

Understanding Lipoid Proteinosis: A Brief Overview

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1. Abstract:

Lipoid proteinosis is a rare autosomal recessive deposition disorder resulting from a loss-of-function mutation of ECM1 on chromosome 1q21. It is characterized by the deposition of hyaline-like material within multiple organs, including the skin, oral mucosa, larynx, and brain. Clinically, the first sign is often a weak cry or hoarseness of voice due to the infiltration of the laryngeal mucosa; hoarseness remains throughout life. Cutaneous lesions occur in two stages, which may be overlapping; the first stage consists of vesicles and hemorrhagic crust on the skin of the face and extremities, which resolves with pock-like scarring. In the second stage, the skin becomes diffusely thickened and waxy yellow. The classical clinical feature is beaded papules linearly arranged over the eyelid margin, known as Moniliform blepharosis. Involvement of the tongue, oropharynx, recurrent parotitis, dental anomalies, and neurological manifestations are other findings. A pathognomonic radiographic finding is bilateral intracranial sickle-shaped calcification in the amygdala. Pink hyaline deposits are found in the dermis in skin biopsy. Lipoid proteinosis is a chronic cutaneous disease with a benign course.

2. Introduction:

Lipoid proteinosis (LP), also known as Urbach-Wiethe disease and Hyalinosis cutis et mucosae, is a very rare autosomal recessive deposition disorder whose true incidence is not known. It is characterized by the deposition of amorphous hyaline-like material within multiple organs, including the skin, oral mucosa, larynx, and brain [1, 2]. An extensive literature search was conducted across multiple databases, including PubMed, Medline, and Cochrane, using keywords and Mesh and non-Mesh words such as 'Lipoid proteinosis,' 'Urbach-Wiethe disease,' 'Moniliform blepharosis,' 'Hoarseness of voice,' 'waxy yellow skin,' 'Pock-like scarring,' 'history,' 'Clinical features,' 'Pathogenesis,' 'histology,' 'dermoscopy,' and 'treatment.' The first research yielded 639 articles. After excluding languages other than English, 500 articles remained.

In 1908, Siebenmann first described Lipoid proteinosis [3, 4]. Later, in 1929, two Viennese physicians, Erich Urbach, a dermatologist, and Camillo Wiethe, an otolaryngologist, established it as a distinct entity by presenting a case series [3, 5]. In 1930, Urbach renamed it as “LP cutis et mucosae [4].” It is more common among Europeans (e.g., Germany) and South Africa but has also been reported from other parts of the world such as India and Japan [4, 5]. The Namaqualand region in South Africa has the largest number of LP patients sharing a common mutation, indicating a founder effect. (6) The incidence of LP is higher in countries where consanguinity is more common [6]. The sex ratio has been found to be equal. (4) Parental consanguinity has been seen in 20% of cases [4]. It has been reported to occur among siblings [4]. About 400 cases have been reported in the literature so far [6, 7]. In India, about 30 cases have been reported [8].

3. Etiopathogenesis:

Lipoid proteinosis is an autosomal recessive disorder due to homozygous or compound heterozygous loss-of-function mutations of ECM1 on chromosome 1q21, which encodes extracellular matrix protein 1, a glycoprotein expressed in various tissues, including the skin [2]. The function of extracellular matrix protein 1 is still unclear, even though a major role in cutaneous physiology and homeostasis has been postulated [9, 10] ECM1 is a secreted glycoprotein that binds to perlecan, the major heparan sulfate proteoglycan of the basement membrane, as well as to fibrillar proteins and growth factors. ECM1 may act as a “biological glue” in the dermis, thus helping to regulate basement membrane and interstitial collagen fibril macro-assembly and growth factor binding. Consequently, the loss of ECM1 may have profound effects on dermal homeostasis, leading to the clinical features of skin infiltration and scarring. Meanwhile, the lack of ECM1 within the epidermis may change the normal pattern of keratinocyte maturation and differentiation, resulting in clinical features of warty hyperkeratosis [10].

Till date, more than 50 mutations have been reported on chromosome 1q21 in the ECM1 gene [11]. ECM1 is comprised of two alternatively spliced isoforms, ECM1a and ECM1b. ECM1b lacks exon 7 of this 10-exon gene (ECM1). Most ECM1 mutations are frameshift or nonsense mutations in exons 6 or 7, resulting in a truncated ECM1 [11]. Usually, mutations outside exon 7 are clinically associated with a slightly more severe mucocutaneous phenotype, but neurological features do not show any such genotype-phenotype correlation [2]. Many LP genotypes and phenotypes are possible since there are several ECM1 splice

variants and mutations [11]. Recently, Khan et al. reported a homozygous nonsense mutation with a C to T substitution at nucleotide position 1246 in exon-8 of the ECM1 gene leading to a stop codon [6].

