IBD LIVE Case Series: Case 10: Out of Sight, Out of Mind; Ocular Complications of Inflammatory Bowel Disease

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Abbreviations: NSAIDs = non-steroidal anti-inflammatory drugs; MRI = magnetic resonance imaging
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LEARNING OBJECTIVES
After completing this IBD LIVE activity, physicians should be better able to:

1. List common ocular extraintestinal manifestations of inflammatory bowel disease (IBD).
2. Describe which ocular extraintestinal manifestations are more likely to occur in patients with Crohn’s disease or ulcerative colitis and which parallel IBD activity.
4. Describe ocular conditions that are associated with medications used to treat IBD.
5. Designate which ocular conditions are most likely to threaten vision.
6. List various types of infectious agents that can cause ocular disease.
7. Convey the predominant means of transmitting Toxoplasma and know which forms of transmission are more common in developed versus developing countries.
8. Characterize which cohorts of the population are at greatest risk for serious infections with Toxoplasma.
9. Recount the medications that may be part of a treatment regimen for toxoplasmosis and know which medications are included in classic triple therapy.
The patient is a 22-year-old Caucasian male who was initially diagnosed with chronic colitis about 3 years ago. At that time, he presented with abdominal pain and diarrhea, and demonstrated mainly proctitis symptoms. Initially, he had a flexible sigmoidoscopy at an outside facility that showed severely inflamed rectal mucosa. The scope was not advanced very far because of the severity of disease. Biopsies that were taken at sigmoidoscopy showed active inflammation, chronic architectural changes and some granulomas. Subsequent computed tomography (CT) enterography suggested that there was ileal inflammation so the thought was that the young man had ileocolonic Crohn’s disease. The patient continued to have significant proctitis symptoms despite receiving several courses of prednisone and bidirectional mesalamine therapy.

When he came to his initial visit at our institution, he was complaining of a recent change in his bowel habits, stating that he now was constipated instead of having loose stools. Review of symptoms was negative for fever, chills, nausea, vomiting, night sweats, and unintentional weight loss. When asked about potential extraintestinal manifestations, he mentioned having bilateral knee discomfort that he attributed to his job as a chef, where he stands for long periods of time. He was not using NSAIDs on a regular basis. His past medical history included only his
Crohn’s disease and he had a negative surgical history. Family history included multiple second and third degree relatives with inflammatory bowel disease and an aunt who died of lymphoma at age 17. His social history was positive for occasionally smoking cigars and drinking alcoholic beverages. He mentioned having an allergic reaction to amoxicillin that manifested as hives. At his initial visit to us, his daily medications included mesalamine 2.4 grams and 9 mg of oral budesonide (Entocort EC).

On physical exam, the patient looked well. He had anicteric sclera and was not jaundiced. There was no evidence of lymphadenopathy and his cardiac and lung exams were benign. On abdominal exam, he had normoactive bowel sounds. On perianal inspection, there was no evidence of current or previous perianal disease. However, on rectal exam, he did have an appreciable, very tight stricture about 2 or 3 cm from the anal verge. The patient came to see us as part of a combined visit with the colorectal surgeons. After he saw us, he went to the proctoscopy room to be evaluated. The surgeons observed the tight stricture and some anorectal inflammation. Later that day, he went to the operating room where the surgeons dilated his rectal stricture and took multiple biopsies. They appreciated an approximately 3 cm fibrotic-type stricture. Biopsies were consistent with Crohn’s disease, showing chronic inflammation but no evidence of dysplasia.

After discussing treatment options with the patient, he was initiated on infliximab monotherapy. Prior to starting infliximab, the patient was tested for latent tuberculosis and his hepatitis B serologies were checked. We then scheduled him to have a colonoscopy because he had never had a full endoscopic exam. We
also ordered a magnetic resonance enterography. Thereafter, we went through our regular healthcare maintenance checklist. The patient had a bone densitometry scan because of his previous prednisone use. We discussed smoking cessation and we reviewed his vaccinations, all of which were up-to-date.

Some images were taken during the patient’s colonoscopy. There is a photo of his ileocecal valve, where you can see that he has a tight stricture (Fig. 1). The valve could not be traversed but it was biopsied. We were able to get the scope up and through the stricture far enough to obtain a porthole view of the terminal ileum and there was one ulcer evident (Fig. 2). There is also a photo of the rectum (Fig. 3) and another one that shows the tight rectal stricture (Fig. 4). Following surgical dilation, a pediatric colonoscope could be passed through the rectal stricture. Pathology read these biopsies as showing chronic active ileitis, with the rectum showing focal active proctitis with no dysplasia.

We had a number of discussions with the patient regarding the best way to manage his rectal stricture. In a multi-disciplinary fashion, we also met with the colorectal surgeons and there was talk of potentially getting a diverting loop ileostomy while we treated him medically. Using shared decision-making, the patient ultimately decided to perform periodic self-dilatations. He was taught how to self-dilate and, at follow up visits, he was doing very well with. He was very happy with his medical therapy and with doing self-dilations. However, unbeknownst to us, while we assumed that he was continuing to be well, he developed an upper respiratory tract infection (URI) and saw his primary care provider. We learned that he had been having fevers for a few weeks and had been started on antibiotics.
He never alerted us to this, which was frustrating because we always tell our patients, particularly those on anti-TNFs, to give our office a call if they get any type of infection. Initially, the patient’s URI symptoms improved but did not go away completely and he starting having some issues with his vision. He noticed flashes and floaters as well as a blind spot. He lived with these problems for a week or so until he mentioned it to his mother and she encouraged him to get a medical evaluation. He then came to our attention at the Emergency Department of Penn State Hershey.

