VOLUME-9, ISSUE-6, JUNE-2020 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Pediatrics

# A RARE CASE OF CELIAC DISEASE IN A YOUNG MALE CHILD WITH HERMANSKY-PUDLAK SYNDROME

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**ABSTRACT** Hermansky-Pudlak syndrome (HPS) is a disorder caused by 10 different genotypes, characterized by oculo-cutaneous albinism, bleeding and systemic manifestation attributed to aberrant vesicle formation occurring in melanosomes, platelet dense bodies and certain lysosomal subtypes.

We report eight year old male with severe anemia and oculo-cutaneous albinism with complaints of bloody diarrhea, vomiting, and abdominal pain since one month. Electron microscopy revealed absent delta granules in platelets, hence a diagnosis of HPS was made. Serological- histopathological findings for gastrointestinal manifestations suggested celiac disease. After this diagnosis, he was started on gluten-free diet to which he responded and improved during his hospital stay but condition at home worsened few months later where he unfortunately expired.

Because of his severe presentation we can consider the course to be complicated by underlying HPS or celiac crises. Our case explores the association, diagnostic and management difficulty of celiac disease and Hermansky-Pudlak Syndrome

**KEYWORDS :**

**Case Description**

An eight year old male child presented with bloody diarrhea, abdominal pain and vomiting since one month. We further elicited a history of poor appetite, weight loss, and easy bruising. Physical examination revealed the child was severely malnourished with a BMI of 14.5, oculo-cutaneous albinism, horizontal nystagmus and photophobia (Figure 1). Pallor, grade 3 clubbing and pedal edema were also seen. His abdomen was tender and per rectal examination was normal. He was dyspneic at rest. Cardiac auscultation revealed gallop rhythm.

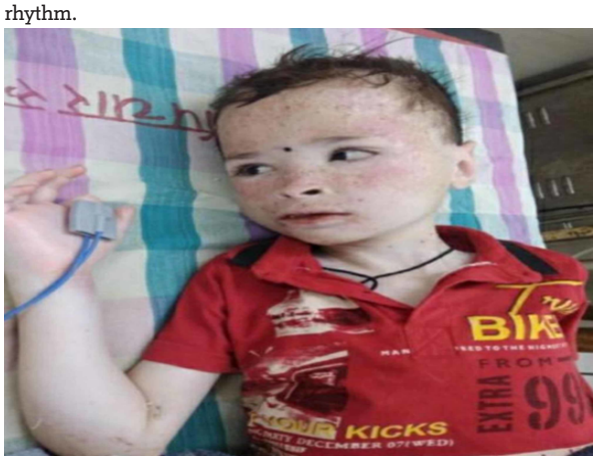


**Figure1: Patient On Presentation With Oculocutaneous Albinism And Horizontol Nystagmus**

Past history revealed that in the last three years the child was admitted multiple times for similar gastrointestinal complaints and bleeding manifestations for which he was symptomatically managed with multiple blood transfusions. No past history of recurring episodes of fever or pyogenic infections. Family history was significant for a paternal aunt diagnosed with albinism who passed away from an unknown cause at the age of 20 years.

**Investigations:**

Baseline investigations done at admission include Hemoglobin 4.5g/dl; platelet count 1.1 lakh/microlit; serum albumin 2g/dl; prothrombin time 22; INR 1.8.

Due to the constellation of all signs and symptoms like, a diagnosis of Hermansky-Pudlak syndrome was considered. For its confirmation we did an electron microscopy study of the platelets which demonstrated absent delta granules. Anti-tissue transglutaminase IgA antibodies were positive. Esophagogastroduodenoscopy showed scalloping of duodenal folds and increased vascularity. Colonoscopy showed edematous mucosa and decreased vascularity (Figure 2). Histopathology reports of biopsies from terminal ileum and sigmoid colon showed villous blunting and atrophy with dense lympho-plasmacytic infiltration (Figure 3&4). Intraepithelial lymphocytes were more than 25/100 epithelial cells suggestive of celiac disease.

