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A Case of Community Acquired *Clostridium difficile* and *Tropheryma whipplei* Co-infection Causing Persistent Joint Pain

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Abstract

Joint pain is a common presenting symptom seen in the outpatient setting. Accurate diagnosis is imperative for providing optimal patient care. Our patient is a 50 year old male who presented with many years of joint pain affecting multiple joints. He was diagnosed with seronegative Rheumatoid arthritis. Despite treatment with immunosuppressive medications, his joint symptoms persisted and he developed abdominal pain and diarrhoea.

In light of these gastrointestinal manifestations, his diagnosis was changed to Chron's disease, and his medications were modified. Yet, his joint and abdominal symptoms remained unremitted; hence he underwent further investigations which led to the diagnosis of Whipple's disease co-infected with *Clostridium difficile*.

To the author's knowledge co-infection of Whipple's disease with *Clostridium difficile* has not been previously reported. Community acquired *Clostridium difficile* infection has been a growing health concern. It can co-infect with other pathogens, confounding the clinical picture.

Keywords: Arthritis; Whipple's disease; *Tropheryma whipplei*; *Clostridium difficile*

Case

A 50 year old male was seen by a Rheumatology consulting service for primary symptoms of joint pain. His symptoms started five years ago when he developed pain in his bilateral hands, wrists, shoulders, knees, and ankles. These joint pains were present in an asymmetric, migratory pattern and symptoms subsided without specific treatment. Additionally, he experienced joint swelling, morning stiffness lasting for a few hours, and intermittent episodes of fever. Initially the patient was diagnosed with Lyme disease and treated with doxycycline 100 mg twice daily for twenty one days and prednisone 10 mg daily for two weeks, decreased to 5 mg daily for four weeks. Symptoms abated with treatment but reoccurred once prednisone was tapered and discontinued, and the patient received a Rheumatology referral.

Rheumatology's evaluation found that the patient's serologies for rheumatoid factor (RF) and anti-cyclic citrulinated peptide (CCP) were negative. Thus, the patient was diagnosed with seronegative rheumatoid arthritis. He was started on methotrexate 15 mg every week, folic acid 1 mg daily, and prednisone 10 mg daily tapered over four weeks. Symptoms improved minimally with these medications and after three months on methotrexate his symptoms continued. Therefore, etanercept 50 mg every week was added to the current medications.

After a period of six months on methotrexate and etanercept, the patient developed abdominal pain, diarrhea, and had lost twenty pounds. He underwent an esophagogasrtroduodonscopy (EGD) and colonoscopy. EGD showed mild erythema of the duodenal wall. Colonoscopy revealed colitis with neutrophilic infiltrates and rare granulomatous changes. Biopsy results from both the EGD and colonoscopy were read as nonspecific inflammation. Based on these findings, he was diagnosed with Crohn's disease with secondary arthritis. Additionally stool enzyme immunoassay (EIA) for *Clostridium difficile* toxin A and B and stool culture for Campylobacter came back positive and the patient was diagnosed with *Clostridium difficile* colitis and Campylobacter infection. He was treated with metronidazole 500 mg three times daily for 14 days for *Clostridium difficile* colitis and with ciprofloxacin 750 mg twice daily for three days for Campylobacter infection. Methotrexate and etanercept were discontinued during this period of acute illness. He underwent a repeat colonoscopy three months later which showed an improvement in inflammation.

One month later he again developed diarrhea and was diagnosed with another episode of *Clostridium difficile* colitis and Norwalk virus infection. He was treated with metronidazole 500 mg three times a day for 14 days for *Clostridium difficile* and received symptomatic management for Norwalk virus infection. Once the abdominal symptoms subsided, he received infliximab 5 mg/kg on weeks 0, 2, and 6 and then every 8 weeks, methotrexate 15 mg every week and folic acid 1 mg every day. On this regimen his abdominal pain worsened and he continued to have joint pain, so he was referred for a second Rheumatology opinion.

