF、A-CCP were all within normal ranges, HLA-B27 was negative. He absented atherosclerotic risk factors other than smoking. Lower extremity vascular ultrasound showed: 1. Bilateral popliteal arteries, peroneal arteries and posterior tibial arteries were occluded, the right tibial anterior artery was occluded, and the left tibial anterior artery was incomplete occlusion; 2. Superficial subcutaneous venous had thrombus of

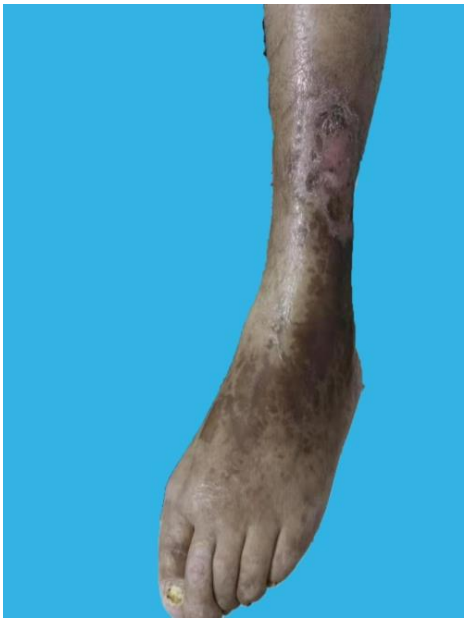

Figure 1. An ulcer about 4*6 cm^2 on the left leg

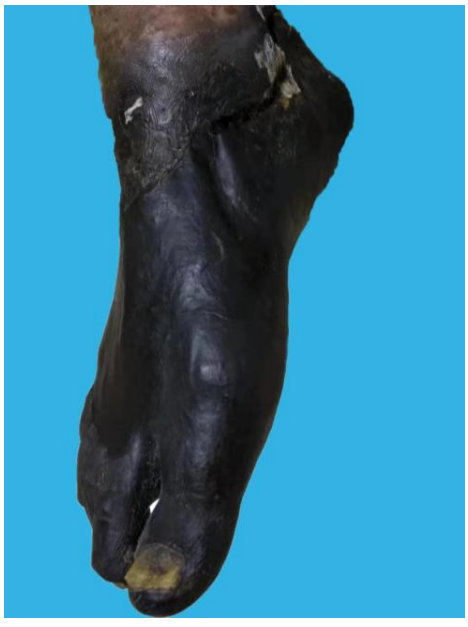

Figure 2. Dry gangrene of the right ankle joint plane and below and a strip of about 10cm rip on the heel

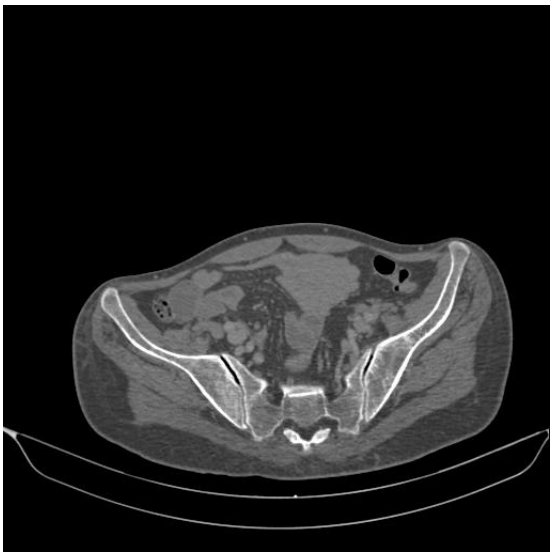

Figure 3. Pelvic CT showed no bone abnormalities

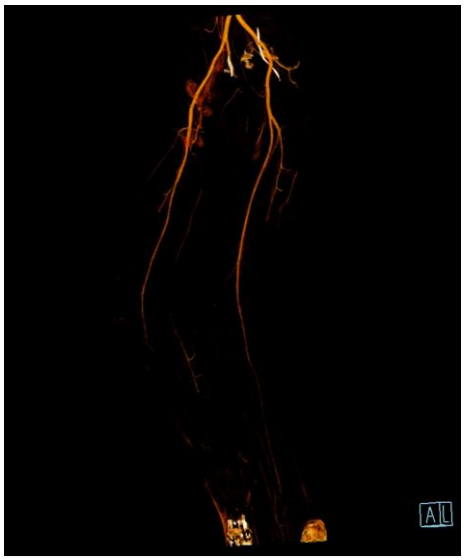

Figure 4. No clear contrast agent imaging was found in the right anterior tibial artery, peroneal artery, left posterior tibial artery and peroneal artery and multiple thrombosis with complete occlusion of the lumen

the right leg. Pelvic CT showed no bone abnormality (Figure 3). Lower extremity X-ray showed bilateral pyogenic osteomyelitis of distal femur and tibia, suppurative arthritis in both knees and ankles. CTA showed that the right anterior tibial artery, the peroneal artery, the left posterior tibial artery and the peroneal artery lumen were completely occluded, no obvious contrast medium imaging was found, and multiple thrombi could be seen (Figure 4). Additionally, he smoked 3-4 cigarettes a day for more than 15 years. According to the Shionoya's criteria [1], he was diagnosed as TAO and underwent amputation of both lower limbs for serious gangrene and infection.

