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Case Report

Urbach-Wiethe disease: a rare pediatric case report

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ABSTRACT

Urbach-Wiethe disease also known as lipoid proteinosis (LP) is a rare autosomal recessive Geno dermatosis.[1] It is characterized by the deposition of an amorphous hyaline material in the skin, mucosa and viscera and is also known as cutaneous-mucosal hyalinosis.[2,3] Parental consanguinities is identified in approximately 20% of Urbach-Wiethe disease cases. The classic manifestation due to laryngeal infiltration is a hoarse cry with its onset in infancy. Skin and mucous membrane changes become clinically apparent important consequences.[4] Rarely, the central nervous system and respiratory tract may be involved resulting in seizures and airway obstruction, respectively. The lifespan is generally normal. We report a case of Urbach-Wiethe disease in a 6-year-old boy with hoarseness of voice who was started on oral acitretin therapy following his diagnosis. Oral acitretin can prove useful in cases of lipoid proteinosis who present with hoarseness of voice or vocal cord palsy. The mutations in the gene encoding extracellular matrix protein 1 (ECM1) have been linked to lipoid proteinosis. Even though no effective treatment is known, acitretin has proved to reverse hoarseness of voice in few reported cases and was started in our case as it was his chief presenting complaint.

Keywords: Acitretin, ECM 1, Hyaline material, Lipoid proteinosis, Hoarseness of voice

INTRODUCTION

Lipoid proteinosis is a rare genodermatosis. It is also known as "Urbach-Wiethe" disease and hyalinosis cutis et mucosae and has a variety of clinical features. It is due to mutation of the extracellular matrix protein 1 (ECM 1) gene that encodes a glycoprotein known as extracellular matrix protein 1.[5] Worldwide more than 300 cases have been confirmed genetically but very few cases have been reported especially from India.[6,7]

CASE REPORT

A 6-year-old boy born of non-consanguineous marriage presented with hoarseness of voice since early infancy and recurrent spontaneous blistering and raw areas over both elbows, upper and lower back and trunk from 3 years of age (Figure 1).

Figure 1: Hypopigmented healed scars over trunk and face and waxy skin.

His dentition was also abnormal with poor oral hygiene (Figure 2).

He had recurrent upper respiratory tract infections and irritation in his eyes and eyelids (Figure 3).

Figure 2: Poor dentition and dental caries and thickened frenulum at the under surface of the tongue.

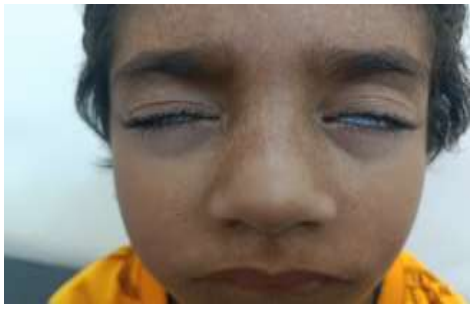

Figure 3: Blepharosis and pearly white deposits around eyelids.

There was no history of breathing difficulty or difficulty in swallowing. No history of alopecia. No history of seizures or development delay. There was no history of allergies, medical or surgical illness or any treatment taken in the past. There was no history of photosensitivity and the lesions did not have a predilection for sun-exposed areas or injury prone sites. There was no similar history in other family members. He was age appropriately immunized with no history of adverse reactions. He was underweight and short for his age and appeared to be moderately nourished (Figure 4).

Figure 4: Short stature in the boy with lipoid proteinosis (height at 3rd centile as per WHO growth chart).

Skin surface examination revealed waxy appearance of facial skin, multiple residual atrophic hypopigmented and hyperpigmented patches over trunk and the lower back (Figure 5).

Figure 5: Hypopigmented scars on back post healing of raw areas of skin and on dorsum of the hands.

Hyperpigmented verrucous plaques were present over bilateral knees (Figure 6).

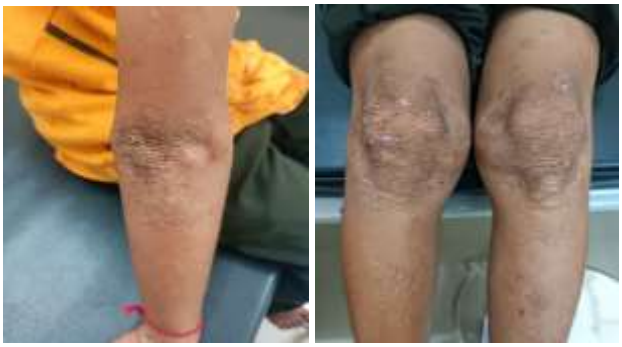

Figure 6: Healed scars post verrucous plaques over both elbows and knees.

