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Case Report

Prolidase deficiency presenting as inflammatory bowel disease in an infant

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ABSTRACT

Prolidase deficiency (PD) is a rare autosomal recessive inborn error of metabolism caused by pathogenic variants in the PEPD gene, leading to impaired collagen degradation and proline recycling. Gastrointestinal manifestations are uncommon and may mimic inflammatory bowel disease (IBD), particularly in early childhood, resulting in diagnostic delay. We report a 16-month-old girl who presented with chronic diarrhoea, failure to thrive, and haematochezia, with endoscopic and histological features suggestive of IBD. Subsequent genetic evaluation revealed a homozygous frameshift mutation in the PEPD gene, confirming prolidase deficiency. This case highlights PD as an important differential diagnosis in very early-onset IBD and emphasizes the need for heightened clinical suspicion in infants with atypical features, consanguinity, and multisystem involvement.

Keywords: Prolidase deficiency, Inflammatory bowel disease, Infant, Very early onset IBD, PEPD gene

INTRODUCTION

Prolidase deficiency is a rare autosomal recessive metabolic disorder resulting from pathogenic variants in the PEPD gene, which encodes the enzyme prolidase (peptidase D).[1,2] Prolidase is a metalloproteinase that catalyzes the final step of collagen degradation by cleaving imidodipeptides containing C-terminal proline or hydroxyproline.[1,2] This process enables recycling of proline for collagen resynthesis and extracellular matrix remodeling.[1] Deficiency of this enzyme leads to accumulation of iminodipeptides and impaired collagen turnover, resulting in multisystem involvement including characteristic facial dysmorphism, recurrent infections, developmental delay, dermatologic manifestations, and variable gastrointestinal features.[1,2] Gastrointestinal symptoms such as chronic diarrhoea, malabsorption, and failure to thrive have been reported.[3-5] However, presentation resembling inflammatory bowel disease (IBD), particularly in infancy, is uncommon but increasingly recognized.[3-8] We describe an infant with PD presenting with clinical, endoscopic, and histologic features suggestive of IBD and review the evolving literature on gastrointestinal and hepatic involvement in PD.

CASE REPORT

A 16-month-old female child, born to third-degree consanguineous parents, presented with chronic diarrhoea for 6 months of age, failure to thrive, intermittent low-grade fever, and haematochezia for 6 weeks. There was a history of recurrent respiratory tract infections and poor weight gain. There was no family history of IBD. On examination, the child was undernourished with weight-for-age<−2 Z score and height-for-age −1 Z score. Dysmorphic features included hypertelorism, epicanthic folds, up slanting palpebral fissures, and anteverted nares.

A 2×1 cm café-au-lait macule was noted in the right axilla, along with generalized hypertrichosis. Perianal excoriations were present. Abdominal examination revealed mild distension without organomegaly.

Laboratory investigations showed microcytic anaemia (haemoglobin 8.6 g/dL), elevated C-reactive protein (28 mg/L), and hypoalbuminemia (2.4 g/dL). Immunoglobulin levels were normal. Stool cultures and parasitological examinations were negative. Fecal calprotectin was markedly elevated (918 µg/g).

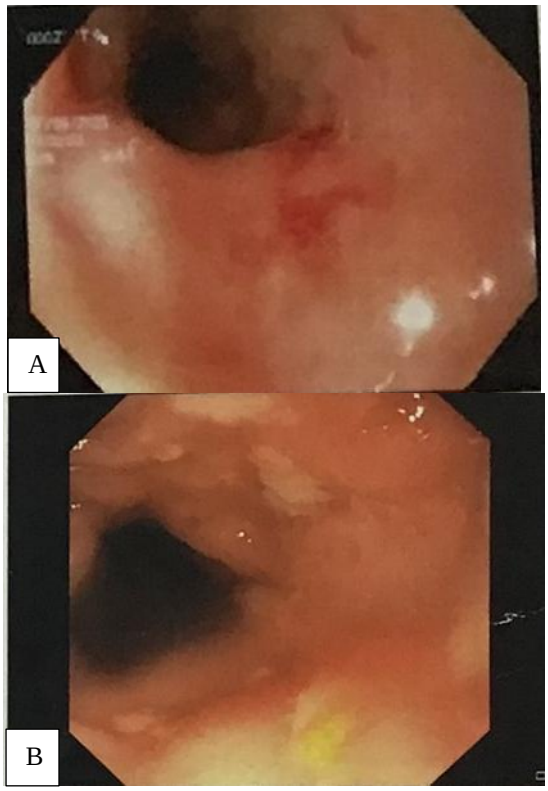

Figure 1 (A and B): Colonoscopy image showing diffuse erythema and friability of the rectosigmoid mucosa with superficial ulcerations.

