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An Amish boy with recurrent ulcerations of the lower extremities, telangiectasias of the hands and chronic lung disease

Jeffrey J. Kelly, DO^a, Alexandra F. Freeman, MD^b, Heng Wang, MD, PhD^c, Edward W. Cowen, MD, MHSc^d, and Heidi H. Kong, MD^d

^aDepartment of Dermatology, Walter Reed Army Medical Center, Washington, DC

^bLaboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD

^cDDC Clinic for Special Needs Children, Middlefield, OH

^dDermatology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

CASE SUMMARY

History

A 6-year-old white male of Amish ancestry with chronic lower extremity ulcers was seen in the Dermatology Clinic at the National Institutes of Health (NIH) Clinical Center in Bethesda, MD. Since the age of 2, the patient had experienced numerous deep ulcers on the thighs, legs, and feet that developed without preceding trauma. His wounds typically healed slowly leaving depressed atrophic scars. At the time of presentation, the patient had ulcers limited to the soles of both feet and difficulty ambulating due to associated pain. The ulcers on the left sole had been present for nine months. His parents reported frequent epistaxis and easy bruisability. At age 4, the patient underwent splenectomy for thrombocytopenia and was found to have esophageal varices and cirrhosis. He also suffered from pulmonary hypertension, recurrent pneumonias with bronchiectasis, recurrent otitis media, and chronic sinusitis. At the time of evaluation, the patient required three liters per minute of continuous oxygen via nasal canula.

The patient's parents were second cousins. Several family members had had similar medical problems: his older brother died at 13 months of age of respiratory failure with history of leg ulcers and recurrent infections; a paternal cousin also died at 13 months of age with recurrent infections, chronic lung disease and pulmonary hypertension; and a living maternal cousin had leg ulcers and recurrent infections. The patient had three healthy siblings. He shared a common ancestry with an Amish kindred several generations earlier who exhibited similar physical findings.

Physical examination

The patient was a Caucasian male appearing smaller than stated age with hypertelorism and a depressed nasal root. On the left foot there were two deep ulcers with irregular borders and

Correspondence to: Heidi H. Kong, MD, Dermatology Branch, Center for Cancer Research, National Cancer Institute, Bldg10/Room 12N238, 10 Center Dr, MSC 1908, Bethesda, MD 20892-1908. konghe@mail.nih.gov.

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yellow adherent material on the heel and lateral mid-sole (Fig 1). The plantar surface of the right foot had multiple smaller ulcers. The ulcerated areas were tender to palpation and prevented normal ambulation. Multiple well-healed depressed scars were present on both soles. Numerous 1–3 cm ovoid depressed, atrophic scars were observed on the lateral and anterior aspects of the thighs (Fig 2). A few scattered telangiectatic vessels were noted on the dorsal feet and anterior thighs. More pronounced densities of telangiectatic vessels were present on the palmar and dorsal surfaces of both hands (Fig 3). There was marked clubbing of all fingers. Oral exam revealed normal mucosa with absence of multiple teeth. The abdomen was distended with a large well healed surgical scar on the right upper quadrant.

Significant diagnostic studies

Notable laboratory results performed at the time of the patient's admission to the NIH included increased white blood cells (41.83 K/ μ L) with neutrophilia (87.6%) and increased platelet count (810 K/ μ L). These hematologic abnormalities were related to his prior splenectomy. He had elevated IgA (306 mg/dL), IgG (2320 mg/dL), and IgE (3065 IU/mL) levels but a normal IgM level (138 mg/dL). PT/PTT and routine urinalysis were unremarkable.

DNA mutation analysis from cord blood at birth indicated a single nucleotide nonsense mutation of the peptidase D* (*PEPD*) gene resulting in a premature stop codon.

Diagnosis

Prolidase deficiency

DISCUSSION

Prolidase deficiency is a rare autosomal recessive inborn error of amino acid metabolism that results from mutation of the human prolidase gene, peptidase D (*PEPD*) on chromosome 19q12-q13.2. To date, at least 13 mutations of *PEPD* have been described.¹ Prolidase is a ubiquitous metalloenzyme involved in the catabolism of dietary and endogenous proteins, especially imino acid-rich proteins such as collagen. Prolidase is important for supplying and recycling proline for protein synthesis and cellular growth through hydrolysis of iminopeptides with C-terminal proline or hydroxyproline.^{2, 3}

Patients with prolidase deficiency have high circulating levels of iminopeptides containing a C-terminal proline with resultant urinary excretion of these iminopeptides. The first description of prolidase deficiency was by Goodman et al in 1968.² The clinical characteristics were further defined by Powell et al. in 1974 with the report of absent prolidase in association with the characteristic clinical features of prolidase deficiency.⁴ Approximately 60 cases have now been described in the literature.⁵

The range in clinical features observed with prolidase deficiency varies from no obvious clinical abnormalities to a constellation of recurrent infections, chronic leg ulcers, characteristic facies, mental retardation, and splenomegaly.^{5, 6} Features of prolidase deficiency typically present at birth or within the first two decades of life. Ulcers are a classic cutaneous finding in prolidase deficiency and are usually irregularly shaped with prominent granulation tissue. These ulcers, which are often slow to heal and resistant to typical wound care, have been described as the most troublesome feature of the disease [6]. The lower extremities are most frequently affected but anogenital ulcers have also been

*The nonsense mutation of *PEPD* in this Amish patient with prolidase deficiency and his kindred was previously reported by Wang, Kurien, Lundgren, et al. (A nonsense mutation of *PEPD* in four Amish children with prolidase deficiency. *Am J Med Genet* 2006;140A:580-5).

