IBD LIVE Case Series—Case 3: Very Early-Onset Inflammatory Bowel Disease: When Genetic Testing Proves Beneficial

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LEARNING OBJECTIVES

After completing this IBD LIVE-CME activity, physicians should be better able to:
1. Identify monogenic causes of early onset IBD.
2. Know when genetic testing might benefit the management of select IBD patients.
3. Be aware of potential clinical, endoscopic and histologic findings in early onset IBD.
4. Understand the pathophysiology and potential clinical course of IBD in patients with XIAP.
5. Be aware of effective treatment among patients with monogenic causes of very early onset IBD.

PRESENTATION

Dr. Whitney M. Sunseri: Pediatric Gastroenterology Fellow I, 2014 to 2015.

The patient is an 8-year-old boy who was diagnosed with Crohn’s disease in March 2013 at 6 years of age. He initially presented with a 2-month history of abdominal pain, diarrhea, vomiting, and a rash that was diagnosed clinically as erythema nodosum. His family history is positive for a maternal half-brother with early-onset Crohn’s disease diagnosed at age 3 that is well controlled with infliximab. He also has an uncle with autoimmune hepatitis.

His initial esophagogastroduodenoscopy in April 2013 showed multiple aphthous ulcers in the middle and lower third of the esophagus and erythematous mucosa in the antrum, cardia, and fundus of the stomach with exudates in the antrum. The duodenal bulb and second portion of the duodenum appeared normal. Colonoscopy showed aphthae and exudate throughout the entire colon and edematous mucosa and exudates in the terminal ileum. Pathology revealed esophagitis with a submucosal epithelioid granuloma, active chronic gastritis, mildly increased intraepithelial lymphocytes in the duodenal epithelium, active chronic ileitis, and active chronic colitis throughout the entire colon including the rectum.

The patient was started on prednisone and subcutaneous methotrexate 15 mg every week. Once he demonstrated a response to the medications, mesalamine was added. Two weeks after completing a steroid taper, the patient had a symptom recurrence including diarrhea, erythema nodosum, abdominal pain, and an 8-pound weight loss. Methotrexate and mesalamine were discontinued, and he was started on 6-mercaptopurine, empiric vancocin, a steroid taper, and a polymeric diet. After showing...
little clinical improvement, the patient was started on infliximab (5 mg/kg at 0, 2, and 6 weeks) in August 2013. His C-reactive protein (CRP) went from 9.9 to 0.2 mg/dL (normal <0.5 mg/dL) during infliximab induction therapy. He developed breakthrough symptoms 6 weeks after the third infusion and his interval was shortened to 5 mg/kg every 4 weeks. He had an incomplete response, and the dose was escalated to 10 mg/kg every 6 weeks.

In April 2014, the patient continued to have colitis symptoms. His laboratory work revealed a rising CRP and undetectable levels of infliximab with weakly positive infliximab antibodies. In May 2014, he was switched to adalimumab. Clinically, he continued to experience symptoms of colitis and oscillating CRP levels that did not fully return to normal (Fig. 1). He was restarted on infliximab 10 mg/kg every 4 weeks in mid-June 2014 and placed on total parenteral nutrition. That same month, he was admitted to the hospital for fever, chills, leukopenia, and symptoms of refractory colitis. His infliximab dosing was increased to every week in July 2014 (Fig. 2).

Given the extreme escalation of dosing without symptom resolution, the patient was presented at IBD LIVE on July 10, 2014. The consensus was that infliximab was not providing symptom control, and other agents, including vedolizumab or ustekinumab, were discussed and also total colectomy with end ileostomy. After considerable deliberation, the patient’s family chose surgery. A repeat colonoscopy was performed that demonstrated discontinuous active inflammation throughout the colon and rectum characteristic of Crohn’s disease. On August 4, 2014, the patient underwent a diverting ileostomy without complication and thereafter received infliximab 10 mg/kg every 5 weeks. The hope was that by diverting the fecal stream and adding infliximab, his Crohn’s colitis would improve and he would be able to have an ostomy takedown in the future.