I have a photo of our patient taken in the Emergency Department when he presented complaining of problems with his vision, including a blind spot. You can see that his left eye is particularly red and injected (Fig. 5). He had a visual exam that showed mildly decreased visual acuity in the left eye (20/25 vs. 20/20 in the right eye). In terms of his visual fields, there was a small inferonasal scotoma in left eye. He had a full evaluation from a retinal specialist who noticed inflammatory changes in both eyes. In the right eye, there was some subretinal whitening and in the left eye, there was a subretinal white lesion with subtle retinal whitening just temporal to this area. The retinal specialist’s impression was that the patient had bilateral panuveitis with whitish subretinal fluid. At this point, I’d like to ask people what their thoughts are regarding this patient and what they think these eye lesions might represent?

Dr. Miguel D. Regueiro (Gastroenterology, University of Pittsburgh)

Andrew, first of all I’d like to thank you for always teaching us new
vocabulary words. You should copyright the term bidirectional mesalamine.

Dr. Andrew Tinsley (Gastroenterology, Penn State Hershey)

Yes, it's a term I use a lot, meaning concurrent use of both oral and topical mesalamine. The two of them together are typically more effective than either one alone for distal colonic inflammation.

Dr. Miguel D. Regueiro (Gastroenterology, University of Pittsburgh)

So the presentation starts off with what seems to be a bread and butter IBD case until there’s a twist when we come across the eye findings. To summarize, this is a young man that initially presented with symptoms of proctitis followed by a change in bowel habits to constipation. He then had some testing done and was shown to have a rectal stricture and some rectal inflammatory changes. He had biopsies taken that showed granulomas in the rectum but on colonoscopy, as well as radiographically, he has what appears to be a stricture at the ileocecal valve with terminal ileal disease.

In regards to his gastrointestinal disease, it sounds as though he has done reasonably well on infliximab monotherapy. The case really seems to begin with what seems to be an upper respiratory infection. He had some lingering fevers but now what seems to be the problem, based on the photos, is obvious eye redness. I’m not an ophthalmologist but I’m just saying what I see. The ophthalmologist’s diagnosis in the Emergency Department was that he had a bilateral uveitis-like picture. We have a lot of sites participating in this conference but let’s go to our
clinicians at Emory first. Robin, what are your thoughts, particularly pertaining to these eye findings?

Dr. Robin E. Rutherford (Gastroenterology, Emory University)

We are thinking that it's probably something viral or perhaps even fungal. A thrombotic manifestation was in my differential until we got to the bilateral uveitis and the conjunctival injection. Now I think it's less likely to be something thrombotic. Initially, I would have put that on a differential because I've seen a few patients that present with some very strange thrombotic phenomenon. This young man's problem seems to be infectious, particularly considering the upper respiratory illness. We think of the herpes virus family; all of them would be in the differential, particularly cytomegalovirus. In young people, I think we have to add herpes simplex to that because it can disseminate whenever patients are taking an anti-TNF. The scotoma in particular made me worry about fungal diseases, such as histoplasmosis. There are a number of other entities that we could list.

Dr. Miguel D. Regueiro (Gastroenterology, University of Pittsburgh)

So initially there were concerns about his visual changes and the visual loss that might be some sort of thrombotic event. But, as you mentioned, this is a young man on infliximab who has had fevers. You're listing an infectious etiology that includes both viral and fungal pathogens and some of these entities might be opportunistic infections. Our colleagues at Maryland, what are your thoughts?
Dr. Raymond K. Cross (Gastroenterology, University of Maryland at Baltimore)

Well, initially when you were talking about the visual issues, I was thinking about some sort of autoimmune phenomenon like multiple sclerosis related to the anti-TNF. Given the patient's ocular findings, that's much less likely. From my days on the Infectious Disease wards about 19 years ago, I know that these white exudates can be a sign of fungal infections. So I agree with Robin. I would have opportunistic infections on my differential. The other intriguing thing is the uveitis. Anti-TNFs should work very well for that so the fact that he has developed uveitis while on the anti-TNF is quite interesting. I have never looked at drug levels and antibodies when we’re dealing with extraintestinal manifestations but I wonder if his dose is inadequate. Obviously, once you have ruled out or taken care of the infection, if you are able to check levels and dose escalate, you might be able to get some of the uveitis symptoms to resolve. If there are antibodies present, then you could switch to another agent.

