Lipoid proteinosis: Report of 2 cases

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Introduction

Lipoid proteinosis also known as Urbach-Wiethe disease is a rare autosomal recessive genodermatosis, that has been first described in 1929. To date only about 300 cases have been reported in the world literature. Although it has been reported from all over the world, the condition appears to be more common in patients of European ancestry. This explains the high prevalence in south Africa (about 25% of the reported cases) where many people are of Dutch or German ancestry[1-3].

The disease is characterized by deposition of an amorphous hyaline material in various tissues. It may display multiple systemic involvement, however skin and mucosal membranes of the upper aerodigestive tract are those that are primarily affected.

Onset is usually in early childhood characteristically presenting with a weak cry or hoarse voice[4], although late presentations have been reported. Cutaneous manifestations may start during the first two years of life. Diffuse skin infiltration and thickening gradually occurs, resulting in papules, plaques and chicken pox-like scars. Virtually any organ may be involved, but visceral involvement rarely leads to clinically significant consequences, except in the cases of respiratory distress due to laryngeal infiltration and neuropsychiatric manifestations that might result from calcifications in the brain[5-6]. The prognosis of LP patients is generally good despite the progressive nature of the disease until early adulthood.

Lipoid proteinosis is characterized, histologically, by intercellular deposits of periodic acid Schiff (PAS) - positive hyaline material in the skin, mucous membranes, and internal organs.

Recently, lipoid proteinosis has been linked to mutations in the gene encoding extracellular matrix protein 1 (*ECM1*) in chromosome 1q21[7]. A positive family history may be elicited as the condition is inherited in an autusomal recessive pattern[14].

Unfortunately, no effective treatment is known to date.

Case 1

Mr DA, a 35 year old patient presented to our dermatology clinic with recurrent vescicles that ulcerated and healed with scarring. His history went back many years starting from early childhood.

First episode occurring one month after birth. He is a product of a non consanguineous marriage and the first medical encounter had been due to development of recurrent blisters, especially on the face and extremities. These blisters had ulcerated and healed with scarring. Initially the possibility of porphyria had been considered although the porphyria screening had been negative. He recalls that from early days he had difficulty in speech with problems in pronunciation. His skin condition had stabilized after several years, being limited to occasional development of new ulcers however the speech difficulties had progressed over the years. The frustration from speech problems had led him to default from schooling and for many years he had been lost to medical follow up. After a period of inactivity, recently he had started developing blisters that quickly ulcerated and this has been associated with ulceration in the oral mucosa as well. He had developed generalized seizures in his mid twenties and is currently on antiepileptic medication. There was no history of frontal headache or behavioral problems and no evidence of other system involvement. Family history revealed that his younger brother was affected with a similar condition however no other relatives appeared to be affected.

Examination revealed skin colored waxy papules and plaques mainly on the face and dorsa of hands with pox like scarring (Figure 1). At each clinic visit he had at least one active ulcer on the skin or oral mucosa. He had limited tongue movements with difficulty in protruding the tongue. Typical beaded appearance of the eye lids described as moniliform blepharosis was noted however examination by the ophthalmologist did not reveal any other eye

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abnormalities. No abnormalities in the dentine were noted. Skull X rays or the CT scan of the brain did not reveal any intra cranial calcifications. Two skin biopsies were taken, one from a new lesion on the neck and the second from an old scar from the face to confirm the diagnosis. Both sections demonstrated dermal deposition of hyaline material, specially around the dermal vessels and connective tissue. Dermis was noted to be extensively expanded due to these deposits. Section from the old scar showed marked epidermal atrophy (Figure 3). PAS positivity was noted. The appearance was reported to be compatible with Lipoid proteinosis.

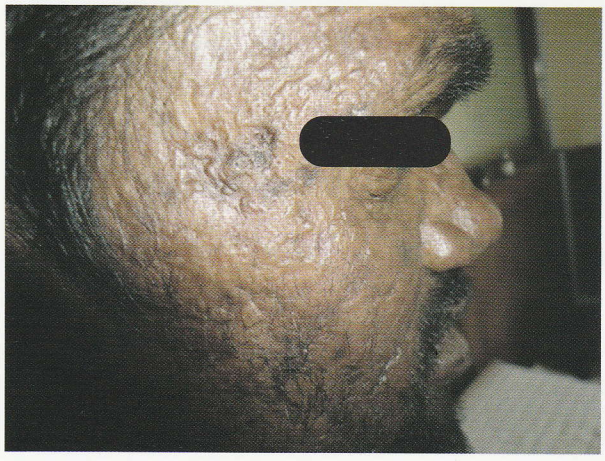

Figure 1.