After surgery, the patient’s Crohn’s disease was relatively well controlled on 10 mg/kg of infliximab every 5 weeks (Fig. 3). His symptoms and laboratory work, including albumin and inflammatory markers, improved until he developed a methicillin-sensitive Staphylococcus aureus line infection that caused a spike in this CRP (Fig. 4). In November 2014, his disease was assessed endoscopically. Esophagogastroduodenoscopy showed mild esophagitis, mild inactive chronic gastritis, and an unremarkable duodenum. Ileoscopy was grossly normal in appearance, whereas colonoscopy showed multiple small erosions in the rectum and sigmoid colon, and a 1-cm pseudopolyp in the sigmoid colon. The colonoscope could not be advanced beyond the sigmoid colon because of a stricture. A long strictured segment of the colon was confirmed by barium enema (Fig. 5).

Secondary to his infliximab infusions, the patient developed severe psoriasis. In January 2015, he was admitted to the hospital to receive IV clindamycin for cellulitis of his right thigh. On returning home, his cellulitis cultures were reported as growing clindamycin-resistant methicillin-resistant Staphylococcus aureus. He was switched to sulfamethoxazole/trimethoprim at home. After finishing this course of antibiotics, the patient represented to the emergency department with reports of having 3 days of spiking.

FIGURE 1. From April 2014 to June 2014, the patient’s rising CRP levels coincided with undetectable infliximab levels. Initiation of adalimumab brought an incomplete response, with oscillating CRP. Infliximab was, thus, restarted. Open blue circles delineate CRP level measurements.
FIGURE 2. In June 2014, the patient was readmitted to the hospital for fever, leukopenia, and refractory colitis. Infliximab was given more frequently. Arrows on the graph designate dosing of infliximab in relation to serum CRP levels (open blue circles).

FIGURE 3. On weekly dosing of 10 mg/kg of infliximab, the patient’s symptoms and CRP levels (open blue circles) were escalating. In August 2014, he underwent a diverting ileostomy. Infliximab was restarted exactly 2 weeks after surgery.
fevers, increasing fatigue, decreased oral intake, and a diffuse morbilliform rash. He was febrile at 39.2°C and had a heart rate of 122 beats/minute, respiratory rate of 24, and blood pressure of 135/71 mm Hg. He deteriorated acutely with altered mental status and was intubated and transferred to the pediatric intensive care unit.

At admission, the patient’s laboratory results were remarkable for pancytopenia with a white blood cell count of 2.3 (normal [nl] 3.9 to 10.7 x 10^3 cells/μL), hemoglobin of 6.6 (nl for 6–12 years of age, 11.5–15.5 g/dL), platelet count of 23 (nl = 150–350 x 10^3/μL), and albumin of 2.5 (nl, 3.5–5.5 g/dL). His international normalized ratio was as high as 1.8 (nl, 1) with mildly elevated transaminases; his CRP was 19.35 (nl, 0.5 mg/dL) and his ferritin was highly elevated at 15,240 ng/mL (nl, 15–200 ng/mL). Given his pancytopenia, liver dysfunction, coagulopathy, neurologic symptoms, and exponentially increased serum ferritin, his clinical picture was consistent with cytokine storm known as macrophage activation syndrome (MAS). With this constellation of laboratory values, clinical picture, and acute decompensation, the patient was started on empiric treatment of MAS with intravenous immunoglobulin, plasmapheresis, and 5.6 mg IV every 12 hours of dexamethasone. Over time, he steadily improved and self-extubated; concomitantly, his laboratory results normalized. Because of the atypical presentation of inflammatory bowel disease (IBD) in this patient, flow cytometry and genetic testing were performed. The flow cytometry showed the absence of X-linked inhibitor of apoptosis (XIAP) on lymphocytes. Genetic testing confirmed the diagnosis of XIAP. XIAP is one of a long list of monogenetic disorders that predisposes to an early refractory form of IBD. Ideal treatment for this patient is hematopoietic stem-cell transplant.

