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Inflicting Confusion

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The Case

A 26-year-old man with recently diagnosed Crohn disease presented to the emergency department with acute-onset abdominal pain, nausea, vomiting, anorexia, and an inability to pass gas. His white blood cell count was elevated and imaging revealed a small bowel obstruction and ileitis consistent with a Crohn flare. The patient was admitted to the medicine team, started on empiric antibiotics, and placed on bowel rest. The medicine team recently managed a patient with Crohn disease and a similar presentation in which a gastroenterology (GI) consult recommended infliximab therapy. After they concluded that this flare was similar in its degree of acuity as the prior patient's, the medicine team preemptively initiated infliximab therapy and called for a GI consultation. GI recommended sending stool studies, including for *Clostridium difficile* infection (CDI), and suggested infliximab therapy should be initiated only after the stool studies were negative for infection. However, while an order was placed for stool studies, the primary team did not discontinue the infliximab. The next day, an hour into the infliximab infusion, a stool study returned and confirmed CDI. Infliximab was discontinued at that point, and the patient was treated for the CDI with eventual improvement in his symptoms.

The Commentary

by Frank I. Scott, MD, MSCE, and Gary R. Lichtenstein, MD

While this case suggests a typical presentation of Crohn disease, it also reinforces the need to carefully consider other diagnoses in such patients. A primary subtype of inflammatory bowel disease (IBD), Crohn disease can cause inflammation in any segment of the alimentary canal, from the oropharynx to the anus.(1) Inflammation may involve the full thickness of the bowel wall, resulting in penetrating complications, both fistulae and abscesses. The ileum is the most common site of inflammation in Crohn disease, and colonic disease is the second most common.(1) Crohn disease is associated with extraintestinal manifestations, including pyoderma gangrenosum, erythema nodosum, urethritis, nephrolithiasis, polyarticular arthropathies, and ocular manifestations, such as uveitis or iritis.

The most common symptoms leading to hospital admission include diarrhea, abdominal pain, and hematochezia. Inflammation or fibrosis of the small bowel can also result in obstructive-type symptoms: abdominal distension, nausea, and vomiting. Penetrating phenomena can result in phlegmon formation or intra-abdominal/pelvic abscesses mandating drainage and parenteral antibiotics. As the current case illustrates, patients with Crohn disease are also at higher risk for infections, particularly *Clostridium difficile* infection (CDI) or cytomegalovirus (CMV), which can present with further exacerbation of diarrhea and abdominal pain.

The initial evaluation and therapeutic strategy depends upon presenting symptoms, and it has two primary goals: (i) stabilization of the patient and (ii) excluding an infectious etiology. Volume resuscitation should be performed when indicated, and basic electrolyte and peripheral blood count studies should be assessed in all patients. Inflammatory markers such as erythrocyte sedimentation rate or C-reactive protein can be helpful in the assessment of systemic inflammation and more severe disease. Negative inflammatory markers may indicate symptoms not related to active mucosal inflammation, particularly in patients with a history of elevations of C-reactive protein with disease flares. Rising values may also indicate loss of response to current therapies. Oral intake should be limited in patients with severe pain, nausea, or vomiting. Patients with significant abdominal pain, obstructive symptoms, history of abscess or penetrating disease, fever, or leukocytosis should receive radiologic evaluation, usually with either computed tomography or magnetic resonance imaging of the abdomen and pelvis with oral and intravenous contrast. In the patient with prior colonic involvement, flexible sigmoidoscopy or colonoscopy with biopsies can be performed to both assess disease severity and rule out CMV.(1)

In patients with increasing diarrhea or abdominal pain, stool studies including *C. difficile* toxin, culture, and ova and parasites, are indicated. CDI, a common form of infectious colitis, is a well-established confounder in patients with IBD.(2) The incidence of CDI seems to be increasing in this patient population.(3) Immunosuppressive therapies used to treat IBD, specifically corticosteroids, increase the risk of CDI and may worsen outcomes, with some studies demonstrating higher mortality, colectomy rates, and length of stay.(2,4) Empiric immunosuppressive therapy is generally not recommended until an infectious etiology has been excluded, particularly considering the rapid turnaround time associated with current assays for detecting CDI.

