IBD LIVE Case Series: Case 11: Yersinia enterocolitica, NSAID use and obstructive symptoms: Is this Crohn's Disease?

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Abbreviations:
MRI = magnetic resonance imaging; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; NSAIDs = non-steroidal anti-inflammatory drugs; anti-TNF = tumor necrosis factor antagonist

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The patient is a 49-year-old male who was referred to our Inflammatory Bowel Disease Center for evaluation of distal ileal ulcers that were found during colonoscopy. The patient initially presented to an outside hospital in April of 2016 complaining of significant abdominal pain, nausea, vomiting and diarrhea. During this hospitalization, the patient was shown to have *Clostridium difficile* (*C. difficile*) and *Yersinia enterocolitica* infections by stool culture. With antibiotic treatment, his diarrhea began to resolve. However, following his release from the hospital, he still had significant left upper and lower quadrant pain as well as suprapubic pain. For these reasons, the patient underwent a follow up colonoscopy that same month that was normal.

At the same outside hospital, he had an esophagastroduodenoscopy and repeat colonoscopy in March of 2017. Random biopsies taken from the stomach, duodenum, and colon showed no pathology. Immunohistochemistry of biopsies taken from the stomach were negative for *Helicobacter pylori*. An ulcer in the terminal ileum was biopsied and showed moderately active ileitis without evidence of dysplasia. Subsequently, the patient had a video capsule endoscopy that demonstrated multiple deep ulcerations in the terminal ileum (Fig. 1) and a normal appearing colon and rectum.

Sometime during the 16 months before he came to our care, the patient was treated for a recurrence of *C. difficile*. He had been given metronidazole for his initial
C. difficile infection but was treated with a four week tapering regimen of vancomycin for the recurrence. Since receiving the vancomycin, his subsequent stool studies have been negative for C. difficile toxin. During this same time period, the patient also had 3 separate computed tomography (CT) scans of the abdomen at the outside hospital, all of which were unrevealing.

Due to his persistent symptoms, the patient was referred to us at Hershey Medical Center for balloon-assisted enteroscopy on June 15, 2017. On exam, 10 cm above the ileocecal valve, the terminal ileum contained a number of ulcers that measured about 1 cm in diameter (Fig. 2). Approximately 20 cm from the ileocecal valve, a benign-appearing, intrinsic moderate stenosis measuring 2 cm in length by 1.2 cm in diameter that could be traversed was noted (Fig. 3). There was one localized, semi-pedunculated, non-bleeding polyp that was 1 cm in diameter in the distal ileum (Fig. 4). Biopsies of the polyp were read as showing mild chronic inflammation and mild villous flattening. About 30 cm from the ileocecal valve, there was a separate, moderate stenotic area measuring about 2 cm in length that was traversed. The cecum was normal on visualization and some biopsies showed inflammation compatible with mucin granuloma while the remainder were unrevealing. The rectum was normal in appearance (Fig. 5). Intact fragments of rectal mucosa showed no pathology. The biopsy samples were sent for cytomegalovirus immunochemistry, which was negative.

On review of symptoms, the patient reports having lower left and upper left quadrant pain without weight loss and a normal appetite. He has a history of C. difficile infection that is now resolved. Currently, he reports having one to two non-
bloody bowel movements per day and also describes occasions in which he has symptoms that are concerning for a bowel obstruction. During these episodes, he has an acute onset of severe abdominal pain coupled with feeling extremely unwell. After having a bowel movement, he has a sudden improvement of these symptoms. He denies having nausea or vomiting during these episodes. Previously, the patient used NSAIDs regularly for knee and back pain, although he has no documented joint disease or pattern indicative of arthritis. He has no mouth ulcers or skin rashes.

The patient's past medical history includes hypertension, hypercholesterolemia, and a meniscal injury of his knee. He has had no previous surgeries. The patient's family history includes a sister with ulcerative colitis but there is no family history of colorectal cancer or celiac disease. He works as a machinist and is married with one child. He is a lifetime non-smoker and non-drinker and does not use recreational drugs. He has not recently traveled outside of the state and he uses his local city source for drinking water. The patient’s current medications include 30 mg of prednisone daily, a probiotic, and acetaminophen as needed. Previously, he used naproxen on a regular basis but stopped 3 months prior to undergoing balloon-assisted endoscopy. He reports an allergy to azithromycin.

On physical exam, the patient's vital signs were normal except that he had a blood pressure of 149/93 mm Hg. His body mass index (BMI) was 34.5 kg/m². His physical exam, including abdominal exam, was unremarkable. A number of laboratory tests were run. The patient had a comprehensive metabolic panel and all of its components, including protein and albumin, were within normal limits. He also had a lipase and amylase level drawn to rule out pancreatitis and a viral
hepatitis panel; these tests were also normal (Table 1). The patient had a complete blood count and iron studies. He was not anemic and had a normal iron with slightly elevated transferrin saturation. His vitamin D level was in the lower range of normal. He tested negative for celiac disease and his inflammatory markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were not elevated. He tested negative for tuberculosis. In the case that he would be started on azathioprine, the patient’s thiopurine methyltransferase enzyme activity was evaluated and found to be normal (Table 2). His stool studies were negative for giardia and C. difficile. Yersinia enterocolitica cultures were also negative but his fecal calprotectin was mildly elevated at 58 (Table 3).

Although stool culture for Yersinia was negative, serology testing by immunoblot showed a positive IgA but a negative IgM and IgG. The titre of IgA was not measured. The patient had a normal bone densitometry. Because of his back pain, a plain spinal film was ordered that also was normal. The patient underwent magnetic resonance enterography of the abdomen that demonstrated segmental foci of stratified enhancement of the bowel wall, with thickening in the terminal ileum and within an adjacent loop of small bowel (Fig. 6). The bowel wall thickening was associated with fibrofatty proliferation. Luminal narrowing was not evident.

