Lipoid Proteinosis: A Rare Case Report and Review of Literature

Dear Editor,

An 8-year-old boy born to non-consanguineous parents presented to our department with the complaints of recurrent episodes of spontaneous blistering and erosions over face, trunk, and extremities and hoarseness of voice from 1 year of age. Lesions healed with scarring and associated with intense itching. There was a history of multiple raised lesions over the extensor surface of the body and thickening of skin and pigmentation over neck, elbows, knees, axilla, and groin from the last 2–3 years. There was no history of similar complaints in the family. There was no history of seizures or any neuropsychiatric disorder.

On examination, the patient had pock-like scars and crusted erosions over face, trunk, and extremities. There were multiple, discrete as well as confluent, waxy, skin-colored to hyperpigmented papules and plaques present over bilateral elbows, wrist, and dorsum of hands and knees. There was diffuse waxy thickness of the skin with hyperpigmentation which was predominantly present over neck, bilateral cubital fossa, buttocks, bilateral popliteal fossa, and extremities [Figures 1a, b and 2a, b]. There was subtle beading of the eyelid margin. Oral examination revealed macroglossia with indentation present at the lateral margins [Figure 2c]. The patient was not able to protrude the tongue properly. There was thickening of the lips with fissures at the commissures. The scalp showed patches of scarring alopecia over temporal and occipital areas. All laboratory investigations including routine hematological and biochemical workup was normal. The ophthalmological evaluation was normal. His intelligence quotient (IQ) score was 87 (verbal IQ was 87, and performance IQ was 86) suggestive of average intellectual and cognitive level. The patient was advised behavioral therapy.

Histopathological evaluation (HPE) with hematoxylin and eosin stain showed compact hyperkeratosis with thinning of the granular layer with parakeratosis. Dermal vascular channels in the papillary and mid-dermis appear ectatic and dilated with mild perivascular mononuclear inflammatory infiltrates. Mild perivascular periodic acid–Schiff (PAS)-positive and diastase resistant hyaline-like amorphous material was deposited in the dermis extending into the fibroconnective tissue [Figure 3]. Contrast-enhanced compound tomography (CECT) of base of skull revealed thickened epiglottis and multiple sub centimetric homogeneously enhancing cervical lymph nodes along with bilateral medial temporal lobe calcification in the region of hippocampus and amygdala [Figure 4a and b]. Genetic study revealed a non-sense homozygous mutation in exon 7 of the extracellular matrix protein 1 (ECM1) gene (c.742G>T, p.Glu248*) on chromosome 1. On the basis of clinical features and genetic analysis, a diagnosis of lipoid proteinosis (LP) was made. The patient was started on oral acitretin (0.4 mg/kg) and is currently under follow-up with significant improvement in the cutaneous lesions.

LP, also known as Urbach–Wiethe disease, is a rare autosomal recessive disorder, characterized by the infiltration of hyaline material into the skin, upper aerodigestive track, and internal organ. It is caused by mutations in the ECM1 gene, located on chromosome 1q21.2, which encodes a secretory glycoprotein that plays an important role in the structural and functional

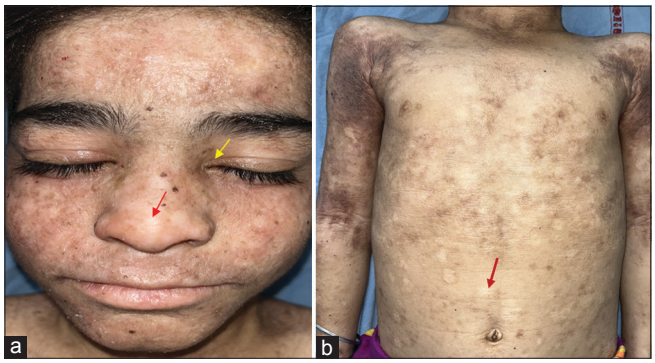

Figure 1: (a and b) Pock-like scars (red arrow) and crusted erosions over face, trunk, and extremities. There is subtle beading of the eyelid margin (yellow arrow)