Literature Review

9 publications which reported the arthritis as the first manifestation in patients with TAO have been found [2-9] . A total of 23 patients presented with arthritis before TAO were diagnosed.18 cases of whom recorded basic information (Table 1) and 15 patients had detailed records of the affected joint sites (Table 2). The sex ratio (M: F) was 11:7 and time from articular symptoms to diagnosis of TAO is 9.5 years (1m-13y). Arthritis manifestations were varied including joint pain, swelling, redness, effusion. Joint ultrasound in some patients presented synovitis, tenosynovitis, carpal tunnel syndrome, joint effusion. Two patients ANAs were positive and one of them even with Anti-M2 (+); two patients had HLA-B27 (+) and one patient had HLA-B35 (+), it was difficult to distinguish rheumatism from TAO. Therefore most of them were mis-diagnosed as rheumatoid arthritis, connective tissue disease, systemic vasculitis and sero-negative spondyloarthropathy. Once diagnosed as rheumatism, patients were treated with related antirheumatic therapy like sulfa-salazine, methotrexate, cyclophosphamide, hydroxychloroquine, cyclosporine, myco-phenolate mofetil, D-penicillamine and so on. However, those therapeutic drugs were almost ineffective. We found that only one patient presented with monoarthritis, one patient presented with carpal tunnel syndrome, and the others presented with polyarthritis. The acute onset was pain and swelling of multiple joints, swelling of surrounding soft tissues, and pain, tiredness and stiffness of nearby muscles. Wrists (73.3%), knees (60%), and ankles (53.3%) involvement were the most in common. Arthritis mainly manifested in bilateral symmetry, a few only involve one side. Compared with small joints of extremities, large joints were more prone to occur arthritis.

Table 1. Relevant information of 18 patients

Gender ratio	M:F=11:7
Age of onset of articular symptoms	34-year-old(12 to 46-year-old)
Time from articular symptoms to diagnosis of TAO	9.5years(1m-13y)
Arthritis manifestations	pain,swelling,redness, effusion, some of them with peripheral soft tissue swelling and muscular aches, tiredness
Rheumatism related test	ANA(+): 2 cases,one of them with Anti-M2(+) HLA-B27(+):2 cases HLA-B35(+):1 cases
Ultrasound manifestations of joints	synovitis, tenosynovitis, carpal tunnel syndrome, joint effusion, without bone erosions
Misdiagnosis of disease	1.Inflammatory joint disease 2.Rheumatoid Arthritis 3.Vasculitis related to Connective Tissue Disease 4.Systemic Vasculitis, 5.Seronegative Spondyloarthropathy
Antirheumatic therapy	sulfasalazine,methotrexate,cyclophosphamide, hydroxychloroquine, cyclosporine, mycophenolate mofetil, D-penicillamine, azathioprine, etanercept, plasma exchange, glucocorticoid

Table 2. Joints involvement in 15 patients

Joint	Total (%)	Bilateral (%)	Unilateral (%)
Hand	6(40)	5(33.3)	1(6.67)
Wrist	11(73.3)	7(46.7)	4(26.7)
Elbow	6(40)	5(33.3)	1(6.7)
Shoulder	2(13.3)	2(13.3)	0(0)
Keen	9(60)	9(60)	0(0)
Ankle	8(53.3)	6(40)	2(13.3)
Foot	6(40)	5(33.3)	1(6.7)
Axial skeleton	1(6.67)	/	/

Discussion

Thromboangiitis obliterans (TAO), or Buerger's disease (BD), is a non-atherosclerotic, acute segmental, inflammatory, thromboembolic and non-destructive vascular disease of unknown origin, which clinically undulating multilocular segmental inflammatory disease affecting small and medium sized arteries and veins[10]. TAO is usually diagnosed in young, male smokers before the age of 50, less than 1% of those affected are women, but recent studies have shown that rates are increasing for more and more women smoking[11]. TAO is thought to tight correlate with the incidence of smoking, and less than 5% of TAO patients are non-smokers. Although it is closely related to tobacco exposure, but the general pathophysiology of the disease remains unclear [12]. These cases might be triggered by cold, frostbite, traumatism of the extremities or even abuse of sympathomimetic drugs. It initially involves the distal and nerves within the neuro-vascular bundles of the legs (the arms and cerebral visceral might be involved, but infrequently) [11-13], Upper extremity involvement is reported to increase during the last decades, about 20 – 25 % of the cases combined upper and lower extremity involvement. The symptoms of TAO include limb ischemia, pain, and intermittent claudication, abated or artery

disappeared foot dorsal pulse and wandering superficial phlebitis. The skin cyanosis, and then the ulcer or gangrene on the toe end becomes black, gradually spreading to the proximal end with the development of the disease. Serious cases can lead to amputation [10].

