Prolidase Deficiency, A Rare Case Report

Humaira Shamim,[1] Usman Saeed,[2] Faizan Kashif,[3] Saba Lateef,[4] Mehwish Jahangir,[5] Nadia Ali Azfar[6]

Abstract

Prolidase deficiency is a rare genetic disorder inherited in an autosomal recessive manner. The culprit Peptidase D (PEPD) gene, has been identified through molecular gene testing. Diagnostic methods include assessing reduced prolidase enzyme activity or imidodipeptiduria. This condition is both a metabolic disease and an inborn error of metabolism, characterized by defects in proline-containing protein breakdown, such as collagen. Patients may exhibit dysmorphic facial features, atopy, telangiectasia, skin ulceration, splenomegaly, and recurring infections. Skin ulcer biopsy can rule out vasculitis, and autoimmune activation may lead to an overexpression of the activation marker Human Leucocyte Antigen (HLA DR) on CD4+ and CD8+ T cells, along with high interleukin 18 plasma levels. Multidisciplinary care is essential for proper management.

Keywords: Prolidase deficiency, leg ulcer, autoimmunity, T cell immunity.

How to cite: Shamim H, Saeed U, Kashif F, Lateef S, Jahangir M, Azfar NA. Prolidase Deficiency, A Rare Case Report. Esculapio - JSIMS 2024;20(03): *443-447*

DOI: https://doi.org/10.51273/esc24.25203.29

Introduction

Prolidase deficiency is a rare autosomal recessive disorder caused by a gene defect involving prolidase encoding.[1] Diagnosis typically occurs around the ages of eight to eleven years.[1] Prolidase acts as a dipeptidase, cleaving the imide bond present in dipeptides with proline or hydroxyproline at the C terminal position, with its highest activity against glycyl proline.[1] Diagnosis is confirmed through prolidase enzymatic activity assessment.[1] Association with chronic lung disease and systemic lupus erythematosus has been noted.[1] Elevated plasma and urine imidodipeptidases are characteristic Prolidase enzyme is crucial in collagen I biosynthesis and degradation, a key component of the extracellular matrix supporting connective tissues such as skin, bone, cartilage, tendon, and ligament.[2] This deficiency manifests with facial dysmorphism, cognitive impairment, splenomegaly, recurrent infections, and lower limb ulcers.[2] Prenatal testing is recommended for high-risk cases.[2]

1,2,4-6. Department of Dermatology Unit II, Jinnah Hospital, Lahore.
3. Department of Pediatrics, Jinnah Hospital, Lahore.

Correspondence:
Dr Humaira Shamim, *Consultant Dermatologist, Department of Dermatology Unit II, Jinnah Hospital, Lahore, Pakistan*
E-mail. Dr.homaira@gmail.com

Submission Date: 16-06-2024
1st Revision Date: 27-07-2024
Acceptance Date: 09-09-2024

Case Report

A 12-year-old male, born to consanguineous parents with four siblings, presented with a history of multiple admissions due to recurrent furunculosis, recalcitrant leg ulcers, and skin infections for the last 4 years. He has a history of multiple admissions for leg ulcers in different hospitals in the past. He had diffused abdominal pain radiating to the left hypochondrium with complaints of anorexia, abdominal distension, and weight loss of four to five kg over the past six months. He was treated with intravenous antibiotics, painkillers, and dressing. His other siblings are healthy. He exhibited a painful ulcer with purulent discharge surrounding swelling associated with pain in the lower half of his right shin for the last 20 days and abdominal discomfort for 15 days in the dermatology outpatient department at Jinnah Hospital, Allama Iqbal Medical College, Lahore. Differential diagnosis of primary immune deficiency, Sickle cell disease, Chediak-Higashi syndrome, Beta thalassemia, Werner syndrome, and Prolidase deficiency was considered.

