Case Report

A Rare Cause of Rectovaginal Fistula in Early Infancy: It is in the Genes!

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Submitted: 17-Jun-2020
Revised: 18-Aug-2020
Accepted: 05-Sep-2020
Published: ***

Abstract

Acquired Rectovaginal Fistula (RVF) is rare in infants. Interleukin10/ Interleukin 10 receptor deficiencies are monogenic disorders presenting as aggressive forms of infantile onset inflammatory bowel disease with perianal abscess and fistula. Genetic studies assist in confirming the diagnosis. We present a two month old infant with rectovaginal fistula, severe colitis, failure to thrive and recurrent infections in whom colonoscopy revealed irregular colonic ulcers, and genetic studies confirmed an IL10RB mutation. Hematopoietic Stem cell transplantation is the definitive therapy for this disorder which the child underwent. We report this infant with an acquired RVF with extraintestinal features due to IL10RB mutation to highlight the importance of thinking beyond the local anatomy and looking into the genetic domain.

Keywords: *Rectovaginal Fistula, Infantile Onset IBD, Monogenic IBD, IL10/ IL10R, Hematopoietic Stem Cell Transplant*

Introduction

Acquired rectovaginal fistula (RVF) due to pediatric inflammatory bowel disease (PIBD) is rare in infancy. Infantile-onset IBD (IOIBD) with the onset of disease before the age of 2 years is associated with a 20%–30% prevalence of monogenic variants.[1,2] Monogenic disorders (MDs) present with colitis, perianal disease, recurrent infections, and failure to thrive. Interleukin-10 (IL-10)/IL-10 receptor (IL10/IL10R) mutations are important MDs causing severe colitis that does not respond to conventional therapy.[3,4] Hematopoietic stem cell transplantation (HSCT) is curative in this disorder.[5] We present an infant with IL10RB mutation, probably the first case from India, with severe colitis and RVF, who underwent HSCT.

Case Report

A 2-month-old female infant born to parents of three-degree consanguinity with a birth weight of 2.77 kg presented with a passage of feces per vagina from 1 week of age. She had a perianal abscess at the age of 25 days, with purulent vaginal discharge at 1 month of age which was treated with antibiotics. During this 2-month period, she was treated for atopic dermatitis, bilateral otitis media, and loose stools. She was on exclusive breast milk feed. There was a history of sibling death at 4 months of age due to diarrhea. On examination, the infant was not sick looking, her weight (3.5 kg) and length (53 cm) were below the 3rd percentile, and a normal BCG scar was seen. The abdomen revealed a soft 3-cm liver but no other organomegaly. The perianal area showed a puckered scar with a perianal tag. Yellow feces was seen in the vulval area. Rectal examination revealed soft stool without blood or mucous on finger stall. Investigations revealed Hb of 11g/dl, white cell count – 23,450 cells/cu. mm, platelet count – 10.77 lakh cells/cu. mm,

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Access this article online

Quick Response Code:

Website: www.jiaps.com

DOI: 10.4103/jiaps.JIAPS_217_20

How to cite this article: Swaminathan A, Sathiyasekaran M, Padankatti S, Padankatti RB, Arulprakash S, Raj R. A rare cause of rectovaginal fistula in early infancy: It is in the genes! J Indian Assoc Pediatr Surg 2020;XX:XX-XX.

