Case Series
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# Monogenic Cases of Infantile IBD with Discrete Pathological Pathways: a Case Series

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**Abstract**

**Objective** – Inflammatory bowel disease (IBD) is a multifactorial auto-immune disease caused by dysregulated immune responses, resulting in chronic intestinal inflammation. IBD in which disease onset is before 2 years of age is known as Infantile IBD. As the disease is rare in this age group, it is often misdiagnosed as infective or allergic colitis. Cases – We present here a case series of three patients with infantile IBD with completely different etiologies, that is, a mutation in the distinct pathways, i.e. the hematological lineage pathway (*IL10 RA*), autoimmunity (*NLRC4*), and immunodeficiency (*IKBKG*). All the cases had chronic diarrhea, however each case was difficult to diagnose conclusively and had a different response to the standard treatment protocol for IBD. **Conclusion** – Our case series shows that genetic mutations and/or primary immunodeficiency play an important etiological role in this subgroup of IBD (infantile onset). It also highlights that patients with infantile IBD are difficult to diagnose, treat, and usually do not respond to conventional treatment.

**Key Words:** Infantile IBD ▪ Monogenic IBD ▪ Pediatric Chronic Diarrhea.

## Introduction

Inflammatory bowel disease (IBD) is a heterogeneous group of complex and multifactorial disorders, and an uncommon disease in young children. The pathogenesis of IBD begins with an altered intestinal response to various external stimuli in a genetically susceptible host. IBD in children is further subclassified on the basis of age of onset as: early (<10 year), very early (<6 year) and infantile (<2 year) (1). Compared to children whose IBD develops later in life, those with Very Early Onset of IBD, and particularly those with infantile IBD, are more likely to have single gene defects that alter their immunity or lead to epithelial barrier dysfunction which may also have a more severe disease course (2).

We present here a case series of three children with infantile IBD, and the different signs and symptoms in each patient. In all three cases whole exome sequencing was done by next generation sequencing, performed on an illumina platform for genetic analysis.

## Case Report

### *Case 1*

An 18-month-old male presented with intermittent fever and loose stools over the previous 2 months. He was having stools 8-10 times per day with watery consistency, associated with blood. There was additional history of moderate abdominal pain and progressive lethargy. He had developed progressive

generalized body swelling and an increased amount of blood in his stools two weeks before admission to our center and received one Packed Red Blood Cell (PRBC) transfusion. He was initially treated elsewhere for infective colitis with multiple broad-spectrum antibiotics, and later for cow milk protein allergy by hydrolyzed milk formula, but with no improvement. He was born full term with no significant antenatal or perinatal history, and had been growing well until 16 months of age. The family history was insignificant, apart from the fact that the 40–year old father had had occasional blood in his stools for a few years, but this had not been investigated further. On physical examination the child was conscious, afebrile, and generalized edema and severe pallor were present. Initial laboratory work up showed moderate anemia and severe hypoalbuminemia, with mildly elevated C reactive protein (CRP) (Table 1). Ultrasonography of the abdomen revealed a thickened wall and edema in the descending colon. Colonoscopy showed a superficial ulcer with surrounding erythema, and a pseudo polyp with loss of vasculature throughout the colon (Fig. 1).

Histopathology of the colonic biopsy showed a focal crypt distortion and cryptitis, suggestive of ulcerative colitis. In view of the very young age of onset of IBD, exome sequencing was performed. On investigation he was non-reactive for HIV, and had normal levels of immunoglobulins and T cell subsets for his age. His bleeding persisted and hemoglobin levels dropped further, and he was again given a PRBC transfusion. He was initially managed on intravenous steroids (2 mg/kg), broad spectrum antibiotics and mesalamine (100 mg/kg). Initially he showed improvement with a decrease in the frequency of stools, a reduced amount of blood in the stools and improvement in his general condition. His medication was changed to oral steroids and oral antibiotics. However, after 3 days he again had a high grade fever and bloody diarrhea, and on investigation he had elevated CRP (90 mg/L) with low hemoglobin (5 gm/dl). He was again started on intravenous steroids. His exome sequencing revealed a heterozygous missense variation in exon 5 of the *NLRC4* gene (*chr2:g.32475610G>T*). He was started on oral cyclosporine (2.5 mg/kg/day) and began showing generalized improvement. Steroids were tapered and stopped as per protocol, and cyclosporine was given for 6 months. He has now been in follow up for one year with no flare up.