Figure 1: *Reveals hypertelorism*

Figure 1: *Prognathism and dysmorphic features*

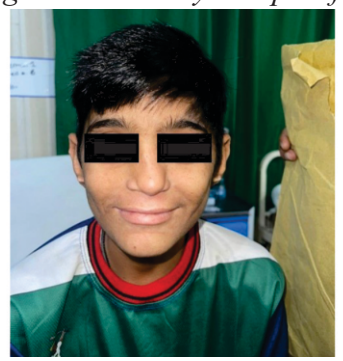


Figure 2 : *Reveal Bitot spots*

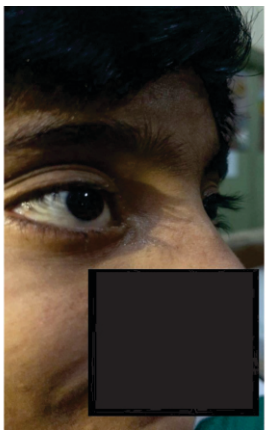


Figure 3:*Reveal Clubbing*

Figure 4: *Leg ulcer with crusting*

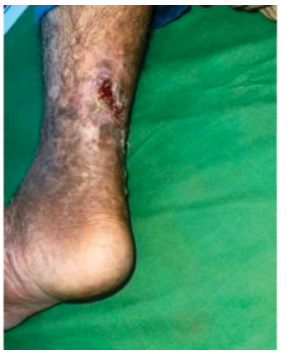


Figure 5: *Leg ulcer with surrounding swelling*

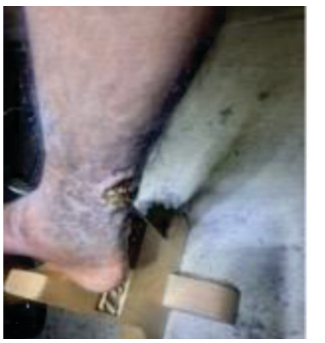


Figure 6: *Chest X-ray PA VIEW*

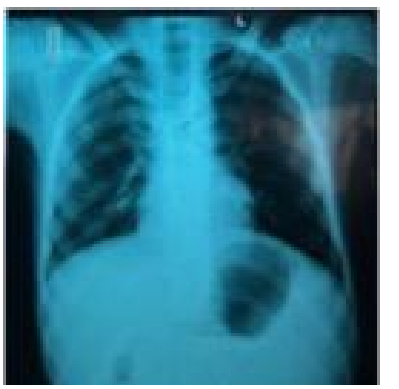


Figure 7: *Teeth of patient*

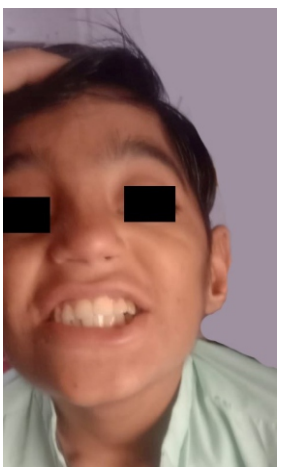


Figure 8: *High arched palate*

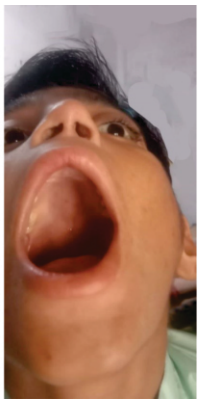


Figure 9: *Cellulitis*

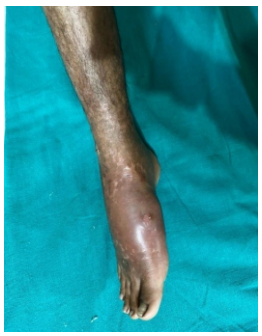


Figure 10: *Cellulitus*

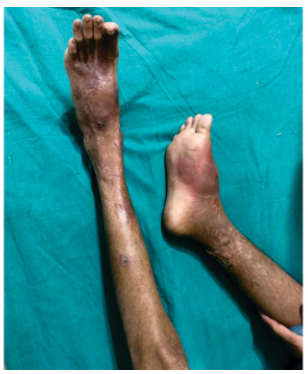


Figure 11: *Leg ulcer with crusting*

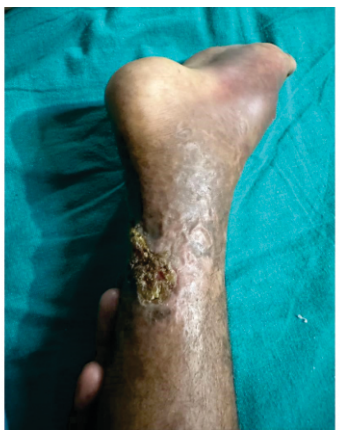
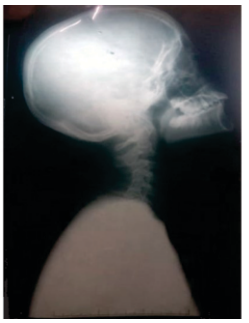


Figure 12: *x ray cervical spine lateral view Generalized decrease bone density*



Sclerosis between C1 and C2 vertebrae, Butterfly vertebrae C2 level C6 vertebral body shows decreased height, omovertebral body at C8 level and exaggerated cervical curvature.

