Prolidase deficiency: a rare cause of lower leg ulceration

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Summary

Prolidase deficiency is a rare, autosomal recessive genodermatosis with features including skin ulceration, intellectual impairment, characteristic facies, skeletal deformities, splenomegaly, hepatomegaly, haematological abnormalities and chronic infections. Deficiency of prolidase leads to increased urinary excretion of glycylproline and other dipeptides containing proline, causing delay in wound healing via impaired collagen synthesis. We report a 61-year-old female with a 4-year history of painful, recalcitrant lower leg ulceration. Additionally she had characteristic facies and haematological abnormalities described in other reported cases of prolidase deficiency. A spot urine test for imidodipeptiduria and subsequent prolidase (PEPD) genotyping confirmed the diagnosis. This condition should be considered in any severe prolonged case of skin ulceration that is unresponsive to therapy, and is diagnostically atypical.

KEY WORDS: leg ulceration; prolidase deficiency.

Case report

A 61-year-old female was referred to Royal Perth Hospital dermatology clinic by the vascular surgeons with a 4-year history of painful, and poorly healing left lower leg ulceration (Figures 1, 2), which commenced after a blister to the left posterior ankle. She was receiving three times per week home dressings and compression stockings, with minimal improvement. Her past medical history included type 2 diabetes mellitus (most recent HbA1c 6.9%), previous left lower limb deep vein thrombosis, hypertension, chronic hip pain, hysterectomy, and left leg skin graft following a traumatic injury (40 years ago). Her medications included metformin, perindopril and ketoprofen. She lived with her husband and was a retired cleaner. She was a non-smoker, and had 2-3 standard drinks of alcohol per month. She had no family history of recurrent, recalcitrant lower leg ulceration.

Investigations revealed a hypochromic, microcytic anaemia and a diffuse gammaglobulinaemia with paraprotein not detected. ESR was slightly increased, with normal liver and renal function tests. Hepatitis B, hepatitis C and HIV were all negative and calcium, vitamin D, ANCA, ANA, RF, C3/C4, quantiferon and cryoglobulins were normal. Urinalysis found trace protein. Protein electrophoresis of urine was normal. Multiple swabs and biopsies for microscopy, culture and sensitivity were performed with no pathogenic organisms found. CT angiogram (abdominal aorta and distal run-off) was performed, showing an occluded left posterior tibial artery beyond mid-calf with large vessels in the left lower leg otherwise patent without clinically significant stenosis.

An incisional biopsy of the left lower leg (Figure 3) showed an ulcer with inflammation undermining the adjacent epidermis, neutrophilic inflammation and many dermal blood vessels containing fibrin thrombi, some with fibrinoid necrosis of their walls. Immunofluorescence was not diagnostic of a vasculitic process. A diagnosis of pyoderma gangrenosum was made. She was managed with 50 mg oral prednisolone daily and regular dressings continued three times per week. She developed significant side effects and the dose was reduced to 25 mg daily, with methotrexate 10mg/week added. Despite this, she experienced persistent pain and no improvement in ulcer size, so her methotrexate dose was increased to 15 mg/week. After an appropriate treatment course, methotrexate was deemed ineffective and cyclosporine 3.5 mg/kg/day was trialled.

After one month she was hospitalised with severe pain as a result of osteomyelitis of the left fibula. Cyclosporine was discontinued and she was treated with intravenous tazocin for two weeks, then augmentin duo forte and ciprofloxacin orally. The vascular surgeons performed a revascularization procedure with minimal improvement in the ulcers and a full biochemical work up for vasculitis was repeated and found to be negative. Infliximab infusion (5 mg/kg at week 0, 2, 6 then 8-weekly) was commenced, with minor improvement only. The differential diagnoses were revisited, with rarer causes of lower leg ulceration considered.

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Urine metabolic screening was performed for imidodipeptiduria and showed marked increases in glycylproline, alanylproline and valinylproline. Prolidase (PEPD) genotyping identified a novel homozygous frameshift variant (c.578_579delAG; p.Glu193GlyfsX7), which introduced a premature stop codon. Other frameshift variants have been reported in prolidase deficiency.

Upon further enquiry, she additionally reported a history of poor healing as a child, teenager and young adult, with mosquito bites becoming secondarily infected and taking months to heal. She found school difficult, leaving at age of 14, and there were some facial dysmorphisms, including frontal bossing, proptosis and a thin vermillion border. However, there was no evidence of hepatomegaly or splenomegaly and no other features of prolidase deficiency listed below.

