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Case Report

# Very Early-Onset Inflammatory Bowel Disease in a Patient with Rare Genetic Syndrome

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## Abstract

An Indian boy of age around 4 years, born out of consanguineous marriage between healthy parents with chalky white skin, brownish hair, and grey eyes, representing oculocutaneous albinism presented with diarrhea, pain abdomen and fever for a duration of 4 months. Past history includes episodes of spontaneous nasal and gum bleed along with recurrent appearance of patches of bluish discoloration of skin involving extremities which resolved spontaneously without treatment. He was evaluated for the same and was diagnosed with Crohn's-like inflammatory bowel disease based on the endoscopic finding of longitudinal ulcerations in the colon and the histopathologic findings of chronic inflammation with granulomas. He was treated with corticosteroids but failed to improve clinically or biochemically. Based on the spectrum of oculocutaneous albinism, probable platelet dysfunction and inflammatory bowel disease a diagnosis of Hermansky-Pudlak syndrome was made which was confirmed on genetic screen using next-generation sequencing in a targeted gene panel analysis for primary immunodeficiency disease and/or inflammatory bowel disease. The patient proved to have homozygous mutation of HPS4 gene resulting in Hermansky-Pudlak syndrome type 4. The patient was started with infliximab which failed to produce sustained clinical response highlighting the difficulties in managing monogenic forms of inflammatory bowel disease.

**Keywords:** Very Early-Onset Inflammatory Bowel Disease; Hermansky-Pudlak Syndrome; Monogenic Inflammatory Bowel Disease; Biologicals

## Abbreviations

HPS: Hermansky-Pudlak Syndrome; IBD: Inflammatory Bowel Disease; VEO-IBD: Very Early-Onset IBD; IFX: Infliximab

## Introduction

Hermansky-Pudlak syndrome (HPS) is a very rare genetic disorder characterised by presence of oculocutaneous albinism, bleeding diathesis and ceroid lipofuscin accumulation in lysosomes [1,2]. It a autosomal recessive, genetically heterogeneous disorder with ten genetic subtypes described [1,3]. Patients with HPS, specifically those with genotype HPS-1, HPS-2, or HPS-4, are predisposed to interstitial lung disease that usually present in late adolescence to mid-adulthood [1]. In addition, some patients with HPS, specifically HPS-1, HPS-4, and HPS-6 develop granulomatous colitis similar to Crohn's disease - Inflammatory Bowel disease (IBD). HPS with IBD can also present at any age, but mostly in adolescence and young adulthood [1,2].

We report a very early-onset IBD (VEO-IBD) patient with HPS-4 who responded to infliximab.

## Case Report

A baby boy born of consanguineous marriage between healthy parents, delivered at full term by normal vaginal delivery with normal birth weight and 2 older healthy siblings was born with chalky white skin, brownish hair, and grey eyes (Figure 1a), indicating oculocutaneous albinism. At a later age (around 1-2 years) he developed horizontal nystagmus and difficulties in vision. Also the boy experienced recurrent patches of bluish discoloration of skin over upper and lower limbs which resolved spontaneously. He also had recurrent spontaneous episodes of nasal and gum bleed which improved on local therapy.

The boy presented to us at the age of 4 years with chronic diarrhoea and fever for a duration of 4 months. He was admitted in the Paediatrics department at our hospital and evaluated for the same.

Laboratory results' include a white blood cell count of 10.8 × $10^9$/dL (normal range, 4.0-10.1); red blood cell count of 5.34 × $10^9$/dL (4.0-5.3); haemoglobin 9.63g/dL (13-17); platelet count 539.7 × $10^6$/dL (150.0-450.0); serum total protein 7.5g/dL (5.3-

7.2); and albumin 3.6g/dL (3.5-4.2). C-reactive protein was 136.52 mg/L (0-6) and erythrocyte sedimentation rate, 71 mm/hr. (< 10). Prothrombin time was 14.6 s (11.0-15.0); activated partial thromboplastin time, 31.4s (24.0-39.0); and bleeding time, 2.3 min (2.0-5.0). Upper gastrointestinal endoscopy showed presence of atrophic duodenal folds with scalloping which on histopathological examination showed features of partial villous atrophy with mild increase in intraepithelial lymphocytes. His stool culture reports were sterile. Abdominal ultra- sonography and computed tomography showed bowel wall thickening in the transverse and descending colon. Lower gastrointestinal endoscopy showed erosive changes, multiple aphthous ulcers, and longitudinal ulcerations in the colon, but normal mucosa in the terminal ileum (Figure 1b and c); endoscopic biopsy specimens from the colon showed nonspecific chronic inflammation with granulomas.