Dr. Miguel D. Regueiro (Gastroenterology, University of Pittsburgh)

Okay, so you're confirming the concern about infection and the uveitis brings up the possibility of an IBD-related problem although it would be a little bit unusual given that he is on infliximab. Nonetheless, you're wondering if maybe drug levels are low and this is the first manifestation of an extraintestinal eye problem. But I think that you're still worried about the infliximab and infection. Let's go to our clinicians at Dartmouth and I'd like you to address something that we are sometimes asked. Say that this young man's infusion is due tomorrow and his
gastrointestinal symptoms are fairly well controlled but we have this curveball of a possible infection. Do we hold the infliximab? Do we give the infliximab? Let’s get your thoughts about this case and the eye manifestations but also, what would you do about the infliximab in the near term?

Dr. Corey A. Siegel (Gastroenterology, Dartmouth)

This is a concerning and interesting case. I don’t think that we’ve seen something exactly like this before. I agree with all of the worries about infection. He is a young male receiving therapy that we know can increase the risk of lymphoma, and we think that he has a family history of lymphoma. We should consider something going on in the central nervous system (CNS) with the worry of both infection and potentially some malignancy. It would be a good idea to scan his brain to make sure that we’re not missing something beyond the eye proper. We probably still have more to learn about these medications. If we had a conversation like this about new onset psoriasis 10 years ago, we all would’ve said that it was strange to get psoriasis while on anti-TNFs, since anti-TNFs treat psoriasis. But we learned over time that this indeed is an adverse event related to anti-TNFs. Just based on the time course in this case, although we haven’t seen this before, I do wonder if this could be a reaction to the infliximab rather than due to not enough infliximab.

I think that following up on the infection clearly needs to be number one. It would be very unusual for him to have a malignancy. However, one of the first malignancies reported with anti-TNF use was a CNS malignancy, so I believe it is worth considering imaging if you can’t identify an infection. Overall, I’m favoring
that this is a reaction to anti-TNFs as opposed to not giving enough anti-TNF. To specifically answer your question about whether the patient should get an infusion if he were coming in tomorrow, I would hold the infusion. I don’t know what is causing this young man’s visual issues but visual loss is a serious and potentially permanent problem. I don’t think that I would take a chance and say, ‘Well, it’s from not giving enough infliximab, so we better give him some more,’ given that this is a first time ocular finding in a patient with inflammatory bowel disease. I would hold off for now and gather a little more information before I give him another infusion.

Dr. Miguel D. Regueiro (Gastroenterology, University of Pittsburgh)

Our differential has expanded. I’ll keep it going and ask our colleagues at Yale and Boston and then our pediatric gastroenterologists in that order. Corey raised two other interesting possibilities. One was whether this might be an infliximab-type reaction. This isn’t something that we’ve seen before but as Corey and Ray mentioned, having uveitis occur in the setting of infliximab is unusual although the same psoriasis story has been out there. And while it might be hard to draw a parallel to this, the question is whether we are going to start seeing some type of manifestation such as this ocular issue that might be anti-TNF mediated. Finally, the idea about lymphoma was raised. Andrew, we can get back to you to answer the question of whether this patient has had a scan of his brain. Let’s go to Yale and then Boston and get your thoughts.
Dr. Myron H. Brand (Gastroenterology, Yale)

We really do not have much to add to what has already been said. After I heard about the scotoma, I wondered about whether the patient might have something like an optic neuritis secondary to the infliximab. I think that the differential has been covered quite well and I don’t have anything else to add at this time.

Dr. Francis A. Farraye (Gastroenterology, Boston Medical Center)

We don’t have much else to add. We would certainly be worried about an ocular fungal infection. Again, in terms of a patient newly diagnosed with rapidly progressive rectal disease who had a very short duration of bowel disease, I wonder if we could be missing the boat. Is it possible that he has a primary infection that involves the gut that was made worse by the anti-TNF? It’s just a thought. However, it does seem that his diagnosis of Crohn’s disease was well established. We would absolutely hold the infliximab and get an MRI scan and some input from neurology and ophthalmology.

Dr. Miguel D. Regueiro (Gastroenterology, University of Pittsburgh)

Why don’t we go to one of our pediatric gastroenterologists and then perhaps back to Hershey for some answers to this patient's problems. So, Alka, do you think that we missing anything regarding this patient?

Dr. Alka Goyal (Pediatric Gastroenterology, Children’s Mercy Kansas City)
I don't think so. I was just doing a literature search and there was a case report that describes infliximab-induced anterior uveitis in a patient with ulcerative colitis.\textsuperscript{1} They treated the patient with topical steroids. Of course, the patient that was presented today demonstrates more findings than just anterior uveitis so we are leaning towards thinking that he has an infection.

Dr. Miguel D. Regueiro (Gastroenterology, University of Pittsburgh)

Alka, you're cheating by using Google and other web search tools, but that's okay because it's what we all do. Andrew, why don't we return to you so you can share the continuation of the case?

Dr. Andrew Tinsley (Gastroenterology, Penn State Hershey)

Everyone did a great job with the differential and introduced many things that we thought of and a few that we did not. At this point, it's a good idea to mention some of the patient's additional, pertinent history that was elicited by the Infectious Disease consultants. We discovered that the patient's mother had a history of histoplasmosis. His maternal grandfather had been diagnosed with chronic ocular toxoplasmosis. He had a paternal grandmother with multiple sclerosis and, as previously mentioned, his maternal aunt died of lymphoma at age 17. The patient also reported that he just moved to a new apartment that he shares with 3 roommates and they have a "big mold problem." Additionally, they have a new cat. Being a chef and an avid hunter, the patient also reports that he both handles and eats lots of raw fish and meat. He does not have any significant travel
history and reports no high-risk sexual behaviors.