Empiric antibiotic therapy should only be considered in those patients with clinical suspicion of intra-abdominal abscess or other bacterial infection. Many small trials have attempted to assess the effect of antimicrobial therapy as primary therapy for Crohn disease (without a concurrent infectious complication).(1) Metronidazole, ciprofloxacin, rifaximin, and mycobacterial-directed combination therapies have been evaluated, with conflicting results.(5-8) Based on limited evidence for efficacy, coupled with the potential increased risks of antibiotic resistance and risk of CDI, empiric antibiotic therapy is currently not recommended in Crohn disease.(1)

Once infectious etiologies have been excluded, the mainstay of initial inpatient management is intravenous (IV) glucocorticoids.(1) Steroids are an effective therapy for induction of remission, and up to 70% of patients will have a clinical response.(1) However, many of these patients subsequently become steroid-dependent. Of patients initiated on steroids, 56% remain steroid-dependent or lose response to steroids at 1 year.(9) Consequently, the use of steroid-sparing maintenance therapy is critical when initiating IV

steroids in patients with moderate to severe Crohn disease.

The anti–tumor necrosis factor alpha therapies (anti-TNFs) are the backbone of treatment for patients with moderate to severe Crohn disease with inadequate response to steroids or immunomodulators such as 6-mercaptopurine or azathioprine.(1) Infliximab is a chimeric monoclonal antibody administered intravenously. Adalimumab is a fully humanized antibody administered subcutaneously and certolizumab pegol is a PEGylated Fab fragment administered subcutaneously. These agents have demonstrated efficacy in the induction and maintenance of remission in Crohn disease.(10-13) The efficacy of the anti-TNF agents can be further augmented when used in combination with antimetabolite therapy, such as a thiopurine.(14) The fact that infliximab can be administered intravenously makes it the most attractive agent for patients who are severely ill in the inpatient setting. Infliximab is initiated at a dose of 5 mg/kg, and should be given via a standardized induction sequence at 0, 2, and 6 weeks, followed by scheduled dosing every 8 weeks. Failure to follow this regimen or episodic dosing, or not using the standardized induction sequence and only treating when symptoms arise, has been associated with increased antidrug antibody formation and reduced efficacy.(15)

There are several unique risks associated with anti-TNF therapies, including activation of latent tuberculosis. This risk mandates screening of all patients for tuberculosis prior to initiation of therapy. Screening can take place either by purified protein derivative (PPD) or QuantiFERON-TB Gold testing, along with chest radiography.(1) Reports of fulminant hepatitis due to hepatitis B virus (HBV) reactivation have also been associated with anti-TNF therapy. Considering this risk, HBV surface antigen, core antibody, and surface antibody status should be assessed, and vaccination should be given when appropriate. Other risks, including other infections, acute and delayed infusion reactions, and lupus-like syndromes are linked to these agents. An increased risk of melanoma has been reported with anti-TNF drugs, mandating frequent dermatologic screening while on these agents.(16) Although early studies suggested an increased risk for non-Hodgkin lymphoma, more recent data suggests this risk is likely due to thiopurine.(17)

Considering the complex safety and administration issues in patients hospitalized with Crohn disease, the admitting physician should explore each of the following: (i) rule out infection, (ii) ensure hemodynamic stability, and (iii) early consultation with a gastroenterologist. Stool culture, CDI testing, and screening for ova and parasites should be considered at admission for all such patients. Testing for reactivation of HBV and tuberculosis testing is also important. Further decisions regarding the timing of steroid or immunosuppressive therapy should be done in collaboration with the gastroenterologist, and anti-TNF agents should not be administered prior to such consultation. At time of discharge, the entire health care team should ensure timely follow-up with a gastroenterologist to confirm appropriate medication management.

Take-Home Points

- Patients with known Crohn disease presenting with an exacerbation or flare should be screened for *C. difficile* infection prior to the administration of steroids or other immunosuppressive therapies.
- Antibiotic therapy should be reserved for those with known *C. difficile* infection, or in those with a high index of suspicion for intra-abdominal infection.

- Prior to initiating anti-TNF therapy, infection must be excluded, a gastroenterologist should be consulted, and screening for latent tuberculosis and hepatitis B must take place.
- Coordination between gastroenterology and the admitting physician (if a non-gastroenterologist) is key to ensure adequate follow-up and management of anti-TNF therapies such as infliximab.

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