Follow-up: On April 23, 2015, the patient underwent umbilical cord stem-cell transplant. As of August 2015, he is doing well.

**CASE DISCUSSION**

**Dr. Miguel D. Regueiro**

Thank you, Whitney, for this outstanding presentation. As an adult gastroenterologist, it is humbling to hear what this young patient went through. I think that the graphs of CRP levels were impressive in that the weekly infliximab treatments corresponded with a low CRP level but the CRP would spike when there was antibody formation and eventually a loss to response. Also pertinent is that now that he is diverted, the barium enema shows a stenotic and somewhat shriveled appearing colon, which affects how you might want to treat this patient. Let us review some of the pathology slides and get Dr. Ranganathan’s feedback on a histologic diagnosis in this patient.

**Dr. Sarangarajan Ranganathan**

The first biopsies were performed in April 2013 at the time of diagnosis. In the duodenum, there is very little inflammation in the lamina propria but a neutrophilic infiltrate surrounds glands in the submucosa. The stomach shows chronic active gastritis with
glandular damage and occasional neutrophils but no granulomas. In the esophagus, there is a submucosal histiocytic aggregate forming a granuloma (Fig. 6A). The terminal ileum was moderately inflamed, demonstrating superficial erosions and aphthous ulcers with cryptitis and crypt abscess formation (Fig. 6B). The ascending colon showed minimal inflammation with a few neutrophils in crypt lumens, but most architecture was preserved. The descending colon had a moderate degree of inflammation with an ulcer and erosions present on the surface with architectural distortion. The rectosigmoid showed a mild degree of inflammatory changes with cryptitis but without crypt architectural distortion. Overall, there was mainly upper gastrointestinal (GI) and terminal ileal involvement with a granuloma in the esophagus. The pattern was highly suggestive of Crohn’s disease. There was discontinuous inflammation and the segments that were inflamed did not show a similar extent of inflammation. This is a critical finding that I use to diagnose Crohn’s disease even if I do not see granulomas.

The second set of biopsies performed in 2014 shows greater inflammation in the stomach and a granuloma. There is a milder degree of inflammation in the terminal ileum than in the previous biopsy with some suggestion of crypt injury and crypt apoptosis. The transverse colon again had a moderate degree of inflammation and architectural distortion, whereas the rectosigmoid showed a greater degree of inflammation than in the previous biopsy, with numerous crypt abscesses. Thus, similar to the previous biopsies, the involvement was skipped, with not every segment being involved to the same degree.

Dr. Miguel D. Regueiro

Dr. Subra Kugathasan at Emory is with us today and I had like to have him discuss the gene chip that Emory uses in evaluating some of their more challenging pediatric cases. Some of the questions that this case raises in relation to genetic testing are 1. Should we send genetic testing for kids with IBD? and 2. in a select cohort of adult patients with IBD, should we send genetic testing?

Dr. Subra Kugathasan

I am a pediatric gastroenterologist with a particular interest in very early-onset and genetic causes of IBD. At Emory, we have been working diligently to create a simple genetic test to help us evaluate these early-onset pediatric patients with IBD, who may have a single genetic reason for the disease—Mendelian monogenic causes of IBD. Ideally, every patient with IBD should have a molecular diagnosis, either monogenic or polygenic. At the current time, however, this is not feasible. Any patient who has early-onset IBD, like the patient presented today, or who comes from a family in which there are multiple family members affected with IBD raises suspicions for having a Mendelian or monogenic disorder. Although there are approximately 65 monogenic disorders recognized as relating to IBD, these are

FIGURE 5. During a November 2014 colonoscopy, the colonoscope could not be advanced beyond the sigmoid because of severe narrowing. Barium enema verified the existence of a long segment colonic stricture.