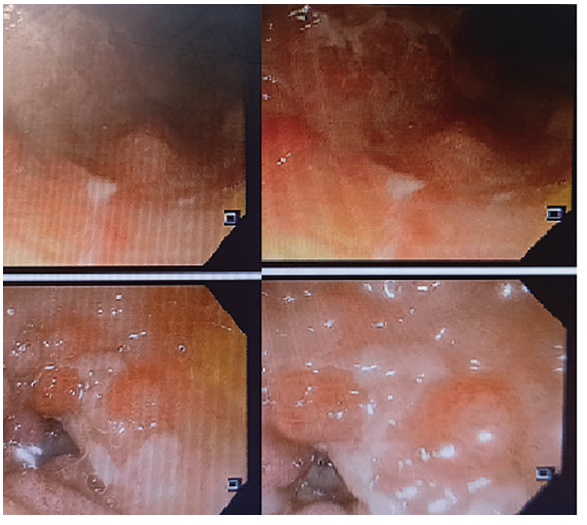

**Fig. 1.** *Colonoscopy finding in Case 1 showing diffuse edematous mucosa with pseudo polyp, superficial ulceration and loss of vascularity.*

### *Case 2*

A 5–month old male was referred to our hospital with the chief complaint of recurrent episodes of fever and bloody diarrhea from day 10 of life, growth failure and perianal lesions. For the first episode he was treated for infectious colitis with broad spectrum antibiotics. He improved initially, but had similar symptoms again and needed rehospitalization at 1 month of age. From then on, he was admitted to hospital every month for fever and blood in his stools, and started developing painful perianal lesions at 2 months of age. He had elevated counts and CRP at every admission. Colonoscopy was done at 3 months of age and showed aphthous ulceration in the colon. Colonic biopsy revealed a dense diffuse inflammatory infiltrate, comprised of lymphocytes, eosinophils and cryptitis (Fig. 2).

He was initially treated for cow's milk protein allergy, however, he showed no improvement. He

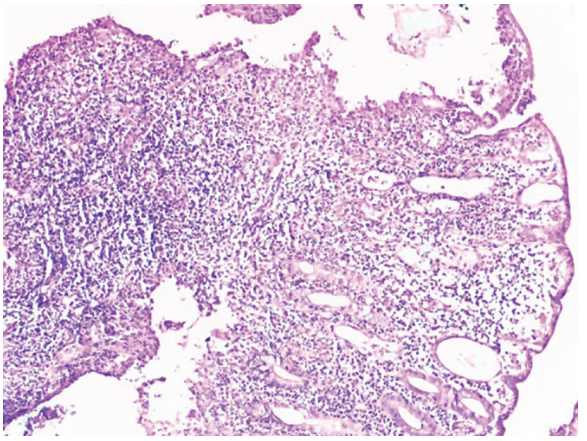

**Fig. 2.** *A dense diffuse inflammatory infiltrate comprised of lymphocytes, eosinophils and cryptitis was seen on the colonic mucosal biopsy in case 2 (H & E stain with 10 × magnification).*

was born full term with no significant antenatal or perinatal history. His father had a history of perianal fistula at the age of 25, and had had surgery twice for fistula. On admission, the patient was febrile but did not appear septic. On examination, his weight and height were both below the 3rd percentile. Perianal tags and multiple perianal fissures were present (Fig. 3).