The pathogenesis is not fully recognized, but it appears to be related to an alteration in the synthesis and metabolism of collagen, leading to an increase in the production of types IV and V collagen by endothelial cells, a glycoprotein substance by fibroblasts, and a decrease in the synthesis of collagen types I and II [7].

4. Clinical Features:

Lipoid proteinosis is clinically heterogeneous, with affected individuals exhibiting variable degrees of scarring and infiltration, hoarseness, respiratory distress, and, in certain cases, neurological abnormalities such as temporal lobe epilepsy [2]. Classical clinical features include skin scarring, beaded eyelid papules, and laryngeal infiltration leading to hoarseness [3] (Figure 1).

5. Cutaneous Manifestations:

Cutaneous lesions occur in two stages, which may overlap. The first stage consists of vesicles and hemorrhagic crust on the skin of the face and extremities, which are often pruritic and resolve with pock-like scarring [3, 4, 7]. In the second stage, the skin becomes diffusely thickened and waxy yellow [3,4]. Patients are highly susceptible to minor trauma, and infections can occur easily [4]. Other cutaneous manifestations typically include waxy papules, nodules, and plaques on the trunk, flexures, and extremities. Verrucous lesions resembling xanthoma are observed over elbows, knees, and buttocks [12]. Seldom, the occurrence of calcinosis cutis has been reported, with the nidus of calcification thought to be the hyaline material in the dermis [7]. Scalp involvement may lead to patchy or diffuse alopecia [4,7,13] Nail dystrophy, along with hemorrhagic blisters on the wrists, fingers, and nailbed, is also a frequent finding [7].

6. Mucosa and Internal Organ Involvement:

Lipoid proteinosis presents with diverse clinical manifestations involving multiple systems, with skin and mucous membranes of the respiratory and digestive systems predominantly affected [9]. The first clinical sign is often a weak cry or hoarseness of voice due to the infiltration of laryngeal mucosa. Hoarseness is present in approximately two-thirds of patients at birth or early infancy and persists throughout life [3,5]. The tongue is usually enlarged due to diffuse infiltration and restricted mobility due to frenulum involvement, leading to speech difficulties [3,4]. Generalized

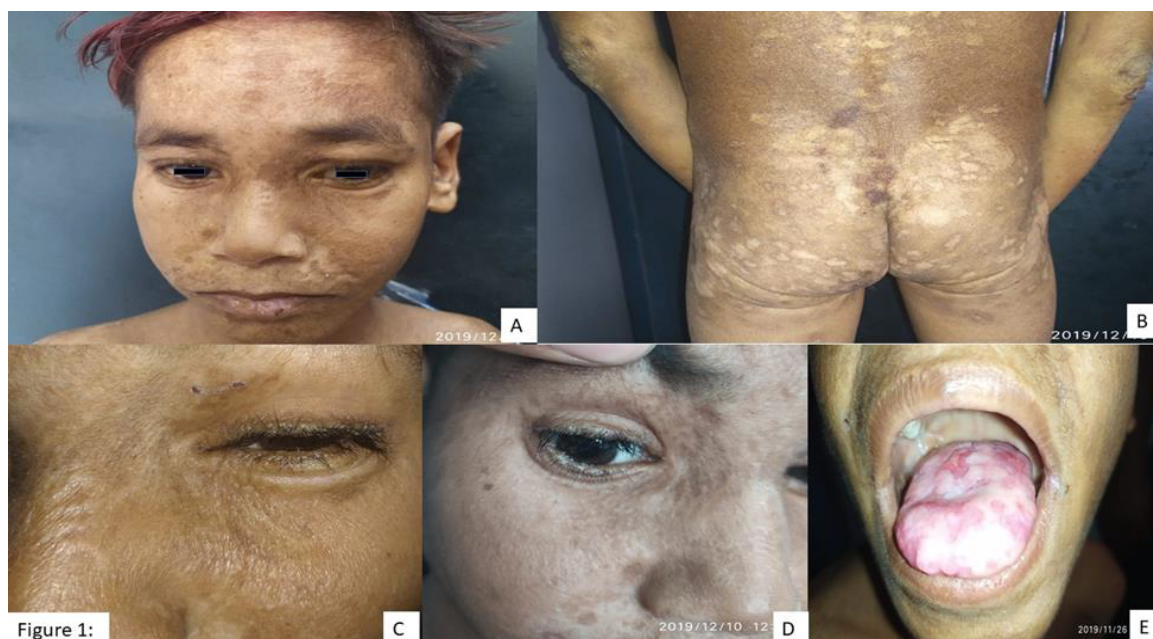


Figure 1: A) Face with waxy skin and multiple pock like scarring; B) Yellowish waxy skin with scarring over buttocks; C) & D) Skin colored waxy papules linearly arranged in both upper lid and lower lid of both eyes ((C) Left eye and (D) Right eye) giving Beaded appearance; E) Irregular nodular infiltration of tongue with ulceration.

