

## Is *Mycobacterium avium paratuberculosis* the Trigger in the Crohn's Disease Spectrum?

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We present and discuss a 30-month investigation of a patient that presented with abdominal pain, postprandial diarrhea, bloating, and night sweats and was treated for Crohn's disease without significant improvement. The patient underwent an ileocectomy with removal of an atonic segment with resolution of functional gastrointestinal symptoms, but profound night sweats continued postoperatively. The patient was presumptively treated for a mixed mycobacterial infection, blood cultures later grew *Mycobacterium avium paratuberculosis* (MAP), and she improved over time. We discuss MAP and its possible relationship to Crohn's disease.

**Keywords.** Crohn's disease; MAP; *Mycobacterium avium paratuberculosis*; night sweats.

Crohn's disease (CD) is a chronic, often debilitating, inflammatory illness that is increasing in incidence and now afflicts over 700 000 Americans [1]. For years, the medical community has treated CD as an illness of unknown etiology that culminates in a waxing waning clinical complex of disordered digestion, pain, and constitutional symptoms. For over 30 years, *Mycobacterium avium paratuberculosis* (MAP) has been suggested as a causative factor or an etiologic cofactor [2]. Nevertheless, most physicians are either unaware or disbelieve the claim of association. We report a case that was clinically treated as CD until MAP was discovered as the probable trigger to the clinical illness.

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## CASE REPORT

The patient is a 29-year-old white female nurse anesthetist of Ashkenazi descent who, in April of 2013, presented with postprandial bloating, postprandial polychexia (Bristol stool scale 5 to 7), and night sweats. Her past medical history was notable for intermittent history of irritable bowel syndrome (IBS) dating back to high school and an infrequent nonsustained history of night sweats while in college. The patient's travel history included a 2-week trip to Patagonia, Argentina (January 2013) with the ingestion of unpasteurized dairy products.

Her symptoms were persistent, particularly the postprandial bloating and night sweats; the latter cycled 3 to 4 times per night necessitating bed clothes and sheet changes. The evaluation included an otherwise negative history and examination and normal laboratory parameters including inflammatory markers. Imaging studies were also normal including computed tomography of the chest, abdomen, and pelvis and upper gastrointestinal (GI) and small bowel follow through. Breath testing for small bowel overgrowth syndrome was negative; nevertheless, treatment with rifaximin provided some relief of bloating. In June 2013, panendoscopy was normal. A thorough infectious disease work up was done, including investigations for unusual pathogens such as tuberculosis (TB).

The patient remained symptomatic. In September 2013, an empiric steroid trial was instituted with a dramatic 2-week response, including significant improvement in bloating and resolution of night sweats. The steroid taper was followed by a return of symptoms incompletely mitigated by mesalamine. In March 2014, a magnetic resonance enterography (MRE) was consistent with ileitis. This was followed by a second colonoscopy in March 2014, including visualization of the terminal ileum, which again showed no mucosal lesions and a negative biopsy for microscopic colitis.

The clinical diagnosis of CD was made in April 2014, and the patient was treated with steroids plus tumor necrosis factor (TNF) blockers (adalimumab followed by infliximab) without a sustained clinical response. She continued with drenching night sweats and postprandial bloating. In January 2015, 6-mercaptopurine was added and not tolerated.

In March 2015, a repeat MRE was done that showed less enhancement of the terminal ileum but thickening. This led to laparotomy in April 2015. She received an intravenous dose of ceftriaxone and metronidazole preoperatively. A section of terminal ileum was pale and flaccid and was resected. The remainder of the intestines appeared normal. The pathology showed lymphoid hyperplasia with drug-induced modulation of associated lymphoid tissue and reduction in neural ganglia

cells. The patient's GI symptoms completely resolved with the ileal-cecal resection. Nevertheless, her night sweats returned 7 days postoperative. All of her laboratory and pathology samples were reviewed—special stains looking for infectious agents were repeated and all were negative. She was also recultured for TB.

In June 2015, a buffy coat blood sample (nucleated cells) was obtained for culture at a specialized laboratory using modified media [1]. The only medication the patient was taking was a tapering dose of prednisone. Contemporaneously, she was started on an empiric 5-drug regimen (rifampin, ethambutol, azithromycin, isoniazid, and levofloxacin) for presumed mixed mycobacterial infection. Within 10 days, the night sweats decrementally improved; and within 6 weeks of treatment resolved completely. Nine weeks after blood sample collection, the culture reading was positive for MAP<sup>1</sup>. The organism's identity was further confirmed by PCR, gel electrophoresis, and deoxyribonucleic acid (DNA) sequencing of the PCR amplicon. The anti-MAP titer from the same blood sample was positive (using MAP whole-cell extract from commercial MAP American Type Culture Collection no. 43545) at a dilution of 1:8 (moderate). The PCR analysis for MAP DNA in the plasma was negative.

