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Case Report

Orolaryngeal manifestations of Urbach-Wiethe disease: a case report

Arunabha Chakravarti*, Varun Kumar

Department of Otorhinolaryngology and Head and Neck Surgery, Lady Hardinge Medical College, New Delhi, India

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***Correspondence:**
Dr. Arunabha Chakravarti,
E-mail: drachakravarti@yahoo.co.in

ABSTRACT

Lipoid proteinosis, also called Urbach-Wiethe disease, is a rare genodermatosis that presents with diverse signs and symptoms. It causes the accumulation of amorphous hyaline deposits in various organs of the body, including mucous membranes, skin and the brain. The disease starts with hoarseness in childhood and then progresses to involve other systems. We report two cases of the disease, one of a 14-year-old girl who presented with hoarseness. The patient had scarring of the skin over the face and upper limb, and deposits were visible in the oral cavity. Office endoscopy revealed laryngeal deposits. On brain imaging, bilateral mesial temporal lobe calcifications were noted. Biopsy of the lesions was suggestive of lipoid proteinosis. Second, of a 2 years old male child, who presented with a weak cry and skin lesions over the upper limbs and was diagnosed by a genomic analysis. This case series adds to the sparsity of the literature with regard to this medical rarity. The girl was started on oral acitretin, topical triamcinolone and speech therapy while the second child was started on oral acitretin. Thus, our case series highlights the diverse nature of this disease, diagnostic modalities and the importance of multimodal therapy for this disease.

Keywords: ECM-1, Hoarseness, Lipoid Proteinosis, Acitretin

INTRODUCTION

Urbach-Wiethe disease also referred to as Lipoid proteinosis or hyalinosis cutis et mucosae, is an uncommon, autosomal recessive genodermatosis, characterised by the accumulation of hyaline like material into the mucous membranes, skin and other organs of the body. The condition was first described by Urbach and Wiethe in year 1929.[1] Since then, fewer than 400 cases have been reported globally.[2] Underlying genetic defect involves mutation in gene encoding for ECM-1 protein located on chromosome 1q21.[3] Earliest consistent feature in patients with this condition is hoarseness, which begins early in childhood, attributed to the thickening of arytenoids and irregular morphology of vocal cords.[4] Additional findings may include thickened epiglottis and arytenoids, pebbled oral mucosa, and woody tongue causing restricted mobility. Dermatological manifestations present as vesicles and papules that heal with pox like acneiform scars over the skin. The highly characteristic feature is the presence of beaded papules along the eyelids-Moniliform blepharosis which is highly pathognomonic.[5] Magnetic resonance imaging of the brain reveals symmetrical calcifications in the amygdala and mesial temporal lobes, a hallmark feature.[6] Histopathology examination of lesions shows deposition of PAS-positive, with/without diastase-resistant hyaline material in the mucous membranes.[1] Management is largely supportive and multidisciplinary. Acitretin, a vit-A derivative has shown partial benefit, improving skin and sometimes voice. In severe cases, surgical excision of laryngeal deposits may lead to voice improvement.[4,7]

CASE REPORT

Patient 1

Patient information

A 14-year-old girl referred to the otolaryngology clinic by dermatologist for the complaints of hoarseness since early childhood, on general examination it was found that

patient had papular deposits along eyelid margins along with thickened, waxy skin over face and upper limbs.

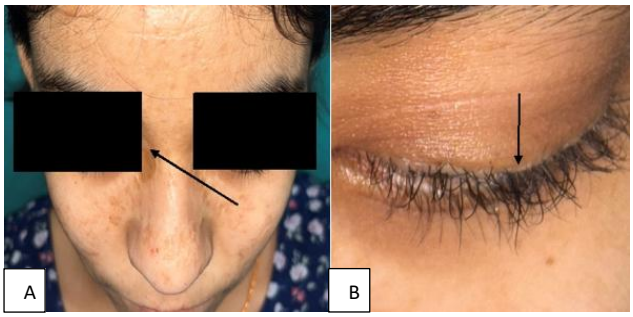

Figure 1 (A and B): Waxy skin and arrow showing pock like scarring over the skin, arrow showing beaded deposits along the eyelid margins.

Clinical findings

Local examination revealed deposits over the lateral tongue border and buccal mucosa with restricted tongue mobility. Office laryngeal examination showed thickened vocal folds, deposits over arytenoids, laryngeal surface of epiglottis and posterior pharyngeal wall.

Diagnostic assessment

Routine haematological and biochemical investigations were normal. In view of patient's mucocutaneous and airway involvement of uncertain cause, a direct laryngoscopy with biopsy was performed. Histopathology demonstrated hyperplastic squamous epithelium with pink amorphous eosinophilic material, which was positive for Periodic Acid-Schiff stain and diastase-resistant. The clinical features, laryngeal and mucocutaneous lesions in conjunction with the characteristic findings and histopathology, led to the diagnosis of Urbach-Wiethe disease. Magnetic resonance imaging of the brain was obtained for further workup, which revealed bilateral symmetrical calcifications in the mesial temporal lobes involving both amygdalae, along with patchy basal ganglia calcifications, although the patient had no neurological symptoms.

