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RESEARCH ARTICLE

CONGENITAL PROLIDASE DEFICIENCY IN TWO SIBLINGS: A RARE CASE REPORT, FROM JAMMU AND KASHMIR, NORTHERN INDIA

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ABSTRACT

This case report describes a pediatric patient with congenital prolidase deficiency, a rare, autosomal recessive metabolic disorder with severe dermatological manifestations, particularly ulcers of the lower extremities. While this condition has been very rarely reported with around 70 cases reported in literature till recently, it may be more common than previously acknowledged. Our case report is about a fifteen year-old girl with prolidase deficiency presenting with ulcerations on the feet and lower legs and her other sib with a similar history of recurrenr ulcerations predominantly on lower extremities. Clinical presentation and the pathogenesis of prolidase deficiency are also discussed.

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INTRODUCTION

Prolidase deficiency (PD) is a rare, inherited, autosomal recessive, inborn error of amino acid metabolism that affects collagen maturation. Eighty-five percent of the patients present with dermatological symptoms, including lower extremity ulcers, with pedal ulcers as the common clinical finding at diagnosis in 50% of the patients (Der Kaloustian *et al*., 1982). These chronic leg ulcers are usually irregularly shaped with prominent granulation tissue. They are often resistant to various topical, systemic, and surgical treatments making them slow to heal (Leoni *et al*., 1987). In 1968, Goodman *et al*., were the first to describe prolidase deficiency (Goodman *et al*., 1968). Powell *et al*., in 1974 further defined the clinical characteristics by documenting the absence of prolidase enzyme in association with the characteristic clinical features of prolidase deficiency (Powell *et al*., 1974). Prolidase enzyme cleaves iminodipeptides with C- terminal proline or hydroxyproline. The gene encoding this enzyme is located at chromosome 19. Prolidase deficiency has an incidence of 1-2 per 1,000,000 persons with an estimated 70 cases described in the literature.

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The clinical features observed with prolidase deficiency vary from asymptomatic to a range of symptoms, including chronic leg ulcers, recurrent infections, characteristic facies, mental retardation, and splenomegaly (Haydar A Nasser *et al*., 2015).These symptoms normally occur in the first year of life but can remain dormant in an affected individual until the second decade of life (Lopes *et al*., 2002). Some authors have even described it in patients in their forth decade of life (BernaSolak *et al*., 2015).

Prolidase deficiency affects the normal physiology of dermal collagen and skin (Lopes *et al*., 2002). Collagen is degraded through several steps to iminodipeptides that are then split to free amino acids by the action of prolidase and other dipeptidases. These amino acids are resynthesized to form new collagen without readily exchanging with those in the general systemic pool. In a prolidase deficient state, iminodipeptides with C- terminal proline or hydroxyproline cannot be split. This causes an abnormal amount of glycine and prolinedipeptides comprising over 30% of the amino acids in the normal dermal layer of collagen to be excreted in the urine and removed from the collagen cycle. Dermal layer collagen synthesis without adequate amounts of proline and glycine causes an irregular cross linking, an atypical basal lamina, and

excessive high levels of type III collagen (Goodman *et al*., 1968; Sekiya *et al*., 1985) Subsequently, the dermal collagen produced in patients with PD has a fragile and dysfunctional structure. In acute ulcerations, vascular changes including occlusion of medium-sized vessels with amyloid deposits and perivascular infiltration of neutrophils have been observed (Ogata *et al*., 1981). Additionally, Pierand, *et al*., cited vascular wall thickening and infiltration of mononuclear cells and neutrophils in pre-ulcerative indurated lesions (Milligan *et al*., 1989). Yasuda, *et al*., believed the difference in the severity of skin lesions and the mental retardation between two patients may have been related to the relative superoxide-generating activity of polymorphonuclear cells (PMN) (Yasuda *et al*., 1999). These vascular and tissue changes result in chronic lower extremity ulcerations and other dermatological conditions, including scarring, scaly abnormally thick skin, photosensitivity telangiectasia, poliosis, and lymphedema (Arata *et al*., 1979). Researchers have yet to determine why these chronic ulcers occur mainly in the lower extremities. Association with solitary mastocytoma has also been seen though very rare (Shirley P Ma *et al*., 2015).

Case Report

A 15-year-old female of was admitted in our emergency department with complaints of Fever, cough and severe pallor with significant history of chronic lower extremity ulcers, since the age of 5years, the patient had experienced numerous deep ulcers on the thighs, legs, and feet that developed without preceding trauma. Her wounds typically healed slowly leaving depressed atrophic scars. At the time of presentation, the patient had ulcers limited to both legs. His parents reported frequent epistaxis and easy bruisability. At the time of evaluation, the patient required fiveliters per minute of continuous oxygen via nasal canula. The patient was a product of non consanginous marriage. Her elder sister had similar medical problem, other two female siblings were normal .No other significant family history. Developmental history was normal.

Physical examination

The patient was a female appearing smaller than stated age with stable vitals. Hypertelorism and a depressed nasal root were prominent features. She had severe pallor with mild respiratory distress. On chest examination crepts were present predominantly on right side. CVS examination was normal .On abdominal examination mildsplenomegaly was palpable. On the right leg there was a deep unhealthy looking ulcers with 3&8cm dimentions, just above the ankle laterally, the one on right leg was healed and was smallerin dimensions with irregular borders just above the ankle laterally. (Figure 1 & 2) 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 .There was marked clubbing of all fingers. Oral exam revealed normal mucosa with absence of multiple teeth. The abdomen was soft non tender with palpable spleen 4cm below costal margin.