We asked the patient to begin tapering his prednisone. We also discussed treating what we felt was likely to be inflammatory bowel disease with azathioprine. However, the patient was reluctant to start the medication, given its many side effects, and he initially refused treatment. Our main questions for the conference participants are:
1. Should we treat this patient as though he has Crohn’s disease?

2. How should we address the positive Yersinia serology? Does he need re-treatment for Yersinia?

3. Should we be concerned about using immunosuppressive treatment with a positive Yersinia serology?

Dr. Kofi Clarke (Gastroenterology, Penn State Hershey)

I have a few comments to add. This gentleman had been to the office a few times before we talked to him about starting medication. We discussed his options and said that he was 49-years old with a history of Yersinia infection and a positive IgA for Yersinia, the meaning of which we can discuss shortly. He has intermittent diarrhea in conjunction with what seem to be episodes of bowel obstruction. So the questions that we’d like to ask the group are whether you agree that the patient has inflammatory bowel disease that should be treated or should the serological results of the Yersinia testing be addressed first? Bear in mind that the patient had been regularly taking NSAIDs up until the last few months.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

Thank you for the excellent case presentation. As you can see, the patient’s issues are not straightforward. From a gastrointestinal standpoint, he had simultaneous Yersinia enterocolitica and Clostridium difficile infections when he first presented. How much time has passed since then? And what was the initial treatment for the Yersinia?
Dr. Kofi Clarke (Gastroenterology, Penn State Hershey)

It has been about 16 or 17 months since he had those two gastrointestinal infections. At the outside hospital where he presented, he was seen by Infectious Disease specialists. They treated him with 10 days of metronidazole and ciprofloxacin for the Yersinia infection, which they felt was adequate.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

I know that the potential confounder with the findings from the patient’s balloon-assisted enteroscopy was his NSAID use. Was he still on NSAIDs when he had the balloon enteroscopy?

Dr. Kofi Clarke (Gastroenterology, Penn State Hershey)

No. He had stopped taking NSAIDs three months before we saw him and performed the balloon-assisted enteroscopy. At his follow up visit, he had not taken NSAIDs in four months and we asked him to continue avoiding them.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

Thanks for clarifying those points. I think that we have a number of issues to address. Let’s first go to Atlantic Health. Joel, this is obviously not a pediatric patient, but how would you manage him?
Dr. Joel R. Rosh (Pediatric Gastroenterology, Atlantic Health)

I’m going to have to plead some ignorance. I don’t have a feel for Yersinia serologies so perhaps somebody else in the room could educate me about them. The chronicity is what I key into. We think of inflammatory bowel disease as a chronic disease and I think that this patient has declared himself as such. I am also impressed that there is a family history of IBD in his sister so that gives me a little more confidence in calling this IBD. The conversation just now was helpful. I wasn’t sure what to do with the results of the balloon enteroscopy but if he had truly been off of NSAIDs for three months and he still has those findings and he is having recurrent, intermittent obstructive type symptoms, I think that you’ve clinched the diagnosis. So I would feel comfortable calling this Crohn’s disease. The question then becomes how comfortable he is with this diagnosis and with medical therapy. I think that he needs to hear that this definitely is what you think that he has and then you can have a conversation about how to best treat it. I am not opposed to his lack of enthusiasm and taking azathioprine. I’m not sure that that is the best drug for him. I would probably think about a biologic considering his impressive small bowel disease.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

Joel, to pin you down, which biologic would you choose? And would you treat the Yersinia?
Dr. Joel R. Rosh (Pediatric Gastroenterology, Atlantic Health)

I would phone an Infectious Disease colleague. I’m not comfortable with my knowledge level about what to do with the Yersinia serology result. It sounds like it has been a long time since it has been treated. I’m not sure how sensitive or specific the immunoglobulin tests are; I don’t have a working knowledge of the test for Yersinia. Once I had established a comfort level with the Yersinia, I would say that our longest experience is with anti-TNF’s. I’m fine with him doing an infusion or injectable anti-TNF, whichever he feels comfortable with. That’s what I would offer him.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

I would like to turn to Rochester and see what your thoughts are. Do you think this is Crohn’s disease? And how would you address the Yersinia, if you think that it’s a problem?

Dr. Arthur J. DeCross (Gastroenterology, Rochester)

I’m a little uncomfortable calling this Crohn’s disease. I would like to see a little bit more of a natural history of how his clinical course is going to evolve. I am uncertain about the Yersinia, although it does raise all sorts of red flags. Yersinia has always enjoyed a special relationship in the history of clinical ileitis with patients being operated on acutely for the wrong reasons. I’m not certain that we know a lot about the time course of how small bowel injury from NSAIDs resolves and I’m concerned about the fact that he is a first degree relative of somebody with
inflammatory bowel disease. When you look at many of these first-degree relatives, they have nonspecific inflammation in the ileum even on biopsies. I’ve often wondered if they are more prone to inflammation because they share the genetics of the reaction to injury in their healing. I wonder if they are more prone to easily manifest injury in the ileum. Are they more susceptible to damage from NSAIDs? Are they more susceptible to damage from infection?

