Seronegative Arthritis as a Complication of Whipple's Disease

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ABSTRACT: Whipple's disease (WD) is an uncommon cause of seronegative arthritis. WD is known for its gastrointestinal symptoms of diarrhea, weight loss, and abdominal pain. However, arthritis may precede gastrointestinal symptoms by 6 to 7 years. We describe a case of an 85-year-old Caucasian male with multiple joint complaints, not responsive to traditional treatments for conditions such as rheumatoid arthritis and osteoarthritis. We suggest that WD be considered for seronegative arthritis especially affecting large joints.

KEYWORDS: Endocarditis, seronegative arthritis, T whipplei, Whipple's disease

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Introduction

Whipple's disease is a rare, chronic, multi-organ systemic illness caused by *Tropheryma whipplei*, that can be potentially fatal if not treated appropriately.[1] Therefore, it is especially important to recognize the signs and symptoms early in the disease course. If treatment is not given appropriately the most devastating consequence is progressive neurologic disease. The neurologic manifestations of WD include dementia, supranuclear ophthalmoplegia, and myoclonus.[1]

Case Presentation

An 85-year-old Caucasian male presented to ambulatory care with asymmetric pain in multiple large joints including right knee, right wrist, and left shoulder.

He had a history of severe mitral regurgitation secondary to *T. whipplei* endocarditis status post mitral valve replacement 2 years prior. At the time, the patient developed symptoms concerning for stroke. He had a brain MRI that revealed scattered bilateral foci of restricted diffusion compatible with acute/subacute infarcts. During a workup for embolic stroke, transesophageal echocardiogram revealed myxomatous degeneration of the posterior mitral valve leaflet, partial flail, severe mitral regurgitation. Several months after this finding he experienced worsening dyspnea on exertion. He presented to an outside hospital for surgical intervention of his mitral insufficiency. At the time of surgery, a sample of the mitral valve was taken. PCR positive for *T. whipplei*. Blood cultures remained negative. He was treated with ceftriaxone for 4 weeks and ampicillin-sulbactam for 6 weeks. He was transitioned to TMP-SMX twice daily for 1 year.

During this current presentation, we looked back into his medical history. It became apparent that he had previously undergone a work up for arthritis. Three years prior to the current presentation, and 1 year prior to mitral valve replacement, the patient began complaining of large joint pain. He developed pain in both of his shoulder joints, right worse than left, and pain in his right hip. He also complained of muscle achiness and stiffness proximal to the joint regions. With this presentation, he was diagnosed with polymyalgia rheumatica because of the stiffness in the proximal muscle groups and osteoarthritis because of the joint pain. There was some initial concern for seronegative rheumatoid arthritis. However, that diagnosis was never formally given. Rheumatoid factor (RF) was negative. Cyclic citrullinated peptide (CCP) antibody was 1.7 U/mL (reference range < 3.00 U/mL). ESR was 28 mm/hour (reference range: 0-15 mm/hour) and CRP was 1.88 mg/dL (reference range < 1.00 mg/dL). He began prednisone 15 mg daily. He tapered down to 5 mg daily over 26 months. He continued to have proximal muscle stiffness and joint pain in his shoulders right greater than left and hip left greater than right.

Furthermore, he noted history of working on farms with close contact to manure during childhood and adolescence but was now retired.

On current presentation, the patient complained of migrating large joint pain. He experienced pain in alternating knees, elbows, and wrists. Three months prior to symptom onset, he completed antibiotic therapy for Whipple's disease. Five months prior to symptom onset, he also discontinued Prednisone therapy. He felt that his pain had improved while on antibiotic therapy for T Whipplei endocarditis. When he presented to our clinic, pain was predominant in his left knee, right elbow, and left wrist. He denied any diarrhea or abdominal pain. He denied any fatigue or weight loss. On physical exam, the left knee was warmer than right with a palpable effusion. Otherwise, knees, shoulders, elbows, and wrist joints had full range of motion without erythema. Left knee arthrocentesis was performed. Synovial fluid was PCR positive for *T whipplei*. Fluid was turbid, negative for crystals, with white blood cell count 23 600 cmm, 80% segmented neutrophils, and red blood cell count 3000 cmm. Serum C-reactive protein was 15.35 mg/dL and rheumatoid factor was 12 IU/mL (reference

range < 14 IU/mL). The patient with diagnosed with presumed recurrence of Whipple's disease. He was started on parenteral ceftriaxone 2 g twice daily for 4 weeks. He was then transitioned to doxycycline 100 mg by mouth twice daily and hydroxychloroquine 200 mg by mouth 3 times daily for 1 year. He is currently on this oral regimen. Most of the joint pains, including knees, elbows, and wrists resolved. Some residual shoulder pain remains.

Discussion

T. whipplei is a ubiquitous organism found in wastewater and transmitted in feces and saliva.[2] The prevalence is higher among farmers and sewage workers.[1,3] It has been postulated that human-to-human transmission is prominent.[4] Most individuals who contract *T. whipplei* infections will be asymptomatic carriers.[1] The prevalence of *T. whipplei* in the asymptomatic general population is 2.3%.[5] An additional source reports detection of *T. whipplei* using PCR assay in saliva of 0.6% and stool 1.5% of the general, asymptomatic public.[5]

The individuals who become exposed and subsequently develop WD are likely to have predisposing immune factors that make them more susceptible to infection.[5] Genetic predisposition is thought to be linked even more specifically to HLA alleles HLA DRB1*13 and DQB1*06.[4] These mutations ultimately lead to impaired macrophage and dendritic cell function.[4] This leads to the accumulation of T whipplei-infected macrophages predominantly in the duodenum and blood.[4] It typically occurs in Caucasian males. One review on 231 patients with WD found 85% of the patients were male.[6]

We would like to highlight the occurrence of arthritis and endocarditis often found together in WD such as how our patient presented. These 2 presenting factors can be without any other manifestations such as gastrointestinal manifestations. Our patient did have arthritis with synovial fluid from knee arthrocentesis PCR positive for T whipplei. In addition, he had endocarditis with tissue sample also PCR positive for T whipplei.

