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Case Report

Urbach-Wiethe syndrome (Lipoid proteinosis): an entity with rare absence of characteristic hoarseness of voice

烏爾巴赫—威士綜合徵（類脂質蛋白沉積症）：一宗罕見地沒有聲音嘶啞特徵的個案

V Kuntoji, C Kudligi, PV Bhagwat, ED Kaivalyam, S Patil, A Bansal

Lipoid proteinosis, also known as Urbach-Wiethe disease, is a rare autosomal recessive disorder characterised by the deposition of an amorphous hyaline material in the skin, mucosa and viscera which results in a myriad of clinical features. Although symptoms can vary greatly among affected individuals, symptoms normally begin in infancy and are typically due to the thickening of the skin and mucous membranes. The first symptom is often a weak cry or a hoarseness of voice due to thickening of the vocal cords which is one of the most striking features of the disease. We report a case of lipoid proteinosis in an adult male who had most of its typical features except for hoarseness of voice which is rarely reported in the literature.

類脂質蛋白沉積症也稱爲烏爾巴赫－威士病，是一種罕見的常染色體隱性遺傳病，其特徵在於在皮膚、粘膜和內臟中沉積著無定形的透明物質，衍生各式各樣的臨床特徵。儘管受影響的個體之間的症狀可能會有很大差異，但症狀通常在嬰兒期開始，由皮膚和粘膜增厚引起。首個症狀通常是由於聲帶增厚而引起的柔弱的啼哭或聲音嘶啞，這是此病最突出的病徵之一。我們報告一例成年男性的類脂質蛋白沉積症，除卻聲音嘶啞之外，他有著衆多其他的典型特徵，這是文獻中罕見的。

Keywords: Hoarseness, hyaline, lipoid proteinosis, scars

關鍵詞：聲嘶、透明的、類脂質蛋白沉積症、疤痕

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Introduction

Lipoid proteinosis (LP) is a rare autosomal recessive congenital disorder which has a vast continuum of ophthalmic, cutaneous, neurological, and oral manifestations characterised by the deposition of hyaline material in various organs.[1] It is more common in the Namaqualand region of South Africa (1 in 300 population). It affects males and females equally. Hoarseness of voice is the earliest finding in LP which usually presents at birth or in the first few years of life.[2] We report a case of LP in an adult

male who had most of its typical features except for hoarseness of voice which is rarely reported in the literature.

Case report

A 25-year-old male presented with gradually progressive skin lesions since the age of six months. There was a history of two types of lesions: (1) clear fluid-filled blisters over the face and trunk which ruptured after a few days to heal with scarring and (2) papular lesions which had initially started on the forehead and progressed to involve the eyelids, trunk, axillae and elbows. He also had difficulty in protruding the tongue. He was on antiepileptic medication for seizures since ten years ago which had been well-controlled. However there was no history of hoarseness of voice, photosensitivity, visual disturbances or joint pain. The patient was born of a consanguineous marriage with uneventful antenatal and perinatal events. There was a family history of similar lesions in his brother. General physical examination revealed a moderately built and well-nourished individual with general appearance appropriate for his age. On examination, there were multiple skin-coloured to hyperpigmented papular lesions on the face, neck, axillae, elbows, knees and thighs. The margin of the eyelids were studded with similar lesions with sparse eye lashes. Multiple erosions and scarring alopecic patches were seen on the eyebrow and beard areas. Facial skin, ears, and lips were thick and infiltrated (Figure 1). Intraoral examination revealed a thickened and firm tongue studded with multiple papules on its surface. The tongue movements were partially restricted. Labial, buccal, and palatal mucosae showed a thickened and nodular appearance. Systemic examination did not reveal any abnormality. Routine blood investigations including serum lipid profile, thyroid profile were within normal limits. Urine and stool examination findings were normal. Electrocardiography, abdominal ultrasound, plain computed tomography (CT) of the brain were normal. Biopsy from one of the representative cutaneous lesions revealed deposition of dense eosinophilic material in the dermis and around blood vessels (Figure 2) and amyloid staining with Congo red (Figure 3) was negative confirming the diagnosis of lipoid proteinosis. However, immunohistochemistry, immunofluorescence labelling, polymerase chain amplification and direct nucleotide sequencing of