As part of his continued workup, he went to the operating room and underwent vitreous sampling. A number of tests were run on those samples. He also underwent a brain MRI to look for more systemic signs of infection or any brain findings beyond the ocular issues, such as lymphoma. He had a number of labs sent, including blood cultures, HIV, urine histoplasmosis/blastomycosis, serum cryptococcal antigen, cytomegalovirus (CMV) polymerase chain reaction (PCR), and serology for herpes simplex virus 1 and 2, varicella zoster virus, coccidiomycosis and toxoplasmosis. He had positive toxoplasmosis IgG and IgM and also had a positive toxoplasmosis PCR from his vitreous sampling. His final diagnosis was bilateral ocular toxoplasmosis, which is quite interesting but given the information that I just shared, it might not be that surprising.

In summary, the patient has been diagnosed with toxoplasmosis and has been treated. He is getting a little bit better although our Infectious Disease team has needed to adjust his toxoplasmosis medications a few times. However, he still has the ileoanal Crohn's disease with a stricture. Moving forward, my question would be how should we proceed with a symptomatic patient whose ocular infection is slowly getting better but still requires some form of immunosuppressive agent for his bowel disease?

Dr. Miguel D. Regueiro (Gastroenterology, University of Pittsburgh)

Andrew, that's very interesting. I'm not sure that I would have thought of toxoplasmosis. The family history and the new pet cat might have been factors that
helped to figure this out. The question that I would like to pose to the group is how would you treat someone that has toxoplasmosis of the eyes who is on infliximab, still with significant IBD? David Binion, what are your ideas?

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

As far as I know, this case has few precedents. Systemic immunosuppression with an agent such as an anti-TNF is going to be a problem for this patient for at least a few months, maybe even for as much as a year. Given the need for immune function to handle the infectious complication, I don’t think that continuing infliximab is a viable option.

We don’t have a wealth of information on the emergence of opportunistic infections amongst large groups of patients on biologic therapy, outside of the original New England Journal of Medicine article that identified reactivation of tuberculosis. If we look at the rheumatologic literature originating from places like South Korea where latent tuberculosis is very common compared to North America and Western Europe, we can identify patterns of infections in response to various immunomodulators and biologic agents. You see the highest rates of infectious complications in patients with rheumatologic problems taking infliximab compared to the other agents such as a subcutaneous anti-TNF or methotrexate.

If we just step back and think about the various biologic agents, infliximab is very powerful but you may pay a price for this potency in the form of higher rates of infectious complications from an anti-TNF. Now, a selective agent that targets the gut would be vedolizumab, which might emerge as a better choice for your patient.
Granted, it is not the most powerful drug for his Crohn’s disease but it might be a better medicine for somebody that may not tolerate systemic immunosuppression due to infectious complications. I don’t know if mucosal addressin cell adhesion molecule 1 (MAdCAM-1) is being expressed by microvascular endothelial cells in any of the areas that are currently affected by toxoplasmosis, but I would doubt it. Based on vedolizumab’s selective inhibition of alpha4 beta7 integrin, the ligand for MAdCAM-1, it should not impact migration of lymphocytes entering the CNS and should not worsen the infection with toxoplasmosis. This is in contrast with natalizumab, which blocks both alpha 4 beta 1 and alpha 4 beta 7 integrins, which will impact CNS leukocyte trafficking and potentially would worsen the CNS infection with toxoplasmosis. However, the number one priority in this patient is treating the toxoplasmosis. If you are concerned that the reduction in immunosuppression may precipitate a significant deterioration of his Crohn’s disease, then I would probably talk to your Transplant Immunology or Transplant Infectious Disease colleagues and ask for their guidance. Our colleagues in solid organ transplantation cannot withdraw systemic immunosuppression for a lung transplant patient in the setting of opportunistic infection, and will frequently need to treat infections while simultaneously preventing allograft rejection. Our colleagues in transplantation are an excellent resource, as are frequently challenged with these types of clinical dilemmas.

Dr. Miguel D. Regueiro (Gastroenterology, University of Pittsburgh)

Andrew, before I turn back to you for the wrap up, why don’t we let a few of
our participating physicians comment on their ideas. Alka Goyal, what do think?

Dr. Alka Goyal (Pediatric Gastroenterology, Children’s Mercy Kansas City)

At this point, I think that decreasing immunosuppression would be a key treatment strategy. Could you consider doing a diverting ileostomy and continue with the self-dilations? If he is given an ileostomy but does not continue with the dilations, the stricture will get worse. I would also suggest using minimal immunosuppression, perhaps in the form of methotrexate if it’s not contraindicated in this case, to help keep him in some type of remission while you treat the toxoplasmosis.

Dr. Miguel D. Regueiro (Gastroenterology, University of Pittsburgh)

So surgery comes up and my sense is that he has significant ileal and rectal disease. Diverting him might be an option but my thought is that, from a gastrointestinal standpoint, clinically he is doing okay. You might have to first resect his ileum and then divert him so that’s a possibility. Methotrexate, if we get into leucovorin, with other folate antagonists, might be an issue. And I see our surgeon Wolfgang Schraut standing up at the back of the room, which is making me anxious. Dr. Schraut, would you like to offer an opinion?

