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A Novel Manifestation of Prolidase Deficiency in a Toddler Diagnosed With Very-early-onset Crohn Disease

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We report a pediatric case of very-early-onset Crohn disease (VEO-CD) in association with the unexpected finding of prolidase deficiency (PD) by whole-exome sequencing (WES). CD is a chronic granulomatous inflammatory bowel disorder that may affect the entire gastrointestinal tract and extraintestinal sites (1). Although the average age of diagnosis of pediatric inflammatory bowel disease (IBD) is 10 to 12 years, the fastest rates of rise in new diagnoses have been in children younger than 5 years (2), which represents the subset of VEO-IBD. Patients with VEO-IBD account for 15% of all pediatric IBD cases and can have a worse prognosis, as they may not respond to conventional therapies. WES has played a vital role in identifying monogenic defect in a subset of VEO-IBD (3).

One such genetic defect is PD, an autosomal recessive disorder of proline and hydroxyproline metabolism. PD leads to impaired collagen synthesis causing delayed wound healing. PD is usually associated with cutaneous ulcers, dysmorphic facies, skeletal deformities, splenomegaly, mental retardation, and recurrent infections. Incidence of PD is extremely rare (1–2 per 1,000,000 individuals); thus far, only 93 cases have been reported in the literature, usually in consanguineous or genetically restricted populations (4). This rare combination of VEO-CD and PD has only been described in the literature once (5) but should be considered in cases of VEO-IBD complicated by recalcitrant skin ulcers and findings not typical of CD.

CASE PRESENTATION WITH IMAGING

A 5-year-old African American boy presented with chief complaints of recurrent scrotal edema, severe cutaneous ulcers, and chronic diarrhea with poor growth for 2 years.

Past medical history was notable for onset of profuse diarrhea, pallor, and fatigue at 3 years of age. At that time, his evaluation was significant for hypoalbuminemia (2.7 g/dL), elevated fecal calprotectin (1374 μg/g), pancytopenia with microcytic anemia, and elevated erythrocyte sedimentation rate, and transaminitis. Due to marked developmental delay including no verbal language and abnormal behaviors typical of autism spectrum disorder, the patient underwent genetic evaluation for Fragile X, chromosomal microarray analysis, and urine organic acids screen, which were all negative. Patient was then lost to follow-up for 2 years.

At current presentation at 5 years of age, his weight was at 38%tile and length at 8%tile for age. Physical examination revealed dysmorphic facies with flat nasal bridge, hypertelorism, large epicanthal folds, misaligned teeth, high-arched palate, splenomegaly, scrotal edema, and a large nonhealing ulcer over dorsum of his left foot.

Laboratory findings were remarkable for elevated fecal calprotectin 1134 μg/g, aspartate aminotransferase (AST) 46 U/L, C-reactive protein (CRP) 58 mg/L, erythrocyte sedimentation rate (ESR) 72 mm/h, white blood cell 15,800/mm^3. Diffuse severe scrotal edema with associated hyperemia was noted on scrotal ultrasound and splenomegaly was confirmed on abdominal ultrasound. Colonoscopy showed pancolitis with serpiginous ulcers and pseudopolyps (Fig. 1), but no perianal disease. Colonic biopsy showed chronic colitis with Paneth cell metaplasia, consistent with very early CD. Abdominal computed tomography with IV contrast did not show any evidence of small bowel disease. After diagnosis, he was started on steroids and sulfasalazine with minimal improvement in diarrhea and cutaneous ulcers.

In order to rule out unusual genetic causes of VEO-CD with associated atypical physical findings, WES was performed, which revealed homozygosity for the c.826G>A mutation in the *PEPD* gene, resulting in a D276N amino acid substitution in the prolidase enzyme. This pathogenic variant is reported in autosomal recessive PD and has not been observed in healthy individuals.

Additional chromosomal testing revealed long contiguous stretches of homozygosity across 5 of his 22 autosomes representing 2% of his total autosomal genomic content. The presence of long contiguous stretches of homozygosities on multiple chromosomes reflected regions by descent, strongly suggesting that his parents share a common ancestor. Although denied by mother, homozygosity of this very rare *PEPD* variant suggests consanguinity. The patient's parents are presumed obligate carriers of the mutation; the biological father was not available for genotyping.

Because of uncontrolled CD symptoms, treatment was changed to infliximab (IFX) monotherapy, but patient developed loss of response and high IFX antibody titers after 3 infusions.

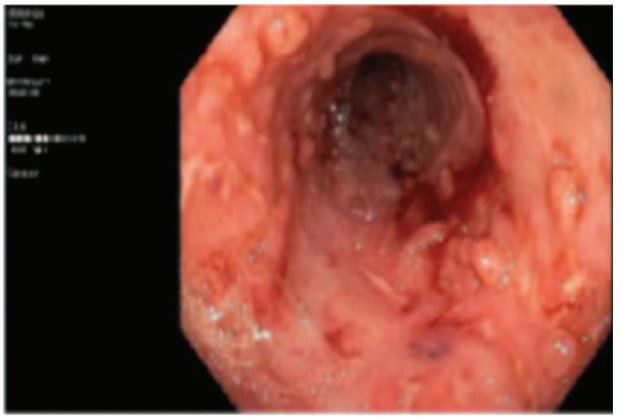

FIGURE 1. Colonoscopy results showing pancolitis with serpiginous ulcers and pseudopolyps.

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Subcutaneous weekly methotrexate as a mild immunosuppressive steroid-sparing agent plus topical tacrolimus was then started, with rapid resolution of his diarrhea and skin ulcers. After 1 year on treatment, his symptoms were minimal with appropriate weight gain, normalization of his labs, and normal repeat colonoscopy.

DISCUSSION

Although CD typically presents with diarrhea, weight loss, anorexia, and abdominal pain, extraintestinal manifestations may complicate definitive diagnosis. These associated symptoms include arthritis, uveitis, erythema nodosum, and pyoderma gangrenosum (6), but isolated scrotal edema is uncommon. The patient's skin lesions were not typical of CD and his overall constellation of symptoms and dysmorphic facial features led to genotyping that revealed homozygosity for rare mutation in the *PEPD* gene that is strongly associated with autosomal recessive PD. Patients with PD have severely impaired prolidase activity and present with unusual chronic skin ulcers, severe intellectual disability, dysmorphic features, recurrent respiratory infections, and occasionally features of hyper-IgE syndrome and systemic lupus erythematosus (1).

Association of PD with autoimmune disease has been described, but only 1 case report has noted an association of IBD with mutations in the *PEPD* gene (5). Our case illustrates a second patient with IBD and PD. Potentially, defects in collagen synthesis and impaired wound healing seen in PD could cause the instability of the mucosal-gut barrier and predispose to a heightened inflammatory response seen in CD. Currently, there are no curative treatment options available for PD. Supportive wound care has shown to be efficacious in most patients. After failing steroids, sulfasalazine and IFX, subcutaneous methotrexate (MTX) was used to treat his CD and cutaneous ulcers, in combination with topical tacrolimus since the resulting immunosuppression is relatively mild. His diarrhea, skin lesions, and growth rapidly improved. Therefore, we propose that subcutaneous MTX plus as-needed topical tacrolimus should be considered as initial treatment for patients with coexistent CD and PD. Lastly, children presenting with VEO-CD, especially those with unusual manifestations, require immune, rheumatologic, and genetic evaluations to rule out syndromes that may require alternative treatments and affect long-term prognosis.

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