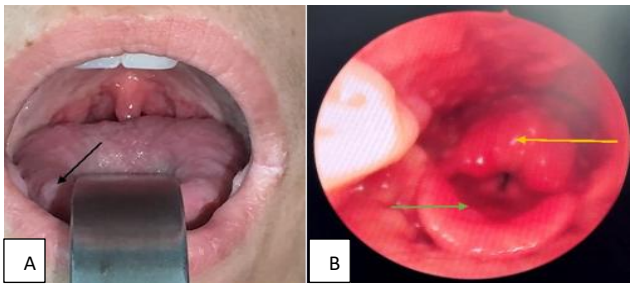

Figure 2 (A and B): Black arrow showing deposits over lateral border of tongue, long yellow arrow shows deposits over arytenoids; green arrow shows thickened epiglottis and deposit over laryngeal surface of epiglottis.

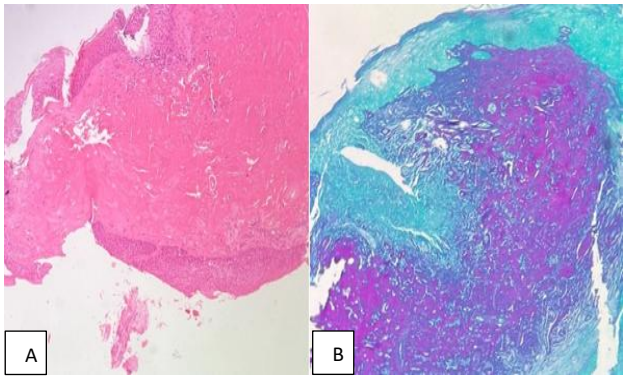

Figure 3 (A and B): Hyperplastic squamous epithelium with pink, amorphous eosinophilic material on haematoxylin and eosin staining beneath mucosa; deposition of periodic acid-Schiff -positive, hyaline-like material on PAS staining on 40× magnification.

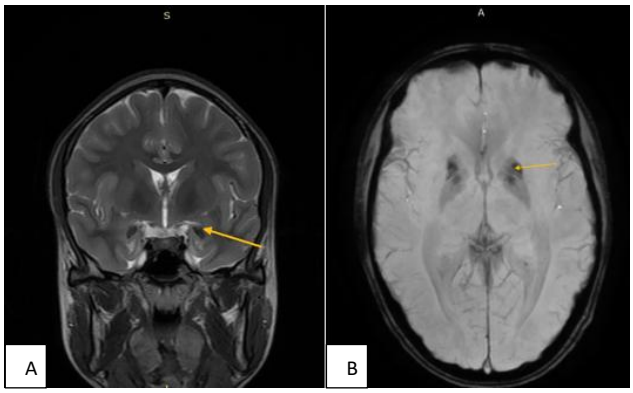

Figure 4 (A and B): Yellow arrow shows T2-hypointense foci involving the bilateral amygdala-suggestive of calcification, small yellow arrow showing loss of signal seen in Basal ganglia region on SWI indicating calcification.

Therapeutic intervention

Serum lipid profile, liver function tests, limb and spine X-rays were obtained followed by the initiation of oral acitretin, intraoral triamcinolone ointment and speech therapy.

Follow-up and outcomes

On a yearly follow-up, the patient reported subjective improvement in her voice quality and skin lesions.

Patient 2

Patient information

Two years old boy was referred to otolaryngology department by dermatologist for evaluation of weak cry since childhood. The patient had pock-like scars over the face and the shoulders and two beaded papules along the right upper eyelid margin.

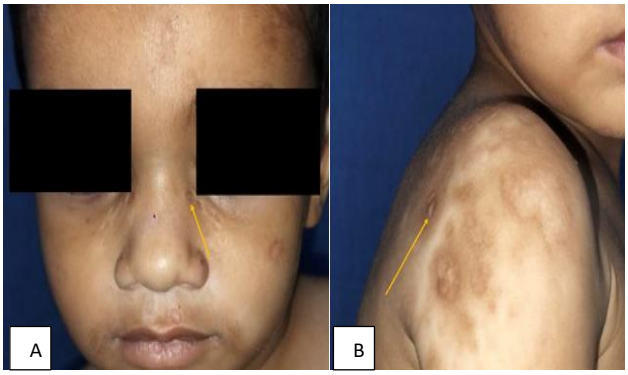

Figure 5 (A and B): Waxy skin and pock-like scars over face and shoulders.

Clinical findings

Tongue was depapillated with reduced mobility and office laryngeal examination showed thickening of true vocal folds but no submucosal deposits.

