CASE REPORT

Lipoid proteinosis: A case report and review of literature

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ABSTRACT

Lipoid proteinosis (LiP) is a very rare, autosomal recessive disorder, characterized by hoarseness of voice, skin scarring, beaded papules along the eyelid margins and an inability to protrude the enlarged tongue. This condition is caused by homozygous or compound heterozygous mutations in the ECM1 gene located on chromosome 1q21. The ECM1 gene encodes an important structural component of the basement membrane and extracellular matrix. The dermatologic manifestations of Lipoid proteinosis, arise from the loss of protein–protein interactions due to ECM1 gene mutations. Lipoid proteinosis was first reported by Seibman in 1908. The disorder was initially observed in South Africa, where the responsible gene was introduced in the mid-17th century by a German settler and his sister. In 1929, Urbach and Wiethe, a dermatologist and otorhinolaryngologist, respectively, from Vienna, described an entity that they called 'lipoidosis cutis et mucosae' on the basis of histological findings of the deposition of a lipid material associated with protein in the skin and mucous membrane. This name was subsequently modified to 'lipoid proteinosis.' It is mainly prevalent in early infancy and childhood and is rare in older adults. In this article, we reported a 22-year-old patient with the skin and orofacial features of lipoid proteinosis, which is very rarely recorded in literature as far as age and oral manifestation are concerned. This is supposed to be the first case to be reported in Bangladesh.

KEYWORDS: Autosomal recessive disease, lipoid proteinosis, hoarseness of voice

INTRODUCTION

Lipoid proteinosis is a rare autosomal recessive disease that presents in infancy with a hoarse cry or voice. It is more common in South Africa. The disease is characterized by the deposition of an amorphous hyaline material in the skin, mucosa and viscera. It is caused by mutations in the extracellular matrix protein 1.[1-3] Patients usually presents with beaded papules in the eyelid magins, sides of the hands, verrucous plaques over the elbows and axilla. The diagnosis can be established on the basis of characteristic clinical symptoms and confirmed by histopathology. The earliest finding in lipoid proteinosis is hoarseness due to vocal cord infiltration, which occurs at birth or in the first few years of life and can progress to complete aphonia.[4,5] Skin lesions usually develop in the first years of life, although the timing of skin eruption is variable. Photoaging of the sun exposed skin may be seen. Two stages of skin lesions can be noted.[6] In first stage there is blistering, which can be extensive enough to resemble epidermolysis bullosa. The blisters

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are non inflammatory, heal with hemorrhagic crust and scar. In some patients blistering is worse during summer months. The scarring usually begins during childhood and often follow trauma or occur spontaneously. The skin lesions of the second stage are better recognized. Beaded papules along the eyelid margins (moniliform blepharosis) are considered a classic clinical finding. Other cutaneous stigmata include generalized skin thickening with a waxy, yellow appearance, areas of distinct papules and nodules. Areas of repeated friction and trauma develop verrucous plaques. Alopecia may occur with variable severity and nails are normal.The mucosae of patients with lipoid proteinosis exhibit infiltration and thickening. In early ages oral erosions may be noted and these may persist. Thickening of lingual frenulum leads to inability to protrude the tongue. The pharynx, tongue, soft palate, tonsils and lips are typically involved. There may be respiratory difficulties, swelling of the salivary glands, xerostomia, and dental caries. Central nervous system involvement is variable with amygdale dysfunction. Neurologic and psychiatric findings include seizures, memory deficit, behavioral changes, paranoid symptoms, mental retardation. Eyelid infiltration may lead to corneal ulceration due to abnormal eyelash positioning. Loss of eyelashes and eye brows may occur. There may be asymptomatic deposition of hyaline materials in internal organs.