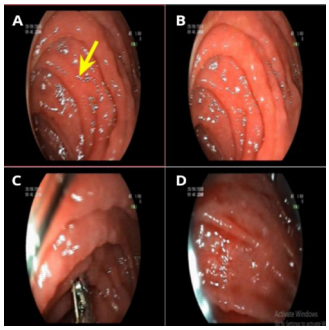


**Figure 2: A&B: Colonoscopy findings showing edematous mucosa; C&D: Esophagoduodenoscopy findings showing scalloping folds**

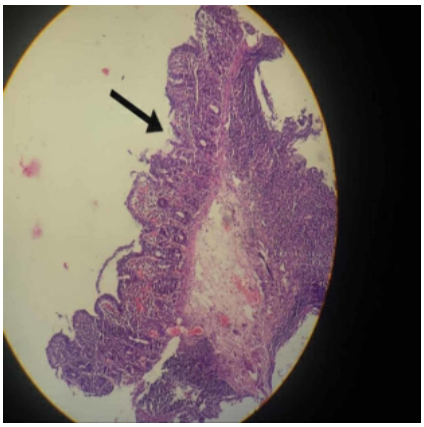

**Figure 3: Histology Of Terminal Ileum And Sigmoid Colon Biopsies Demonstrating Villous Blunting And Atrophy.**

2D echocardiogram was suggestive of global left ventricular hypokinesis. Abdominal CT and HRCT of chest was normal.

**Differential Diagnosis:**

The presence of oculo-cutaneous albinism (OCA), bleeding diathesis and gastrointestinal involvement suggested the diagnosis of syndromic OCA subtypes such as Chediak-Higashi or Hermansky-Pudlak syndrome or Griscelli syndrome. In our case, Chediak-Higashi syndrome was ruled out due to absence of repeated pyogenic infections and neutropenia. Griscelli syndrome is usually characterized by silver-gray hair, and melanin pigment aggregation in the hair shaft was not seen in our patient and was hence ruled out. A diagnosis of Hermansky-Pudlak syndrome was suggested and it was supported by the absence of platelet delta granules on electron microscopy study. Gastrointestinal investigations gave strong evidence to confirm the diagnosis of celiac disease.

Thus, we made a final diagnosis of Hermansky-Pudlak syndrome with celiac disease.

**Management And Follow-up:**

The patient's fluid and electrolyte imbalances on admission were corrected with fluid replacement. He received multiple blood transfusions for his ongoing hematochezia and severe anemia. He was kept on parenteral nutrition initially and slowly oral feeds were uptitrated. Third generation cephalosporins were given 5 days when all the septic work-up came out negative. Gluten-free diet was started and compliance was ensured. He responded well to this diet in the form of decreased frequency of loose stools, as well as a regain of appetite and weight. He was discharged after 35 days of hospitalization and the parents were advised to adhere to a strict gluten-free diet. After discharge, the patient came for regular follow ups and even showed signs of improvement. However, two months later, his condition relapsed when he was still at home, which led to his unfortunate demise.

## DISCUSSION

HPS can be caused by 10 different genotypes. These aberrant genes cause abnormal vesicle biogenesis and trafficking involving melanosomes, platelet dense bodies, and a subset of lysosomes resulting in visual impairment, skin hypopigmentation, and increased risk of bleeding [1]. Impaired secretion of lytic granules by cytotoxic T cells predominantly leads to the primary immunodeficiency seen in some subtypes of HPS [2]. Gastrointestinal complications are an important manifestation in patients with HPS but their pathogenesis remains unclear. Schinella et al first reported granulomatous colitis as a complication in HPS.