pearly papular yellowish deposits may be seen in the oral mucosa [7]. Irregularly thickened lips with gingival hypertrophy are often found [7]. Oropharynx is also involved, and oral ulcerations have also been reported [2,3,7].

Infiltration of the respiratory mucosa may lead to respiratory difficulty, especially following upper respiratory tract infections [2]. The mucosa of the labia and vagina may also be similarly involved [4]. Recurrent parotitis and submandibular gland inflammation cause hyposalivation/xerostomia, leading to poor oral hygiene and dental caries [7].

The classical and universal clinical feature is beaded papules linearly arranged over the eyelid margin, known as Moniliform blepharosis, seen in about two-thirds of patients [4,10,13]. Hyaline deposits have also been reported in the conjunctiva, cornea, trabeculum, and retina, with secondary glaucoma due to infiltration in the trabeculum or corneal opacities appearing later [7,10]. Epiphora is one of the reported ocular signs [7].

Additionally, the central nervous system, respiratory system, upper gastrointestinal tract, blood vessels, and lymph nodes may also be affected [7]. Central nervous system involvement is seen in 50% - 75% of individuals, with neurological symptoms like epilepsy, memory loss, mental

retardation, emotional changes, schizophrenic behavior, depression, anxiety disorder, and other neuropsychiatric abnormalities observed [2,5,7]. In CNS involvement, hippocampal capillaries are common sites of infiltration, along with wall thickening and subsequent perivascular calcium deposition [5]. The radiographic finding is bilateral intracranial sickle-shaped calcification in the amygdala or hippocampus or temporal lobes, with amygdala involvement being pathognomonic and more prominent with a longer duration of the disease [2, 3, 5]. Lung and bronchial involvement have also been reported [9]. An association with diabetes mellitus has been reported, postulated to be due to the deposition of amorphous material in the capillary vessels in the pancreas. Likewise, deposition of hyaline material in the intestine may cause intestinal bleeding [9].

7. Differential Diagnosis:

Differential diagnoses include amyloidosis, erythropoietic protoporphyria, and lichen myxedematous. The distribution of hyaline-like material and staining for PAS and amyloid are frequently used to differentiate among these conditions [11].

8. Investigations:

Histopathology, direct laryngoscopy and Imaging studies can be done for evaluation.

9. Histopathology:

Histopathology reveals the epidermis with hyperkeratosis, focal parakeratosis, acanthosis, papillomatosis, and overlying elongated rete ridges. Disruption and/or duplication of the basement membrane, along with the deposition of dense eosinophilic hyaline material at the dermo epidermal junction aligned perpendicular to the epidermis in the papillary dermis, and as thick perivascular mantles surrounding capillaries and around adnexal epithelia with the appearance of sweat coils, are observed [7]. This hyaline material is PAS positive and diastase resistant [4]. Immunohistochemical skin labeling for antibodies against the ECM1 protein has shown reduced expression in Lipoid proteinosis. Staining with anti-type III, anti-type IV, anti-V collagen, or anti-type VII collagen antibodies reveals bright, thick bands at the dermo epidermal junction and a reduction of types I and III collagen around blood vessels [7,12] (Figure 2).

10. Direct Laryngoscopy:

Direct laryngoscopy confirms the presence of fleshy deposits on the palate and vocal cords with restricted movement.(7)

11. Imaging:

Imaging studies, including computed tomography (CT),

show bilateral true vocal cord mucosal irregularity with hyperdense depositions, bilateral medial temporal amygdala parallel bean-shaped calcification (a pathognomonic sign), and bilateral striatal (caudate and putamen) hypoattenuation. On magnetic resonance imaging (MRI), the signal intensity of the lesions is low in T1 and T2 and is well-highlighted in T2* gradient echo (GRE) images. CT or MRI features are unremarkable in the absence of brain calcifications.(5)

