

Inflammatory Bowel Disease: Early-Onset Cases and the Role of Genetic Testing

Cases of early-onset inflammatory bowel diseases (IBD), such as Crohn's disease in individuals under the age of 10, that present in an atypical manner and are refractory to standard treatment regimens and surgery may be the result of an underlying genetic defect contributing to the condition. Children who present with various IBD diagnoses before the age of 8 have an increased frequency of having a particularly severe immune defect presenting as IBD. Genetic screening for mutations in this patient population may provide faster identification of the root contributing factor, avoidance of complications or surgical procedures, and the application of appropriate therapies, such as stem cell transplant for those patients with monogenic defects. For patients with some monogenic defects, stem cell transplantation may provide an ultimate cure for the underlying defect contributing to or causing their IBD.

Case Overview:

Initial Presentation and Medication Regimen

An 8-year-old boy (ZS) and his maternal half-brother were initially diagnosed with Crohn's disease at 6 and 3 years old, respectively, by David Keljo, MD, PhD, and the Pediatric Gastroenterology team at Children's Hospital of Pittsburgh of UPMC. ZS was diagnosed in March 2013 after presenting with symptoms over a two-month period. Symptoms included abdominal pain, diarrhea, and vomiting. Initial endoscopic studies showed aphthae in the proximal $\frac{2}{3}$ of the esophagus and scattered throughout the colon. There were deeper linear ulcerations in the ileum and transverse colon. Pathological findings indicated the presence of esophagitis, active chronic gastritis, active chronic ileitis, and chronic colitis along the entire colon.

His disease settled down on prednisone, but the prednisone could not be weaned to either methotrexate or 6-MP. He was started on infliximab in August 2013 with clinical improvement, but he required progressively increasing doses and shorter and shorter intervals between infusions. A brief trial of adalimumab led to much worsened disease, and more aggressive infliximab therapy was pursued. Because of severe symptoms, in August 2014 a diverting

ileostomy was performed. The patient did well and went home on total parenteral nutrition (TPN) only to return with fever a week later. He was hospitalized again; cultures were negative, but he developed a transient pancytopenia, which was felt to be viral in etiology. The patient did reasonably well, but a month later was hospitalized with an MRSA abscess of the thigh, which subsequently responded well



David Keljo, MD, PhD, in clinic with a patient.

to antibiotics. In November, he developed psoriasis. By January 2015, the psoriasis was quite severe, and he was hospitalized with another abscess in the thigh. He responded to trimethoprim/sulfamethoxazole and was discharged. Soon after completing the therapy he returned to the emergency room with fevers, increasing fatigue, and a diffuse erythematous rash. While he was in the emergency room his clinical status rapidly deteriorated, and he was admitted to the Pediatric Intensive Care Unit (PICU) with presumed septic shock. In the PICU, he developed progressive confusion and was intubated. His blood cultures were negative, and he developed a severe pancytopenia with markedly elevated ferritin. These lab values, along with the patient's neurological symptoms, pointed to cytokine storm — macrophage activation syndrome (MAS).

Continued on next page

Inflammatory Bowel Disease *Continued from previous page*

Identifying the Genetic Underpinnings of the IBD

As a result of the patient's acute MAS episode, along with his atypical IBD refractory to various treatments, follow-up testing was conducted. Flow cytometry showed the absence of X-linked inhibitor of apoptosis (XIAP) on lymphocytes, and subsequent genetic testing confirmed a diagnosis of XIAP absence. XIAP is one of many monogenic conditions that is related to early-onset forms of IBD that are refractory to treatment. XIAP deficiency also plays a role in MAS, because one of its causes is a defect in T-lymphocyte function. In XIAP deficiency, the T-cells themselves are excessively susceptible to dying in response to a variety of stimuli, inhibiting the ability to eliminate cell-bearing antigens.

The PICU was crucial for identifying the XIAP defect and successfully treating the patient for the macrophage activation syndrome.

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The exact trigger for the MAS in this patient is not known; however, it may have been the Staphylococcus infection itself or some kind of reaction to the antibiotic regimen prescribed to treat it. Macrophage activation syndrome has

a very high mortality rate, and it requires significant intensive care expertise to recognize what the problem is and successfully manage it. His treatment included IV immunoglobulin, plasmapheresis, and IV dexamethasone. ZS' lab results normalized, and he was discharged to home on February 6. Allogeneic stem cell transplant was planned to correct his XIAP deficiency. He was maintained in the interim on steroids and infliximab.