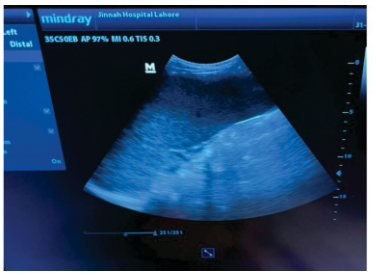


Figure 13: *Ultrasound demonstrating splenomegaly of 22.5 cm*

Table 1: *Complete Blood Examination*

	Param		
1	WBC	4.1	10^9/L
2	LYM%	44.1	%
3	MID%	10.4	%
4	GRAN#	45.5	%
5	LYM%	1.8	10^9/L
6	MID%	0.4	10^9/L
7	GRAN#	1.9	10^9/L
8	RBC	4.23	10^9/L
9	HGB	8.6	g/dl
10	HCT	26.9	%
11	MCV	63.6	fL
12	MCH	20.3	pg
13	MCHC	31.9	g/dl
14	RDW_CV	18.3	%
15	RDW_SD	44.9	fl
16	PLT	73	10^9/L
17	MPV	9.7	fl
18	PCT	0.07	%
19	P_LCR	35.3	%
20	P_LCC	25	10^9/L
21	PDW_SD	18.2	fl
22	PDW_CV	19.8	%

Table 2: *Immunoglobulin Levels*

Serum Immunoglobulin E	**19238.9**
Serum Immunoglobulin A	5.23 g/L High
Serum Immunoglobulin G	68.2 g/L High

Table 3: *Gamma-glutamyltransferase Level*

Serum Gamma-glutamyltransferase	89 U/L High

Table 4: *Complement C3 Level*

	Serum Complement-3 (C3)	**120**
1	Female 1 - 14 years:	82 - 173 mg/dL
2	Female > 15 years:	83 - 193 mg/dL
3	Male 1 - 14 years:	80 - 170 mg/dL
4	Male > 15 Years:	82 - 185 mg/dL

Table 5: *Complement C4 Level*

	Serum Complement-4 (C4)	**26**
1	Female 1 - 14 years:	13 - 46 mg/dL
2	Female > 15 years:	15 - 57 mg/dL
3	Male 1 - 14 years:	14 - 44 mg/dL
4	Male > 15 Years:	15 - 53 mg/dL

General Physical Examination:

The patient appeared pale and afebrile, with vital signs within normal limits with a pulse rate of 82 per minute, respiratory rate of 16 per minute, and blood pressure of 120/80. Physical examination revealed pallor, high-arched palate, clubbing, hypertelorism, low-set ears, a depressed nasal bridge, hyperflexible joints, dry skin, trichomegaly, and Bitot spots in the eyes.

Systemic Examination:

Abdominal examination revealed a palpable spleen. Cognitive impairment and the psychiatric evaluation revealed conversion disorder.

Cutaneous Examination:

A 4cm x 6cm leg ulcer with an overlying crust was observed.

The patient was managed with oral antibiotics and daily dressing with pyodine along with oral Vitamin A and Vitamin D, nutritional support was advised by a nutritionist, and psychological counseling of the patient and her family was done. The patient was advised to follow up.

Surveillance:

Skin ulcer follow-up for malignant transformation, eye evaluation, dental examination, Counselling for the avoidance of rigorous sports, timely diagnosis of chest infections, and addressing educational needs of the patient.