Typically, clinical features of gastrointestinal involvement include signs and symptoms of inflammatory bowel disease, like abdominal pain, bloody diarrhea, symptoms of bowel constriction, and perianal fistula. They usually present in the first few decades of life. Colonoscopic findings range from mild hyperemia to linear ulceration and fissuring. Microscopically, the bowel shows areas of hyperemia and denuded epithelium with non-necrotizing granulomas. Ceroid deposits may be identified in the intestinal lesions [3]. In a retrospective study conducted on patients with HPS by Hussain et al, inflammatory bowel disease (IBD) was found to be the most common gastrointestinal manifestation. In our patient, the gastrointestinal symptoms of bloody diarrhea and colonoscopic findings suggestive of colitis do raise the probability of IBD similar to those reported in literature, however histopathologic findings did not coincide, and instead provided conclusive findings of celiac disease. We are therefore inclined to explain the diarrhea by celiac disease and the hematochezia as part of the bleeding diathesis in HPS due to platelet dysfunction. Considering the age of onset of IBD in HPS and the early demise of our patient, it is difficult to say whether our findings of non-specific colitis represented the early beginnings of IBD.

Celiac disease is an immune-mediated enteropathy characterised by injury to the intestinal mucosa, affecting mostly the small intestine. It is triggered by dietary intake of gluten in genetically susceptible individuals with class II human leukocyte antigen (HLA) DQ2 and DQ8. It is one of the most common causes of malabsorption with progressive villous atrophy which limits both production of digestive enzymes and production of iron and some vitamins especially fat soluble vitamins such as A, D, E and K. Celiac disease is diagnosed by serologic evaluation (anti-tissue transglutaminase (TTG) antibody, anti endomysial antibody, anti Deaminated Gliadin Peptide (DGP) antibody), genetic testing for HLA DQ2/DQ8 and small intestinal biopsy. Histologic findings include intraepithelial lymphocytes, loss of villi, flat mucosa and crypt hyperplasia [4]. Typically, clinical response to a gluten-free diet is faster in children; the mean time to symptom relief is four to eight weeks and serologies often improve within six months and normalize within 12-18 months. Celiac disease rarely presents with life-threatening complications, however there have been a few documented cases of celiac crisis, mainly in children [4,5].

It is known that inflammatory diseases of the gut are commonly encountered in patients with primary immune deficiencies. The exact pathogenesis of gastrointestinal diseases in the setting of primary immunodeficiency remains unknown, however, both humoral and cell-mediated immunity appear to play a role in preventing intestinal inflammation. This is why patients presenting with atypical gastrointestinal disease and/or failure to respond to conventional therapy should be evaluated for an underlying primary immune disorder.

The severity of clinical presentation of our patient at the time of admission went beyond the features of regular celiac disease. We could consider the course to be complicated by underlying Hermansky-Pudlak Syndrome, but our patient showed no other overt signs of primary immunodeficiency such as neutropenia or recurrent infections which could have contributed to a complicated celiac disease presentation. We did, however, find celiac crisis to be a worthy explanation of this fulminant clinical course.

The term "celiac crisis" has been used since the 1950s. Traditionally, celiac crisis was associated with a high mortality rate. Celiac crisis can be defined as acute as well as rapid progression of gastrointestinal symptoms attributable to CD which requires hospitalization and parenteral nutrition

along with signs of severe dehydration and at least two of the following: hemodynamic instability, neurologic dysfunction, renal dysfunction, metabolic acidosis, hypoproteinemia, dyselectrolytemia, and weight loss [5,6]. Our patient showed four of the above manifestations making celiac crisis a likely explanation. Even though our patient responded to treatment during hospitalization, we can only speculate that his untimely death was at the hands of a fatal bout of celiac crisis. Adherence to strict gluten-free diet is difficult and costly. In a resource-limited environment such as ours, it is not uncommon to see poor compliance to this diet.

The clinical findings of oculocutaneous albinism in combination with the absence of platelet delta granules on whole-mount electron microscopy are enough to establish a diagnosis of HPS. However, we were unable to confirm it or determine the subtype of HPS with genetic testing due to financial restrictions. Despite this drawback, the uniqueness of our case warrants its reporting.

## CONCLUSIONS

To our knowledge, this is the first case reporting celiac disease in a patient with Hermansky-Pudlak Syndrome. This association should be explored with further studies to determine if it was coincidental or if there is any pathogenic link between HPS and celiac disease.

Celiac crisis is often the initial presentation of celiac disease as in our case. Physicians should consider the differential of celiac crisis in an individual presenting with gastrointestinal disturbances, hemodynamic instability, hypoproteinemia and dyselectrolytemia.

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