Stem Cell Transplant Therapy and Recovery

ZS was admitted to Children's Hospital on April 8, 2015, for the transplant process and discharged on May 20. The actual transplant procedure occurred on April 23. Prior to the transplant, the patient received an institutional reduced-intensity conditioning therapy for nonmalignant diseases, using chemotherapeutic agents only, for three days. This non-myeloablative, reduced-intensity protocol was developed by transplant physician Paul Szabolcs, MD, chief, Division of Blood and Marrow Transplantation and Cellular Therapies.

The patient received an allogeneic hematopoietic stem cell transplant — derived from donor umbilical cord blood — to address the underlying XIAP deficiency, leading to a cure for the patient's IBD. Autologous transplants for this condition are not favorable, as there are concerns about:

- Having enough stem cells for a successful transplant
- The reality that with an autologous transplant protocol the patient's underlying genetic position remains unchanged, thereby making the return of the disease a real fear

Additionally, with this particular patient, there was some concern with the volume of the cell dose from the cord blood transplant due

to the patient's size (47 kg) at the time of transplant. The Crohn's disease-type symptoms were a concern, as any inflammation in the body prior to the transplant, whether in the skin or the gut, can flare up and lead to eventual graft versus host disease. This is a concern, even if the transplant is considered to be successful.

The patient engrafted remarkably fast, which speaks to not only the quality of the cord blood, but also to the transplant protocol at Children's Hospital with the reduced-intensity chemotherapy conditioning regimen. Median engraftment time with the Children's Hospital protocol is approximately 14 days. No significant complications, such as end-organ toxicities, PICU transfer, or the requirement of oxygen, were observed with the patient. Transfusions received by the patient the first week after the transplant produced an engraftment syndrome, which was successfully treated with low-dose prednisone. The patient was discharged from the hospital to home on May 20, 2015, without active graft versus host disease or infections. This particular patient was able to be withdrawn from immunosuppression therapy (cyclosporine and tacrolimus) quickly without observed issue or complication, four and a half-months post-transplant. At nine-months posttransplant, the patient exhibited full donor engraftment with no complications, graft versus host disease, or infection. At this point, the likelihood of relapse is extremely low.

In April 2016, the patient had a repeat colonoscopy, which showed a stricture involving the transverse and descending colon. Biopsies showed mild colitis. Ileoscopy with biopsies was normal. In June, he underwent takedown of the ileostomy with subtotal colectomy and ileal-proximal rectal anastomosis. There was no evidence of active Crohn's disease on pathology. He is clinically doing well.

His half-brother, with the same XIAP deficiency, underwent successful allogeneic stem cell transplant in December 2015, and as of July 2016, has no evidence of inflammatory bowel disease.

Genetic Screening Is Appropriate for Early-Onset, Aggressive Cases

It is clear that blanket usage of genetic screening for early-onset cases of IBD is not appropriate or necessarily warranted. However, in those cases that are particularly aggressive, with symptoms that are refractory to standard treatments, a familial history, or other related conditions such as infections or HLH-like aspects, a genetic screening may reveal a genetic factor at play, some of which can be effectively dealt with using stem cell transplant therapy.

With ZS and his maternal half-brother, this appears to be one of the few circumstances in which Crohn's disease can actually be cured. For these particular patients, the underlying XIAP defect was dominant, and many of the other gene defects that are part of the immune system would be expected to be cured by a stem cell transplant. However, Crohn's is a polygenic disease, and it is possible that the other implicated genes (e.g., those involved in the maintenance of epithelial integrity) could conspire to represent with Crohn's in the future, and if that is the case, it seems likely that the disease course would be much less aggressive. •

ABOUT THE DIVISION

The Division of Pediatric Gastroenterology, Hepatology, and Nutrition provides a wide range of treatment options for patients with conditions of the gastrointestinal tract, liver, and pancreas. Some of the conditions that we treat include:

- Abdominal pain
- Gastroesophageal reflux and esophagitis
- Inflammatory bowel disease
- Intestinal failure
- Liver transplantation
- Small bowel transplantation
- Pancreatitis
- Metabolic disorders

Specialized Programs and Centers

- Inflammatory Bowel Disease Center
- Hepatology Center
- Intestinal Care and Rehabilitation Center (ICARE)

Clinical Research

The Division has a large research program, and taken a leading stance in investigations for numerous conditions and therapies. Some of the current research in the Division includes the following studies. For a complete listing of current clinical studies, please visit CHP.edu.