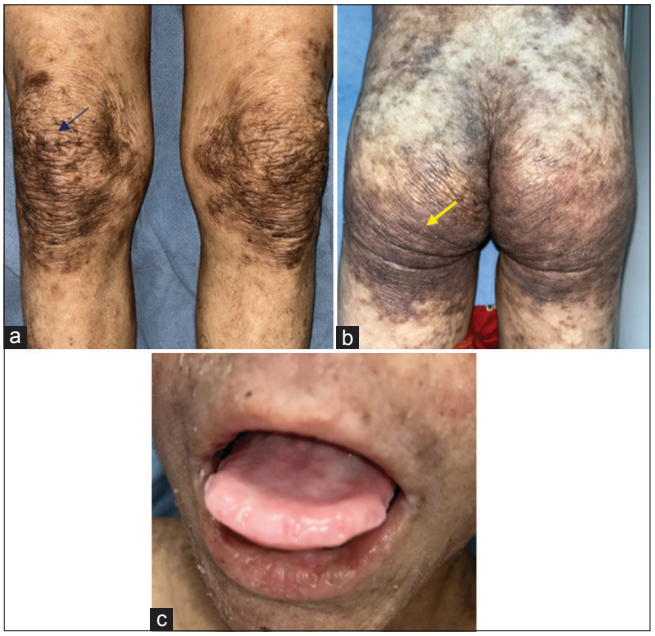

Figure 2: (a) Multiple, discrete as well as confluent, waxy, skin-colored to hyperpigmented papules and plaques present over knees (blue arrow). (b) Diffuse waxy thickness of the skin with hyperpigmentation over infragluteal folds (yellow arrow). (c) Macroglossia with indentation present at the lateral margins

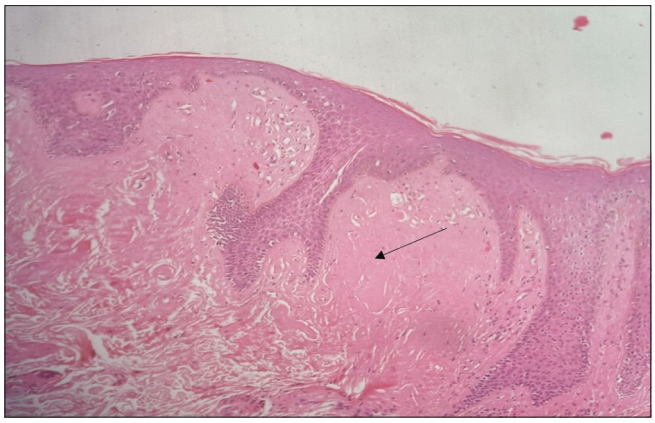

Figure 3: Compact hyperkeratosis with thinning of granular layer with parakeratosis. Hyaline-like amorphous material (PAS-positive and diastase resistance) is deposited in perivascular area in the dermis (black arrow) (H&E, 100x)

integrity of the skin and homeostasis.[1] Although LP occurs worldwide, ~25% of all case reports have been observed in South Africa. To the best of our knowledge, approximately 50 cases have been reported from India till date in which genetic analysis was conducted in only a few cases.[2]

The classic presenting symptom of LP is a weak cry and a persisting hoarse voice during the first year of life that is caused by the deposition of hyaline material within the laryngeal mucosa. It can rarely lead to stridor and breathing difficulties. Infiltration of the oral mucosa during childhood results in stiffening of the frenulum and macroglossia with lateral crenation and restricted protrusion of the tongue. Cutaneous manifestations start in early childhood. There is skin fragility resulting in spontaneous or trauma-induced vesicles or blister formation over the face and extremities, which heals with pock-like scarring, which usually appears during the first 2 years of life. This later on leads to waxy, verrucous, and hyperkeratotic plaques over frictional areas, such as knuckles, elbows, knees, buttocks, and axilla. The presence of beaded papules over the eyelid margin (moniliform blepharitis) is quite characteristic and is seen in two-thirds of the cases, but was not very prominent in our patient.[3] Other cutaneous manifestations include alopecia and palmoplantar keratoderma.

Extracutaneous manifestations, such as neuropsychiatric complications, are less commonly seen and usually associated with calcification of temporal lobe or hippocampi.[1] The most characteristic radiological findings are intracranial calcification in amygdala or temporal lobe, which is more evident in adults and can be seen in 50% of the cases and was present in our case also. Histopathology shows prominent deposition of an eosinophilic, PAS-positive hyaline material deposition around the blood vessels and appendages.[4]

Loss-of-function mutations in the gene encoding ECM1 on chromosome 1q21 have been identified in LP. Forty-six mutations in the ECM1 gene have been identified so far;

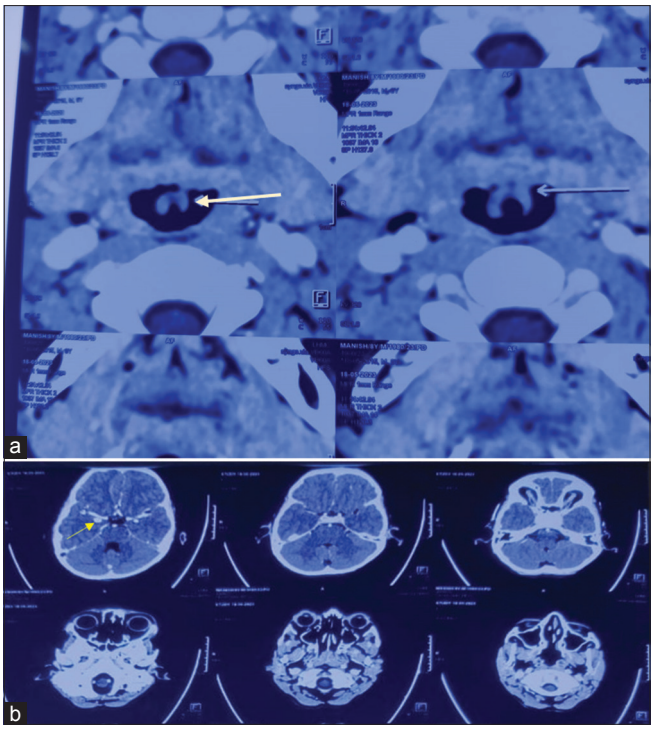

Figure 4: CECT of base of the skull revealed (a) Thickened epiglottis (white arrow) and (b) Multiple subcentimetric homogeneously enhancing cervical lymph nodes along with bilateral medial temporal lobe calcification (yellow arrow) in the region of hippocampus and amygdala