Light microscopic evaluation of the lesional sections reveals deposition of amorphous eosinophilic material at the dermoepidermal junction, perivascularly and along adnexal epithelia. The hyaline material is periodic acid-Schiff positive and diastase resistant. Immunohistochemical staining of skin biopsy specimen may show absence or attenuation of ECM-1. The differential diagnosis of this pathological entity includes erythropoietic protoporphyria, where the lesions are restricted to sun exposed areas and there is no beading of eyelid margins.[3,4] CT scan of the brain reveals bilateral anterior medial temporal lobe calcification, especially within the amygdale. The prognosis of lipoid proteinosis is variable. Often there is progressive worsening of cutaneous features, with clearance during childhood of blistering lesions and progressive development of infiltrative lesions. Most patients have a normal life span, although some patients have experienced respiratory tract complications from upper respiratory tract infiltration. The disfiguring nature of the skin lesions, along with abnormal voice, significantly impacts the interactions of lipoid proteinosis patients with others. Due to rarity of the disease, there are no long case series to evaluate the therapeutic options. Many patients have been treated with systemic retinoids with improvement. Retinoids are proposed to modulate the metabolism of basement membrane and inhibit collagen production. Via this inhibitory effect, acitretin may decrease the deposition of hyaline material in dermis and restore the basement membrane.[7] A dose of acitretin 0.5 mg is well tolerated and improves hoarseness of voice more than skin lesions.[1] As skin lesions are not prone to natural involution, surgical therapy e.g. dermabrasion and CO_2 laser, chemical peeling is required to eliminate papular, nodular, vegetative lesions and improvement of skin thickening and yellowish color.[8]

CASE REPORT

A 22-year-old taxi driver presented to the outpatient department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University with gradual development of yellowish non pruritic papular lesion over dorsum of both hands for 8 years. There were similar skin colored papular lesions over his eyelid margins and verrcous plaques over the elbows, knees, axillae for same duration. He also complained of hoarsening of his voice since childhood and a vesicular eruption on the trunk which healed with atrophic scars. He had no history of headache, visual disturbance, epilepsy. His parents were consanguineously married and no family members were affected.

On physical examination, he was with average body built and normal vital parameters. On integumentary system examination, increased wrinkling of the face, skin colored papules coalescing to form linear plaques along the eyelid margins of both upper and lower lids on both sides; hyperpigmented macules and patches over the face and trunk. There were atrophic scars over the trunk. Hyperpigmented, verrucous plaques were present over both elbows, knees, axillae. Hyperpigmented papules coalesing to form plaques over the side of both hands. Lips were thickened with hyperpigmented patches, pinkish induration of the oral mucosa and tongue with inability to protrude; teeth were normal. Scalp hair was normal but there was loss of body hair. Nails were normal, there was accidental loss of distal phalanx of right ring finger. Routine laboratory tests included complete blood count, urine routine and microscopic study, chest X ray, SGPT and serum creatinine were normal. Skin biopsy for histopathology was taken from papules of the hand and it revealed diffuse dermal deposition of eosinophilic hyaline material around the blood vessels which is congo red and crystal violet negative but positive for periodic acid-schiff staining. Thyroid function tests and fasting lipid profile were normal.

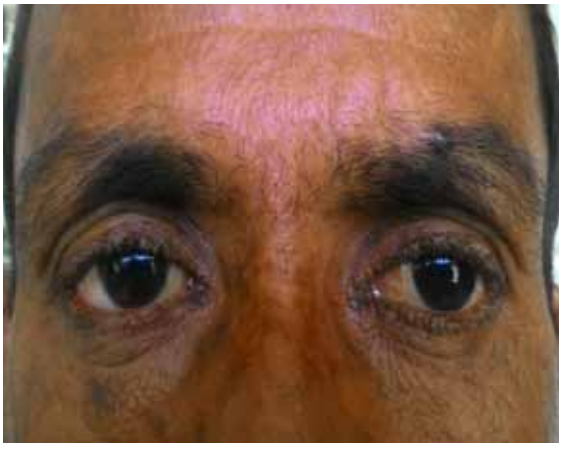

Fig. 1 Beaded papules in eyelid margins.