I would probably approach this patient with the mindset that there is no rush to treat. There is no evidence that a significant amount of the small bowel surface is injured or diseased. His albumin levels are good. His iron levels are good. His CRP is not elevated. I think that I would probably contact an Infectious Disease consultant or do some research on my own to figure out what to do with that Yersinia serology. I might just sit tight and watch and wait and repeat some of the studies six months from now. And I would keep him off of NSAIDs.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

Our Hershey colleagues alluded to what we are starting to hear, which is a level of discomfort in stating definitively that this is Crohn’s disease. Art, I like that you brought up the special relationship of Yersinia to ileitis. That’s a nice way of putting it. And the NSAIDs may still be something of a confounder. And you’re wondering, if we did a balloon enteroscopy on all family members of an IBD patient, would you see ulcers and would this truly represent disease? So, I’ll go to Hans at the University of North Carolina. After Hans, we will go to Emory and to Rhode Island. Hans, what do you or your colleagues think?
Dr. Hans H. Herfarth (Gastroenterology, University of North Carolina)

I have a question. How did the patient respond to the prednisone? Did he feel better and experience pain relief after receiving it?

Dr. Kofi Clarke (Gastroenterology, Penn State Hershey)

He said that he felt fine when he was taking 40 mg of prednisone but when he started reducing to about 30 mg he reported having increased symptoms. Whether this was accurate or not was difficult to determine.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

Hans, everyone will feel better on 40 mg of prednisone. What do you make of that?

Dr. Hans H. Herfarth (Gastroenterology, University of North Carolina)

Clearly there seems to be a steroid dependent problem here that he feels well on higher doses but, on lower dose, he starts to feel poorly. You have an MRI that shows fibrofatty proliferation. We know that there are short segment strictures that appear to be longer than what we normally expect for NSAID-induced strictures in the small bowel. We have the capsule showing multiple ileal ulcerations. I’m not sure if the patient was still on NSAIDs at this time or not. With the findings of the balloon enteroscopy, I tend to be thinking that this is more likely to be Crohn’s disease of the small bowel. I would probably treat the patient with budesonide
(Entocort EC). Then I would repeat the exams after three months to see how the patient is doing. If he has continuing obstructive symptoms while on the budesonide, I would be very aggressive and start him on an anti-TNF. I think with the fibrofatty proliferation and the stricture of 2 to 3 cm seen on the MRI and confirmed by small bowel enteroscopy, I feel pretty confident that the patient probably has Crohn’s disease. I agree that there is a question because of his use of NSAIDs. I don't think that we have to rush to an anti-TNF immediately. I would first try and see if I can calm his symptoms down with 9 mg daily of budesonide. But overall, I think this is Crohn's disease.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

So Hans, we have this concept that if we put patients on steroids and they get better, we give a biologic because we say that this is an inflammatory-mediated IBD process. So if I were hearing you correctly, if the patient gets better with budesonide, then you would probably go to an anti-TNF. What happens if he doesn’t get better with budesonide?

Dr. Hans H. Herfarth (Gastroenterology, University of North Carolina)

I would still go to an anti-TNF. The reason that I would initially give the budesonide is because there is still some room for discussion with the patient regarding medications. I thought that the patient was not accepting the diagnosis yet and was not ready to start any type of immunosuppressive treatment. I know
that only azathioprine was discussed but I believe that he may have the same reservations with anti-TNF therapy.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

So it sounds like your advice is to give him some mental time to accept the diagnosis and ameliorate some of the inflammation on budesonide and then switch him over to an anti-TNF. Two sites are a little bit reluctant to say that this is Crohn’s disease. Hans is coming out and saying that this is Crohn’s disease and whether or not the patient responds to budesonide, he should eventually be put on an anti-TNF agent. Emory, what are your thoughts and are you worried about the Yersinia?

Dr. Cary G. Sauer (Pediatric Gastroenterology, Emory)

I think that we collectively agree with Joel. It’s walking like a duck and quacking like a duck so it is probably Crohn’s disease. While those deep ulcers comprise a minimal portion of the small bowel, they do put him at risk for higher rates of complications that we often see in Crohn’s disease. We would also phone a friend about the Yersinia and we would likely treat him because there are enough data about concomitant infections at the time of presentation of inflammatory bowel disease, whether they are C. difficile or Yersinia or both in this case. Having these types of infections puts you down a different path that could be more severe. I think that we all here would likely agree that this is Crohn’s disease and would be comfortable calling it such, contacting an infectious disease specialist about the
Yersinia and most likely starting steroids, likely in the form of prednisone, and then switching over to the anti-TNF biologics.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

We have another vote for initiating anti-TNF therapy once the Yersinia issue has cleared some or at least been validated by Infectious Disease consultants. I’d like to ask our colleagues at Rhode Island what your thoughts are?

Dr. Colleen R. Kelly (Gastroenterology, Rhode Island)

We were just discussing the case and we were wondering, how symptomatic is the patient at this time? It sounds as though his diarrhea has resolved. He has these pain episodes that come periodically but we are wondering how frequent they occur? Is this a day-to-day issue for him or is it every couple of weeks or every few months that his stomach hurts? It would help guide us a little bit in our recommendations, especially whether you would want to go to steroids.

Dr. Kofi Clarke (Gastroenterology, Penn State Hershey)

He has obstructive-like abdominal symptoms with pain approximately every other week. It’s worth noting that he feels better when he’s on 40 mg of prednisone, including his diarrhea, which is better on 40 mg of prednisone. But when he tapers his prednisone below that amount, he reports having diarrhea and an increased frequency of abdominal pain.
Dr. Samir A. Shah (Gastroenterology, Rhode Island)

We were talking here and we are somewhere in the middle. We think that the patient is probably manifesting Crohn’s disease. We would like to have more definitive evidence. We do think that it would be good to treat that the Yersinia and also to treat the patient’s small bowel disease with budesonide short-term, eventually moving him up to an anti-TNF. We feel that this strategy makes sense.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

So you agree with Hans and would give him budesonide before moving to an anti-TNF. Let’s hear from David Keljo at Children’s Hospital in Pittsburgh and then move on to Maryland before getting some more commentary from our presenters at Hershey.