At this time the patient's primary complaints were generalized joint and abdominal pain and episodes of non-bloody diarrhea. Review of symptoms was negative for nausea, vomiting, rash, photosensitivity, alopecia, oral and nasal ulcers, ocular symptoms, cough, shortness of breath, and inflammatory back pain. There was no family history of autoimmune disease, and the patient denied smoking, alcohol use, and recreational drug use. He had medical history of well controlled asthma, for which he used an albuterol inhaler as needed.

Physical examination was unremarkable except for a diffusely tender abdomen; he had normal bowel sounds with no organomegaly. Joint examination found tenderness present over glenohumeral, wrist and ankle joints. No joint effusion, dactylitis and enthesitis were identified.

Lab investigations showed normocytic anemia (hemoglobin 12.2 gm/dl, reference range: 13.5-17 mg/dl), leukocytosis (white blood cell count: 12.2×10^9/liter, reference range: $3.5\text{-}10.5 \times 10^9$), thrombocytosis (platelet count: 480, reference range 150-450 K/cumm), elevated C reactive protein (CRP) level of 38, (reference range: 0-8) and elevated erythrocyte sedimentation rate (ESR), of 65 mm/hr (reference range: 0-20 mm/hr.). Antinuclear antibody (ANA), extractable nuclear antigen, antineutrophil cytoplasmic antibody, Quantiferon test for Mycobacterium tuberculosis, human immunodeficiency virus serology, hepatitis B and C virus serology, urinalysis and blood culture were negative. Liver and kidney function tests were within normal limits. Radiographs of bilateral hands and feet did not show erosions.

Because of the persistence of the abdominal pain, the patient had a repeat EGD and colonoscopy. EGD showed duodenal mucosal erythema. The biopsy samples taken during EGD revealed active duodenal inflammation; periodic acid shiffs stain (PAS) was positive for macrophages and PCR was positive for *Tropheryma whipplei*. A colonoscopy showed tiny aphthous ulceration of terminal ileum but otherwise unremarkable ileal and colonic mucosa. PCR and PAS stains on colonic biopsy were positive for *Tropheryma whipplei* Blood and CSF PCR for *Tropheryma whipplei* were negative.

Based on many years of constitutional abdominal and joint symptoms and positive PCR on duodenal and colonic biopsy, the patient was diagnosed with Whipple's disease. He was treated with intravenous Ceftriaxone 2 gm/day for four weeks followed by Trimethoprim/Sufamethoxazole (TMP/SMX) double strength tablet twice daily for one year. His immunosuppressive therapy was discontinued.

On follow up his diarrhea and abdominal pain had subsided and there was marked improvement in the joint symptoms.

Discussion

Whipple's disease (WD) is a chronic, systemic illness caused by *Tropheryma whipplei*. *T. whipplei* is an actinobacteria and is phyogenetically related to actinomycetes and cellulomonades. WD is characterized by arthralgias, diarrhea, and weight loss, and commonly affects middle aged Caucasian men. Because of its variable manifestations, there is often a delay of about seven years before the diagnosis is established, as seen in our patient. Diagnosis is made by duodenal or jejunal biopsy showing macrophage containing periodic acid Schiff (PAS) positive material and by polymerase chain reaction (PCR) based detection of *T. whipplei* from intestinal tissues [1].

Here we report a case of WD associated with community acquired *Clostridium difficile* infection, a circumstance of which we could not find a previous description. Community acquired *Clostridium difficile* infection is defined as *Clostridium difficile* infection in a person who had no overnight stay in a health care facility within the 12 weeks prior to infection. *Clostridium difficile* is a gram positive, spore forming, obligate anaerobe bacillus that is transmitted through fecal-oral route. Infection is transmitted by spores which are plentiful in the environment, allowing for community transmission. The spores are extremely resistant and can persist for more than twelve months. The pathogenesis of *Clostridium difficile* is based on the action of two major toxins, A and B, which bind to glycoprotein receptors on intestinal cells. The toxins irreversibly inactivate Rho family guanosine triphosphatase (Rho GTPases), leading to disruption of cytoskeleton and tight junctions, and resulting in subsequent cell rounding, detachment, and cell death [2].