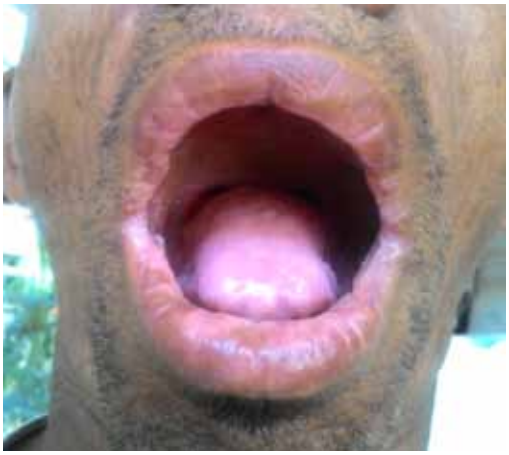

Fig. 2 Infiltration of lips and tongue.

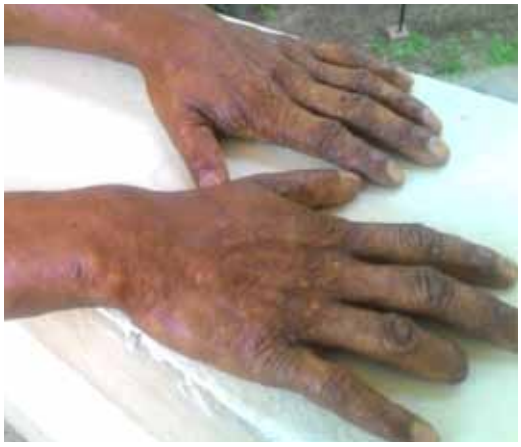

Fig. 3 Yellowish papules in the hands.

Fig. 4 Verrucous plaques over the elbows.

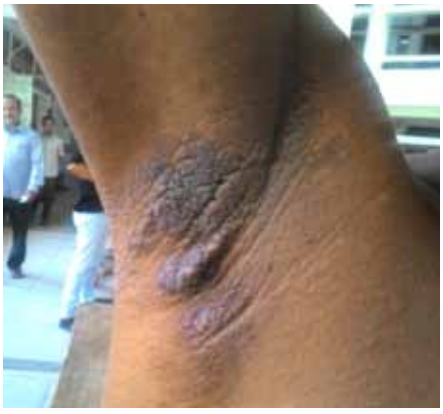

Fig. 5 Verrucous plaques in right axilla.

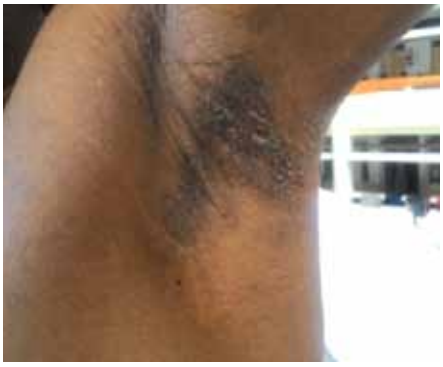

Fig. 6 Verrucous plaques in left axilla.

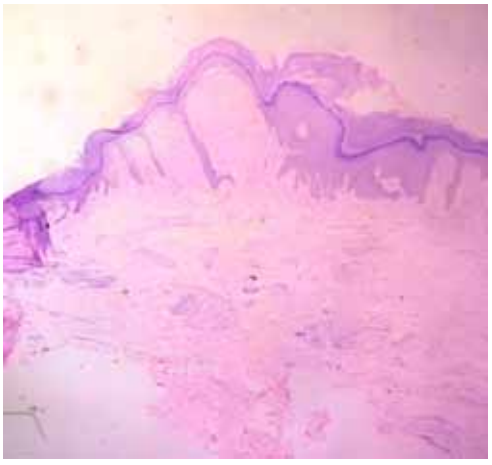

Fig. 7 Acanthosis and deposition of eosinophilic hyaline material in dermis (10x).

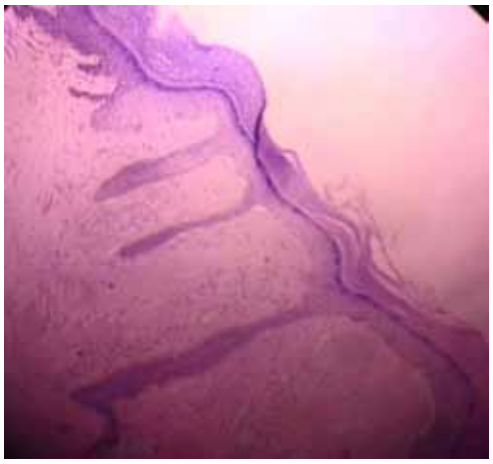

Fig. 8 Deposition of hyaline material in dermis (40x).