Alagille Syndrome and LUM001: The IMAGINE Study

Primary Investigator: Robert Squires, MD

This study is looking at long-term safety and durability of the therapeutic effect of LUM001, an apical sodium-dependent bile acid transporter inhibitor (ASBTi), in the treatment of cholestatic liver disease in pediatric subjects with Alagille Syndrome.

ICARE Research Registry (Intestinal Care and Rehabilitation Center Database)

Primary Investigator: Jeffrey A. Rudolph, MD

This registry is a central repository of information about pediatric patients who have been treated by the Intestinal Care and Rehabilitation Center (ICARE) at Children's Hospital of Pittsburgh of UPMC. The registry serves as a means to identify the clinical characteristics of patients being followed, assess clinical outcomes, and evaluate the long-term medical and nutritional management issues in children with intestinal disease.



IBD Treatment with Remicade®: The ADAPT Study – Phase IV

Primary Investigator: Sapana Shah, MD

This multicenter research study is to determine if pediatric patients with inflammatory bowel disease (IBD) who have lost response to infliximab, also known as Remicade®, at the standard approved dose of every eight weeks would benefit from an increase in their dose. •

DIVISION NEWS

At the 5th World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition (WCPGHAN), held from October 5-8, 2016, in Montreal, several faculty members from the Division presented on a number of topics, including:

Immune Tolerance and Rejection

Patrick J. McKiernan, MD
Director, Pediatric Hepatology Program

Steatorrhea: What if it's not cystic fibrosis?

Mark E. Lowe, MD, PhD
Chief, Division of Pediatric Gastroenterology

Acute Liver Failure — Pathogenesis and Management

Robert H. Squires, MD, *Medical Director, Pediatric Liver Transplantation*, and Anil Dhawan, MD

Inflammatory Responses — Healing in Pancreatic Injury

Sohail Husain, MD
Co-director, Pediatric Exocrine Pancreatic Disorders Program

RECENT PUBLICATIONS

Below is a sample of recent publications from researchers and clinicians in the Division.

George Mazariegos, MD, FACS; Patrick McKiernan, MD; and Robert Squires, MD, were published in the April 2016 issue of *Hepatology* for the paper "Primary Prophylaxis of Variceal Bleeding in Children and the Role of MesoRex Bypass: Summary of the Baveno VI Pediatric Satellite Symposium."

Sohail Z. Husain, MD, was published in the April 2016 issue of the *Journal of Pediatric Gastroenterology and Nutrition* for the article "Toxic-metabolic Risk Factors in Pediatric Pancreatitis: Recommendations for Diagnosis, Management, and Future Research."

David Keljo, MD, PhD, and Arvind Srinath, MD, were published in the March issue of the *Journal of Pediatric Gastroenterology and Nutrition* for the article "Effect of Psychotherapy on Healthcare Utilization in Children with Inflammatory Bowel Disease and Depression." •

CONTINUING MEDICAL EDUCATION

The free courses below are available online by visiting UPMCPhysicianResources.com/Pediatrics.

Acute Liver Failure in Children: Story of a Lifetime

Robert Squires, MD, reviews the history, diagnosis, and studies for acute liver failure in children.

Living Donor Liver Transplant: Update in Hepatology, Gastroenterology, and Transplantation

Christopher Hughes, MD, and Abhinav Humar, MD, discuss living donor liver transplantation and the process that a transplant center needs to go through in order to get a patient transplanted. •

ABOUT CHILDREN'S HOSPITAL OF PITTSBURGH OF UPMC

Children's Hospital of Pittsburgh of UPMC is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists.

Children's is consistently recognized for its research and clinical achievements, including ranking tenth among children's hospitals and schools of medicine (FY15) in NIH funding for pediatric research, and being named to the 2016-17 *U.S. News & World Report* Honor Roll of America's Best Children's Hospitals.