Dr. David J. Keljo (Pediatric Gastroenterology, Children’s Hospital of Pittsburgh)

I’m going to be a little bit contradictory and say that I think that the Yersinia is entirely a red herring. I may be willing to say that this is Crohn’s disease but looking at that small bowel enteroscopy, I don’t see anything that is narrow enough to cause him obstructive symptoms. I would be hesitant to label this as Crohn’s just because the patient has obstructive symptoms. There was a study recently published in Lancet about risk stratification in cohorts of IBD patients. The study took newly diagnosed patients with Crohn’s disease and stratified them by disease severity and whether they got early infliximab. The interesting finding from the study was that infliximab did not prevent strictureing complications although it did
prevent penetrating complications. This makes me think that I would probably not
go with infliximab if we were treating the patient as though he had Crohn’s.

His disease looks relatively mild. I might think about something more like 6-
mercaptopurine, which is heretical for a pediatrician. One pediatric diagnosis that
I’d like to mention just for thought is that the patient has a polyp. In pediatrics,
Crohn’s disease aside, we think about this sort of picture with something like
intermittent intussusception, which certainly could occur with a polyp as a lead
point. You might be able to get somewhere with ultrasound to bring him out of pain,
although I don’t know if this works as well for adults as it does for kids. That’s just a
thought.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

So, similar to Art, David is wondering whether the patient really has Crohn’s
disease and is wondering whether we should be pushing an anti-TNF. We could take
a step back. Even if it is Crohn’s disease, starting an anti-TNF may not prevent that
stricturing complication, as referenced in the Lancet article. Maryland, let’s get your
thoughts and then we’ll go back to Hershey for some more input for discussion.

Dr. Raymond K. Cross (Gastroenterology, University of Maryland)

One thing that to note is that, before referring to a referral center, the patient
has had two upper endoscopic exams, two colonoscopies, a video capsule
enterography, and three CT scans. Perhaps we even have too much information
here. I think the patient probably has Crohn’s and I think that there are separate
problems to address. There is probably a fibrostenotic stricture that is causing him to have issues and it doesn’t matter which therapy you give him. Regardless of what the Lancet paper showed, I think that those kids might’ve already had fibrostenotic disease that was undiagnosed and that is why infliximab therapy did not help their situation. So I think that you may have to do something mechanical with that narrowing. Balloon dilation is probably what I would do if he has symptoms despite an anti-TNF. I would give him anti-TNF monotherapy. He is a large man with a BMI of almost 35 so I would give him infliximab as opposed to an injectable fixed dose. I think this is Crohn’s disease. I agree that I would also call an Infectious Disease specialist to get information about the positive IgA. But, as Dave said, I think that the Yersinia is probably a red herring. In my opinion, this is stricturing Crohn’s.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

So we have more definitive thoughts on giving the patient an anti-TNF and thoughts that this is Crohn’s with a mechanical issue that should be addressed. Let’s go back to Hershey. What did you do with this patient since his balloon enteroscopy and how did you address the Yersinia?

Dr. Kofi Clarke (Gastroenterology, Penn State Hershey)

I am somewhat reassured that there has been a lot of discussion along the same lines that we had in the office. I was not certain what the relevance of the Yersinia infection was, since it was about 15 months before came into our care. So I spoke to our Infectious Disease specialists and they recommended that we do the
Yersinia serologies first before running other tests. So if you were wondering, the Yersinia serology was not something that I thought of because I’m savvy about Yersinia. I received the results and spoke to our Infectious Disease colleagues and they told me that they weren’t certain what to do with them. So this ended up not being very helpful.

During his office visit, I offered to start him on budesonide. However, his insurance would not cover the budesonide so I just left him on prednisone. He agreed to stay off of the NSAIDs and we decided to speak on the phone after I obtained some additional information. Based on the Yersinia serologies, I decided to give him some more antibiotics. When we spoke on the phone again, he declined all therapy. He wanted to stay on the prednisone until I could assure him that he had IBD. I tried to meet him halfway and suggested azathioprine but he was not willing to start azathioprine based on its side effect profile.

We cultured the patient’s stool for Yersinia and the test was negative. Therefore, I met with the patient once again and together we decided that the patient would initiate anti-TNF therapy. We preferred infliximab but he lives about 100 miles from our institution and there was nobody in his local vicinity that was able to give him infliximab but they are able to administer adalimumab. As I was leaving the office, I bumped into Walter and he told me that he could give me a diagnosis in three hours. All he had to do was resect him.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

Is that what you did?
Dr. Kofi Clarke (Gastroenterology, Penn State Hershey)

No, I declined. But Walter is right here so I’ll let him share his opinion.

Dr. Walter A. Koltun (Colon & Rectal Surgery, Penn State Hershey)

Sometimes we do diagnostic surgery. I think that he might be a candidate for that. I want to incidentally mention that there is this phenomenon that we sometimes see with patients that have perineal Crohn’s disease, before we put them on infliximab another anti-TNF, we sometimes get upstream studies first. If there are strictures, I’m a little bit uncomfortable. I have operated on at least 3 patients that had acute obstruction because of having an upstream stricture who were put on some of the newer anti-TNF antagonist. I think there is a phenomenon of rapid healing that occurs with anti-TNF like infliximab that worsens a stricture. Instituting an anti-TNF with upstream strictures in this patient, you should keep in mind there is that occasional phenomenon that takes place of worsening the obstruction.