FIGURE 6. A, An image of the mid-esophagus section showing a histiocytic aggregate with multinucleate giant cell in lamina propria (H&E, ×200). B, An image of terminal ileum showing neutrophilic infiltrate in lamina propria and epithelium and a small aphthous ulcer (H&E, ×100).
exceedingly rare. They may exist in only 1 in 100,000 individuals or even fewer than that. For instance, we hear a lot about IL-10 and IL-10 receptor-associated genetic defects, but, in aggregate, there have only been approximately 30 to 35 patients with one of these mutations described worldwide by various investigators. So the dilemma becomes how to make a test for these disorders that is cost effective. At Emory, we have developed a chip that is both CLIA (Clinical Laboratory Improvement Amendments) and CAP (College of American Pathologists) certified. The quality control that we went through in developing this chip was very well regulated, and there is approximately an 80% to 90% chance that insurance companies will cover the cost of the test.

After completing a form, the patient just needs to have approximately 5 cc of blood collected in an EDTA tube at the patient’s own laboratory. There are approximately 50 different genes on the chip. A number of genes that are well known to cause early-onset IBD are included in our panel (Table 1). Our approach is to exome sequence all genes, but only reports the genes of interest as our first interpretation. The reason that we do this is due to the clinical utility of being able to go back and look at the genes specifically or to expand our search to additional lesser-known genes of interest, if requested. For example, if you have a clinical suspicion that the patient has an IL-10 disorder, but you do not identify a previously identified mutation, you have the ability to go back and look at the promoter and the interior coding regions. In this manner, we can see if there are known mutations and also new mutations in the IL-10 gene or even new genes. The final report that we present to the patient is first tier reporting and just shows the genes and whether they are present. Our aim is not to give the patient extraneous information but, rather, to answer questions like those that have been raised in the case today. We have a website that provides more information and instructions on how order the test to be sent to our laboratory.²

**Dr. Miguel D. Regueiro**

These disorders are very rare but genetic testing confirmed the diagnosis and had a big impact on this child’s treatment. My understanding is that his lack of response to traditional IBD treatment is not unexpected and he will benefit greatly from a stem-cell transplant. Subra, given your expertise in genotype-phenotype correlations in IBD and the genetic answer to the fascinating case that Whitney presented, what is the cost of the early-onset gene panel?

**Dr. Subra Kugathasan**

At the current time, the cost is in the range of $3000.

**Dr. Miguel D. Regueiro**

This child is young and has a very strong family history of Crohn’s disease with involvement throughout the GI tract from esophagus to rectum. He required very high doses of infliximab but still did not maintain a response to medication. Specific cases similar to this patient may be of particular interest in looking at genetic associations. Corey Siegel, MD at Dartmouth and Ray Cross, MD at University of Maryland, I am curious to know whether you have sent genetic tests previously or are there adults for whom you would consider doing genetic testing?

**Dr. Corey A. Siegel**

No, I have not sent genetic testing for this type of patient but I do not treat pediatric IBD. However, we do occasionally send a panel for functional immune deficiency testing. These genetic tests are a great addition to our armamentarium but speaking as an adult gastroenterologist, I wonder whether we should be looking more from the other side of things at the functional standpoint of testing. I would be thrilled if someone could provide strong guidance about which 5 or 10 tests we should be running when we suspect an immunodeficiency syndrome that might be linked to one of these genetic disorders. When I see an adult patient with a complicated and nonresponsive disease course, I could see value in working with Subra to discern how genetic testing could help us with these more difficult cases, but for now, we focus on testing the function of the immune system.

**Dr. Raymond K. Cross**

I have not been sending genetic tests but I think that what Subra has discussed for both children and adults can be seen as a segue into precision medicine and personalized medicine. In the next 10 years, we should have cheaper diagnostics and, as Corey described, functional studies that will help us to be more accurate in our medication selection. Who would I consider for genetic testing before it becomes mainstream? I think that most of the patients presented at our IBD LIVE conferences and national IBD symposia who have refractory disease are appropriate candidates. If you have a patient who is not responding to anti-TNFs and has ongoing, confirmed inflammation of the GI tract, I think that it would make sense to review the patient’s family history and

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**TABLE 1. Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis**