DISCUSSION

Giandomenico et al reported a 6-year-old girl, presented with progressive skin and mucous membrane changes since early childhood. The patient had developed hoarseness during the first few months of life and at age 3 years, started to develop multiple warty papules on the dorsum of the hands, on the face and eyelid margins. Most papules were skin-coloured. Scarring was also evident. She had no history of frontal headache, seizures or visual disturbance. The patient underwent indirect laryngoscopy, on account of severe dysphonia, which showed thickening of the vocal cords and hyaline deposits in the larynx, oral cavity and oropharynx. As proposed elsewhere, the patient was submitted to a logopaedic programme; when this failed, the lesions were removed surgically, for temporary functional purposes. Light microscopy examination of laryngeal biopsy tissue showed massive deposits of homogeneous, eosinophilic, hyaline-like material in the lamina propria, without inflammation. The material was strongly PAS positive and diastase resistant, revealing the glycoproteic nature of the substance. The most recent follow-up showed a slight improvement

in the clinical appearance of the vocal cords, but little change in the dysphonia. The patient has recently started a new logopaedic programme, but prognosis has not changed.[9]

Kabre et al reported a 19-year-old male with a complaint of multiple large ulcerations on his tongue since 1-week with associated burning sensation and fever. There were no previous episodes of similar ulcerations in the oral cavity. He gave the history of hoarseness of voice, alopecia, cracked skin over soles, repeated vomiting, and loose stools since childhood. Extraoral examination showed multiple ulcerations with discharge over both upper limbs. There were multiple nonpruritic yellowish papules and warty lesions on the neck. Right submandibular lymphadenopathy was present. Intraoral examination revealed multiple nontender ulcerations covered with slough measuring about 1-1.5 cm. Entire floor of the mouth, palate and bilateral buccal mucosa were coated with scrapable curdy white patches. All second premolars were missing along with retained[53,82,83] and supernumerary tooth between 14 and 16 were noticed. Skin biopsy confirmed to be of Lipoid proteinosis. Radiographic examination showed no evidence of any calcifications. Blood investigations revealed leukocytosis with increased monocytes (12.8%). Serum iron level was slightly low (36 μg/dL), with raised total iron binding capacity (471 μg/dL). Folate levels were also increased (>20 ng/dL). Patient was a known case of Lipoid proteinosis, the facial and oral findings were considered to be due to the same condition. An additional diagnosis of pseudomembranous candidiasis was also given. The treatment plan for the patient included debridement with hydrogen peroxide and betadine solution under topical LA. Patient was instructed to maintain good oral hygiene and follow liquid diet till the ulcers heal. Antiseptic mouthwash and 1% clotrimazole mouth paint were prescribed. Debridement was carried out for the next 4 days, and healing of tongue ulcers was appreciated on the last visit.

An 11-year-old boy also reported by Kabre et al with a complaint of multiple ulcers on the tongue and hoarseness of voice since 6 months of age with similar ulcerations on bilateral buccal mucosa in the past and was associated with recurrent throat pain and dysphagia from past 2 to 3 years. He also had recurrent episodes of cough, cold and fever occurring once every month. On general examination, multiple shiny skin-colored papules were present over forehead, nose and malar region in a background of thickened waxy skin with few comedones and multiple hyperpigmented papules bilaterally over both the eyelid margins. Few skin-colored papules were found on the neck. There was erythema, edema, and tenderness of both the pinnae of ears. Few circular linear atrophic scars were noticed on the face. Hyperpigmentation and verrucous surface skin were seen over both the elbows, knuckles, sides of fingers, and over the palmar surface of hands and digits. Few crusted healing erosions were seen around elbows. Nails were normal. On intraoral examination, whitish plaques were seen over the bilateral buccal mucosa, lips, sublingual mucosa, and palate. There was a restriction of tongue movements with thickening of the lingual frenum. Erosions, few fissures, and whitish plaques were noticed on the tongue. Based on the clinical findings and considering the patient being a known case of