Dr. Kofi Clarke (Gastroenterology, Penn State Hershey)

My thought is to leave him on adalimumab for about six months. I will see him in the clinic after three months to see how he is doing and then scope him again at six months.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)
I know that we have some people at Pittsburgh that would like to speak. I think that Andrew Watson would like to share some of his ideas and then David Binion will have some comments.

Dr. Andrew R. Watson (Colorectal Surgery, University of Pittsburgh)

Walter, thank you for weighing in. I just want to say that living with a bowel obstruction is no fun, especially symptomatically. And as Ray Cross from Maryland said, the patient has had an extensive work up. Walter is right. A diagnostic laparoscopy is a relatively simple process and at that time you can run the entire small bowel, which will go well beyond the visualization of a CT scan. On occasion, CT scans will over or under read a patient’s situation. However, if you do a laparoscopy and you do find disease, you get a diagnosis and can symptomatically make them better. The only issue with this patient is how much terminal ileum above the ileocecal valve is normal. I have gone down to about 4 to 5 cm above the ileocecal valve and put in an end-to-end anastomosis, preserving the valve. It works very well and we haven’t had any leaks from this procedure. This is something to consider here. I’m with Walter. Symptomatically, this man is suffering and a quick diagnostic laparoscopy is the way to go. Additionally, if you wanted to get a biopsy, you could because it’s a same-day procedure.

Dr. Miguel D. Regueiro Dr. (Gastroenterology, Cleveland Clinic)

I think that a laparoscopy would be diagnostic. Walter, I don’t want to put words in your mouth, but you could also possibly do a resection, which would serve
as the ultimate diagnostic and therapeutic intervention in a 49-year-old. I was happy to hear these recommendations because I had been waiting for surgeons to chime in. I couldn’t believe that this case went so far before Ray brought up the mechanical process occurring in the terminal ileum.

Dr. David G. Binion (Gastroenterology, University of Pittsburgh)

I echo the comments about the obstructive symptoms. Patients that have a partial small bowel obstruction will often have a post-obstructive diarrhea because luminal contents will accumulate and then “release” when the obstruction resolves. I think I recall a comment that the patient had a very intense pain and then a rapid resolution, which would happen about every two weeks, which is also suggestive of intermittent partial obstruction. Distention is a powerful trigger for pain, but this will alleviate when the partial obstruction is resolved. Another consideration would be the presence of multiple web strictures in the small bowel, which may be difficult to demonstrate radiographically, but would be seen on enteroscopy. Some individuals will develop a series of web strictures in the small bowel, which may be a combination of factors, such as underlying Crohn’s disease and/or the effect of non-steroidal anti-inflammatory drugs. The potential for NSAIDs to contribute to ulceration and web stricture formation in the small bowel was described by Allison and colleagues in 1992 in a paper published in the New England Journal of Medicine. These authors looked at an autopsy series of patients who had been prescribed long acting non-steroidal anti-inflammatory drugs and found 8% of individuals that had been using chronic NSAIDs had small bowel lesions and web
strictures. The mechanism for the small bowel injury may be related to the long-acting nature of the preparation. Long-acting pill formulations that are designed for either once or twice daily dosing are actually designed to remain intact and pass through the small bowel and release drug in the cecum. So if there is a stricture in the small bowel, these long-acting agents are likely to hang up at the stricture and cause damage, potentially leading to another stricture immediately upstream from the location of the pill retention. So I would not be surprised if there are a series of web strictures in the small bowel.

The negative effect of multiple small bowel web strictures on intestinal physiology and function is multiplicative, as resistors in series have a more powerful effect on the flow dynamics. So even though the web strictures are shallow and might not look that impressive, they may pose an even greater challenge to the flow dynamics in the intestine. Given the propensity to develop partial obstruction, this patient needs to be educated to chew food thoroughly, particularly fibrous foods. If he were to eat an apple rapidly, swallowing larger pieces of fibrous material, one of these fragments could easily lodge proximal to one of the web strictures, which would cause cramping abdominal pain. I have one last comment concerning steroids and how they may benefit these types of obstructive lesions. Corticosteroids have additional potentially beneficial effects on tissues, which are distinct from their anti-inflammatory properties. Steroids will reduce edema in tissues, which can improve the luminal diameter, which is very helpful at areas of stenosis. Tissue edema frequently accompanies partial obstruction in the small bowel and steroids may help to alleviate this. The Calgary IBD group has done
studies associating ultrasound findings with clinical parameters and bowel wall thickness at the terminal ileum, demonstrating that tissue edema will resolve rapidly with steroid exposure in the setting of partial obstruction. However, in this individual, I feel that surgery will be the best approach. When obstruction is the presenting symptom, this may not be the opportune time to initiate an anti-TNF agent. If we first correct the stenosis in the bowel, and thus “fix the plumbing,” attempts to use anti-TNF biologic therapy may be more effective to control and prevent recurrence of inflammation in the post-operative time period.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

I see that Hans wants to make a comment.

Dr. Hans H. Herfarth (Gastroenterology, University of North Carolina)

I’m just wondering because it did sound like the patient had only obstructive symptoms. I don’t think we saw any radiographs showing a partial bowel obstruction. Of course, if the patient says ‘I have some belly pain every 2 weeks,’ that is different than ‘I am in the Emergency Room every 2 weeks because I just don’t know what to do anymore.’ I think that decision whether or not to go to surgery depends on the severity of symptoms. I felt that his symptoms were present but not to the degree that he would need to go to surgery for an unknown extent of stricturing disease. And I wanted to say to David that his strictures were too long to be just webs, which I think is why his diagnosis favors Crohn’s disease. Two to 3 cm
of stricture, that's not a web. And the fibrofatty proliferation is not something that would be a consequence of NSAID use.