Dr. Wolfgang H. Schraut, MD (Surgery, University of Pittsburgh)

If you divert him, he will never be taken down because his rectum will shut down. Treating him with infliximab right now might be helping his ileal disease but
you’re not doing anything for his rectal disease. And if you have guided him to do self-rectal dilatations, that is marvelous. That will solve that problem, probably. I would just resect the guy and forget the infliximab and just move on because you’re treating a disease that, in the end, you will not be able to influence. No matter how long you give him infliximab or any other anti-TNF medication, his rectal disease will never go away. Why are you treating established hyperstenosing rectal disease with a TNF antibody anyway? It will not work. It may postpone an operation but it will not obviate the need to fix the problem.

Dr. Miguel D. Regueiro (Gastroenterology, University of Pittsburgh)

Like a proper surgeon, Wolfgang is focusing on when he’ll need to operate on this patient and questioning the effectiveness of his medical therapy. About a decade ago, we worried that anti-TNFs could precipitate the formation of strictures and cause intestinal obstruction. The current consensus is that anti-TNFs are unlikely to be of benefit when there’s an established stricture. That said, the main function of the biologics is to decrease inflammation and improve intestinal healing, which might lessen the probability of new stricture formation. Andrew, why don’t you provide us with some follow-up on your patient?

Dr. Andrew Tinsley (Gastroenterology, Penn State Hershey)

Since the end of this presentation, the Infectious Disease specialists and the ophthalmologist have become more involved with this patient’s care. Strangely enough, theoretically they were initially okay with concurrent anti-TNF
immunosuppression in combination with treatment for his toxoplasmosis in the form of chronic trimethoprim/sulfamethoxazole or something similar. However, the young man’s eye problems did not completely improve and I was not comfortable with continuing infliximab. What we chose to do is to have him continue with the periodic self-dilations of his rectal stricture and we switched to vedolizumab for the reasons that David Binion mentioned. He will stay on the trimethoprim/sulfamethoxazole to try to decrease the risk of having a recurrence of the infection. As of now he’s doing well. The thought is that the vedolizumab will help with his ileal disease and, hopefully, will be a safer medication choice for him particularly since his ocular toxoplasmosis is still not completely better.

**DISCUSSION**

Eye problems are routinely encountered in patients with Crohn’s disease and ulcerative colitis. Ocular disease may be described as primary or secondary in nature, with primary ocular ailments being an extraintestinal manifestation of inflammatory bowel disease (IBD) while secondary ocular issues often occur as a consequence of treatment. Primary ocular manifestations of IBD characteristically present as inflammation localized to one or more structures of the eye. Although as many as one-third of individuals with IBD will exhibit extraintestinal manifestations, ocular manifestations are less common, occurring in only 4% to 12% of IBD patients. Ocular manifestations often coincide with extraintestinal manifestations of the joints and skin and they occasionally precede the diagnosis of
IBD. A basic understanding of the components of the eye helps to understand ocular findings and facilitate discussions with eye specialists (Fig. 6, Table 1).

Non-Infectious Ocular Disease

The cornea is not frequently affected in IBD patients although keratopathy, a non-inflammatory condition of the cornea, may be a complication of problems in other parts of the eye and can lead to corneal ulcerations and keratinization. Patients with keratopathy often complain of eye pain and irritation and feeling as though there is a foreign body in the eye. On exam, small grayish-white infiltrates can be seen on the cornea. The lesions are often bilateral and will not compromise vision unless they occur in the center of the cornea. Keratopathy due to lipid malabsorption and subsequent vitamin A deficiency may impact vision, particularly at night.

Episcleritis is the most common extraintestinal manifestation of IBD. The episclera is a thin, loose connective tissue layer beneath the conjunctiva with a rich blood supply. Episcleritis is usually a benign cause of redness of the eye that may be accompanied by mild eye soreness or discomfort, typically without changes in vision. Episcleritis may be localized or diffuse and usually parallels IBD activity. The sclera is the avascular, "white" of the eye that is composed of dense collagen fibers, receiving its nourishment from the episclera above it and the choroid plexus below it. Scleritis is an ocular inflammation that characteristically presents with dull or aching pain, photophobia, double vision, and increased tearing. Scleritis is about twice as common in women than in men and may
precede the diagnosis of IBD. While episcleritis and scleritis are similar sounding terms, scleritis is a more serious condition that may lead to complications, including uveitis, ulcerative keratitis, and diminished vision. Treatment with cool compresses or corticosteroid eye drops is typically effective for episcleritis while scleritis almost always requires systemic treatment in the form of NSAIDs, oral corticosteroids, or immunosuppressive agents in addition to corticosteroids.