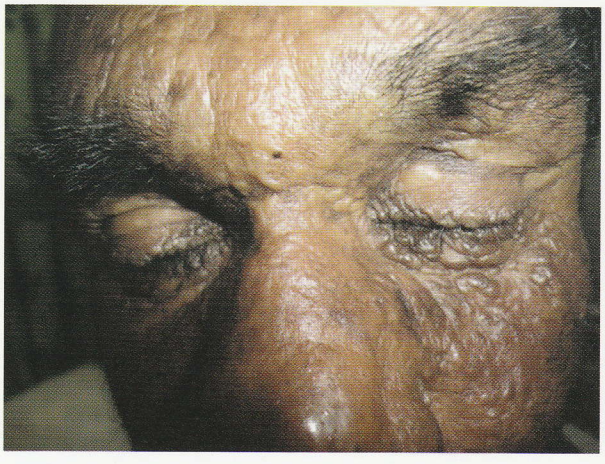

Figure 2.

Case 2

Mr SA is the brother of our first patient. We got him down to the clinic after obtaining the family history of our first patient. Similar to his brother he had also started developing spontaneous blisters and ulcers that healed with scarring few months after birth. He recalls thickening of the skin over the face and dorsa of hands from early childhood. Together with his brother he had been seen by many doctors regarding his skin changes without a satisfactory answer. He had more severe speech difficulties than his brother and at the time of presenting to the clinic was almost incapable of coherent speech. He did not have a history of seizures, headaches or behavioral changes. His skin examination revealed a similar picture to that of his brother with waxy skin colored papules and plaques and pock like scars on the face and hands with prominent moniliform blepharosis (Figure 3). In addition he also had thickened hyperkeratotic areas over the elbows. Indirect laryngoscopy revealed thickening of the vocal cords with hyaline deposits on the cords as well as the oropharynx. A biopsy taken from these deposits in the larynx showed classical histological features of lipoid proteinosis confirming the diagnosis. Surgical removal of some of the deposits from the vocal cords and the pharynx gave a satisfactory improvement of his speech, although this may be transient. Ophthalmic examination did not reveal any abnormalities. He did not show evidence of other system involvement.

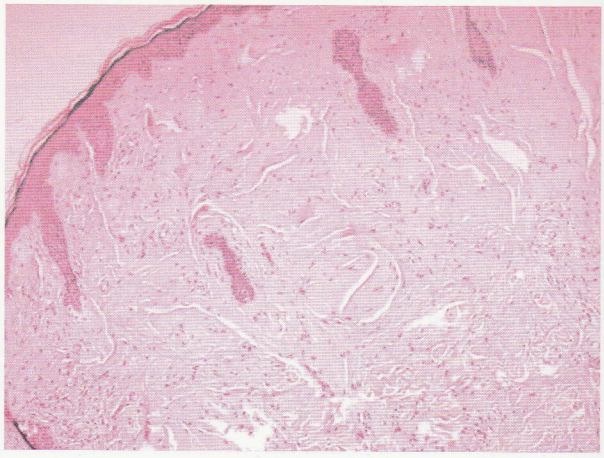

Figure 3.

Discussion

In 2002, loss of function mutations in the gene encoding extracellular matrix protein 1 (*ECM1*) on band 1q21 had been identified as the cause of lipoid proteinosis[7]. The *ECM1* gene product is a glycoprotein with functional roles in skin physiology and homeostasis. *ECM1* is involved in keratinocyte differentiation in the epidermis and in regulation of basement membrane integrity, interstitial collagen fibril macroassembly, and growth factor binding in the dermis[15-16]. The disease is characterized by

deposits of hyalinelike material in skin, mucosa, and viscera and is also referred to as hyalinosis cutis et mucosae. The loss of normal function of *ECM1* in lipoid proteinosis is associated with a wide range of clinical abnormalities due to infiltration of the skin and viscera with hyaline like material. Its role in wound healing, scarring, and aging is speculated but not yet defined.

The first clinical manifestation of lipoid proteinosis is usually progressive hoarseness caused by diffuse deposition of hyaline material in the mucous membranes of the vocal cords[4]. This hoarseness may be present at birth, as a weak cry, or develop later, within the first few years of life.

The hallmarks of cutaneous involvement are; yellowish warty papules, pox like scars together with beaded appearance of eye lid margins known as moniliform blepharosis[9]. However the cutaneous features may manifest in sequential but overlapping stages.

1. Initially, an inflammatory, vesicular eruption may appear on the face and extremities. They occur predominantly in sites of trauma, and ultimately heal with scarring[8].
2. The second stage is characterized by dermal deposits of amorphous hyaline material, creating a diffuse, waxy, thickened appearance.
3. Verrucous papules and plaques arise later on surfaces subject to friction, such as the elbows, knees, and hands.

The skin of patients with lipoid proteinosis is highly susceptible to damage, explaining the predominant involvement of skin over extremities and areas subjected to friction.

Although autopsy findings of patients with Lipoid proteinosis have demonstrated microscopic deposits of hyaline proteins in almost all tissues, in clinical practice involvement of other organs is not a major problem. It's rarely a life threatening condition except in patients with diffuse infiltration of the pharynx and larynx that may cause respiratory distress, at times requiring tracheostomy. Other more common features in the oral cavity include, thickening of the sublingual frenulum and the tongue leading to speech difficulties due to limited tongue movements. More diffuse involvement of the oral mucosa may cause xerostomia and dysphagia as well. Both our patients (more severe in Case 2) had limited tongue movements with difficulty in speech but no respiratory distress.