LiP, a diagnosis of oral manifestations of LiP was given. X-ray skull showed focal areas of increased density, projected over the dorsum sellae. Lateral view showed probable suprasellar calcification with normal size of sella. Histopathologic examination revealed a diagnosis of LiP showing hyperkeratosis, acanthosis, and elongated rete ridges along with deposition of dense eosinophilic material in the superficial dermis. Patient was instructed to maintain oral hygiene and to be under liquid diet. Antiseptic mouthwash was advised to be used thrice daily after foods. Patient was recalled after 1-week during which there was a considerable improvement in the healing of the intraoral lesions.[10]

Prakash et al reported a 32-year-old male patient with complain of dermal eruptions in the mouth for the previous 25-30 years. Family history was noncontributory, with the absence of consanguinity. The face revealed multiple acneiform scars; beaded papules on the eyelids; as well as papulovesicular lesions, scars, and hyperkeratosis on the upper and lower extremities, face, and pinnae. Alopecia was also observed. Extra oral examination revealed lacerations on the upper and lower lip secondary to injury. Intraoral examination revealed a thickened, pale, firm, and enlarged crenated tongue, with yellowish white papule on its surface and a cobblestone appearance. The tongue movements were restricted. Other findings included hyperkeratosis on the labial, buccal, and palatal mucosa, which gave a thickened and nodular appearance. Throat examination by indirect laryngoscopy revealed headed deposits over the epiglottis and vocal cords. Based on the clinical history of the case, a provisional diagnosis of LiP was made while the diagnoses of myxoedema, erythropoietic protoporphria, and xanthomas were ruled out. The patient was subjected to an oral mucosal biopsy, which revealed the presence of hypertrophied squamous epithelium showing acanthosis, hyperkeratosis, parakeratosis, and koilocytosis. The underlying fibrous tissue displayed focal areas of hyaline eosinophilic material deposits. These findings confirmed the diagnosis of LP. A proper oral hygiene regimen was initiated, and the carious breakdown of the teeth was treated. The patient was referred to a dermatologist for the skin changes, followed by proper evaluation and treatment by an otorhinologist for the hoarseness of voice.[11]

Sadaksharam et al reported a 61-year-old male patient with stiffness of his tongue, slurred speech, and hoarseness of voice for the past 6 months. Patient developed hoarseness of voice 6 months before, which was followed by slurred speech and dysphagia to solid food insidiously. Before developing these symptoms, he was apparently normal; even during infancy and adulthood, no significant complaints were reported. Family history and personal history was non-contributory. None of the family members were affected and no history of consanguinity was recorded. Patient was otherwise apparently healthy; no significant systemic illness was noted. No history of seizures, visual disturbances, photosensitivity, or respiratory obstruction were reported. Skin of face and neck showed multiple acneiform scars and beaded papules along the margins of the eyelids. Intraorally, the tongue was firm, enlarged, crenated, with yellowish white papule on its surface. The tongue movements were restricted due to infiltration of the yellowish