## DISCUSSION

We postulate that a MAP infection likely caused an ileitis with destruction of the neural ganglia, which caused the terminal ileum to become atonic. The patient was treated as having CD and was given high-dose steroids, TNF blockers, and immunomodulators without sustained clinical response. Finally, persistent right lower quadrant pain, polychazia, bloating, and night sweats led to ileal resection with resolution of the GI symptoms but not the night sweats. These have resolved with anti-MAP antibiotics.

We recognize case reports as one of the lowest levels of evidence; nonetheless, they have an important role in medical advances [3], such as acquired immune deficiency syndrome being described in Los Angeles in 1980. The *Helicobacter* story reminds us that commensals once considered to be harmless can, under certain clinical conditions, cause disease. These case reports inspired our curiosity to explore the unexpected.

We believe a chronic subclinical MAP infection, which may have begun years before, was responsible for the patient's preceding intermittent IBS symptoms and then, once chronically activated, caused ileitis. Unlike typical CD, no mucosal

changes were ever discovered, but damage occurred to the ganglionic cells that led to an atonic terminal ileum. Removal of the atonic segment remedied the functional postprandial bloating and other GI symptoms. Mesalamine (5-ASA), which has mild antibiotic activity against MAP [4], may have also given some partial relief. Intravenous ceftriaxone and metronidazole at surgery may have temporarily been responsible for 1 week of night sweats abatement. However, until MAP was treated with a sustained multidrug regimen, the night sweats continued. A mixed mycobacterial infection was also considered as a cause, perhaps *Mycobacterium bovis*; however, we were unable to culture this, and both her purified protein derivative and QuantiFERON Gold tests were negative.

*Mycobacterium avium paratuberculosis*, a thick-walled triminarian organism, is the etiologic agent responsible for Johne's disease, a chronic intestinal infection in ruminates that leads to malabsorption, wasting, and death [5]. Transmission from cow to calves by milk is known to occur. *Mycobacterium avium paratuberculosis* is not routinely killed by pasteurization, and even infant formula can be found to occasionally contain MAP [6].

There are formidable resistances against the notion that MAP may be a cause of CD. A 2007 Australian, randomized, prospective, clinical trial of anti-MAP antibiotics versus placebo concluded that MAP was not causative [7], and this has been generally accepted by the GI community despite multiple criticisms on experimental design as well as using subtherapeutic antibiotic dosing [8].

There are reasons to believe that MAP (soil commensal) is a causative pathogen. It is very slow to grow in culture and requires special media. Routine blood culturing practices have a very low likelihood of success [9]. The organism can lose its cell wall to form spheroplasts once ingested into cells such as macrophages; the forms are not acid-fast positive.

*Mycobacterium avium paratuberculosis* is zoonotic. It is possible that MAP infects an individual, and an immune response ensues that limits but does not eradicate the organism, leaving it to survive in macrophages and other reticuloendothelial cells. For reasons that are unclear, this latent infection responds to a "triggering event" that leads to disease. This is analogous to *Mycobacterium tuberculosis*, which causes a latent infection; the infection activates when immune status changes in the host.

## CONCLUSIONS

For this patient, we suggest that MAP was ingested at some time in the remote past and became latent. There may have been a transient period of reactivation in college, including night sweats and IBS symptoms. The sustained infection likely began in early 2013 in the terminal ileum with local damage producing GI symptoms and eventually an atonic ileum. Cytokine release from the reticuloendothelial system infected with intracellular spheroplasts produced the night sweats. The

<sup>1</sup>Performed at PZM Diagnostics, a specialized microbiology laboratory of Peilin Zhang, MD, PhD (Charleston, West Virginia). Nucleated cells were cultured using PZM media consisting of Middlebrook 7H9 broth and 7H10 plate with various supplements including Mycobutin J. The culture is incubated at 37°C for 2–4 weeks. An aliquot of culture is removed, polymerase chain reaction (PCR) analysis is performed. The PCR product is examined on agarose gel electrophoresis and subsequently deoxyribonucleic acid (DNA) sequencing analysis. The PCR amplicon is compared with GeneBank DNA sequences using BLAST program available at NCBI.NLM.NIH.GOV.

positive serology for MAP suggests infection and the positive blood culture is confirmatory. It is still possible that the patient has a mixed mycobacterial infection, and she continues on an 18-month antibiotic regimen. Although her clinical course is not typical of CD, perhaps MAP causes a variable clinical spectrum of CD.

Since this patient's MAP infection was documented, in a general internal medicine practice, 3 of 3 tested patients with refractory CD have been found positive for MAP: 3 of 3 with positive MAP titers and 2 of 3 with positive cultures. We suggest that refractory Crohn's patients should be investigated for MAP infection, using advanced laboratory techniques.

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