

## CASE REPORT

# Lipoid Proteinosis—A Pediatric Otolaryngologist's Perspective: A Case Report and Review of Literature

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## ABSTRACT

Lipoid proteinosis (LP) is a rare autosomal-recessive hereditary disorder with multisystemic involvement manifesting in infancy and early childhood. These children may present to a pediatric otolaryngologist with hoarse voice. Here, we report a case of a child with LP with a pediatric otolaryngologist's perspective.

**Keywords:** Autosomal recessive, Lipoid proteinosis, Pediatric hoarseness.

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## INTRODUCTION

Lipoid proteinosis (LP) is a rare autosomal-recessive hereditary disorder, primarily affecting children.<sup>1</sup> It was first described by Siebenmann in 1908. Twenty years later, on the basis of histologic findings, it was established as a distinct entity by two Viennese physicians, Erich Urbach, a dermatologist, and Camillo Wiethe, an otorhinolaryngologist.<sup>2</sup> It is also known as "Urbach—Wiethe disease" or "Hyalinosis Cutis et Mucosae."<sup>3</sup> Parenteral consanguinity has been reported in few cases.

Less than 300 cases have been reported in the literature till date. Although LP occurs worldwide, approximately 25% of all reported cases have been observed in South Africa, where many of the patients are of Dutch or German ancestry.<sup>4</sup>

Infants and children presenting with hoarse cry are difficult to diagnose as examination of larynx is difficult. Lipoid proteinosis often presents in early infancy, and

signaled by a weak and hoarse cry due to laryngeal infiltration.<sup>5</sup> The examination of skin gives a vital clue to the diagnosis. Despite the rarity of the condition, hoarse cry in a child voice with skin and mucosal lesions is characteristic.

## CASE REPORT

A 7-year-old boy presented to pediatric otolaryngology and dermatology outpatient department of our institution with complaints of hoarseness of voice for 4 years. He also complained of lesions over the skin for 2 years, which were gradually increasing in both number and size. There was no associated photosensitivity or blisters. He had no associated dyspnea or dysphagia. He was the third child from a second degree consanguineous union and history of death of the two older siblings due to unknown cause during infancy.

On head to toe examination, there was diffuse waxy appearance of the face with few interspersed yellowish papules and atrophic scars over the nose, elbows, forearms, dorsal aspect of hands, knees and buttocks (Figs 1A and B). Mucosa of oral cavity and oropharynx was normal. On fiberoptic nasopharyngolaryngoscopy, right vocal cord flaccidity with phonatory gap was noted (Figs 2A and B). Skin biopsy from one of the yellowish papules on the chin showed eosinophilic hyaline thickening of papillary dermal capillaries and around the eccrine ducts in an onionskin arrangement. The hyaline material stained positively with periodic acid-Schiff stain and was resistant to diastase (Figs 3A to C). Erythropoietic protoporphyria was ruled out with a negative RBC



**Figs 1A and B:** (A) Diffuse waxy appearance of the face with few interspersed yellowish papules and atrophic scars over the nose and (B) atrophic scars over the elbows and forearms