The term uveitis describes a heterogeneous group of diseases characterized by inflammation of intraocular structures. Uveitis is a substantial cause of blindness worldwide. Uveitis can be classified into different types based on the affected structures of the uvea (Table 2). Uveitis is less common amongst IBD patients than episcleritis and scleritis. While episcleritis and scleritis have a stronger association with Crohn’s disease, uveitis is more frequently observed in patients with ulcerative colitis. Females are at greater risk of developing uveitis than males and it often does not coincide with IBD activity. The presentation of uveitis often includes pain that develops steadily over the course of a few hours to days, redness, photophobia, blurred vision, and increased tearing. Uveitis may also be asymptomatic, particularly in younger patients.

Anterior uveitis, particularly iritis, has been associated with HLA-B27. Therefore, IBD patients that develop acute anterior uveitis may have other illnesses associated with B27, such as ankylosing spondylitis and peripheral or psoriatic arthritis. There should be a high degree of suspicion that a patient has uveitis if he or she has characteristic insidious eye symptoms and concomitant joint complaints. Posterior uveitis is less common than anterior uveitis as an
extraintestinal manifestation of IBD but uveitis that involves the posterior segment is more likely to impact vision.4

Less common ocular presentations in IBD include retinal vascular disease, which can be subclinical in nature or present acutely as an arterial or venous occlusion.28, 29 Disorders in immune-regulation, inflammatory response, or coagulation may play a role in retinal vasculitis.30 Orbital inflammation (orbital pseudotumor) and acute inflammation of the optic nerve (optic neuritis) are two other rare extraintestinal manifestations of IBD that can endanger vision.31 There is no agreement regarding treatment of these entities, outside of systemic corticosteroids.32 For any of these rare ocular presentations, consultation with an ophthalmologist is imperative to determine the best course of treatment.

Ocular symptoms can be non-specific in nature and are not always indicative of eye inflammation.6, 33, 34 For example, in a cross-sectional survey of 305 IBD patients (228 with Crohn’s disease), 32% reported having at least one eye symptom, such as eye irritation, eye redness, and blurred vision; by ophthalmologic exam, the most frequent finding was dry eye.33 A community-based, prospective cohort study noted that IBD patients were significantly more likely to report ocular symptoms than controls, particularly dry eye, which was corroborated on ophthalmologic exam.35 In this study, the use of 5-aminosalicylate medications was significantly associated with dry eye in IBD patients.

Secondary ocular problems arising from IBD treatment are not uncommon. A number of medications are known to affect the eye.7 For instance, long-term use of
glucocorticoids can cause cataracts as well as steroid-induced glaucoma.\textsuperscript{36,37} Ophthalmologic toxicities linked to the use of cyclosporine include ophthalmoplegia, nystagmus, and optic neuropathy that may lead to optic atrophy and visual loss.\textsuperscript{38} Conjunctivitis is a rare adverse reaction to 5-aminosalicylates (mesalamine).\textsuperscript{39} There have been case reports in which IBD patients on infliximab or adalimumab developed optic neuritis.\textsuperscript{40,41} Patients taking more potent immunosuppressants are at risk of developing lymphoma, which infrequently may extend into the eye, particularly the orbit.\textsuperscript{42} Lymphomas seem to show the greatest association with combined therapy of an immunomodulator and an anti-TNF.\textsuperscript{43,44}

**Infectious Ocular Disease**

Many types of pathogens affect the eye (Table 3). Some highly contagious infections, such as conjunctivitis, are caused by viruses or bacteria and are not specific to IBD patients. Conjunctivitis may be more likely to occur in children or young adults that are often in group settings (e.g. day care, dormitories). Disseminated infections with the parasites Baylisascaris procyonis (raccoon roundworm) and Toxocara canis (canine helminth) can cause chorioretinitis, even in immunocompetent individuals.\textsuperscript{45-47} Potent biologic and immunomodulator medications increase the risk of infections in IBD patients.\textsuperscript{48-50} Patients with severe immunodeficiencies and those taking immunosuppressants for a sustained period of time have been noted to develop ocular diseases such as chorioretinitis due to opportunistic infection with cytomegalovirus (CMV), Epstein-Barr virus, herpes zoster, varicella zoster, fungi such as *Aspergillus fumigatus* and *Candida albicans*,


bacteria (*Chlamydia trachomatis*), mycobacteria (mycobacterium tuberculosis), and parasites such as *Toxoplasma gondii*.

In a combined study involving a community-based comprehensive ophthalmologist practice and a hospital-based tertiary uveitis referral center, CMV retinopathy, *Toxoplasma* chorioretinitis, and HLA-B27-associated anterior uveitis were three of the five most common diagnoses.

With greater international travel, a number of novel infectious agents are now recognized as causing various types of ocular disease in human beings. Some of these entities include West Nile virus, *Borrelia* species (Lyme's disease), dengue virus, chikungunya virus, Rift Valley Fever, *Bartonella* species, *Brucella* species, and *Rickettsia* species. Many of these pathogens are better known for insect-borne illnesses that can affect animals and humans. *Rickettsia rickettsii*, for instance, is the agent responsible Rocky Mountain spotted fever in the Americas but common ocular manifestations of rickettsial disease include retinitis with retinal detachment and optic neuropathy.

Taking a detailed medical history that includes lifestyle factors and recent travel can help to elucidate the infectious agent responsible for ocular symptoms.