Discussion

Prolidase deficiency was first described by Goodman et al. (1) in 1968, although prolidase activity was never measured. The clinical characteristics were further defined by Powell et al. (2) in 1974 with the presence of absent prolidase in association with characteristic clinical features of prolidase deficiency. It is a rare autosomal recessive metabolic disorder that leads to skin fragility and recurrent ulceration (3-13). The ulcers result from impaired recycling of proline, which constitutes 20% of total amino acid in collagen and is important for tissue repair (9). It is caused by mutation in the prolidase gene (PEPD; OMIM #170100) (3-7, 10-12). There are approximately 90 affected individuals reported in the literature, with <1 in 1,000,000 newborns affected (3, 4, 7). Prolidase deficiency features typically present at birth or within the first two decades of life (2, 3, 12), although pres-
entation with persistent leg ulceration has been reported later in life (3-5, 14). Prolidase deficiency is likely to be under diagnosed due to a lack of recognition by clinicians (3). It should be considered in any persistent and severe case of skin ulceration at any age, particularly if the presentation does not typically fit into a well defined diagnostic category.

The hallmark of prolidase deficiency is severe, chronic, recalcitrant, and painful skin ulceration of lower extremities, particularly feet (2-7, 9-19). Other cutaneous findings can precede the ulceration by many years and include telangiectasia of the face and hands, atrophic scarring, premature greying of the hair and scaly and erythematous maculopapular lesions (2-5, 7, 9-12). Other clinical features include recurrent infections (3-7, 9-14, 17) particularly of the skin and respiratory tract, dysmorphic facial features (3-11, 14-17), variable intellectual disability (3-8, 10-14), hepatomegaly with elevated liver enzymes (4, 5, 10), splenomegaly (3-5, 7, 10-16), anaemia (3-7, 10, 12, 17), thrombocytopenia (3, 4, 10), hypergammaglobulinaemia (3, 4, 10, 12, 17), hypocomplementaemia (3-5, 10), skeletal deformities (6, 12, 14), and ocular involvement including keratitis, myopia and other corneal ulcerations (4, 12). An association between systemic lupus erythematosus and prolidase deficiency has also been reported in the literature in at least 10 cases (3-5, 7, 12). Chronic lung disease with digital clubbing and cystic fibrosis phenotype including elevated sweat chloride and transepithelial potential difference has been described (3, 5, 8). There is marked variability in the clinical presentation of prolidase deficiency regarding features seen and severity of disease (3, 7, 10). In some individuals skin ulcerations lead to toe amputation (3, 19), whereas other remain asymptomatic (3, 13, 15). Severity of the condition can vary among affected individuals within the same family (3, 5).

The diagnosis is established by either decreased prolidase enzyme activity or pathogenic variants in the PEPD gene in a proband with characteristic clinical findings and dipeptiduria (3, 7). Due to the wide phenotypic variance, extended family studies may be required. Carrier testing for relatives and prenatal testing for pregnancies at increased risk is also potentially available (3).

Unfortunately no curative treatment is available for prolidase deficiency (3, 4, 9, 10, 14, 15). Many experimental treatments have been trialled with variable success to assist in the management of this condition (4, 9). Apheresis exchange of prolidase-deficient red blood cells with normal filtered cells, blood transfusions (3, 13-15), and a combination of systemic and topical growth hormone (10, 14-16) may result in transient improvement of skin ulcers. Corticosteroid pulse therapy followed by a moderate dose of prednisolone improved the preulcerative indurated lesions and ulcers, however skin lesions reappeared when the dose was weaned. Moderate doses of oral corticosteroids alone were not found to be effective (4, 9-11). Other therapies including 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 success (4, 9-14, 16-18). Topical 5% proline in white soft paraffin ointment was successfully used to manage leg ulceration due to prolidase deficiency in a case by Dunn et al. (9), with marked improvement in the ulcers and decreased frequency of hospitalizations for cellulitis.

Supportive treatment of skin, lung and immunologic manifestations has been shown to be beneficial in some patients (3, 10). Patients who have undergone splenectomy should be appropriately vaccinated, with prompt treatment with antibiotics at the first sign of infection with consideration of prophylactic antibiotics.
if clinically indicated (3). Splenomegaly patients should avoid contact sports due to the increased risk of splenic rupture (3).

Ferreira et al. (3) recommend annual full skin examination for evidence of malignant transformation in patients with chronic recalcitrant skin ulceration, as well as annual full blood count, liver function tests and abdominal ultrasonography to assess size of liver and spleen.

Prolidase deficiency has an autosomal recessive mode of inheritance and hence it is appropriate to offer genetic counseling to patients who are carriers or are at risk of being carriers. The parents of an affected child are obligate heterozygotes and the offspring of an individual with prolidase deficiency are obligate heterozygotes for a pathogenic variant in PEPD. Molecular genetic testing is the preferred method of prenatal testing if both PEPD pathogenic variants in an affected family member have been identified. This testing may be available from a clinical laboratory that offers either testing of this gene or custom prenatal testing. Measurement of prolidase activity in amniocytes has also been used for prenatal diagnosis (3, 19). Prenatal genetic counseling is complicated by the marked heterogeneity of prolidase deficiency (5, 19).

References