Laboratory workup revealed anemia, leukocytosis, thrombocytosis, hypoalbuminemia, and elevated CRP (Table 1). He was non-reactive for HIV and had normal levels of immunoglobulins and T cell subsets for his age. Fecal calprotectin was elevated. A diagnosis of infantile IBD was made, and his clinical exome was sent in view of suspected monogenic IBD. He was started on intravenous methylprednisolone(2 mg/kg) and azathioprine (2 mg/kg). He initially showed improvement for 10 days but when the steroids were tapered, he again started having fever and flare ups. Exome sequencing identified a homozygous 3' splice site variation in intron 3 of the *IL10RA* gene (chr11:g.117993240G>A). He was started on infliximab (10 mg/kg) but showed no improvement. He started developing rashes in the perioral area and hands. He was planned for Hematopoietic Stem Cell Transplantation (HSCT) but in the meantime he developed intestinal perforation, and an emergency exploratory laparotomy

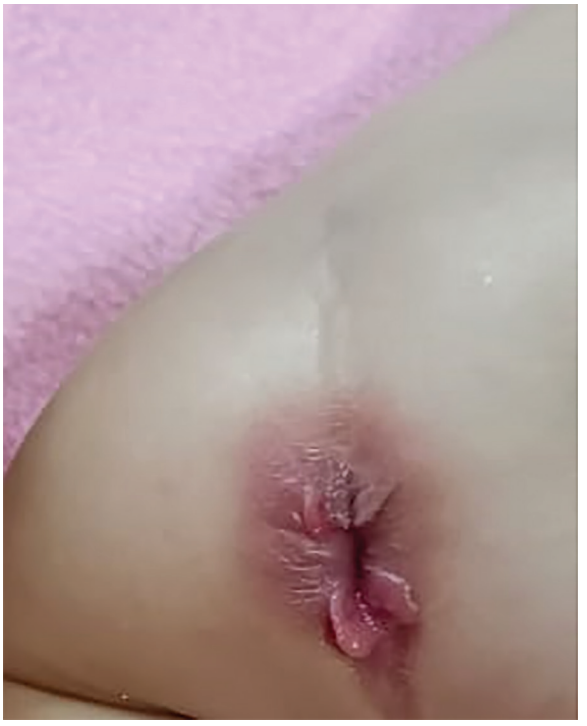

**Fig. 3.** *Perianal lesions in the form of multiple fistulae and perianal tags in Case 2.*

was done in which a perforation of the transverse colon was found. A colostomy stoma was put in place, however he again needed exploration for abdominal distension, and died after 10 days due to sepsis.

### *Case 3*

A 22–month old male presented with intermittent fever, recurrent respiratory tract infection, failure to thrive and loose stools requiring multiple hospitalizations from the age of 6 months. He was born to non-consanguineous parents, with no significant antenatal, perinatal or family history. Infectious causes for diarrhea were ruled out. There was no history of any joint pain or swelling, perianal abscess, ear discharge, mouth ulcers, bleeding from any site, or decreased oral intake. In infancy he had a history of recurrent lower respiratory infections with diarrhea. Colonoscopy showed a few aphthous ulcers throughout the colon, and colonic biopsy revealed chronic inflammation. Total leucocyte count

Table 1. Characteristics of the Infantile IBD* Patients

| Characteristics | Presentation of cases | | |
|---|---|---|---|
| | Case 1 | Case 2 | Case 3 |
| Age (months) | 18 | 5 | 22 |
| Sex | Male | Male | Male |
| Age of onset of symptoms | 16 months | 10 days | 6 months |
| Hemoglobin (g/dl) | 6.2 | 8.4 | 8.1 |
| TLC† (cu.mm) | 10750 | 22700 | 17000 |
| Platelets (lacs/cu.mm) | 3 | 6 | 4.5 |
| Albumin (gm/dl) | 1.3 | 1.8 | 2.1 |
| CRP‡ (mg/l) | 10.6 | 54 | 17 |
| Fecal calprotectin (µg/g) | 250 | 750 | 180 |
| Gene mutation | *NLRC-4* | *IL10-RA* | *IKBKG* |

*Inflammatory bowel disease; †Total leucocyte count; ‡C reactive protein.