Dr. Miguel D. Regueiro (Gastroenterology, Cleveland Clinic)

Well, Kofi and Ehsan, you have been given a number of differing opinions regarding the best course of action for your patient. One thing that I will comment on is that how you chose to handle this patient really does depend on the frequency and severity of his symptoms.

**Follow Up**

The patient agreed to start treatment with adalimumab. After his induction course of adalimumab, he still was experiencing persistent severe abdominal pain unrelated to food intake. His abdominal pain worsened significantly when his prednisone dose was reduced to fewer than 20 mg daily. He was admitted to the hospital electively for further evaluation and surgery. Small bowel follow-through in November of 2017 showed luminal narrowing without obstruction. In December of 2017, the patient underwent single site laparoscopic ileocecectomy with side-to-side ileocolonic anastomosis. Pathologic examination of the resected section of terminal ileum showed chronic active ileitis with ulcers, architectural distortion, acute and chronic mucosal inflammation, blunted villi, submucosal fibrosis and perivascular chronic inflammation characteristic of Crohn’s disease. The latter was
focally organized as large and confluent lymphoid aggregates, mostly concentrated in the submucosa. His cecum and appendix were normal on histology.

Following surgery, the patient had an uneventful hospital course and was discharged home. He resumed his adalimumab after surgery to prevent recurrence of his Crohn’s disease. On December 28, 2017, Dr. Kofi Clarke saw him in the office. He reported that he was doing very well after surgery and was not having any abdominal pain although he’d had some mild bile salt diarrhea that was well managed on cholestyramine. He had a repeat colonoscopy on April 18, 2018 that demonstrated a normal neo-terminal ileum and a normal, well-healed anastomosis, as well as a normal colon and rectum.

DISCUSSION

Enteric pathogens play a complicated role in inflammatory bowel disease (IBD). Occasionally, a gastrointestinal infection will precede the diagnosis of IBD. Enteric infections also may predispose to the development of IBD by promoting chronic inflammation and eliminating immune tolerance to commensal bacteria. Additionally, the symptoms of enteric infections, such as Yersinia and *Escherichia coli* O157:H7, may closely resemble Crohn’s disease. *Clostridium difficile* (*C. difficile*) is capable of mimicking IBD, complicating treatment, and predisposing to a flare of IBD due to promoting inflammation. Rates of *C. difficile* infection have doubled in recent years and the infection has been especially troublesome for IBD patients.
The patient described in today’s conference initially presented with concomitant *Yersinia enterocolitica* (*Y. enterocolitica*) and *C. difficile* infections. Due to its severity and increased incidence, knowledge concerning the management of *C. difficile* has been mounting. In contrast, *Yersinia enterocolitica* is less familiar to many clinicians. *Yersinia* species are gram-negative, facultative anaerobic coccobacilli. *Y. enterocolitica* and *Y. pseudotuberculosis* are the two agents that may cause enterocolitis, although *Y. enterocolitica* is the pathogen more frequently associated with bowel disease.\textsuperscript{13-16} *Y. enterocolitica* is a foodborne illness and outbreaks are most frequently associated with contaminated pork, milk, or water.\textsuperscript{17-20} *Yersinia enterocolitica* is the agent that causes yersiniosis. According to the Centers for Disease Control and Prevention, symptoms typically develop 4 to 7 days after exposure and may last 1 to 3 weeks or longer.\textsuperscript{21}

The symptoms of *Yersinia enterocolitica* infection include diarrhea, fever and acute abdominal pain with nausea and vomiting. In severe cases, patients may have bloody diarrhea.\textsuperscript{22} *Yersinia* enteritis has a similar presentation to appendicitis, particularly among children, and has prompted unnecessary surgeries.\textsuperscript{23-28} On colonoscopy, aphthous ulcerations are often present in the terminal ileum, cecum, and ascending colon.\textsuperscript{29} *Yersinia enterocolitica* may behave as an opportunistic infection in IBD patients regularly taking potent immunosuppressants, with bacteremia and mesenteric lymphadenitis often occurring amongst this cohort.\textsuperscript{30,31}

Serotypes of *Y. enterocolitica* that are recognized as being predominantly pathologic among humans include 0:3, 0:5,27, 0:8, 0:9.\textsuperscript{32} These strains possess some or all virulence genes that are absent in “avirulent” strains.\textsuperscript{33} In the past,
serologic evaluation of *Yersinia enterocolitica* antibodies were used to determine if an individual was infected.\textsuperscript{34} The IgM class of antibodies persists for only about 1 to 3 months after initial infection.\textsuperscript{35} Earlier studies asserted that elevated *Y. enterocolitica* IgM titers correlated with acute bowel infection while persistent elevations of IgA tended to be associated with an arthritis pattern.\textsuperscript{35, 36} In chronic infection, persistent IgA and IgG reactivity may be observed.\textsuperscript{37} There is no consensus on how to interpret IgA antibody reactivity for a *Y. enterocolitica* infection that was diagnosed over a year previously. Currently, *Y. enterocolitica* infection is best established by isolating the bacteria from blood, bile, stool, skin lesions, mesenteric lymph nodes, peritoneal fluid or cerebrospinal fluid.\textsuperscript{21} For patients with intestinal symptoms, the gold standard for diagnosis is established from stool cultured on the selective agar base medium cefsulodin-irgasan-novobiocin (CIN) or an equivalent medium.\textsuperscript{21, 30, 38}