TAO-lesions are classifed in acute, subacute, and chronic types, the latter is difficult to distinguish from other forms of chronic arterial occlusive disease [10]. It distinguishes from other types of vasculitis based on its occurred in most young male smokers, mainly involved in lower limb vessels and nervesthe, laking of systemic signs and symptoms and serological immunol-ogical markers [11]. Although systemic symptoms and signs are very rare in patients with TAO, joint symptoms are common in patients with TAO and usually occur before diagnosis. About 12.5% of patients suffer from these symptoms in the pre-occlusion stage. Patients' present recurrent episodes of arthritis of the large joints, with transient, migratory single-joint episodes accompanied by local signs of inflammation joint problems precede the diagnosis of TAO for an average of about 10 years. Recognizing TAO at this stage is a challenge for the rheumatologists [6].Nevertheless, if joint symptom occur before ischemia, it is difficult to distinguish them from rheumatic diseases. Therefore, autoimmune diseases and other types of vasculitis should be excluded at first, which are including palindromic rheumatism, rheumatoid arthritis, spondyl-oarthritis, systemic erythematosus lupus, systemic vasculitis and so on. It has even been reported that some TAO patients antinuclear antibodies or HLA-B27 was positive by Xavier Puechal[6] and Sarah Steib-Furno[3] ,which increased more difficult to diagnose TAO for rheumatologists. Otherwise, arteriosclerosis, diabetes, proximal embolic source, and hypercoagulable states also should be exclude. The patient of this case presented with joint swelling and pain repeatedly as the first symptom in this case. Except for ESR and CRP elevated, the autoimmune antibodies profile and HLA-B27 were all negative. Ultrasound prompts synovitis in the right ankle and there were nosymptoms of lower limb ischemia (such as intermittent claudication, Raynaud phenomenon and ulcer) in the early stage. Therefore he was misdiagnosed as "SpA ". However, the lower limb swelling, stiffness, skin itching, pigmentation and ulcer were gradually appeared in the long-term follow-up, the symptoms above may be related to lower limb vascular embolism. At this time, rheumatologists should be wary of the misdiagnosis of SpA, which was rarely manifested as cutaneous vasculitis in our past experience. Synovitis may occur in some patients with TAO. Previous studies on TAO had failed to elucidate the mechanisms of joint pain and swelling. These attacks may result from ischemia due to mircrothrobotic arterial or venous thromboaniitis of the small synovial tissue blood vessels [5, 6]. Though ischemia for a long time can also cause osteoporosis, but TAO almost did not because bone erosion, which can be distinguished from the rheumatic diseases mentioned above. Unfortunately, there is no effective treatment for TAO and the aetiology of the disease is unknown. There are currently no treatment guidelines or protocols for TAO patients who suffered from critical limb ischemia [12, 14]. Because Tao is mainly influenced by young smokers, quitting smoking is considered to be the most effective treatment for Tao at present. But, smoking cessation alone is not enough to save the affected limbs in TAO patients with severe limb ischemia, appropriate treatment should be accompanied by smoking cessation to achieve better results [14]. Some studies have found that immunosuppressants (including glucocorticoids, cyclophosphamide, etc.) were effective in the treatment of TAO, but the sample size of patients were too small and the research mainly focused on the changes of inflammatory markers. There were no long-term follow-up results and no mention of amputation rate, either [10, 15]. Although immuno-suppressants and biological agents have been used for a long time, the patient's final amputation may confirm that immunosuppressants may ineffective in the long-term treatment of TAO. Through a retrospective study, Alexandre Le Joncour ect. found that the 10-and 15-year amputation rate was 26% and 34% of TAO. Amputation was closely related to limb infection, but not to the age of smoking at onset and the amount of tobacco exposure at diagnosis. The risks of amputation in patients who

stopped smoking are lower than those who continued [12].

Conclusions

This case represents rheumatic symptom as the first symptom before ischemia in patient with TAO, who was misdiagnosed as SpA and eventually amputated. In addition, TAO with arthritis as the first manifestation of patients were analyzed retrospectively, including their basic information and characteristics of joints involvement. As a rheumatologist, we should be aware that some TAO patients will have joint symptoms (including joint swelling, pain, synovitis, etc.), so we can reduce the rate of misdiagnosis.

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Conflict of interest statement

The authors have declared that they have no conflicts of interest.

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