Diagnostic assessment

Biopsy of the skin lesions revealed hyperkeratosis and irregular acanthosis but no amorphous material was identified. Owing to high suspicion genomic analysis was obtained which revealed frameshift mutation at Exon 7/Exon 10 of ECM-1 gene confirming the disease.

Therapeutic intervention

Lipid profile and liver function tests were obtained followed by oral acitretin therapy.

Follow-up and outcomes

The child is kept on a close follow up.

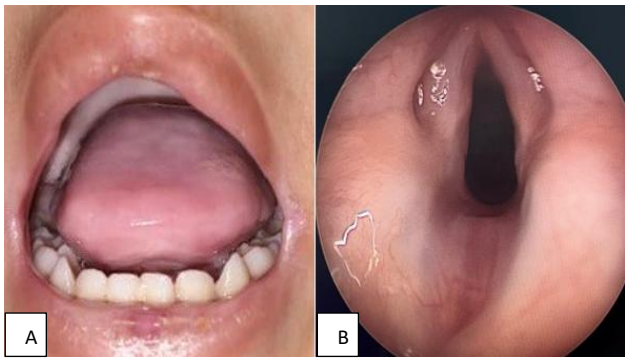

Figure 6 (A and B): Depapillated tongue, Thickening of bilateral true vocal folds.

Table 1: Summary of clinical features.

Age (years) / sex	Hoarse voice / weak cry	skin lesions	Moniliform blepharosis	Oral mucosa	Laryngeal involvement	Diagnosis method	Treatment	Response
14/F	+Hoarseness since childhood	Acneiform scars (face, upper limbs)	+Both eyes	Tongue thickening, restricted mobility	Vocal fold, arytenoid, epiglottic deposits	Biopsy (PAS+, diastase resistant) + Imaging	Acitretin + topical tri-amcinolone + speech therapy	Mild improvement
2/M	+ Weak cry since childhood	Pock-like scars (face, shoulders)	+Right upper eyelid	Tongue depapillated, reduced mobility	Bilateral true vocal fold thickening	Genetic testing (ECM1 mutation, exon 7/10 frameshift)	Acitretin	Under follow-up

DISCUSSION

Lipoid Proteinosis, also known as Urbach-Wiethe disease, is a rare autosomal recessive condition affecting skin and the mucous membranes characterized by the systemic deposition of amorphous, hyaline-like material in the skin, mucous membranes, and other internal organs.[8] While it occurs globally, a significant portion of cases are concentrated in South Africa.[3]

Pathogenesis and genetics

The disease occurs from loss-of-function mutations in the extracellular matrix protein-1 (ECM-1) gene.[9] ECM-1 is a secreted glycoprotein that functions as a "biological superglue", regulating basement membrane integrity and skin homeostasis. It has a role in endothelial cell proliferation, angiogenesis, epidermal differentiation, binding of dermal collagens and proteoglycans, therefore, helps in wound healing.[10,11] Mutations in this gene disrupts these functions and protein interactions, leading to duplication of the basement membrane and the subsequent accumulation of hyaline material. Research indicates that exons 6 and 7 are the most common sites for these mutations.[8,10] Although some reports suggest that mutations in exon 7 may result in a slightly milder phenotype in regards to skin and airway, it is also seen that severe hoarseness and skin manifestations can occur regardless of the specific mutation site.[12]

Clinical manifestations

The clinical presentation of Lipoid Proteinosis is remarkably consistent across different populations. Similar to our patient, the earliest hallmark feature is often a weak cry or hoarseness caused by hyaline

infiltration of the vocal cords.[13] Disease activity in early phase is marked by vesicles and haemorrhagic crusts, seen at the sites of friction or minor trauma.[14] These lesions eventually heal, leaving behind acneiform or pock-like scars, particularly on the face and extremities. A pathognomonic sign is moniliform blepharosis, a row of beaded papules along the eyelid margins.[13] The tongue and frenulum as seen in the oral cavity examination becomes thickened and woody, which restricts lingual movement and further hinders speech. Patients develop bilateral intracranial calcifications within the amygdala and temporal lobes. Although our patient was asymptomatic, but, these neurological changes can manifest as epilepsy, memory impairment, or neuropsychiatric disorders such as schizophrenia.[14]

Management and prognosis

There is currently no curative treatment for lipoid proteinosis, management focuses on symptom reduction and preventing complications.[15] Pharmacological approaches include the use of oral retinoids like acitretin, which may improve cutaneous lesions and hoarseness in some patients.[16] Other treatments such as dimethyl sulfoxide (DMSO) and D-penicillamine have not yielded promising results.[15] Recent researches highlights a hybrid approach involving surgery followed by intensive voice therapy, which has shown significant objective improvements in vocal mass and glottic closure.[16]

CONCLUSION

In conclusion, lipoid proteinosis is generally compatible with a normal life span. It is a progressive condition that may require multidisciplinary inputs from otolaryngologists, dermatologists and neurologists. Although tracheostomy is rarely required, early recognition and examination is vital to manage respiratory risks and provide genetic counselling for affected families.

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