It is estimated that in the United States community-acquired *Clostridium difficile* infections have an incidence of 20-50 cases per 100,000 people, which is 20-28% of all *Clostridium difficile* infections [3].

In WD patients, *T. whipplei* multiplies in macrophages, and infected macrophages appear unable to degrade bacterial antigens efficiently [4]. IL-12 and IFN-γ are important mediators of cell mediated immunity induced by bacterial antigens [5,6]. IL-12 is produced by macrophages after ingestion of infectious agent. One of its major functions is induction of IFN-γ production by T-helper cells [5], which is important in macrophage activation. IFN-γ induces macrophages to ingest and kill bacteria [6]. In WD patients, inadequate production of IL-12 by macrophages prevents the development of effective type 1 helper T-cells, leading to diminished IFN-γ production and defective macrophage activation and function [7]. Serum immunoglobulin IgG2 is dependent on IFN-γ secretion and is deficient in WD patients [7]. Humoral immunity directed against *Clostridium difficile* toxin A and B play an important role in *Clostridium difficile* infection [8]. Immunoglobulin subclass IgG2 is deficient in patients with *Clostridium difficile* infection [9]. Thus, defective humoral immunity in WD may predispose to *Clostridium difficile* infection, as in our patient. Tumor Necrosis Factor (TNF) inhibitor (etanercept, infliximab) therapy, which our patient was taking, suppresses IFN-γ levels. This further impairs macrophage function and IgG2 secretion, increasing the risk of WD and CDI [10].

We could not find a previous description of WD along with community acquired *Clostridium difficile* infection; however, studies have reported WD co-infection with other enteric pathogens [11-13]. In their case control study, Fenollar et al. described a 16% prevalence of Giardiasis in WD patients [11], which is significantly higher than the 2-5% prevalence seen in the general population. They suggested a common source of infection may be responsible for concurrent disease, as both microorganisms are present in soil and water [14]. *T. whipplei* leads to destruction of IgA type mucosal plasma cells [15], which results in diminished secretion of IgA and a predisposition to Giardia infection.

Raoult et al. [12] reported that 15% of children between 2-4 years of age with gastroenteritis were positive for *T. whipplei*. Children infected with *T. whipplei* were co-infected with an associated pathogen more often than those without *T. whipplei* infection. They suggested *T. whipplei* infection is contagious and transmitted by fecal-oral route or through saliva in children 2-4 years of age along with other enteric pathogens. In their study one child had Giardia duodenalis, one had both Campylobacter and rotavirus, as seen in our patient, and five children had rotavirus. Gautret et al. [13] proposed that *T. whipplei* may be associated with travelers' diarrhea. They found *T. whipplei* in rectal swabs taken from individuals during episodes of diarrhea but swabs taken before and after diarrhea episodes were negative, suggesting a causal role of *T. whipplei* in travelers' diarrhea.

Our patient received biologics: Etanercept and Infliximab. Biologics increase the risk of developing infections including tuberculosis, bacterial, viral and fungal infections, hence prior to initiation of

biologic we screen patient for hepatitis B and C virus, HIV and latent tuberculosis infection. While on biologics we monitor patients for signs of infection, obtain complete blood count with differential every 8-12 weeks and annual quanteferon test for latent tuberculosis infection.

Conclusion

WD patients may be a cause of unremitting arthritis. It can be co-infected with other enteric pathogens. Environmental presence of *Tropheryma whipplei* and common sources of transmission predisposes to co-infection.

Antibiotics are necessary for treatment of systemic infectious disease and should be given for recommended duration.

Patient should be followed closely after initiation of treatment to monitor response to therapy and any complications arising from therapy.

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