The patient from today's session was diagnosed and treated for ocular toxoplasmosis. Close to one-third of the world’s population has been exposed to *Toxoplasma gondii* (*T. gondii*). *Toxoplasma* is an obligate intracellular parasite, whose definitive host is the feline, the only host in which sexual reproduction takes place. If a cat eats an animal infected by *T. gondii*, the parasite may invade the cat's intestinal mucosa and form oocytes that are excreted in the cat's feces.
Intermediate hosts ingest feces-contaminated soil or water and *T. gondii* will form inactive cysts that become embedded in their muscle or brain tissue.\(^66\)

The Centers for Disease Control and Prevention describes four principal ways in which Toxoplasma can be transmitted to humans.\(^67\) Foodborne illness results from the ingestion of infected meat. In the United States, toxoplasmosis infection is most commonly associated with eating undercooked meat, often beef or pork.\(^68, 69\) Handling meat and using contaminated utensils may also lead to infection. Secondly, zoonotic transmission manifests between animals and humans, frequently when handling cat feces, such as when emptying a cat’s litter box. Waterborne toxoplasmosis infection may also come from drinking unsafe water, such as well water or unsanitary tap water, that may have come in contact with infected fecal material.\(^70\) This means of transmission tends to be observed in less developed countries as well as in Brazil, where a highly infectious serotype of *T. gondii* is endemic.\(^71-73\)

A third type of transmission may occur from mother to fetus in pregnant women because *T. gondii* can cross the placenta. There is an increased risk of spontaneous abortion and stillbirth following primary infection in pregnant women.\(^74, 75\) Congenital abnormalities from Toxoplasma often involve the brain and nervous system and may include microcephaly, cerebral palsy, deafness, and retinal damage leading to blindness.\(^74-76\) Finally, in rare instances, Toxoplasma infections have arisen in recipients of allogeneic bone marrow or solid organ transplantation.\(^77-83\) While some of these cases may have represented reactivation, seroconversion was
noted in a number of transplant recipients, representing initial Toxoplasma infection.\textsuperscript{81}

For the majority of people, toxoplasmosis is a benign infection that may be subclinical or cause mild, flu-like symptoms.\textsuperscript{84} However, Toxoplasma is a common opportunistic infection in HIV/AIDS patients, where it is associated with encephalitis in addition to other serious neurological problems as well as ocular disease.\textsuperscript{64, 76, 85, 86} The elderly, patients who use corticosteroids continuously, and those on immunosuppressants, also have an elevated risk.\textsuperscript{84} The most frequent eye problem consequent to Toxoplasma infection is chorioretinitis, also known as retinochoroiditis.\textsuperscript{72, 87} Evidence-based standards for treating ocular toxoplasmosis have not been established. Although many low-risk individuals do not require treatment, there is consensus that congenital infections, infections in pregnant women, and infections in individuals that are immune suppressed require treatment.\textsuperscript{88, 89} Classic treatment of toxoplasmosis includes pyrimethamine and sulfadiazine in addition to oral corticosteroids.\textsuperscript{90} Quadruple therapy involves the addition of clindamycin to the above regimen.\textsuperscript{91} Treatment with trimethoprim/sulfamethoxazole instead of pyrimethamine and sulfadiazine may be of equal efficacy in terms of preserving visual acuity, reducing retinal lesion size and diminishing the likelihood of recurrence.\textsuperscript{87} For patients that do not tolerate more traditional treatment, tetracycline, minocycline, azithromycin, spiramycin, and antiparasitic agents such as atovaquone have been used.\textsuperscript{92, 93} Many patient symptoms and acute eye findings, such as subretinal fluid, will resolve with treatment.\textsuperscript{94}
Ocular toxoplasmosis has a high rate of recurrence and can reactivate months or years after its primary manifestation, each time causing additional retinal damage. In a study of 59 individuals with active toxoplasmosis chorioretinitis, recurrence occurred in 10.6% at 24 month follow up. If the central structures of the retina are involved during recurrence, progressive loss of vision may lead to blindness. Recurrence is most likely to occur in the first year following the initial ocular presentation. Strategies for decreasing recurrence include intermittent or chronic prophylactic treatment with trimethoprim/sulfamethoxazole. For example, Silveira et al. recruited a total of 124 patients with a history of recurrent toxoplasmosis chorioretinitis and noted that 61 patients treated with 1 tablet of trimethoprim-sulfamethoxazole (160/800 mg) every 3 days for as many as 20 consecutive months experienced significantly fewer ocular recurrences than 63 patients that received no treatment ($P = .01$). Kopec et al. treated two immunocompetent patients, both of whom had a history of numerous toxoplasmosis chorioretinitis recurrences, with trimethoprim-sulfamethoxazole (160/800 mg) twice daily. Both patients were recurrence-free at 18-month follow up.

EDITOR’S COMMENT

Ocular complications are fairly common in IBD patients. Some complications are reflective of systemic disease and dysregulated immunity that manifests as ocular inflammation. However, not all ocular issues presenting in an IBD patients are extraintestinal manifestation. Some eye problems are a side effect of medications while others may not have an association with IBD or its treatment.
Patients taking immunosuppressive medications have an elevated susceptibility to pathogens, especially viral, bacterial, fungal and parasitic agents that cause opportunistic infections.