There was reduced mouth opening and he had difficulty in protruding his tongue and a thickened frenulum. The dorsum of the tongue was studded with multiple white colored papules. Eye examination was otherwise normal except for the blepharosis and his vision was normal. Direct laryngoscopy depicted enlarged pyriform sinuses, bulky arytenoids with dilated laryngeal ventricles and glottic folds appeared thickened and abducted with a glottic gap. From the history and clinical examination alone a diagnostic possibility of this rare disease was considered and the child was investigated further. Routine laboratory investigations including lipid profile were within normal limits. Contrast enhanced CT scan of the neck and from skull base to diaphragm done revealed impaired mobility of true vocal cords and vocal cord paresis and thickened base of epiglottis. Skin biopsy was deferred due to parent unwillingness. Electron microscopy and genetic mutation analysis were not done due to financial constraints. He was started on acitretin at a dose of 10mg daily continued for 3 months along with other routine supplements and emollients for his skin. Previous studies have reported improvement in hoarseness of voice with acitretin therapy and hence this was started after

parental consent. No new skin and mucosal lesions were observed during the course of treatment. There were no side effects during treatment. The plan is to continue with maintenance dose of acitretin for a year and regular use of emollient containing urea and lactic acid for the recurring verrucous plaques. The parents were counseled regarding the prognosis and regular monthly follow up thereafter to monitor the improvement.

DISCUSSION

Examination of larynx in children is a difficult task and diagnosis in a child with hoarse cry is challenging. Examination of the skin and oral cavity can give valuable information in diagnosis of this rare condition. Urbach-Wiethe disease is one of the few skin conditions which may manifest with hypophonia or hoarse voice in childhood (Table 1).[8]

Table 1: Disorders associated with hoarseness of voice.

Type	Disorders
Metabolic disorders	Hypothyroidism
	Lipoid proteinosis/Urbach-Wiethe disease
	Farber's disease
	Systemic amyloidosis
	Lichen myxedematosus
Infections	Leprosy
	Syphilis
	Epidemic typhus
	Rhinoscleroma
Autoimmune connective tissue disorder	Relapsing polychondritis
	Dermatomyositis
	Systemic lupus erythematosus
	Sjogren's syndrome
Genetic disorders	Epidermolysis bullosa laryngoonychocutaneous syndrome
Miscellaneous	Sarcoidosis
	Infantile hemangioma involving the upper airway
	Cornelia de Lange's syndrome

The occurrence isn't gender specific and can present in both males and females with equal frequency. 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 one of the first clinical manifestations. The hoarseness may present at birth or develop later within the first few years of life. Hofer reported that voice change was the most common symptom. The deposition of hyaline occurred early in the larynx and hoarseness can manifest soon after birth which often progresses during the patients lifetime. Subepithelial hyaline deposition in the vocal cord leads to incomplete closure of the vocal cords with phonatory gap and impaired wave formation leading to hoarseness of voice.

In this case, the presenting complaint was hoarseness of voice and was present since early infancy. Many cases have been reported with upper airway obstruction as well requiring tracheostomy as an emergency. In our case the child had no upper airway obstruction presently. Skin lesions include vesicles, pustules, bullae and hemorrhagic crusted eruptions on the face and limbs that are more extensive in areas of trauma.[9] Skin lesions heal with 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. Monoliform blepharosis is one of the classical features with hyaline deposition over the eyelids leading to beaded pattern over the lids.[10] Oral manifestations of lipoid proteinosis 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.

Few of these features were observed in our case. Other manifestations 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 lipoid proteinosis which is related to defective osteoblasts that are biologically similar to fibroblasts. Our child presented with short stature as well.

Pathology

The major clinical manifestations of Lipoid Proteinosis 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 non-collagen 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. Little is known about the initial stage of the disease. H & E -stained sections of early lesions reveal pink, hyaline -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 hyaline 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.

Hamada et al recently discovered that lipoid proteinosis is caused by loss-of-function mutations in the ECM 1 gene. ECM 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, ECM 1 binds to perlecan and thereby may help to regulate basement membrane production.

Management

The prognosis for lipoid proteinosis is variable depending upon the clinical manifestations and there is no known cure. Most of the cases present early in life. Death 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. Parent and patient education and counselling will go a long way and play a very important part in the wholesome management.

CONCLUSION

Lipoid proteinosis should be part of differential diagnosis in infants and young children presenting with hoarseness of voice or hypophonia with coexisting skin and mucosal lesions. Despite the rarity of the condition hoarseness of voice with characteristic skin and mucosal lesions is diagnostic. The beneficial effects of acitretin in the treatment of lipoid proteinosis underlies in its inhibitory effects on collagen production and thereby decreasing the hyaline material deposition in dermis and restoring the basement membrane.[11] The management is multidisciplinary and the role of other specialists along with the pediatrician lies in early diagnosis as well as assuring follow up and explaining the outcome which may not be as good with no definitive available treatment.[12]

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