about half of them are found to be located in exon 6 or 7.[5] Therefore, sequencing of these two exons has been suggested as the initial step in efficiently determining the molecular pathology in new cases of LP. Genetic analysis by Chan Ien *et al*.[2] in two Indian siblings revealed non-sense mutation in exon 7 of the ECM1 gene, which was also noted in our case. Some authors have suggested that the patients harboring mutations in exon 7 could have a less severe skin and respiratory tract phenotype as compared to cases bearing mutations not affecting exon 7.[6] Our patient despite the presence of mutation in exon 7 exhibited a severe phenotype in the form of hoarseness of voice and skin manifestations beginning during the first months of life. This finding favors the hypothesis that the isoform containing exon 7 is of fundamental biological importance. However, no specific correlation between genotype and neurological manifestations has ever been shown.[3]

This entity must be differentiated from erythropoietic protoporphyria (EPP), papular mucinosis, amyloidosis, and xanthomatosis [Table 1].

As the exact pathogenesis of this disease is unknown, there is no effective therapy for LP. Various treatment modalities include retinoids, penicillamine, surgical procedures, dermabrasion, and Carbon-dioxide (CO2) laser.[7] The overall prognosis of the condition is good, and the patient usually has normal life expectancy despite the progressive nature of the disease until early adulthood. Diagnosis of LP should be considered in a child or adolescent presenting

Table 1: Differential diagnosis of lipoid proteinosis

Disorder	Clinical features	Histopathological features	Differentiating features
Erythropoietic protoporphyria	• Autosomal semidominant mode of inheritance due to deficiency of ferrochelatase enzyme. Early childhood onset. • Cutaneous manifestations—erythema, edema, crusting, purpura, skin thickening, and waxy scars, primarily on face and dorsum of hands. • Biochemically, increase in free protoporphyrin levels in erythrocytes, plasma, feces, and other tissues.	• Deposition of homogenous pale eosinophilic PAS-positive, diastase resistance material around the blood vessels with sparing of adnexa.	• Lesions are predominantly present in the sun-exposed area. • Mucous membrane is not involved. • No blistering usually seen. • Severe liver disease can occur. • Adult-onset form can be associated with myeloproliferating or myelodysplastic disease.
Papular mucinosis	• Chronic idiopathic disorder characterized by symmetrical, numerous firm papules and area of induration over head and neck, upper trunk, forearms, hands, and thigh. • Associated with paraproteinemia.	• Diffuse dermal mucin deposition stained with alcian blue or colloidal iron. • Fibroblast proliferation and fibrotic collagen seen.	• Age of presentation—middle age. • Mucous membrane spared. • No blistering.
Amyloidosis	• Variable clinical presentation depending on the type. • Waxy translucent to yellowish papules, nodules, or plaques. • Can be associated with paraproteinemia and autoinflammatory disorders.	• Amyloid appears as amorphous, eosinophilic fissured mass in the dermis. • With Congo red stain, orange–red color seen on routine microscopy, while green birefringence seen on electron microscopy.	• Hyalinization is milder, more focal and superficial and rarely involves the eccrine gland. • Usually, late age of onset. • No blistering usually.
Xanthomatosis	• Variable clinical morphology. • Yellowish skin papules, nodules, or plaque over extensor surface, buttocks, and thighs. • Associated with dyslipidemia, thyroid disorders, or paraproteinemia.	• Lipid–laden foam cells in the dermis or subcutis with areas of cholesterol cleft.	• Not very common presentation in childhood. • Rare mucosal involvement. • No blistering seen.

with hoarse cry, recurrent blister healing with pock-like scars, and diffuse waxy thickening of frictional areas. Through our case, we want to highlight the importance of early recognition, role of genetic testing, counseling, and symptomatic management of this rare disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Damini Verma, Vibhu Mendiratta, Vidya Yadav, Anjali Birla, Amol Srivastava[1]

Department of Dermatology, Lady Hardinge Medical College and Hospitals, New Delhi, [1]Department of Radiology, Institute of Liver and Biliary Sciences, New Delhi, India

Address for correspondence:
Dr. Vidya Yadav,
Department of Dermatology, Lady Hardinge Medical College, Connaught Place, New Delhi, India.
E-mail: vidyadermdoc@gmail.com

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