Although most enteric infections do not cause long-standing complications, lumen perforation and paralytic ileus have occurred in individuals with *Yersinia enterocolitica*.\textsuperscript{39, 40} Well-recognized post-infectious complications of yersiniosis are arthropathy and erythema nodosum.\textsuperscript{30, 41} A number of extraintestinal manifestations of *Y. enterocolitica* have also been documented, including glomerulonephritis, encephalopathy, osteomyelitis, endocarditis, cellulitis, conjunctivitis, and abscess formation.\textsuperscript{42-47} Yersiniosis tends to be a self-limited illness that does not require treatment. In severe cases, first line therapies for isolates of *Y. enterocolitica* include trimethoprim-sulfamethoxazole and aminoglycosides such as gentamicin, while third-generation cephalosporins,
doxycycline, and fluoroquinolones may also be used, but sporadic treatment failures with fluoroquinolones have been noted.\textsuperscript{15, 21, 48}

Although it frequently affects the distal ileum, not all cases of terminal ileitis are due to Crohn’s disease.\textsuperscript{49, 50} Pathogens that preferentially infect the terminal ileum include Yersinia, cytomegalovirus, campylobacter, \textit{Mycobacterium tuberculosis}, \textit{Mycobacterium avium complex}, and salmonella.\textsuperscript{49, 51-53} Independently, NSAIDs are also known to cause damage to the terminal ileum.\textsuperscript{54} The patient’s previous NSAID use was regarded as a confounder due to the gastrointestinal toxicity associated with this type of medication.\textsuperscript{55} While NSAIDs are well known for causing gastric ulceration and bleeding, they can affect any part of the gastrointestinal tract and comparable mucosal lesions have been noted in the small bowel of longer-term NSAID users.\textsuperscript{56, 57} Ileal lesions such as bleeding ulcerations typically resolve when NSAID use is stopped and will recur following NSAID resumption.\textsuperscript{54}

The use of NSAIDs has also been associated with accentuated plicae circulares that create fixed mucosal septal projections into the small intestine called diaphragms or webs. Endoscopically, they appear as thin, concentric fibrotic ridges interspersed randomly between sections of normal bowel.\textsuperscript{58} Small bowel diaphragms in association with NSAID use were first described in 1988 by Lang et al. and are now considered to be specific to NSAIDs and a rare cause of bowel obstruction.\textsuperscript{59-61} Additional enteric lesions that have been noted in the ileocolonic region of NSAID users include reddened folds, mucosal breaks, strictures, denuded
areas, and perforation. NSAIDs may also increase the risk of \textit{C. difficile} infection, which can intensify enteric injury.

In today's case, some clinicians were hesitant to diagnose Crohn's disease in a patient with a history of NSAID use as well as \textit{Y. enterocolitica} and \textit{C. difficile} infections. Patient factors that argued against a diagnosis of Crohn's disease included the patient's normal serum protein and iron levels and the lack of elevated inflammatory markers. However, many patients with Crohn's disease may not be deficient in protein and iron. A European systematic review and data analysis of 2192 IBD patients, the majority of which were treated in tertiary referral centers, noted an overall prevalence of iron-deficiency anemia in patients with Crohn's disease of 27\%. Normal CRP levels also do not rule out Crohn's disease. As evidence, a study of 260 well-characterized, consecutively recruited Crohn's disease patients with follow up noted that 32.3\% had normal CRP levels at diagnosis. Other variables that seemed uncharacteristic of someone with Crohn's disease were that the patient had not reported weight loss and had a high BMI. However, weight loss in Crohn's disease may not be remarkable amongst patients that demonstrate limited disease, like the patient described herein. Additionally, rates of obesity have been rising amongst IBD patients in recent years. A study of 581 IBD patients identified from the IBD registries of the Dallas Veterans Affairs Medical Center and Parkland Health and Hospital Systems who were seen between January 1, 2000 and December 31, 2012 observed an obesity rate of 30.3\% among patients with Crohn's disease. A separate study of 1494 patients with IBD noted that 71.9\% were above their ideal BMI and 31.5\% were obese. Carrying excess weight is not just a
problem for adults with IBD. A multicenter registry study of 1598 children with IBD noted that 23.6% were either overweight or obese. Obese IBD patients may be less likely to be treated with biologic medications or purine analogs and have higher rates of diabetes, hypertension, and hyperlipidemia, but there is no evidence to date that they have higher rates of surgery or hospitalization.

Certain factors helped to substantiate a diagnosis of Crohn’s disease. During balloon-assisted enteroscopy, multiple strictures measuring up to 2 cm in length were noted. Diaphragms associated with NSAID use tend to be shorter in length (<5 mm) when compared to strictures characteristic of Crohn’s disease, although multiple diaphragms in close proximity may lead to similar obstructive symptoms. One study of 10 patients with small bowel diaphragms associated with NSAID use noted that none of these lesions were located in the terminal ileum, which is where disease from today’s patient was concentrated. Histologically, small bowel diaphragms have submucosal characteristics that are indistinguishable from neuromuscular and vascular hamartomas, namely disorganized smooth muscle, fibrous tissue, nerve tissue bundles and vascular elements; these features are absent in IBD. Also in favor of Crohn’s disease were the presence of thickened loops of small bowel and fibrofatty proliferation noted on magnetic resonance enterography. Fibrofatty proliferation—also known as fat wrapping or creeping fat—is not a typical feature of diaphragm disease but it is a mesenteric change that is frequently noted on imaging in patients with IBD. Fibrofatty proliferation of the mesentery is frequently noted adjacent to involved bowel segments in Crohn
disease and represents hypertrophy of the subserosal fat due to chronic inflammation.25

EDITOR’S COMMENT

Establishing a diagnosis of Crohn’s disease can be a clinical challenge, particularly when an individual presents with a concomitant gastrointestinal infection. Symptoms of an enteric infection with Y. enterocolitica can mimic or complicate IBD. They can also lead to a delay in diagnosis. Abdominal pain, diarrhea, ileitis and ileocolonic ulcers can be present in both Y. enterocolitica infection and in Crohn’s disease. NSAID use is associated with numerous forms of enteric injury, including ulcerations and the formation of mucosal diaphragms, or webs, that can result in partial to complete small bowel obstruction. Strict avoidance of NSAIDs for a period of many months prior to endoscopy and biopsy is ideal.