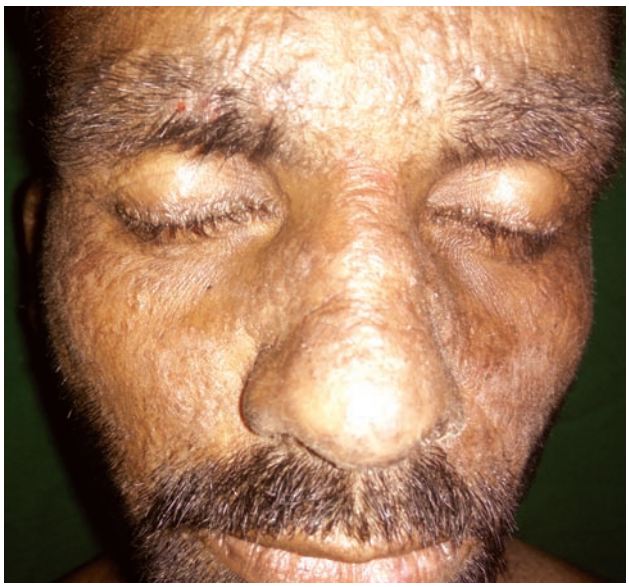

Figure 1. Multiple skin coloured to hyperpigmented papular lesions dispersed over the face, beaded appearance of eyelid margins, scarring alopecic patches involving eyebrows.

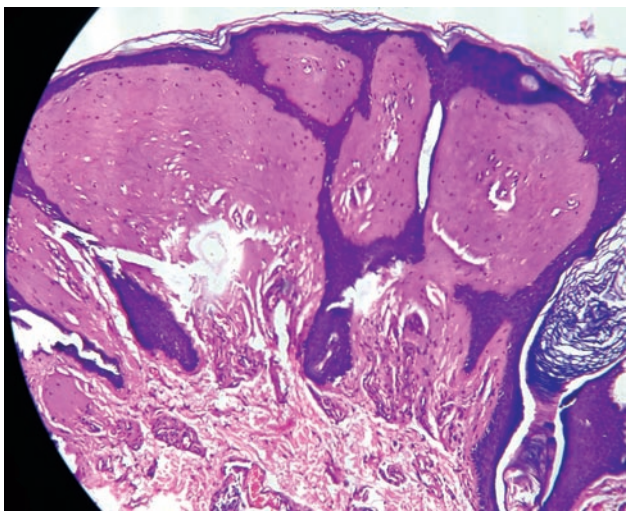

Figure 2. Biopsy of the papular lesion showing deposition of dense eosinophilic material in the dermis and around blood vessels (H and E: x40).

ECM 1 gene could not be performed due to financial constraints.