papule in frenulum region. Oral mucosa showed generalized thickening with yellowish papular infiltration. The yellowish papule was widespread throughout the oral mucosa including buccal mucosa and labial mucosa. No abnormality was noted in the dentition and it was found to be normal for this age. Xerostomia and dysphagia were also found to be present on detailed evaluation. Routine hemogram, renal and liver function tests were normal. Radiographic examination of the skull was found to be unremarkable, with no evidence of calcification noted. Endoscopy was also performed, but no significant abnormality was detected. MRI of brain was taken to rule out any neurological abnormality; no relevant positive findings were noted. Based on the clinical evidence, the case was provisionally diagnosed as LiP and possible differential diagnoses of amyloidosis, xanthoma, porphyria, and myxedema were also given. Incisional biopsy was carried out in the lower labial mucosal region and histopathologic examination showed fibrous tissue with focal areas of hyaline amorphous eosinophilic material deposits. Periodic acid-Schiff (PAS) test was positive around the blood vessel. These findings confirmed the diagnosis of LiP. Patient was then referred to gastroenterologist for opinion regarding dysphagia and hoarseness of voice. Oral prophylaxis was carried out and the patient was then advised D-pencillamine 600 mg/day for 6 months, which resulted in improvement in oral symptoms. Patient is under regular follow-up; no significant adverse effect has been noticed till date.[12] Thaddanee et al reported an 11-year-old male patient, born to consanguineous parents, presented with hoarseness of voice since early childhood, multiple scars over the skin of face and dorsum of hands, and papules over elbows and buttocks. One of his two younger sisters, 9 years old, had similar complaints. Patient was normal at birth, but after 3 days of life developed weak cry and hoarseness of voice. At 2 months of age skin lesions began to appear. Initially, only face was involved; subsequently, lesions appeared over the buttocks, knees, and elbows. At presentation, both siblings had multiple brownish atrophic scars over the face. Hypertrophied and hyperkeratotic nodules were present over the elbows. Beaded papules were seen along the margins of the eyelids. The tongue was thick and could not be protruded. Patchy diffuse alopecia was seen in both the siblings. Under general anesthesia, direct laryngoscopic examination was done in the male patient. Both vocal cords were thickened, though the glottic space was adequate. The mucosa over rest of the larynx was pale and irregular. Histopathology of a verrucous papule from the elbow revealed diffuse dermal deposition of a pale, homogenous, eosinophilic, hyaline-like material around blood vessels and adnexa (sweat glands), which was Congo-red-negative and Periodic acid-Schiff (PAS) positive. Epidermal hyperkeratosis was also noted. Radiograph of the skull did not reveal any calcifications. Biochemical parameters were within normal limits.[13]

REFERENCES

1. James WD, Berger TG, Elston DM. Andrews' diseases of the skin. USA: Elsevier. 2016:537-38.
2. Vempali IZ, Ravikanth L, Sakinala S. Lipoid proteinosis: a case report. Perspectives in Medical Research 2014. 2 (1):33-36.
3. Lima LR, Mulinari-Brenner FA, Manfrinato LC.

Lipoid proteinosis - a report of two cases. An bras Dermatol, Rio de Janeiro 2003; 78 (6):723-27.

4. Wollina U, Konrad H, Schonlebe J. Lipoid proteinosis. Acta Dermatoven APA 2004; 13 (4):131-34.
5. Swain SK, Panda M, Patro N.. A rare cause of hoarseness of voice: Lipoid proteinosis of the larynx. International Journal of Phonosurgery and Laryngology, 2014; 4 (1):23-26.
6. Goldsmith LA, Katz SI, Gilchrest BA et al. Fitzpatrick's dermatology in general medicine. USA: McGraw-Hill. 2012; 1644-47.
7. Gunduz O, Sahiner N, Atasoy P. Acitretin treatment for Lipoid proteinosis. Case reports in Dermatological Medicine 2012; ID 324506:1-4.
8. Oliveira GB, Rossi NCP, Antonio CR. Twenty-five year follow-up of a case of lipoid proteinosis. Surg Cosmet Dermatol 2014; 6 (1):86-89.
9. Giandomenico SDi, Masi R, Cassandrini D, El-Hachem M, Vito R De, Bruno C, et al. Lipoid proteinosis: case report and review of the literature. Acta Otorhinolaryngol Ital. 2006 Jun; 26 (3):162-67.
10. Kabre V, Rani S, Pai KM, and Kamra S. Lipoid proteinosis: A review with two case reports.Contemp Clin Dent. 2015 Apr-Jun; 6 (2):233-36. doi: 10.4103/0976-237X. 156053.
11. Prakash SMR, Verma S, Sumalatha MN, Chattopadhyay S. Oral manifestations of lipoid proteinosis: A case report and literature review. The Saudi Dental Journal 2013; 25 (2):91-94.
12. Sadaksharam J, Karthikeyan B, Mahalingam S, Kessavalou S. Lipoid proteinosis with oral manifestation in a geriatric patient: A unique case report. J Indian Acad Oral Med Radiol 2015; 27:428-31.
13. Thaddanee R, Khilnani AK, Pandya P, Chaturvedi M. Lipoid proteinosis (Urbach-Wiethe disease) in two siblings. Indian Dermatol Online J 2014; 5 (2):95-7.