erythrocyte sedimentation rate – 61 mm/h, CRP – 61.8 mg/l, serum albumin – 2.4 g/dl, procalcitonin – 0.35 ng/ml (normal <0.05 ng/ml), creatinine – 0.5 mg/dl, and sugar – 72 mg/dl; HIV serology were negative; and ultrasound of the abdomen and echo were normal. Two weeks later, she developed another perianal abscess. Pus from the abscess grew *Pseudomonas aeruginosa* sensitive to piperacillin-tazobactam and amikacin. The child was hospitalized, and parenteral antibiotics were administered. Examination under anesthesia revealed a rectovaginal fistula. Diversion sigmoid colostomy was done. The feculent vaginal discharge ceased following colostomy, but a mucoid discharge was seen intermittently. In view of the sibling death and history of infections in the index child, further workup to exclude MD was initiated. Serum immunoglobulin levels and T- and B-cell markers were normal. Nitroblue tetrazolium dye reduction test was negative. Targeted gene sequencing for primary immunodeficiency panel was performed which revealed a homozygous single-base pair deletion in exon 3 (c. 313 del) of the IL10 receptor B gene in chromosome 21. A diagnosis of secondary RVF due to a novel variant in IL10RB mutation was made. Prophylactic antibiotics were added. A distal loopogram at 4 months of age showed a reduced caliber of distal loop with contrast seen flowing freely through the vagina and anal canal [Figure 1]. Upper gastrointestinal endoscopy was done which showed mild scalloping of the duodenal mucosa. Colonoscopy through stoma and anus revealed skip lesions, multiple irregular ulcers of varying sizes, longitudinally aligned and covered with exudates [Figure 2], and pseudopolyps in the descending and transverse colon. Ileum was normal. A fistulous opening was noted in the anterior aspect of the lower rectum, anal opening was cicatrized and scarred, and anal skin tag was noted. Histopathological examination (HPE) showed blunting of the villi in the duodenum and increased cellularity of the lamina propria with lymphocytes, neutrophils, plasma cells, and eosinophils with no evidence of cryptitis, crypt abscess, or granuloma in the colonic mucosa. Although the macroscopic findings on colonoscopy were suggestive of Crohn's disease, the HPE was indicative of inflammatory bowel disease-unclassified (IBDU). At 7 months of age, magnetic resonance imaging pelvis was done which showed a tract between 11 mm from the anal verge to the posterior wall of the lower vagina. Anterior sagittal anorectoplasty was performed by the pediatric surgeon at 9 months of age. Diversion colostomy was retained and closure planned after HSCT. Parents were counseled by the hemato-oncologist and advised early HSCT. The father's human leukocyte antigen typing showed a 100% match with the child, and he was chosen as the donor. Hematopoietic Stem Cell Transplantation was performed at 11 months of age. The conditioning regimen comprised thiotepa, treosulfan and fludarabine. The neutropenic period was complicated by mucositis and frequent loose stools. She tolerated the transplant well, was engrafted by day 14 and is currently on follow up.

Discussion

Congenital RVF occurs in 4%–6% of anorectal malformations and is a rare, complex entity in female infants.[6] Acquired RVF due to IOIBD which constitutes 2%–3% of PIBD is very uncommon.[1,7] IOIBD has a higher prevalence of IBDU (30%) and MD (20%–30%) compared to older age onset polygenic PIBD.[1,2] A recent analysis from Toronto of 1005 children with PIBD revealed a monogenic cause in 3%.[7] An aggressive type of infantile IBD, with extraintestinal manifestations, recurrent infections, failure to thrive (as seen in this child), and poor response to conventional therapy, is highly suggestive of MD.[1] MD includes a diverse spectrum of >50 Mendelian inherited diseases, mainly primary immune deficiencies,

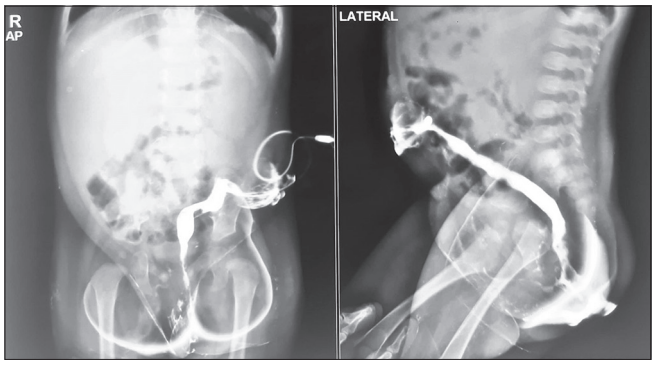

Figure 1: Loopogram showing reduced caliber of distal loop with contrast flowing freely through the vagina and anal canal

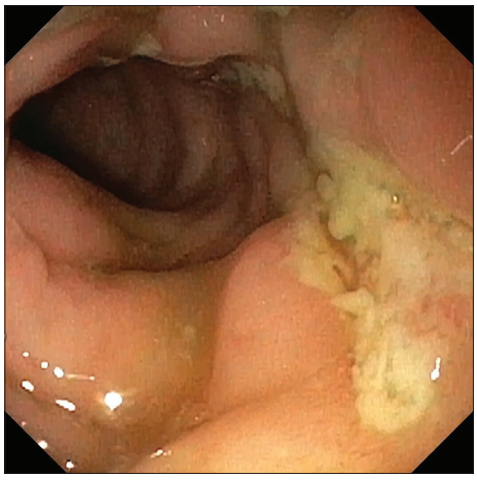

Figure 2: Colonoscopy showing longitudinal ulcer covered with exudates and skip lesions