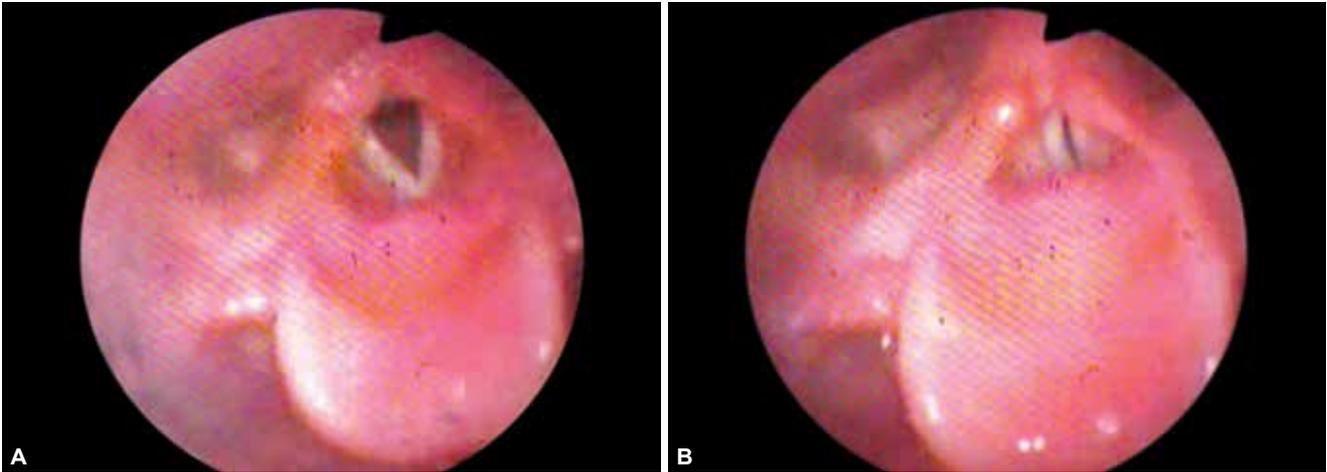
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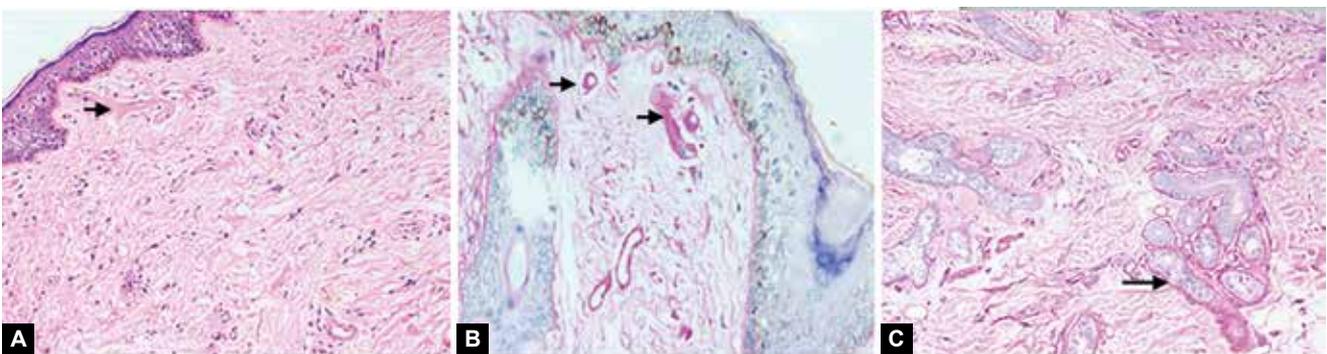
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**Figs 2A and B:** (A) Larynx during inspiration and (B) on phonation with a phonatory gap



**Figs 3A to C:** (A) Pale eosinophilic hyaline deposits around small calibre blood vessels in the superficial dermis, highlighted by arrow head H&E stain, (B) PAS-D stains at 100x magnification, and (C) PAS-D positive hyaline around sweat gland complexes in the deeper dermis 100x magnification

fluorescence study and direct immunofluorescence test. Thus, the diagnosis of lipoid proteinosis was made. The child was initiated on Cap. Acitretin at 0.5 mg/kg for the hoarseness of voice and is on follow-up.

**DISCUSSION**

Examination of larynx in children is a difficult task and diagnosis in a child with hoarse cry is challenging. Examination of skin and oral mucosa can give valuable information in diagnosis of this rare condition. Lipoid proteinosis is one of the few dermatological conditions which may manifest with hoarseness of voice in childhood (Table 1).

Lipoid proteinosis occurs with equal frequency in both males and females. The signs and symptoms of the disease are related to hyaline deposits in skin, mucosae, and internal organs. Laryngeal deposits lead to hoarseness, which is often the first clinical manifestations.<sup>3</sup> The hoarseness may present at birth as a weak cry or develop later, within the first few years of life.<sup>6</sup>

Hofer reported that voice change was the most common early symptom.<sup>7</sup> The deposition of hyaline occurred early in the larynx and hoarseness can manifest soon after birth which often progresses during the patient’s lifetime.<sup>8</sup> Subepithelial hyaline deposition in the vocal

cord leads to incomplete closure of the vocal folds with phonatory gap and impaired wave formation leading to hoarseness of voice. In this case, the presenting complaint