12. Treatment:

There is no effective treatment for Lipoid proteinosis. Dermabrasion and chemical peels can be performed in some patients [7]. Treatment with dimethyl sulfoxide, D-penicillamine, acitretin, etretinate, oral steroids, and intralesional heparin has also been tried but without any promising results [7,10] Mucosal stripping, laser micro laryngoscopy, or dissection of the vocal cords and excision of deposits may be carried out to improve the quality of voice. In very severe cases, when there is diffuse infiltration of the pharynx and larynx causing respiratory distress, tracheostomy may be required [7]

13. Course and Prognosis:

Lipoid proteinosis is a chronic cutaneous disease with a slowly progressing benign course [4] If the lesions begin at

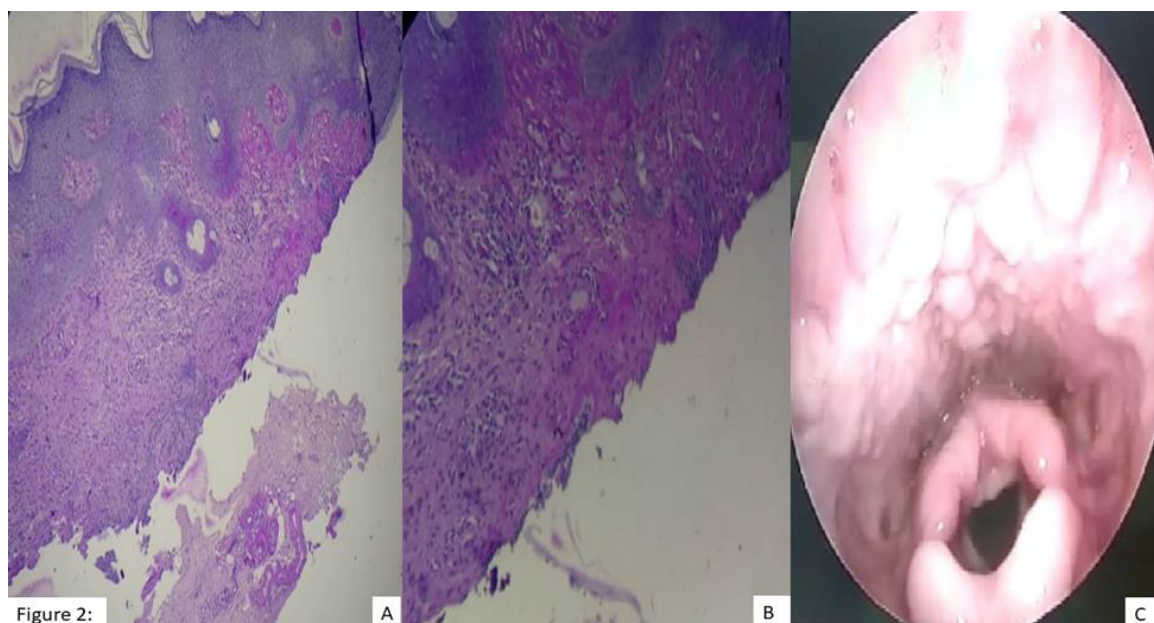


Figure 2: A) Low power (10x) view of Histopathology slide with PAS staining: Hyperkeratosis, acanthosis, PAS positive hyaline material in papillary dermis, perivascular and peri adnexal region; B) High power (40x) view focusing, PAS positive hyaline material in papillary dermis and perivascular area; C) Fiber optic Laryngoscopy showing granulomatous deposits in posterior pharyngeal wall and post cricoid area with thickening and congestion of aryepiglottic fold.

an early age, it is found to be self-limiting [7]. It can affect the quality of life due to its disfiguring scars and systemic complications [4,7]. Counseling should be provided to the parents of affected children regarding the risk of having another affected offspring [7].

14. Complications:

It rarely causes death by laryngeal obstruction [4]. Airway obstruction, seizures, and spontaneous CNS hemorrhage are the most severe complications. Hyaline deposition within the small bowel can cause gastrointestinal bleeding. Complications can also occur as a result of surgical intervention on the vocal cords or larynx, including bleeding, infection, and vocal cord scarring. Certain patients may be taking systemic medications to manage their disease, such as antipsychotic, antiepileptic, and dopamine-modifying agents, which can have a variety of drug-specific side effects [11].

15. Conclusion:

Lipoid proteinosis is a rare genetic disease that demands interprofessional collaboration for optimal patient care. A comprehensive workup with several specialists, including a dermatologist, neurologist, psychiatrist, otolaryngologist, dentist, and geneticist, is required in patients with suspected Lipoid proteinosis. It is important to determine the disease burden, quality of life, and any possible life-threatening manifestations. In addition, genetic counseling should be offered to patients for a better understanding of their condition and its mode of inheritance [11,15].

16. Acknowledgements: Nil

17. References

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