It is critical to determine the underlying cause of a patient’s ocular disease. Infectious etiologies require specific treatment and judicious use of immunosuppressive medications while non-infectious eye manifestations may respond to newer IBD therapies, as well as topical or systemic corticosteroids. The patient described in our conference had a URI that preceded the development of bilateral panuveitis, with some visual loss in his left eye. Although blood tests and vitreous sampling confirmed the diagnosis of ocular toxoplasmosis, taking a detailed medical history would have offered numerous clues to the source of his eye problem. Multi-disciplinary interactions with colleagues from Ophthalmology, Neurology, and Infectious Disease may be necessary to formulate treatment plans whenever ocular diseases arise in IBD patients.
**Tables**

**Table 1: Parts of the Eye and Their Function**

<table>
<thead>
<tr>
<th>Part</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cornea</strong></td>
<td>Outermost layer that covers the eye and is involved in focusing vision.</td>
</tr>
<tr>
<td><strong>Episclera</strong></td>
<td>Thin, highly vascular layer of connective tissue beneath the conjunctiva and above the sclera. Blood vessels of the episclera provide oxygen and nutrients to the sclera.</td>
</tr>
<tr>
<td><strong>Sclera</strong></td>
<td>Dense connective tissue that forms the white outer wall, covering almost the entire eye. It protects the inner components of the eye and is considered avascular although a few blood vessels pass through it.</td>
</tr>
<tr>
<td><strong>Iris</strong></td>
<td>The colored tissue at the front of the eye. Muscles of the iris control how much light enters the pupil.</td>
</tr>
<tr>
<td><strong>Ciliary body</strong></td>
<td>Between the iris and the choroid, it makes the fluid that fills the eye. It also includes the ring-shaped muscle that changes the size of the pupil and the shape of the lens when the eye focuses.</td>
</tr>
<tr>
<td><strong>Choroid</strong></td>
<td>A thin, pigmented highly vascular coat of the eye that provides the retina with oxygen and nutrients.</td>
</tr>
<tr>
<td><strong>Lens</strong></td>
<td>Transparent flexible structure behind the iris that bends light rays to form an image on the retina</td>
</tr>
<tr>
<td><strong>Vitreous humor</strong></td>
<td>Clear gel that makes up the eye's interior and helps it maintain its round shape</td>
</tr>
<tr>
<td><strong>Retina</strong></td>
<td>Layer of cells lining the back of the eye that converts light to nerve impulses that pass from the optic nerve to the brain</td>
</tr>
<tr>
<td><strong>Optic Nerve</strong></td>
<td>Cranial nerve II that carries sensory information from the ganglion cells in the retina to the brain</td>
</tr>
</tbody>
</table>
### Table 2: Classification of Uveitis

<table>
<thead>
<tr>
<th>Location</th>
<th>Area(s) Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>Iris (iritis)</td>
</tr>
<tr>
<td></td>
<td>Iris and ciliary body (iridocyclitis)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Vitreous (vitritis/pars planitis)</td>
</tr>
<tr>
<td>Posterior</td>
<td>Choroid (choroiditis)</td>
</tr>
<tr>
<td></td>
<td>Choroid and retina (chioriretinitis)</td>
</tr>
<tr>
<td>Panuveitis (diffuse uveitis)</td>
<td>Iris, ciliary body and choroid</td>
</tr>
</tbody>
</table>

### Table 3: Infectious Agents That May Cause Ocular Disease

<table>
<thead>
<tr>
<th>Infectious Agents</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td>Cytomegalovirus, Epstein-Barr, herpes zoster, varicella zoster, herpes simplex 1 and 2, West Nile, Rift Valley Fever, chikungunya, dengue</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Chlamydia trachomatis, Treponema pallidum, Brucella sp., Rickettsia sp., Bartonella sp., Borrelia sp.</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Protozoa/Parasites</td>
<td>Baylisascaris procyonis, Toxoplasma gondii, Toxocara cani, Toxocara cati, Leishmania, Plasmodium, Giardia duodenalis/lambia, Cysticercus cellulosa, Onchorcerca volvulus</td>
</tr>
<tr>
<td>Fungi</td>
<td>Aspergillus, Candida, Histoplasma, Cryptococcus, Pneumocystis, Coccidiomycosis, Blastomycosis</td>
</tr>
</tbody>
</table>

sp. = species
Figures

Figure 1. Photo taken during colonoscopy shows an inflamed, strictured ileocecal valve, with an opening that was too narrow to be fully traversed.

Figure 2. With the colonoscope providing a limited porthole view through the ileocecal valve, one ulcer is evident in the terminal ileum (outline).

Figure 3. Photo of the rectum taken at colonoscopy shows patchy erythema and pale mucosa.
Figure 4. Colonoscopy photo demonstrating patchy and inflamed appearing mucosa of the rectum with narrowing of a tight rectal stricture.

Figure 5. Photo of the patient taken in the Emergency Department when he complained of flashes, floaters, and a blind spot (scotoma) in his left eye. Note that the left eye is diffusely injected in comparison to the right eye.

Figure 6. Diagram of the parts of the eye with delineation of the structures that comprise the uvea (Photo credit: National Eye Institute, National Institutes of Health)
References