1. A molecular diagnosis consistent with HLH; these include the identification of pathologic mutations of PRF1, UNC13D, or STX11, OR
2. Fulfillment of five of the eight criteria below:
   - Fever (>100.4°F)
   - Splenomegaly
   - Cytopenias affecting at least 2 of 3 lineages in the peripheral blood
     - Hemoglobin <9 g/100 mL (for infants <.4 wks: hemoglobin <10 g/100 mL)
     - Platelets <100 x 10⁹/L
     - Neutrophils <1 x 10⁹/L
   - Hypertriglyceridemia (fasting, ≥265 mg/100 mL) and/or hypofibrinogenemia (≤150 mg/100 mL)
   - Ferritin ≥500 ng/mL
   - Hemophagocytosis in the bone marrow, spleen, or lymph nodes
   - Low or absent NK cell activity
   - Soluble CD25 (soluble IL-2 receptor) >2400 U/mL (or per local reference laboratory)
medical history to be certain that you are not missing one of these rare disorders before you just reach for another medication.

**Dr. Miguel D. Regueiro**

Subra, I think that this is the first time that you have been involved in IBD LIVE, but we have many cases that would be appropriate for genetic testing, especially the patients seen by David Keljo and Alka Goyal at our children’s hospital. I had like to have David Keljo make some final remarks on this case.

**Dr. David J. Keljo**

I have always believed of genetic testing as having limited value in making a diagnosis of Crohn’s disease. After hearing about the chip, I now realize how valuable this type of genetic testing could be in diagnosing severe defects contributing to IBD. I am not sure what the cost would be at our institution, but I think that we now will be evaluating everyone under the age of 10 if they have an atypical and refractory IBD disease course as in the case that was just presented. Over time, we have had a number of refractory cases that have graduated to the adult world and I can think of some that might have benefitted from genetic testing. If the chip covered most immune defects, I would assume that it would be cheaper than running functional assays.

**Dr. Subra Kugathasan**

For future testing, instead of having the patient’s institution attempt to turn in the claim, I would suggest having Emory do the paperwork. Filing the insurance claim through Emory will give the patient a better chance of having insurance cover the cost than the individual’s referring institution. Since the time when we launched the chip, we have had approximately 80 cases analyzed. With each patient tested and the data we derive, we attempt to refine and improve the chip. Over time, we hope to make the chip more affordable and more widely available across the country.

**DISCUSSION**

The patient described in this case had a complicated presentation and disease course. His symptoms escalated rapidly and he was minimally responsive to IBD treatment. The patient was admitted to the pediatric intensive care unit meeting the criteria for hemophagocytic lymphohistiocytosis (HLH) or MAS (Table 2).

HLH is characterized by an overwhelming activation of cytokine release that is most commonly related to defects in natural killer (NK) cell function or activity. A simplified explanation would be that the failure of NK cells to destroy large numbers of antigen-bearing antigen-presenting cells leads to the continued stimulation of inflammation. This cytokine storm is triggered by intra-cellular infections such as cytomegalovirus, herpes simplex virus, Epstein-Barr virus and influenza H1N1, rheumatologic disorders, leukemia, and immunosuppressive therapy. An example of an NK defect would be perforin deficiency, whereas defects in XIAP may cause enhanced NK cell destruction. Common triggers would include Epstein-Barr virus infection in children with XIAP deficiency and influenza H1N1 in adults with partial NK cell defects.

Similar to the approach taken with our patient, treatment of MAS is to control or eliminate the infectious triggers. As previously noted, these triggers are frequently viral infections. Intravenous immunoglobulin helps bind the offending agent, whereas it can be eliminated with plasmapheresis. Another treatment approach is to block T-cell proliferation and activation with medications such as dexamethasone or etoposide.

Three prevailing clinical manifestations of XIAP deficiency include IBD similar to Crohn’s disease, recurrent splenomegaly, and frequent, potentially fatal bouts of HLH. Our patient was found to be XIAP deficient, although the trigger for his specific occurrence of HLH was not identified.

