ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Assessing Extraintestinal Manifestations of IBD

Millie D. Long, MD, MPH
Assistant Professor of Medicine
Department of Medicine
Division of Gastroenterology and Hepatology
University of North Carolina School of Medicine
Chapel Hill, North Carolina

G&H What are the most common extraintestinal manifestations of inflammatory bowel disease?

ML The most common extraintestinal manifestation of inflammatory bowel disease (IBD) is arthritis in the central and peripheral joints. Numerous types of skin manifestations also are common. These include erythema nodosum, which causes nodules on extensor surfaces, and ulcerating skin lesions such as pyoderma gangrenosum, which can occur anywhere and often can be seen on the extremities or in the perineal area. Some patients also experience systemic manifestations, such as eye inflammation. Episcleritis, for example, presents as a red and somewhat swollen eye. Mouth ulcerations can make swallowing difficult and painful.

Some clinicians also categorize primary sclerosing cholangitis—inflammation and narrowing of the bile ducts—as an extraintestinal manifestation, although it can also occur as a separate disorder.

These extraintestinal manifestations can occur together or independently. They can appear even when the bowel is not inflamed, so their timing does not always correlate with increased gastrointestinal symptoms.

G&H Do these extraintestinal manifestations sometimes appear before the diagnosis of IBD is made?

ML Yes. For some patients, the appearance of these extraintestinal manifestations is what brings them to the doctor. A workup of the manifestation leads to recognition of the underlying IBD. A skin manifestation may be mistaken for an infection until the physician sees that the problem is inflammatory in its etiology. This correct diagnosis is a necessary component of selecting appropriate treatment for the extraintestinal manifestation.

It is more common to have a diagnosed bowel disorder before extraintestinal manifestations arise. However, there are cases in which a patient has mild bowel symptoms but has come to the doctor for a different reason. If IBD is on the physician's differential diagnosis, then he or she will likely ask whether the patient is experiencing any bowel discomfort. An endoscopic evaluation then reveals the bowel inflammation.

G&H What are the rates of occurrence of these different manifestations?

ML A paper by Vavricka and colleagues in the *American Journal of Gastroenterology* examined the prevalence of extraintestinal manifestations among individuals in the Swiss Inflammatory Bowel Disease Cohort Study. Arthritis occurred in approximately one-third of patients with Crohn's disease. Approximately 20% of patients with ulcerative colitis had arthritis.

Other manifestations occurred less frequently. The rate of oral ulcerations ranged from 4% to 10%, as did the rate of skin manifestations. Primary sclerosing cholangitis was less common, occurring in approximately 1% to 4% of individuals with IBD.

In general, these manifestations were more common among patients with Crohn's disease than among patients with ulcerative colitis, with the exception of primary sclerosing cholangitis, which was seen more often with ulcerative colitis.

G&H Why are these particular manifestations linked to IBD?

ML We do not know why these specific manifestations occur with IBD. The underlying mechanisms have not been elucidated. Most likely, a systemic immune system response

causes the arthritis as well as the skin and eye issues. When we treat IBD with proper medications, the extraintestinal manifestations improve as well.

Primary sclerosing cholangitis seems to be a separate autoimmune disorder that is not caused by the same systemic inflammatory response that is linked to IBD.

G&H Can extraintestinal manifestations of IBD be treated in the same way they would be if they occurred on their own?

ML No. It is important to recognize that these manifestations should not necessarily be treated with traditional therapies. If someone has arthritis, it is natural for that person to consider taking ibuprofen or another anti-inflammatory medication. However, these drugs can be very irritating to the lining of the gastrointestinal tract and may even cause a flare of the underlying IBD.

Treatment for extraintestinal manifestations of IBD should focus on medications that are used primarily to treat bowel inflammation. Acetaminophen and similar drugs can help relieve joint pain in the short term, but pain medications do not treat the underlying inflammation. Once the bowel inflammation is treated with appropriate medications, often the arthritis resolves as well.

G&H Are some patients with IBD more susceptible than others to extraintestinal manifestations?

ML There are not any well-defined subgroups of patients who are more at risk for extraintestinal manifestations. Patients with colonic inflammation may have a higher incidence of some complications, but the difference is not dramatic. Extraintestinal manifestations can be associated with subsequent flares in a patient with IBD, but this is not always the case.

G&H Is it important to diagnose these extraintestinal manifestations if they tend to resolve when the underlying IBD is treated?

ML Yes, it can be. As mentioned earlier, sometimes the bowel inflammation is in remission but the extraintestinal manifestations are still active. In addition, unfortunately, not all extraintestinal manifestations respond to traditional IBD therapy.

For example, pyoderma is characterized by deep red ulcers with sharply defined borders that are extremely painful. The best treatment for these ulcers is an anti–tumor necrosis factor (TNF) drug. This class of medications is the only one that has shown efficacy in a randomized clinical trial. A study by Brooklyn and colleagues (published in *Gut* in 2006) that investigated infliximab (Remicade, Janssen) for pyoderma demonstrated a superior clinical response compared with placebo (46% vs 6%) among 30 patients.

However, a 46% response rate means that many patients do not benefit from infliximab, and many other immunosuppressive therapies are therefore also used to treat the extraintestinal manifestation. Other treatment options can include specific antibiotics, corticosteroid injections at the area of the ulcer, and even hyperbaric oxygen. Pyoderma is painful and negatively impacts quality of life, and sometimes it can be more difficult to treat than the underlying bowel inflammation. Therefore, it is definitely important to make these diagnoses and treat the extraintestinal manifestations appropriately.