The rare ophthalmological complications include corneal opacities and secondary glaucoma due to infiltration of traberculum. Extramucocutaneous features include neurological manifestations such as epilepsy (which our first patient had) memory loss and behavioral changes which may be associated with intracranial calcifications, especially in the temporal lobe[5-6].

LP usually has a slow progressive course until early adulthood and stabilizes. Affected individuals usually have a normal life span unless affected by airway obstruction. Unfortunately there is no universally effective therapy currently. Approaches reported in the literature include oral and topical steroids, dimethyl sulphoxide[11], intralesional heparin, D-penicillamine[10] and acitretin[12]. Laser microlaryngoscopy[13], dissection of the vocal cords and excision of deposits may be performed to preserve or improve the voice. Microdermabrasion and chemical peels have been reported to improve the appearance of the skin. Counseling of the parents regarding the risk for future pregnancies is an important part of the management.

References

1. Heyl T. Geological study of lipoid proteinosis in south Africa. *Br J Dermatol* 1970; **83**: 338-40.
2. Hofer PA. Urbach-wiethe disease (lipoglycoproteinosis; lipoid proteinosis; hyalinosis cutis et mucosae): a review. *Acta Dermatol Venereol* 1973; **53**(suppl 71): 1-52.
3. Van hougenhouck-tulleken W, Chan I, Hamada T, Thornton H, Jenkins T, Mclean WHI, *et al.* Clinical and molecular characterization of lipoid proteinosis in namaqualand, South Africa. *Br J Dermatol* 2004; **151**: 413-23.
4. Savage MM, Crockett DM, Mccabe BF. Lipoid proteinosisof the larynx: A cause of voice change in the infant and young child. *Int J Pediatric Otol* 1988; **15**: 33-8.
5. Friedman L, Mathews RD, Swanepoel PD. Radiographic and computed tomographic findings in lipid proteinosis. A case report. *S Afr Med J* 1984; **65**: 734-5.
6. Kleinert R, Cervos-Navarro J, Kleinert G, Walter GF, Steiner H. Predominantly cerebral manifestation in urbach-wiethe's syndrome (lipoid proteinosis cutis et mucosae): a clinical and pathomorphological study. *Clin Neuropathol* 1987; **6**: 43-5.
7. Hamada T, Mclean WHI, Ramsay M, Ashton GHS, Nanda A, Jenkins T, *et al.* Lipoid proteinosis maps to 1q21 and is caused by mutations in the extracellular matrix protein 1 gene (ecm1). *Hum Mol Genet* 2002; **11**: 833-40.
8. Gutte R, Sanghvi S, Tamhankar P, Khopkar U. Lipoid proteinosis: is opathological characterization of early papulovesicular lesions. *Indian Dermatol Online J May* 2012; **3**(2): 148-9.

9. Callizo M, Ibáñez-Flores N, Laue J, Cuadrado V, Graell X, Sancho JM. Eyelid lesions in lipoid proteinosis or Urbach-Wiethe disease: case report and review of the literature. *Orbit* Oct 2011; **30**(5): 242-4.

10. Kaya TI, Kokturk A, Tursen U, Ikizoglu G, Polat A. D-penicillamine treatment for lipoid proteinosis. *Pediatr Dermatol* 2002; **19**(4): 359-62.

11. Wong CK, Lin CS. Remarkable response of lipoid proteinosis to oral dimethyl sulphoxide. *Br J Dermatol* 1988; **119**(4): 541-4.

12. Akoglu G, Karaduman A, Ergin S, Erkin G, Gokoz O, Unal OF. Clinical and histopathological response to acitretin therapy in lipoid proteinosis. *J Dermatolog Treat* 2011; **22**(3): 178-83.

13. Kroukamp G, Lehmann K. Treatment of laryngeal lipoid proteinosis using CO2 laser. *S Afr Med J* 2007; **97**(2): 90-92.

14. Salih MA, Abu-Amero KK, Alrasheed S, Alorainy IA, Liu L, McGrath JA, et al. Molecular and neurological characterizations of three Saudi families with lipoid proteinosis. *BMC Med Genet* 2011; **12**: 31.

15. Han Z, Ni J, Smits P, Underhill CB, Xie B, Chen Y, *et al.* Extracellular matrix protein 1 (ECM1) has angiogenic properties and is expressed by breast tumour cells. *FASEBJ* 2001; **15**: 988-94.

16. Smits P, Poumay Y, Karperien M, Tylzanowski P, Wauters J, Huylebroeck D, *et al.* Differentation-dependent alternative splicing and expression of the extracellular matrix protein 1 gene in human keratinocytes. *J Invest Dermatol* 2000; **114**: 718-24.