Arthritis and arthralgia are common presenting symptoms for many patients.[6] This patient did not have the common triad of diarrhea, weight loss, or fever. The triad for Whipple's disease previously recognized is diarrhea, weight loss, and fever.[7] However, polyarthritis can precede any other symptoms. In approximately 75% of cases, arthritis preceded the common symptoms of weight loss and diarrhea by 6 years.[6]

Especially in a patient with culture-negative endocarditis, there is a strong link between polyarthritis related to *T. whipplei* and endocarditis caused by *T. whipplei*.[8] In one retrospective report of 4 cases, all patients had vegetation on various cardiac valves. In each case, they had previous arthritis or arthralgia. One patient had severe refractory seronegative polyarthritis of ankles, knees, hips, and wrists for twenty years. One patient had arthralgia of wrists and hips for many years. One patient had an 8-month history of knee, shoulder, and hand arthralgia and 1 patient had polyarthralgia for 2 years.[8]

Furthermore, the polyarthritis this patient did have on this most recent presentation was the large joint, migratory, asymmetric, and seronegative arthritis described as occurring in WD. He had specific involvement of knees, elbows, and wrists. Previous lab results had negative RF and normal CCP. In WD, polyarthritis typically involves large joints.[6] The patient will go through periods of remission and then relapse into polyarthritis. There may also be associated myalgias and muscle cramps.[5] Joint involvement (from most common to least common) includes knees (50%), wrists and ankles (40%), hips (25%), elbows (20%), and hands and shoulders (10%).[6] The characteristics of the arthritis or arthralgia can be broken into migratory, which is usually also intermittent, versus chronic. Migratory is more common.[6,9]

Treatment is with 160 mg trimethoprim and 800 mg sulfamethoxazole twice per day for 1 to 2 years, usually preceded by parenteral administration of streptomycin (1 g per day) together with penicillin G (1.2 million U per day) or ceftriaxone (2 g daily) for 2 weeks.[5] Diagnosis can be made via PCR.[3] In a patient with focal manifestations such as arthritis or endocarditis, then sampling is of the focal region. For example, in a patient with arthritis, a synovial fluid sample to PCR is adequate. Equally, for endocarditis, sample the cardiac valve itself.[5]

We can confirm synovial fluid PCR positive for T whipplei. This with his PCR positive endocarditis makes clear the diagnosis of WD in an older Caucasian male. His presentation could represent recurrent T whipplei infection or undertreated T whipplei infection. With initial presentation of seronegative arthritis preceding the diagnosis of PCR positive T whipplei endocarditis he likely had arthritis secondary to WD several years ago. With recent PCR positive T whipplei synovial fluid he most likely also has arthritis secondary to WD now. Regardless, the focus is on the awareness of the diagnosis of WD in the setting of seronegative arthritis.

Another possibility is immune reconstitution inflammatory syndrome (IRIS). IRIS has been found to occur after treatment initiation in WD.[10] In a cohort study of 187 patients, Feurle et al diagnosed IRIS in approximately 10% of patients based on 3 criteria. (1) The patients had a positive response to antibiotic treatment of WD within 3 weeks of beginning therapy. (2) The patients had symptoms that lasted more than 1 week. (3) Antibiotic therapy was effective. This included recurrent sample of tissue was PCR negative for T whipplei.[10] Furthermore, most of the patients had this recurrence of symptoms soon after initiation of antibiotic treatment. Within the group that had what was classified as IRIS, most had fever and recurrent arthritis.[10] There was also a higher risk of IRIS as a complication if immunosuppressive therapy such as if steroid was administered prior to treatment with antibiotics.[10] IRIS is a possibility for our patient. He presented with recurrent arthritis though no febrile episodes and he had previously been on

intermittent prednisone therapy. However, several factors make this less likely. For one, the timeline does not quite fit. Our patient had begun initial antibiotic therapy for WD greater than 1 year ago and had subsequently completed 1 year of therapy. Also, our patient had PCR positive T whipplei synovial fluid whereas based on the cohort study completed by Feurle et al, 1 of the 3 criteria to diagnose IRIS is PCR negative tissue sample.[10] Our patient did improve with this most recent initiation of antibiotics. However, remembering that IRIS is possible in WD, especially shortly after initiation of antibiotic therapy is important when caring for WD patients.

Conclusion

Whipple's disease should be on the differential in patients with seronegative arthritis of large joints that is refractory to therapy for more common conditions such as rheumatoid or other causes of arthritis. In some cases, it can also exist with myalgias. *T. whipplei* PCR positive vegetations on cardiac valves may be preceded or concurrent with *T. whipplei* PCR positive synovial fluid collection of large joints. Once the diagnosis of Whipple's disease is made, even after guideline directed therapy is completed, the disease should be considered in the future.

Author Contributions

All authors have made a substantive contribution to the article.

Patient Consent

Patient consent was secured to publish the findings of this case study.

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