G&H Are extraintestinal manifestations of IBD underrecognized by clinicians?

ML I think so, particularly some of the skin manifestations. It is important to recognize that skin conditions stemming from IBD can take on a wide range of appearances. Cutaneous skin manifestations of Crohn's disease can appear very different from one patient to the next. It is important to be aware of the whole range of potential systemic complications. Prompt referral to a dermatologist and a biopsy of the lesion are usually the next steps. These steps can be crucial in the management of extraintestinal manifestations. Although therapies targeting the bowel inflammation may help, other add-on therapies targeting the skin manifestation itself may need to be employed.

G&H Would a patient with an eye manifestation be referred to an ophthalmologist?

ML Yes. For episcleritis and other forms of eye inflammation, it is important to have an ophthalmologist involved in patient care. Often, the patient needs not only systemic treatment but also therapy specifically for the eye condition, such as topical corticosteroid eye drops. If some forms of eye inflammation are not treated appropriately, the patient may suffer vision loss or other issues.

Treating IBD requires a multidisciplinary approach. As someone who treats IBD, I often work with ophthalmologists for eye conditions, dermatologists for skin manifestations, rheumatologists for joint manifestations, and hepatologists for the biliary tract disease resulting from primary sclerosing cholangitis. Patients need this multidisciplinary, collaborative care because of the systemic nature of the inflammation.

G&H Can permanent damage result if certain extraintestinal issues are not resolved?

ML In some instances, yes. Still, the first step is usually to treat the IBD with appropriate medical therapy. Then,

if the extraintestinal manifestations do not improve, additional treatments can be introduced. The exception is eye inflammation, which needs to be evaluated quickly. There are many different types of eye inflammation seen with IBD, and appropriate management is crucial for preventing long-term consequences.

G&H If the eye inflammation occurred before IBD was diagnosed, would an ophthalmologist consider the possibility of IBD?

ML Yes. In one case, I had a referral from an eye doctor who had prescribed corticosteroid drops to treat a patient with episcleritis. The inflammation would get a bit better, but not really improve. Over the course of several months, the patient mentioned that he was experiencing gastrointestinal symptoms, and the doctor referred the patient to me. I diagnosed the patient with Crohn's disease and prescribed systemic therapy. The active bowel inflammation from Crohn's disease and the episcleritis both resolved with systemic medical therapy. The patient has not experienced a recurrence.

Sometimes, the initial referral will come from a dermatologist or even a gynecologist because many skin lesions can occur labially or in the perianal region in women with IBD.

G&H What are the most pressing research needs in this area?

ML It would be helpful to know specific risk factors and specific prognostic factors associated with response to various medications. As mentioned earlier, our best data on the treatment of pyoderma show a response rate of 46% to anti-TNF medications. For patients who do not respond, physicians cycle through other treatment options, some of which can have significant complications. If there were specific factors (whether genetic or clinical) that predicted a response to certain classes of medications, we could choose medications more effectively.

Research in this field is making headway. A few genetic factors have been linked to pyoderma and erythema nodosum. However, there is no commercial assay to check for these variants.

G&H Do you advise patients to be on the lookout for extraintestinal manifestations?

ML Yes. Education is a very important tool here. When a patient is newly diagnosed with IBD, I inquire about any previously experienced extraintestinal manifestations. Many patients note such issues but had never made the connection to IBD. Even when there is no prior extraintestinal manifestation, I discuss the possible signs so that patients know to call me if they arise. This counseling is very useful because when issues do occur, patients know to call, and then the problem can be resolved efficiently.

G&H Has there been a change in the incidence of extraintestinal manifestations over the years?

ML I think there is a detection bias that has led to a greater number of diagnoses. We do not have a time-trend study, but anecdotally I think we are seeing more of these extraintestinal manifestations. How much of this increase in the number of cases of extraintestinal manifestations is related to rising incidence, vs improved awareness on the part of physicians, is unknown.

G&H Can some IBD medications also cause extraintestinal side effects?

ML Yes. We consider these issues under a separate umbrella. Therapy-induced complications can manifest in the skin, for example. One example is psoriasis, which can occur as a result of anti-TNF medications. For the most part, the psoriasis can be managed with topical agents, and the primary anti-TNF therapy can be continued. However, sometimes the anti-TNF agent needs to be stopped in order to resolve the skin lesions. Additionally, some therapies, such as azathioprine and anti-TNF agents, are associated with an increased risk of nonmelanoma skin cancer. Anti-TNF agents also are associated with an increased risk of melanoma. For these reasons, I counsel patients using these medications to wear sunscreen and have dermatologic evaluations. It is important for clinicians to be aware of these problems, too, and to differentiate them from the extraintestinal manifestations resulting from the IBD itself so that appropriate treatment can be provided.

Dr Long has served as a consultant for AbbVie, Salix, and NPS Pharmaceuticals.

Suggested Reading

Brooklyn TN, Dunnill MG, Shetty A, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut*. 2006;55(4):505-509.

Isene R, Bernklev T, Høie O, et al; on behalf of the EC-IBD Study Group. Extraintestinal manifestations in Crohn's disease and ulcerative colitis: results from a prospective, population-based European inception cohort [published online December 23, 2014]. *Scand J Gastroenterol*. doi:10.3109/00365521.2014.991752.

Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology*. 2012;143(2):390-399.e1.

Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol*. 2011;106(1):110-119.

Weizman AV, Huang B, Targan S, et al. Pyoderma gangrenosum among patients with inflammatory bowel disease: a descriptive cohort study. *J Cutan Med Surg*. 2014;18(5):361.