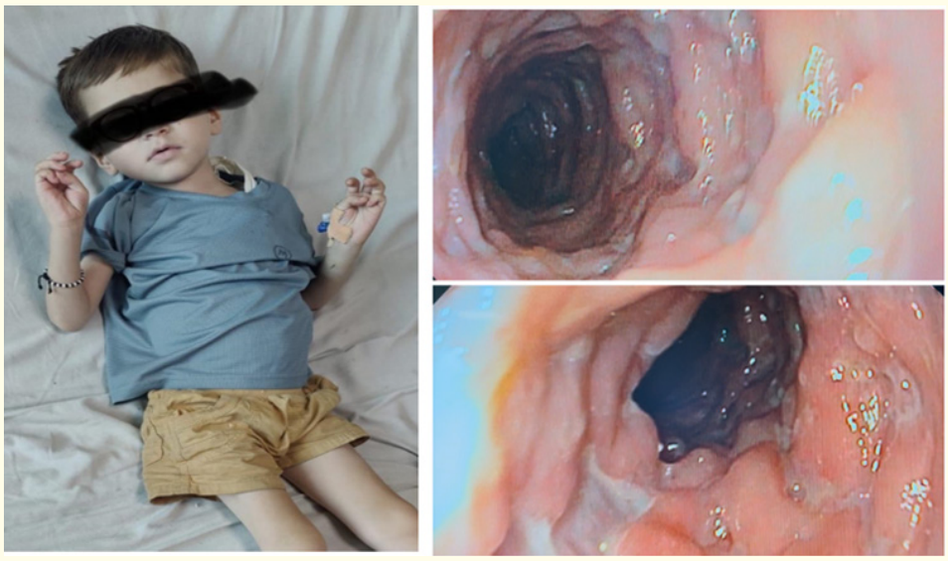

**Figure 1:** Clinical appearance of the patient demonstrating oculocutaneous albinism (a). Endoscopic findings - Endoscopy showed erosive changes, multiple aphthous ulcers, and longitudinal ulcerations in the colon but normal mucosa in the terminal ileum (b and c).

Based on clinical, laboratory, endoscopic and histopathological findings, the patient was diagnosed with IBD Crohn's disease. He was started on corticosteroids as per body weight and followed up. Both fever and diarrhoea worsened on the aforementioned treatment. Given a lack of improvement he was transferred to the Gastroenterology department of our hospital. He was extensively re-evaluated. Infective causes for the same particularly tuberculosis (being highly endemic in the region) were ruled out. Suspicion of monogenic forms of IBD was made; in view of presence of probable platelet dysfunction and oculocutaneous albinism along with IBD. The patient was started on Infliximab (6.5 mg/kg at 0 weeks, being repeated at 2 and 6 weeks). Concurrently, platelet morphology was evaluated. Electron microscopy showed absence of dense bodies in platelets, which was consistent with a diagnosis of HPS. Following parental informed consent, genetic screening using next-generation sequencing in a targeted gene panel analysis for primary immunodeficiency disease and/or IBD was performed (Additional file 1) [1,4]. A homozygous frameshift mutation was identified in the HPS4 gene (c.827del; pLeu276fs*18) on chromosome 22. These mutations have been identified in the patients of HPS type 4 and are associated with oculocutaneous albinism, platelet dysfunction and monogenic forms of IBD. The patient was diagnosed with HPS type 4 . To our knowledge no case reports or documentation for the disease has been previously done in India.

Following initiation of Infliximab, the clinical condition of the patient improved -stool frequency decreased and fever declined. However; the improvement was transient and following a short period of remission of around a month, patient again presented with increased stool frequency. Drug and antibody levels were measured to look for reasons for lack of efficacy but were found to be within normal range. Currently, the patient is being evaluated for other biological agents. This failure of response to standard medical therapy further highlights difficulty in treating monogenic forms of IBD.

## Discussion

HPS is a rare and heterogenetic syndrome predominantly occurring in the Caribbean island of Puerto Rico. HPS can be caused by 10 different genotypes involving various chromosomes. The genetic mutations cause abnormal vesicle formation involving melanosomes, platelet dense bodies and a subset of lysosomes. This results in visual impairment, skin hypopigmentation, and increased risk of bleeding [1,3]. Infantile and very early onset IBD has been reported in patients with HPS-1, HPS-4 and HPS-6; the pathogenetic mechanisms are thought to involve autoinflammatory pathways [1,2].

IBD in HPS shows pathologic features similar to Crohn's colitis: involvement of large bowel with sparing of ileum, large bowel showing irregular distribution of superficial and deep ulcers over inflamed mucosa interspersed with normal mucosa. Histopathological analysis of the same shows cryptitis, crypt abscess, inflammatory cell infiltrates and granulomas in involved areas [2,6,7]. In a study of 122 subjects with HPS, 8% overall were found to have IBD; among those with gastrointestinal symptoms, 33% were diagnosed with IBD [2]. IBD in HPS can present at any age including early childhood but most commonly becomes evident in adolescence and young adulthood.

In certain patients with HPS, conventional treatment of IBD including aminosalicylates and corticosteroids has been unsuccessful. Ongoing reports keep up with that immunosuppressants and anti-tumour necrosis factor α therapy such as Infliximab may be effective for IBD in patients with HPS [2,6,7].

Patients with rare genetic disorders can present with IBD, a situation referred to as monogenic IBD [4,8,9]. Patients with these disorders often develop symptoms during infancy or early childhood, along with endoscopic or histologic features of Crohn's disease, ulcerative colitis, or unclassified IBD. HPS is considered one of the monogenic IBDs [1,2,8]. Recognizing monogenic structures among IBD patients under 6 years of age can be vital in deciding the best treatment. Genetic screening using next-generation sequencing is a highly useful approach to diagnosis of patients with monogenic IBD [4,8,9]. In this patient, the clinical features of oculocutaneous albinism with nystagmus are consistent with an underlying diagnosis of HPS [1]. Such characteristic features may aid in diagnosing specific etiologies of infantile-onset IBD. In conclusion, to the best of our knowledge we consider our patient to be the first known HPS-4 patient with a very early-onset of IBD in India.

## Conclusion

Monogenic variants of IBD are rare and most occur in syndromic forms. High suspicion in presence of multisystem involvement for monogenic forms of IBD should be held as they fail to respond to the conventional therapies and can worsen rapidly. Physicians should consider genetic screening using next-generation sequencing when they treat patients with very early-onset IBD suspected to be monogenic.

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