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Case report

Atypical focal forms of Whipple's disease seen by rheumatologists

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ABSTRACT

We report two atypical cases of focal Whipple's disease with rheumatic presenting symptoms. In one of these cases, the patient presented with chronic intermittent polyarthritis, systemic inflammation, and leukocytosis. Tests were positive for rheumatoid factor and anti-cyclic citrullinated peptide antibodies. There was no structural joint damage. Combined glucocorticoid and methotrexate therapy was only partially effective. Endocarditis requiring emergency valve replacement surgery occurred 4 years later. Evaluation of this event led to the diagnosis of *Tropheryma whipplei* infection responsible for both the endocarditis and the joint disease. The other patient presented with subacute inflammatory low back pain. His medical history was chiefly remarkable for intermittent inflammatory involvement of the wrists and right knee replacement surgery for osteoarthritis followed by a febrile effusion of the operated knee. Radiographs showed destructive lesions of the wrists. Magnetic resonance imaging findings suggested L2-L3 diskitis. A PCR assay on biopsy specimens from the disk lesions recovered *T. whipplei*, thus establishing the cause of the diskitis and previous joint manifestations. Combined doxycycline and hydroxychloroquine therapy was followed by full resolution of all clinical and laboratory abnormalities in both patients.

1. Introduction

Whipple's disease is a rare chronic infection with a broad array of presentations that often results in diagnostic delays [1–5]. The cause is the intracellular Gram-positive bacterium *Tropheryma whipplei*. For many years, Whipple's disease was viewed as a primarily gastrointestinal condition. In most patients, however, joint symptoms are inaugural, preceding not only the gastrointestinal, but also the cardiac, neurological, and ophthalmological manifestations, by several years. Although the joint symptoms exhibit a characteristic intermittent course, they can raise difficult diagnostic challenges for the rheumatologist. We report two atypical cases in patients seen initially in rheumatology.

2. Case #1

In 2006, a 54-year-old man sought medical advice for intermittent flares of polyarthritis, each of which lasted about 1 week. His first joint manifestation had been monoarthritis of the right knee 1 year earlier with persistent systemic inflammation and no response to non-steroidal anti-inflammatory drug therapy. The pain had an inflammatory time pattern and extended gradually to the wrists and fingers, then to the ankles. Synovitis developed at one of the metacarpophalangeal joints of the left hand. The manifestations were intermittent, resolving fully between flares.

This patient had a long history of heavy drinking and smoking (34 pack-years) and was treated in 2007 for vocal cord cancer. He had no history of psoriasis, inflammatory back pain, decline in general health, or fever.

Aspiration of the right knee recovered sterile fluid containing 21,310 leukocytes/mm^3 and no crystals. The blood workup showed leukocytosis (14 G/L); inflammation (erythrocyte sedimentation rate, 33 mm/h; and C-reactive protein [CRP], 43 mg/L); and positive titers of antinuclear antibodies 1280, $n < 80$, anti-cyclic citrullinated peptide antibodies (anti-CCP, 196, $n < 20$), and rheumatoid factor. Tests were negative for anti-dsDNA and anti-ENA antibodies; HLA-B27; and serological markers for hepatitis B, hepatitis C, and the HIV. The only radiographic abnormality was lateral tibiofemoral osteoarthritis in both knees; no erosions were visible at the hands or feet. Magnetic resonance imaging (MRI) of the right knee showed a tiny meniscal crack and thickening of the synovial membrane. Examination of the synovial biopsy from the right knee showed non-specific chronic synovitis with synovial lipomatosis.

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Non-erosive rheumatoid arthritis with positive tests for rheumatoid factor and anti-CCP antibodies was considered the most likely diagnosis. Combined treatment with prednisone 10 mg/day and methotrexate 15 mg/week was only partially effective and the patient continued to require more than 7.5 mg/d of prednisone. He experienced recurrent flares of joint symptoms with systemic evidence of inflammation but did not develop any structural damage.

In November 2012, he experienced the sudden onset of right heart failure with myalgia and diffuse arthralgia. Although his body temperature remained normal, he had a decline in general health and exacerbation of the systemic inflammation (leukocytes, 16.98 G/L; CRP, 115 mg/L). A vegetation was visible on the aortic valve by transesophageal echocardiography. Blood cultures were negative. Emergency aortic valve replacement was performed.

Examination of the aortic valve using a polymerase chain reaction (PCR) assay with probes specific for *T. whipplei* [1] was positive, establishing the diagnosis of *T. whipplei* endocarditis. Results were negative from PCR assays on duodenal biopsy specimens, blood, saliva, and stool. The periodic acid-Schiff stain was negative on stored knee synovial specimens.

Combination therapy with doxycycline (200 mg/d) and hydroxychloroquine (600 mg/d) was given. At last follow-up 18 months later, his clinical and laboratory abnormalities had resolved fully.