Upper gastrointestinal endoscopy was normal. Colonoscopy demonstrated diffuse erythema, friability, and superficial ulcerations involving the rectum and sigmoid colon, with a normal terminal ileum. Histopathological examination revealed focally ulcerated colonic mucosa with cryptitis and crypt abscesses. The lamina propria showed a mixed inflammatory infiltrate comprising neutrophils, eosinophils, lymphocytes, and plasma cells, with focal histiocytic aggregates suggestive of ill-formed granulomas. These findings were consistent with IBD. Granulomatous inflammation was suggestive of a Crohn's disease like inflammation.

The child was initially treated with oral prednisolone for induction of remission along with mesalazine. She relapsed after six months and required a second course of steroids. Following confirmation of normal thiopurine methyltransferase activity, Azathioprine was initiated as a steroid-sparing agent, and mesalazine was continued. She has remained in clinical remission for three years.

Given the very early age of onset, very early-onset IBD was considered, and whole-exome sequencing was performed. Genetic analysis revealed a homozygous frameshift mutation in the *PEPD* gene (NM_000285.4, exon 12, c.825del; p.Phe275LeufsTer46), confirming PD. Both parents were heterozygous carriers of the same pathogenic variant. This mutation has not been reported hitherto.

DISCUSSION

PD is a rare autosomal recessive inborn error of metabolism caused by pathogenic variants in the PEPD gene, leading to reduced or absent prolidase activity.[1,2] Impaired collagen degradation and defective extracellular matrix remodelling explain the multisystem manifestations characteristic of this disorder.[1,2] Early descriptions of PD emphasized biochemical heterogeneity and systemic involvement, including recurrent infections, organomegaly, autoimmune features, hematologic abnormalities, and neurodevelopmental delay.[1,2] Gastrointestinal involvement was recognized in early clinical series, with reports describing chronic diarrhoea and enteropathy.[4] A major advancement in understanding the natural history of PD came with the quantitative systematic review by Rossignol et al in 2021.[5]

This analysis of 161 reported patients provided robust frequency estimates of organ involvement and documented hepatomegaly in 13.5% and elevated transaminases in 6.7% of cases, confirming that hepatic abnormalities represent a reproducible component of the PD phenotype.[5] The association between PD and IBD–like colitis has emerged over the past decade. Roy et al first described PD presenting with IBD-like colitis in 2014.[3] Shortly thereafter, Kuloglu et al in 2015 reported a young girl with PD who developed chronic colitis mimicking IBD.[6]

The patient exhibited persistent diarrhoea, mucosal inflammation, and histologic findings compatible with IBD. Rizvi et al in 2019 further strengthened this association by reporting a toddler with PD diagnosed with very-early-onset Crohn's disease.[7] Subsequent observations from India by Madhusudan et al in 2021 described PD presenting as very-early-onset IBD, highlighting its relevance among monogenic causes of early childhood IBD.[8] Beyond inflammatory colitis, gastrointestinal involvement may extend to other complications. A 2022 case report described PD presenting with upper gastrointestinal bleeding, suggesting possible vascular fragility or impaired mucosal repair related to defective collagen metabolism.[9]Hepatic involvement in PD, once considered incidental, is increasingly recognized as clinically significant. While mild transaminase elevation and

hepatomegaly were noted in earlier reports, systematic quantification was provided by Rossignol et al.[1-5] More recently, Gopalakrishna et al in 2024 described a case series of chronic liver disease in patients with PD.[10] Their findings included persistent liver enzyme abnormalities, hepatosplenomegaly, nodular regenerative hyperplasia, and bridging fibrosis, indicating potential progression to chronic liver disease.[11] Further expanding the hepatic phenotype, Castro et al in 2025 reported a paediatric patient with PD who developed porto-sinusoidal vascular disorder and non-cirrhotic portal hypertension. Histopathology demonstrated sinusoidal dilatation and nodularity, and the patient developed oesophageal varices.[11]

These findings suggest that impaired extracellular matrix remodelling may contribute to abnormal hepatic vascular architecture and portal hypertension. Mechanistically, collagen is critical for intestinal barrier integrity and hepatic sinusoidal structure.[1,2] Impaired collagen turnover may predispose patients with PD to mucosal inflammation, vascular remodelling, and progressive fibrosis. Additionally, immune dysregulation described in PD may further contribute to chronic inflammation.

Chronologically, the understanding of gastrointestinal and hepatic involvement in PD has evolved from recognition of nonspecific enteropathy to identification of IBD-like phenotypes and more recently, progressive chronic liver disease including vascular disorders.[3,4,7,8,10,11] Clinicians should therefore maintain a high index of suspicion for PD in children presenting with very-early-onset IBD, unexplained chronic liver disease, or portal hypertension, particularly when accompanied by dysmorphic features, recurrent infections, or consanguinity.

CONCLUSION

PD should be considered in infants presenting with severe or atypical IBD-like colitis, especially in the presence of consanguinity, dysmorphic features, recurrent infections, and poor growth. Early genetic evaluation facilitates accurate diagnosis, prevents inappropriate prolonged immunosuppression, and enables appropriate counselling and surveillance for potential hepatic complications.

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