XIAP deficiency has been linked to early-onset IBD. Pathologically, the gastrointestinal inflammation noted among individuals with a defect in XIAP could be related to enhanced destruction of XIAP-deficient enterocytes and also defective NOD2 signaling. Patients with XIAP have presented with IBD similar to Crohn’s disease at time points ranging from infancy to 41 years of age with disease that is typically very difficult to control. Additionally, symptomatic female heterozygous carriers of XIAP mutations have been identified. Allogeneic stem-cell transplant can cure both immune defect and the associated IBD.

There are many other IBD or IBD-like syndromes associated with known monogenic mutations. These include, but are not limited to chronic granulomatous disease, mevalonate kinase deficiency, IL-10 receptor defects, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome, and Wiskott–Aldrich syndrome. A number of treatment options provide symptom relief for these syndromes, although allogeneic stem-cell transplant early in the disease course is highly effective for many of these illnesses; gene therapy is a promising future treatment. Severe illness in childhood is a hallmark of many of these syndromes, although the age of presentation of GI inflammation can be well beyond childhood. A gene chip has been developed, which detects these and various additional defects associated with early onset IBD.

Presentation of IBD-like symptoms in children with a genetic defect may be similar to other children with IBD, although certain features make genetic or immunodeficiency-related disease more likely, including the following:

1. Very young age of onset
2. Family history of IBD and/or immunodeficiency in multiple family members, particularly with male predominance or consanguinity
3. Recurrent infections or unexplained fevers
4. Associated autoimmunity (e.g., arthritis, primary sclerosing cholangitis, anemia, or endocrine dysfunction)
5. Very severe IBD and/or resistance to conventional therapies for IBD
6. Hemophagocytic lymphohistiocytosis
7. Lymphoid abnormalities such as splenomegaly
8. Lesions of the skin, nails, or hair
9. Tumors.

**EDITOR’S COMMENTS**

This case raises 2 important questions in regard to the evaluation of patients with IBD, namely:

1. What role should genetic testing take in the evaluation of pediatric patients with IBD?
2. Should genetic testing be a selective part of the IBD management of adults?

TABLE 2. Genes Associated with Disorders Where Early Onset IBD Is Well Recognized. Broader Function of the Genes/Pathways Is Indicated in the First Column. Emory’s Early Onset IBD Gene Panel Includes 26 Genes from the List Below

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<th>Gene</th>
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Some data in this table was found in Uhlig HH. Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease. Gut. 2013;62:1795–1805.

Without question, the greatest number of positive genetic tests will be made among very early-onset (<10 years of age) patients with IBD. Nonetheless, evidence has shown that some patients with genetic causes of gastrointestinal inflammation that are phenotypically similar to IBD may present well into adulthood. Illnesses that were once believed to be present only in males, such as chronic granulomatous disease, have also been diagnosed in females either through separate gene defects or selective inactivation of the wild-type allele.

It would be advantageous for a defect like XIAP deficiency to be discovered before the patient has had to experience the risks associated with intensive immunosuppressive therapy or the
consequences of anatomy-altering surgery. A strong case can be made for performing this sort of genetic testing on patients who present with severe and medically refractory IBD before the age of 10. Given the spectrum of defects and varying age at presentation, this same type of genetic testing may also be appropriate for adults who do not respond to standard IBD therapies and certainly for the rare adult patient who develops HLH.

This IBD LIVE case provides a “real-world” narrative of a young patient with refractory IBD who is found to have a rare disease based on genetic testing. The clinicians treating this patient should be applauded for their aggressive treatment efforts and unremitting search for an answer. Although routine genetic testing in patients with IBD is neither affordable nor considered standard of care, rare and atypical presentations, especially in patients under 10 years, should be considered. There is great hope that, someday, genetic testing in a young patient with refractory IBD who is found to have a rare disease based on genetic testing. The clinicians treating this patient may help patients know their genetic profile, immune and microbiome “make up,” and, most importantly, the precise treatment that will provide symptom control and disease resolution.

REFERENCES