This case also highlights the need to know which method is the best for establishing whether a particular gastrointestinal infection exists, with stool antigen assays and refinements in culture proficiency now producing more reliable results than serological testing.76 Histological evaluation of the affected area of the gastrointestinal tract can be helpful in discerning whether a patient has findings consistent with IBD rather than another entity. Sometimes, the combination of patient history, imaging studies, stool studies, and histology does not lead to a
definitive diagnosis. When a diagnosis remains questionable and obstructive symptoms persist, laparoscopy may prove to be both diagnostic and therapeutic.77

Table 1: Complete Metabolic Panel; Viral Hepatitis and Pancreas Enzymes

<table>
<thead>
<tr>
<th>Electrolytes</th>
<th>Result</th>
<th>Normal Range</th>
<th>Hepatobiliary &amp; Pancreatic Function</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>140</td>
<td>135-145 mmol/L</td>
<td>Alkaline phosphatase</td>
<td>46</td>
<td>40-120 U/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.1</td>
<td>3.5-5 mmol/L</td>
<td>AST (aspartate aminotransferase)</td>
<td>11</td>
<td>≤ 35 U/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>102</td>
<td>95-105 mmol/L</td>
<td>ALT (alanine aminotransferase)</td>
<td>30</td>
<td>≤ 35 U/L</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>31</td>
<td>23 to 31 mmol/L</td>
<td>Total bilirubin</td>
<td>0.4</td>
<td>&lt; 1.3 mg/dL</td>
</tr>
<tr>
<td>BUN (Blood Urea Nitrogen)</td>
<td>21</td>
<td>8-21 mg/dL</td>
<td>Total protein</td>
<td>7.7</td>
<td>6-8.3 g/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.1</td>
<td>0.8-1.3 mg/dL</td>
<td>Albumin</td>
<td>4.5</td>
<td>3.5 – 5.0 g/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>99</td>
<td>65-110 mg/dL</td>
<td>Viral hepatitis panel</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Calcium</td>
<td>9.9</td>
<td>8.5-10.2 mg/dL</td>
<td>Amylase</td>
<td>46</td>
<td>25-140 U/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lipase</td>
<td>113</td>
<td>≤ 160 U/L</td>
</tr>
</tbody>
</table>
Table 2: Complete Blood Count, Iron Studies, Inflammatory Markers and Additional Tests

<table>
<thead>
<tr>
<th>CBC and Iron Studies</th>
<th>Result</th>
<th>Normal Range</th>
<th>Additional Tests</th>
<th>Result</th>
<th>Normal Range or Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>7.21</td>
<td>4-11x10³ per µL</td>
<td>T-spot tuberculosis</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>15.6</td>
<td>14-18 g/dL</td>
<td>TPMT Enzyme Activity</td>
<td>27.5</td>
<td>&gt;21.0 EU/mL</td>
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<tr>
<td>Hematocrit</td>
<td>45.0</td>
<td>40-54%</td>
<td>Vitamin D</td>
<td>28</td>
<td>20-100 ng/mL</td>
</tr>
<tr>
<td>Platelets</td>
<td>219</td>
<td>150-450 x10³ per µL</td>
<td>tTG-IgA Ab</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Iron</td>
<td>141</td>
<td>55-160 µg/dL</td>
<td>IgA</td>
<td>127</td>
<td>70-400 mg/dL</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>51%</td>
<td>20-50%</td>
<td>High sensitivity CRP</td>
<td>0.29</td>
<td>&lt;0.7 mg/L</td>
</tr>
<tr>
<td>Total iron binding capacity</td>
<td>277</td>
<td>40 to 450 µg/dL</td>
<td>Erythrocyte sedimentation rate</td>
<td>1</td>
<td>0-22 mm/hr</td>
</tr>
</tbody>
</table>

TPMT = Thiopurine methyltransferase

*Note: Serology tests for Yersinia enterocolitica— IgA positive, IgM and IgG negative

Table 3: Findings from Stool

<table>
<thead>
<tr>
<th>Stool Studies</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yersinia enterocolitica Culture</td>
<td>Negative</td>
</tr>
<tr>
<td>Giardia antigen</td>
<td>Negative</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Negative</td>
</tr>
<tr>
<td>Fecal Calprotectin</td>
<td>58 (50 to 150 µg/g are considered borderline)</td>
</tr>
</tbody>
</table>
Figures

Figure 1. Video capsule endoscopy demonstrates multiple, erythematous ulcerations in the terminal ileum. The colon and rectum appeared normal.

Figure 2. On balloon-assisted enteroscopy, ulcerations measuring about 1 cm in diameter were evident in the terminal ileum (arrow).

Figure 3. Balloon-assisted enteroscopy photo shows a stenotic area approximately 2 cm in length by 1.2 cm in diameter.
Figure 4. An enteroscopy photo demonstrates a single, semi-pedunculated, non-bleeding polyp in the distal ileum that measured approximately 1 cm.

Figure 5. The patient’s rectum was normal in appearance on enteroscopy.

Figure 6. Abdominal magnetic resonance enterography shows stratified enhancement of the bowel wall, with thickening in the terminal ileum (arrows).
References