of which defects in IL10/IL10R signaling pathway have been evaluated in depth. IL10/IL10R defects are autosomal recessive disorders with 100% penetrance for IBD like illness and have been reported worldwide but are more prevalent (38%–50%) in Asia.[1,3] Infants with IL10/IL10RA/IL10RB mutations have a similar phenotype, such as onset before 3 months of age, colitis, perianal fistulae, abscess, folliculitis, arthritis, and recurrent infections. Colonoscopy shows deep irregular ulcers, with neutrophilic infiltrates as noted in this child. IL10 is an important anti-inflammatory cytokine secreted by various cells such as monocytes, macrophages, eosinophils, NK cells, B-lymphocytes, dendritic, epithelial, and mast cells, and CD4+ T-cell subsets (including Th2 cells, Th1 cells, Th17 cells, and Tregs). IL10 maintains immune homeostasis by its proinflammatory response suppression through binding to the IL10 receptor (IL10R), which comprises 2 distinct chains: 2 molecules of IL10R1 (A chain) and 2 molecules of IL10R2 (B chain). This binding activates the JAK1/STAT3 cascade, which subsequently limits proinflammatory gene expression.[3] This infant had a homozygous mutation in IL10RB chain with the phenotype as described. About 78 cases of IL10, IL10RA, and IL10RB have been published till 2019 from Korea, China, Japan, Europe, and the USA but none from India to the best of our knowledge.[8] Huang *et al*. from China reported the largest cohort of 42 IOIBD with IL10R mutations in whom 97.6% were IL10RA and only 2.45% IL10RB deficiencies, and perianal fistula was documented in 58%.[9] In another study of 38 infants with IOIBD, 63% had IL10RA mutation in whom rectovaginal fistula was a manifestation in 37.5%.[10] However, Crowley *et al*. have reported only one (3.2%) IL10RB defect in their group of monogenic variants. This interesting observation may be due to the different ethnicities. IL10R mutations seem to be more common in the East than the West.[3,7] These infants do not respond to conventional therapy of PIBD such as enteral nutrition, steroids, immunomodulators, or biologics. HSCT is the definitive therapy for this disorder and was first reported in 2009 by Glocker *et al*.[11] Till date, about 25 cases have undergone HSCT with resolution of symptoms in about 80%.[8] This case report is to increase the awareness of this rare IL10RB mutation presenting with a rectovaginal fistula, a surgical problem, and the role of genetic studies and HSCT in the management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Uhlig HH, Schwerd T, Koletzko S, Shah N, Kammermeier J, Elkadri A, *et al*. The Diagnostic Approach to Monogenic Very Early Onset Inflammatory Bowel Disease. Gastroenterology. 2014; 147(5): 990–1007.
2. Kammermeier J, Dziubak D, Pescarin M, Drury S, Godwin H, Reeve K, *et al*. Phenotypic and genotypic characterisation of inflammatory bowel disease presenting before the age of 2 years. J Crohns Colitis 2017;11:60-69.
3. Zhu L, Shi T, Zhong C, Wang Y, Chang M, Liu X. IL-10 and IL-10 receptor mutations in very early onset inflammatory bowel disease. Gastroenterol Res 2017;10:65-69.
4. Kelsen JR, Sullivan KE, Rabizadeh R, Singh N, Snapper S, Elkadri A, *et al*. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Evaluation and Management for Patients With Very Early-onset Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr. 2020;70: 389–403.
5. Engelhardt KR, Shah N, Faizura-Yeop I, Kocacik Uygun DF, Frede N, Muise AM, *et al*. Clinical outcome in IL-10-and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. J Allergy Clin Immunol 2013;131:825-830.
6. Minneci PC, Kabre RS, Mak GZ, Halleran DR, Cooper JN, Afrazi A, *et al*. Screening practices and associated anomalies in infants with anorectal malformations: results from the Midwest Pediatric Surgery Consortium. J Pediatr Surg 2018;53(6):1163–1167.
7. Crowley E, Warner N, Pan J, Khalouei S, Elkadri A, Fiedler K, *et al*. Prevalence and Clinical Features of Inflammatory Bowel Diseases Associated With Monogenic Variants, Identified by Whole-Exome Sequencing in 1000 Children at a Single Center. Gastroenterology 2020;158:2208–2220.
8. Almana Y, Mohammed R. Current concepts in pediatric inflammatory bowel disease; IL10/IL10R colitis as a model disease. Int J Pediatr Adolesc Med 2019;6:1-5.
9. Huang Z, Peng K, Li X, Zhao R, You J, Cheng X, *et al*. Mutations in Interleukin-10 receptor and clinical phenotypes in patients with very early onset inflammatory bowel disease: a Chinese VEO-IBD collaboration group survey. Inflamm Bowel Dis. 2017;23:578–590.
10. Ye Z, Zhou Y, Huang Y, Wang Y, Lu J, Tang Z, *et al*. Phenotype and Management of Infantile-onset Inflammatory Bowel Disease: Experience from a Tertiary Care Center in China. Inflamm Bowel Dis 2017;23:2154–2164.
11. Glocker EO, Kotlarz D, Boztug K, Gertz M, Schaffer AA, Noyan F, *et al*. Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor. N Engl J Med. 2009 10; 361(21): 2033-2045.