3. Case #2

In October 2013, this 82-year-old man was admitted for subacute low back pain with an inflammatory time pattern. He had a history of intermittent pain and swelling of the hands and of right knee replacement surgery for osteoarthritis 1 year earlier. In June 2013, a febrile effusion of the right knee prompted aspiration and lavage of the joint with the collection of multiple specimens using standard aseptic precautions. Findings were negative from universal 16S rRNA gene PCR. A single specimen showed delayed growth of *Staphylococcus aureus* and *Staphylococcus epidermidis*. Infiltrates of lymphocytes and plasma cells forming nodular foci were seen by histological examination, suggesting chronic infection. Contamination of the specimen was deemed likely and the previously initiated antibiotic therapy with penicillin M combined with gentamicin initially then ofloxacin was rapidly discontinued.

The patient described the low back pain as having begun 1 month earlier in the absence of any triggering factor then worsening gradually and having recently started to cause nocturnal awakenings. Overall limitation of lumbar-spine range of motion was noted. Palpation of the L3 and L4 spinous processes elicited pain with a spasm of the left paraspinal muscles at the same level. A fairly large chronic effusion of the right knee was apparent, as well as limitation of wrist flexion-extension on both sides. The rest of the physical examination was unremarkable.

Blood tests indicated systemic inflammation (ESR, 67 mm/h; and CRP, 128 mg/L). Cultures of blood and urine specimens were negative. Tests were negative for rheumatoid factor, antinuclear antibodies, anti-CCP, anti-ENA, anti-dsDNA, and anti-neutrophil cytoplasmic antibody.

Radiographs of the hands showed erosions, bilateral wrist arthritis with joint space narrowing, and arthritis of the carpometacarpal and radiocarpal joints (Fig. 1). Non-concentric osteoarthritis of the glenohumeral joints was noted, with chondrocalcinosis on the right side. At the feet, narrowing of the talonavicular joint space was visible on the right side. MRI of the lumbar-spine showed abnormalities at L3-L4 consisting of low signal on T1 images, high-signal kissing lesions on T2 images, and gadolinium enhancement, suggesting infectious diskitis without epidural involvement (Fig. 2). Findings were normal from an echocardiogram and a computed tomography scan of the chest, abdomen, and pelvis.

Examination of disk and vertebral biopsy specimens taken at L3-L4 showed non-specific subacute-to-chronic diskitis and osteitis. The universal 16S rRNA gene PCR on these specimens was positive for *T. whipplei*. PCR assays on blood, saliva, stool, and gastric biopsy specimens were negative. The diagnosis was focal *T. whipplei* diskitis possibly associated with specific joint involvement (wrists, knee, and foot). Doxycycline therapy (200 mg/d) was started, in combination with hydroxychloroquine (600 mg/d). All clinical and laboratory abnormalities had resolved fully at last follow-up 9 months later.

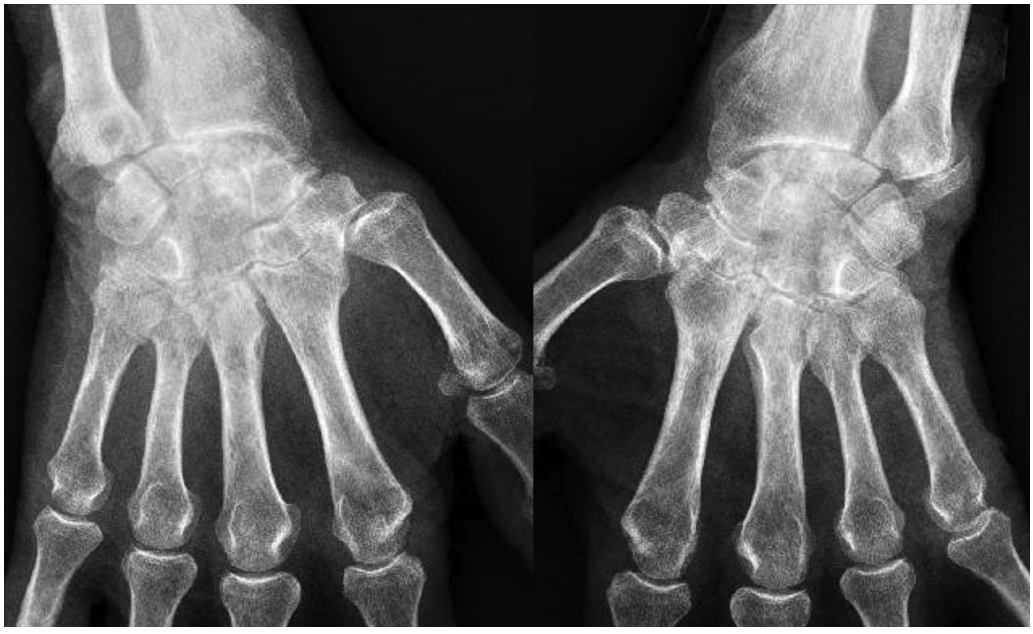

Fig. 1. Radiograph of the hands of patient #1: bilateral and symmetric partial carpal and bilateral radiocarpal joint space narrowing. Note the sparing of the metacarpophalangeal joints.