Discussion

Lipoid proteinosis also known as Urbach–Wiethe syndrome or hyalinosis cutis et mucosae, was first described by E. Urbach and C. Wiethe in 1929.[1,3] Mutations in the *ECM 1* gene on chromosome 1q21 resulting in dysfunctional extracellular matrix protein 1 was suggested as the cause of LP.[4] However, the exact correlation between genetic mutations and clinical manifestations of the disease remains unclear. To date, about 41 distinct germline, missense, nonsense, splice-site, and small and large deletions and insertions have been identified with also two new mutations being reported in two unrelated patients of German and Arab-Israeli race.[5] The most common presentation of LP is progressive hoarseness which may be present at birth or early childhood due to diffuse infiltration of hyaline material in the mucous membrane of the vocal cords.[6] They have a thickened sublingual frenulum which prevents protrusion of tongue, hence the clinical clue "Listen to them talk and have them stick out their tongues".[7] However our patient surprisingly had no hoarseness of voice though there was difficulty in protrusion of the tongue. Since it is an autosomal recessive disorder, all the family members should be screened. In our case, the patient's brother younger by four years was affected and had similar clinical features. Typical involvement of the eye includes whitish, beaded papules along the upper and lower eyelid margins, a pathognomonic finding present in 50% of patients, termed "Moniliform blepharosis". Cutaneous lesions include yellowish or waxy papules on the lips, over the knuckles, sides of the hands, on the knees, elbows and in the axillae. Sometimes vesiculo-bullous eruptions or acneiform lesions may be present, which are followed by nodules or plaques or pock-like scars,[8,9] predominantly on the face and the extremities. Most of these features were seen in our patient. As a multisystem disease, LP occasionally involves the CNS. CNS infiltration occurs predominantly around the amygdala and hippocampal capillaries, resulting in wall thickening, which later progresses to perivascular calcium deposition. Microscopic findings include gross amorphous calcifications encompassed by gliotic tissue and calcified thickened capillary walls.[10] Interestingly, in our patient, plain CT imaging did not reveal any abnormality although he was suffering from seizure disorder. This can be explained as the radiological investigations can be completely normal in the absence of calcification.[10] Lipoid proteinosis must be differentiated from erythropoietic protoporphyria, xanthomatosis, amyloidosis, myxoedema and lichen myxedematosus.[11] We ruled out the possibility of these disorders based on clinical clues (such as the involvement of covered areas, scars, typical involvement of eyelids and oral cavity, absence of photosensitivity), normal blood investigations including complete haemogram, serum lipid levels and thyroid hormones, normal urine and stool examinations and typical histological findings which were consistent with LP. Specific and

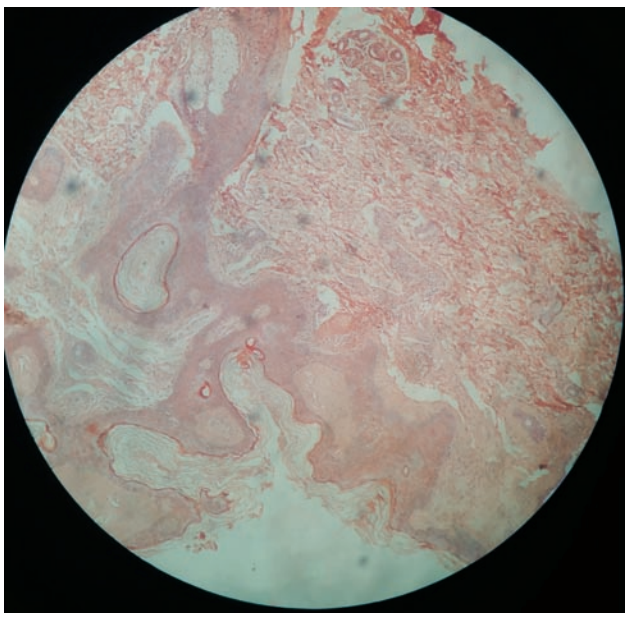

Figure 3. Photomicrograph showing the absence of characteristic orange red deposits of amyloid in the dermis (Congo red stain, x40).

effective treatment is not available for this condition. Various medical and surgical modalities such as oral steroids, dimethylsuphoxide, intralesional heparin, etretinate, penicillamine, dermabrasion, chemical skin peeling, blepharoplasty, and CO_2 laser therapy have been tried with variable success.[11,12]

Conclusion

The present case is reported for its rarity. To the best of our knowledge, less than 500 cases have been reported in the literature. Although there are many classical features, hoarseness of voice which is characteristically present in most of the reported cases was absent in our case. The disease may be misdiagnosed due to its vast spectrum of manifestations hence clinical practitioners need to be aware of this entity.

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