Discussion

Prolidase deficiency is an inborn error of amino acid metabolism and the first case was reported by Goodmen et al. in 1968.[2] Ninghty three cases of prolidase deficiency have been reported in the literature so far.[2] The literature about the Pakistani study shows two cases of prolidase deficiency in Pakistan.[2] Its incidence is estimated at 12 per 1,000,000 births.[2] Multidisciplinary management is essential for prolidase deficiency and genetic counseling is recommended.[3] Insulin therapy has been associated with improved wound healing in ulcers due to prolidase deficiency,[4] with topical insulin therapy emerging as a novel treatment modality to minimize systemic side effects like hypoglycemia and hypokalemia. Topical insulin application promotes macrophage infiltration and phagocytosis.[4] Interleukin 10 levels play a role in angiogenesis and granulation tissue formation, facilitating keratinocyte migration and elevating keratinocytes, fibroblasts, and endothelial cells at the wound site. Associated conditions include Crohn's disease, arthritis, uveitis, erythema nodosum, and pyoderma gangrenosum.[5] Colonoscopy may reveal pseudopolyps, serpiginous ulcers, and pancolitis, necessitating immune and rheumatologic evaluations in patients with prolidase deficiency and Crohn's disease.[5] Associations with systemic lupus erythematosus, juvenile idiopathic arthritis, psoriatic arthritis, and elevated ANA levels have been identified.[6] The gene responsible for prolidase deficiency is located on the long arm of chromosome 19 Immunological impairment may manifest as elevated Immunoglobulin A, Immunoglobulin G, and Immunoglobulin M levels, along with decreased complement levels C1q, C3, and C4.[7] Supportive therapy includes a diet supplemented with amino acids, ascorbic acid, and manganese.[7] Alongside topical treatments such as proline, five percent glycerin ointment, and topical tacrolimus.[8] Oral vitamin C and low molecular weight heparin are beneficial for patients at risk of thrombosis.[8]

Conclusion

Prolidase deficiency presents a wide clinical spectrum with multisystem involvement, often involving autoinflammatory processes indicated by elevated interleukin 18 levels. Patients require immunological, rheumatologic, and genetic evaluations for proper management. Oral vitamin A drops can support Bitot spot treatment, while consultation with a nutritionist and psychologist contributes to overall patient well-being.

References

1. Rossignol F, Moreno MS, Benoist JF, Boehm M, Bourrat E, Cano A, Chabrol B, Cosson C, Díaz JL, D'Harlingue A, Dimmock D. Quantitative analysis of the natural history of prolidase deficiency: description of 17 families and systematic review of published cases. Genetics in Medicine. 2021 Sep 1;23(9):1604-15.
2. Hintze JP, Kirby A, Torti E, Batanian JR. Prolidase deficiency in a Mexican-American patient identified by array CGH reveals a novel and the largest PEPD gene deletion. Molecular Syndromology. 2016 Apr 14; 7(2):80-6.
3. Asly M, Eljazouly M. Osteoarticular Manifestations of Prolidase Deficiency and Disability: Case Reports of Two Moroccan Sisters. Cureus. 2021 Sep 10;13(9).
4. Edek YC, Aral HN, Adışen E, Aksakal AB, ADIŞEN E. Topical Insulin Application in the Management of Resistant Leg Ulcers in a Patient With Prolidase Deficiency: A Case Report. Cureus. 2023 Oct 25;15(10).
5. Rizvi SA, Elder M, Beasley G. A novel manifestation of prolidase deficiency in a toddler diagnosed with very-early-onset crohn disease. Journal of Pediatric Gastroenterology and Nutrition. 2019 Sep 1;69(3): e89-90.
6. Rossignol F, Moreno MS, Benoist JF, Boehm M, Bourrat E, Cano A, Chabrol B, Cosson C, Díaz JL, D'Harlingue A, Dimmock D. Quantitative analysis of the natural history of prolidase deficiency: description of 17 families and systematic review of published cases. Genetics in Medicine. 2021 Sep 1;23(9):1604-15.
7. Lopes I, Marques L, Neves E, Silva A, Taveira M, Pena R, Vilarinho L, Martins E. Prolidase deficiency with hyperimmunoglobulin E: a case report. Pediatric allergy and immunology. 2002 Apr;13(2):140-2.
8. Alrumayyan N, Slauenwhite D, McAlpine SM, Roberts S, Issekutz TB, Huber AM, Liu Z, Derfalvi B. Prolidase deficiency, a rare inborn error of immunity, clinical phenotypes, immunological features, and proposed treatments in twins. Allergy, Asthma & Clinical Immunology. 2022 Feb 23;18(1):17.

Authors Contribution

HS: Conceptualization of Project
SR: Data Collection
MJ,US, FK, SL: Literature Search
NAA: Drafting, Revision
HS: Writing of Manuscript