**Table 1:** Dermatological conditions associated with hoarseness

Metabolic disorders	Hypothyroidism Lipoid proteinosis Farber’s disease Systemic amyloidosis Lichen myxedematosus
Infections	Hansen’s disease Syphilis Rhinoscleroma Epidemic typhus
Autoimmune connective tissue disorder	Sjogren’s syndrome Dermatomyositis Systemic lupus erythematosus Relapsing polychondritis
Genetic disorders	Pachyonychia congenital type I and II Inherited Epidermolysis bullosa (EB)-like Junctional EB laryngoonychocutaneous syndrome
Miscellaneous	Sarcoidosis Infantile hemangioma involving the upper airway Cornelia de Lange’s syndrome



was hoarseness and was present since the age of 3 years. Many cases have been reported with significant upper airway obstruction requiring tracheotomy.<sup>8</sup> The child in our case had no upper airway obstruction presently. Symptoms of LP in the newborn include a hoarse cry and skin manifestations. The symptoms occur in sequence and include vesicles, pustules, bullae, and hemorrhagic crusted eruptions on the face and limbs that are more extensive in areas of trauma. Skin lesions heal with pox-like acneiform atrophic scarring and extracutaneous expressions from the intrusion of hyaline-like material in the skin, larynx, and various organs. Subsequently, cutaneous manifestations become more visible, and the skin eventually becomes thick, yellowish, and waxy. Later, papules, verrucous plaques, and nodules arise on the face, axillae, and scrotum.<sup>2</sup> Monoliform blepharosis is one of the classical features with hyaline deposition over the eyelids leading to beaded pattern over the lids. In the present case, the onset of skin lesions was only 1 year after the onset of hoarseness. He presented with multiple thick, yellowish-waxy lesions over the upper limbs.

Oral manifestations of LP include papules on the tongue, frenulum, and lips. These papules cause pebbling of the oral mucosa and a woody tongue that impairs tongue protrusion, leading to impaired speech and gustation, transient swelling, and ulceration of the lips and tongue. They can also present with hyperplasia or aplasia of the teeth, as well as recurrent inflammation of the parotid and submandibular glands. Similar features were not observed in our case.

Systemic manifestations of LP include changes in learning and behavior, seizures, dysphagia, and dyspnea. Generalized dystonia and gastrointestinal bleeding are also reported. Short stature has been reported by several authors in LP which is related to defective osteoblasts that are biologically similar to fibroblasts.<sup>9</sup> Our case did not have any of the above features.

*Pathology:* The major clinical manifestations of LP are related to the deposition of an amorphous or laminated material around blood vessels and in the connective tissues. The amorphous deposits consist primarily of noncollagen proteins, while the concentric layers of basement membrane-like material contain collagen (types II and IV) and laminin. In addition, the deposits are PAS-positive and diastase-resistant, indicating the presence of neutral mucopolysaccharides.<sup>10</sup>

Little is known about the initial stage of the disease. H&E-stained sections of early lesions reveal pink, hyalin-like thickening of the capillaries within the papillary dermis, and in one patient, vesicles were due to non-dyskeratotic acantholysis. Older lesions are characterized by hyperkeratosis, occasionally papillomatosis, and a thickened dermis in which bundles of pink hyalin

deposits are found in a diffuse pattern. There are smaller scattered deposits of hyalin in the lower dermis. Hyalin mantles can surround the eccrine glands as well as the hair follicles, sebaceous glands and, rarely, erector pili muscles.<sup>10</sup>

Hamada et al recently discovered that LP is caused by loss-of-function mutations in the extracellular matrix protein 1 (ECM1) gene.<sup>1</sup> Extracellular matrix protein 1 encodes a secretory glycoprotein that has been shown to act as a negative regulator of endochondral bone formation and promotes angiogenesis. In the dermis of the skin, ECM1 binds to perlecan and thereby may help to regulate basement membrane production.

*Management:* The prognosis for LP is variable and there is no known cure. Most cases present early in life. Although death due to respiratory obstruction has been reported in the earlier literature, it can be avoided by early recognition of the disease and maintenance of the airway. Primary aim of the treatment is to reduce the morbidity and to prevent complications. Patient education and counseling is a very important part of the management.

## CONCLUSION

Lipoid proteinosis should be part of differential diagnosis in infants and young children presenting with hoarse cry with coexisting skin and mucosal lesions. The management is multidisciplinary and the role of pediatric otolaryngologist is critical in early diagnosis as well as in management of airway complications.

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