(TLC), CRP and Fecal calprotectin were elevated (Table 1). The clinical exome revealed a hemizygous frameshift mutation in *Exon 1* of the *IKBKG* gene (*c.105P_106delCA*). He was started on mesalamine (100 mg/kg) along with cotrimoxazole prophylaxis. The child responded partially, but has had recurrent flare ups of diarrhea which were treated symptomatically. He has been in follow up for one year, but still has faltering growth. Considering the insignificant improvement, his parents have been advised that he should undergo HSCT, and he is currently in follow up.

## Discussion

The pathophysiology of infantile IBD is usually an inherited genetic abnormality that causes immunological dysregulation, leading to epithelial barrier dysfunction. Early age of onset, a strong family history of IBD and/or immunodeficiency, indicate monogenic IBD, as in two of our patients with undiagnosed gastrointestinal symptoms (3). Usually, the onset of IBD is insidious, blood and mucus-stained, small volume loose watery stools are a common symptom. Initial presentation may mimic infective colitis or cow's milk protein allergy, as happened in all our cases, leading to delayed treatment (4). Elevated CRP, fecal calprotectin and perianal lesions are strong indicators of IBD (5). Sometimes the histology of a colonic biopsy in young infants does not show any features consistent with IBD, leading to misdiagnosis, as in our second case. A persistent perianal lesion is a major clue for IBD, and if it responds poorly to pharmacological therapy, ruling out mutations in the *IL10* and *IL10 receptors* is a must, since they respond well to HSCT, if done at an early age. Mutations in the IL-10 receptor genes *IL10RA* and *IL10RB* and defects in *IL-10* itself can lead to early-onset enterocolitis, triggering hyperinflammatory immune responses in the intestine due to dysfunction of the regulatory T cells and immune dysregulation. Extraintestinal manifestations of IL10-related defects are folliculitis, arthritis, recurrent infections and B-cell lymphoma (6). *NLRC4*-related gain-of-function mutations are characterized by autoinflammation and infantile enterocolitis (AIFEC). *NLRC4* is one of the cytoplasmic NOD-like receptors which detect pathogen-associated molecular patterns and initiate inflammatory responses by activating caspase-1. Mutant *NLRC4* leads to production of the interleukin family IL-1 and IL-18, macrophage activation, and increased cell death, eventually leading to an autoimmune reaction. Defects in the *NLRC4* gene have also been reported to cause recurrent fever and severe systemic inflammation, such as macrophage activation syndrome (7). Autoimmune diseases in general are found to be strongly associated with

primary immunodeficiency conditions, and the same is seen in infantile IBD. Primary immunodeficiencies are also a recognized cause of infantile IBD, due to the interaction of the immune system with the luminal contents of the gastrointestinal tract, one of which is the *IKBKG* gene. A mutation in the *IKBKG* gene causes defects in the epithelial barrier and epithelial response, which lead to IBD. The *IKBKG* gene codes for nuclear factor-kB essential modulator protein (NEMO), and mutations in this gene cause defective NF-kB signaling, which leads to proinflammatory cytokine-mediated apoptosis of intestinal cells (8). This case series specifically demonstrates the aggressive and severe course of the disease early in life, and the importance of timely and correct management of the disease. Our series also shows that clinical remission is difficult in monogenic causes.

## Conclusion

This series highlights the importance of a genomic work-up in infantile IBD and early detection of the disease, to provide specific treatment at the proper time, as monogenic IBD patients do not usually respond to conventional treatment of IBD. This series also shows there are varied presentations of the disease, unlike adult IBD where the disease has specific and fixed signs and symptoms.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

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