Significant diagnostic studies

Notable laboratory results performed at the time of the patient's admission includedHb of 6.9g/dl, white blood cells (7.5000 /µL) with neutrophilia (78%) and decreased platelet count (1.0 lac /µL). Both MCH and MCV were significantly decreased.PBF was suggestive of moderate degree of hypochromia with both macro and microcytes.PT/PTT and routine urinalysis were unremarkable.Bone Marrow done in view of severe anemia was suggestive of hypercellular marrow especially myloid hyperplasia consistant with underlying chronic inflimatory disorder, and dual deficiency anemia.CXR PA view was suggestive of right lowerzone consolidation.Patient was managed as consolidation with severe dual deficiency anemia with appropriate antibiotic cover and packed red cell transfusion .In view of history and clinical examination findings, along with similar history of recurrent lower limb ulcerations in other sibling,Prolidase deficiency disorder was strongly suspected hence urinary proline and hydroxyproline were measured in both the sibs which were significantly increased thus further supporting the diagnosis.Erythrocyte Prolidase activity was done in both the sibs and the reports showed significant decrease in level of Prolidase activity which estabilished the diagnosis of congenital Prolidase deficiency

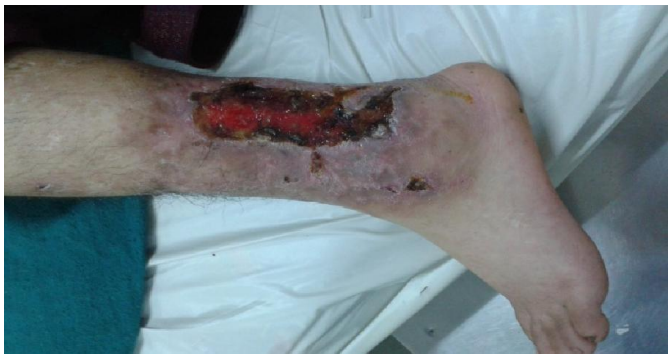

Figure 1. Showing large unhealthy ulcer on left leg just above ankle laterally

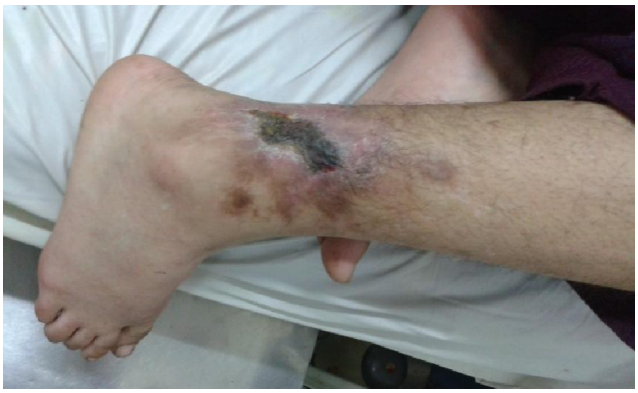

Figure 2. Showing healed leg ulcer on right leg just above the ankle

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 (Hershkovitz *et al*., 2006). 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 (Goodma *et al*., 1968; Yaron *et al*., 1993). 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. 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 prolidasedeficiency (4). Approximately 70 cases have now been described in the literature (Lupi *et al.,* 2006). 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 (Lupi *et al*., 2006; Milligan *et al*., 1989). 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 (Milligan *et al*., 1989). The lower extremities are most frequently affected but anogenital ulcers have also been described. Facial dysmorphisms include hypertelorism, saddle nose deformity, frontal bossing, dull expression, mild ptosis, micrognathia, mandibular protrusion, and exopthalmus (Wang *et al*., 2006) are also associated features in some cases. 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 (Milligan *et al*., 1989; Kokturk *et al*., 2002). Laboratory abnormalities associated with prolidase deficiency include iron deficiency anemia, thrombocytopenia, elevated liver enzymes, and elevated serum immunoglobulins including serum IgE (Wang *et al*., 2006; Cleary *et al*., 1994).

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 (Cleary *et al*., 1994). Although recurrent non-infectious lower extremity ulcers beginning in childhood are characteristic of prolidase deficiency, ulcers accompanied by telangiectasias may be seen in cutis marmoratatelangiectatica congenital (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.

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 (Holland *et al*., 2007). Although several clinical findings, including high-arched palate, joint laxity, oesteoporosis, and elevated serum IgE, are found in both prolidase deficiency and HIES, it is not known if the two syndromes are mechanistically related (Hershkovitz *et al*., 2006). 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 (Milligan *et al*., 1989). Prolidase enzyme activity also can be measured in erythrocytes, leukocytes, or cultured skin fibroblasts (Viglio *et al*., 2006). Definitive treatment for patients with prolidase deficiency is not available. Oral proline supplementation has not shown any clinical benefit (Cleary *et al*., 1994; Isemura *et al*., 1979; Sheffield *et al*., 1977) and reliable enzyme replacement therapy is not yet available but is under investigation (Viglio *et al*., 2006). 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 .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 (Wang *et al*., 2006; Kokturk *et al*., 2002; Viglio *et al*., 2006 and Monafo *et al*., 2000)

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