described. Other reported dermatologic manifestations include skin fragility of the lower extremities and anogenital region, atrophic scarring, pruritic eczematous lesions, necrotic papules, telangiectasias, hyperkeratosis of knees and elbows, purpuric lesions, low hairline, poliosis, premature graying, lymphedema, photosensitivity, and impetigo-like eruptions.⁶⁻⁸

Facial dysmorphisms include hypertelorism, saddle nose deformity, frontal bossing, dull expression, mild ptosis, micrognathia, mandibular protrusion, and exophthalmus.⁸ Other manifestations include splenomegaly, protuberant abdomen, joint laxity, short stature, deafness, osteoporosis, high-arched palate, erosive cystitis and mental retardation. Recurrent infections such as sinusitis, otitis media and upper respiratory tract infections are common.^{6, 7} Laboratory abnormalities associated with prolidase deficiency include iron deficiency anemia, thrombocytopenia, elevated liver enzymes, and elevated serum immunoglobulins including serum IgE.^{8, 9}

The underlying immunodeficiency related to development of recurrent infections has not yet been elucidated. Hypocomplementemia (C3, C4, CH50) and hypergammaglobulinemia have been noted in several cases. Abnormal neutrophil chemotaxis has been documented in patients with recurrent infections.⁹

Although recurrent non-infectious lower extremity ulcers beginning in childhood are characteristic of prolidase deficiency, ulcers accompanied by telangiectasias may be seen in cutis marmorata telangiectatica congenita (CMTC). Unlike prolidase deficiency, widespread large reticulated vascular patterns are seen in CMTC. Multiple cutaneous ulcers develop in patients with vasculitides, coagulopathies, or autoimmune conditions. However, ulcers associated with prolidase deficiency typically manifest at an earlier age and are accompanied by additional findings such as facial dysmorphisms and recurrent infections.

Widespread cutaneous telangiectasias are present in hereditary hemorrhagic telangiectasia (HHT), but the mucosal distribution of the telangiectasias and the visceral arteriovenous malformations associated with HHT are not characteristic of prolidase deficiency. Diffuse telangiectasias, skin fragility and photosensitivity are present in patients with Kindler Syndrome. However, the skin fragility of Kindler syndrome is associated with blistering, not spontaneous ulceration.¹⁰

Hyper-immunoglobulin E syndrome (HIES) associated with STAT3 mutations is characterized by elevated IgE with recurrent cutaneous and pulmonary infections, facial dysmorphism, and eczematous eruptions.¹¹ Although several clinical findings, including high-arched palate, joint laxity, osteoporosis, and elevated serum IgE, are found in both prolidase deficiency and HIES, it is not known if the two syndromes are mechanistically related.¹ Features of HIES such as cold staphylococcal abscesses, coarse facial features, retained primary teeth, and normal intelligence distinguish HIES patients from patients with prolidase deficiency.

These disorders can be differentiated from prolidase deficiency by screening for elevated levels of urinary imidodipeptides yet this solitary finding is not diagnostic for prolidase deficiency. Increased urinary imidodipeptides reflecting collagen degradation may also occur in hypophosphatemic (vitamin D resistant) rickets or hyperparathyroidism but at levels lower than prolidase deficiency.⁶ Prolidase enzyme activity also can be measured in erythrocytes, leukocytes, or cultured skin fibroblasts.¹² As our patient had family members with known prolidase deficiency, he was diagnosed by DNA mutation analysis from cord blood collected at birth.⁸

Definitive treatment for patients with prolidase deficiency is not available. Oral proline supplementation has not shown any clinical benefit.¹³⁻¹⁵, and reliable enzyme replacement

therapy is not yet available but is under investigation.¹² Current therapy for patients with prolidase deficiency focuses on treatment of skin manifestations. Many topical and systemic treatments have been instituted, but satisfactory or consistent outcomes have not been reported. Apheresis exchange of prolidase-deficient red blood cells with normal filtered cells, blood transfusions, high-dose pulsed systemic corticosteroids, and a combination of systemic and topical growth hormone may result in transient improvement of skin ulcers.^{16–19} Other therapies including an ointment containing L-proline, a combination ointment of glycine and proline, combination oral supplementation with vitamin C and manganese, topical antibiotics, oral dapsone, and skin grafting have demonstrated limited benefit.^{7, 8, 12, 18} The patient described here had tried several of these therapies including topical growth hormone; transient improvement was seen with many therapies, but response was not sustained.

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KEY TEACHING POINTS

- Prolidase deficiency is a rare autosomal recessive condition associated with mutations of the gene encoding Peptidase D (*PEPD*). Recurrent infections, abnormal facies and mental retardation are common manifestations.
- The classic cutaneous features of prolidase deficiency are recurrent leg ulcerations with scarring which usually manifest early in childhood. Other dermatologic manifestations include telangiectasias, eczematous lesions, and photosensitivity.
- Management of leg ulcers is challenging. Further investigation is required to identify effective treatments. Early diagnosis of prolidase deficiency will allow initiation of genetic counseling in family members.

Fig 1.
Irregularly shaped ulcers with necrotic debris in variable stages of healing on the plantar foot with atrophic depressed scars and telangiectatic vessels.

Fig 2.
Multiple atrophic, depressed, porcelain-white scars on anterior and lateral right thigh.

Fig 3. Numerous telangiectatic vessels on the ventral palms and fingers with clubbing of the distal fingers. Similar telangiectasias were present on the dorsal aspect of the fingers.