Case Reports

Lipoid proteinosis

A report of 2 siblings and a brief review of the literature

Sahar H. Al-Natour, *MD, KFUFD.*

ABSTRACT

يعتبر مرض التدسم الجلدي المخاطي Lipoid proteinosis من الأمراض الوراثية النادرة، ويتميز بترسب مادة شفافة داخل الجلد في الأغشية المخاطية للفم والبلعوم والقصبة الهوائية وغيرها من الأنسجة. ما يلى هو مراجعة موجزة لتاريخ هذا المرض، وتقرير عن حالة لشقيقين سعوديين ظهرت عليهما العوارض المميزة للمرض في الجلد والأنسجة المخاطية، بالإضافة إلى مظاهر شائعة ونادرة لهذا المرض مثل تكلس في الدماغ Hippocampus، وتغيرات غير محددة في الرسم الكهربائي للدماغ. نحن نستعرض هذه الحالة لتأكيد وجود هذا المرض في المملكة العربية السعودية، ولتحديث المعلومات وآخر التطورات فيما يتعلق بهذا النوع من الاعتلال.

Lipoid proteinosis is a rare autosomal recessive inherited metabolic disorder characterized by deposition of a hyaline-like material in the skin, oral laryngeal mucosa, and in other sites. In this report, the author describes 2 Saudi siblings who had characteristic skin findings, oral and mucosal lesions, histological findings along with few rarely encountered manifestations including pathognomonic calcifications in the hippocampus, electroencephalogram findings and briefly reviews the literature. These cases are presented to emphasize the occurrence of this condition in Saudi Arabia, and to update information on the latest developments of this disorder.

Saudi Med J 2008; Vol. 29 (8): 1188-1191

From the Department of Dermatology, King Faisal University, College of Medicine, Dammam, Kingdom of Saudi Arabia.

Received 8th April 2008. Accepted 29th June 2008.

Address correspondence and reprint request to: Dr. Sahar H. Al-Natour, King Fahd Hospital of the University, PO Box 2208, Al-Khobar 31952, Kingdom of Saudi Arabia. Tel. +966 (3) 8957886. Fax. +966 (3) 8944370. Tel. +966 5054845523. Email: saharnatour@yahoo.com

Lipoid proteinosis (LP) also known as hyalinosis et mucosae or Urbach-Wiethe disease (UWD) first described in 1929, is a rare autosomal recessive (AR) metabolic disorder characterized by the deposition of a hyaline-like material in the mucosa of the larynx, skin, and various other organs.[1] The disease presents in early infancy with hoarseness followed by a manifold of distinctive skin lesions. Over 300 cases of this rare disorder have been described.[2] Lipoid proteinosis in siblings is rarely reported.[3] In 2002, this disorder was mapped to chromosome 1q21, and pathologic loss-of-function mutations were delineated in the extracellular matrix protein one (ECM 1) gene.[4]

Case Report. A 14-year-old boy (Case 1), and his 13-year-old sister (Case 2), born to Saudi consanguineous parents presented with hoarseness since birth and asymptomatic skin lesions from infancy. The siblings were referred from the Department of Otolaryngology, King Fahd Hospital of the University, Al-Khobar, for the evaluation of their skin lesions. Detailed history revealed that the hoarseness manifested soon after birth as a weak cry in both but became more obvious as they started to talk at the age of 11 months. There was no history of dysphagia, dyspnea, or stridor. The skin lesions started at the age of 2 years as non-pruritic yellowish papules and hemorrhagic vesicles that ruptured spontaneously and with minimal trauma, and healing with scars over the face, trunk, and limbs. Progressive thickening of the skin, and hair loss was noticed subsequently. Systemic review was insignificant with no similar skin lesions in their parents or other 8 siblings. A history of seizures, and photosensitivity was denied in both siblings. Both received repeated courses of antibiotics for "recurrent laryngitis" since infancy, and have undergone speech therapy for several months prior to presentation without any improvement. On examination, both siblings exhibited extensive yellowish waxy thickening of the skin most evident on the face but also of the trunk and limbs. "Ice pick" atrophic scars (**Figure 1**) (Case 1), and

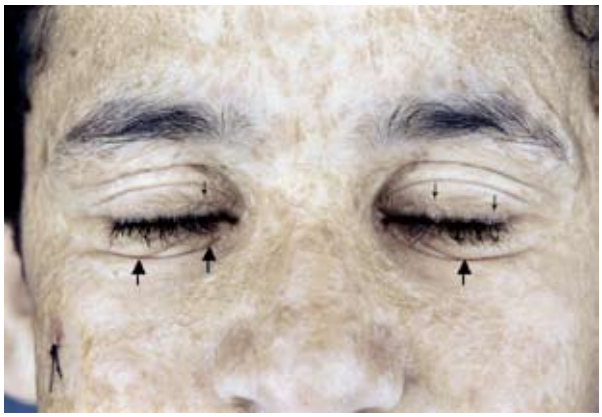

Figure 1 - Diffuse thickening and pigmentation of the skin of the face with acneiform scarring. The classic beaded papules along the upper (↓ top) and lower (↑ bottom) eyelid margins (Case 1).

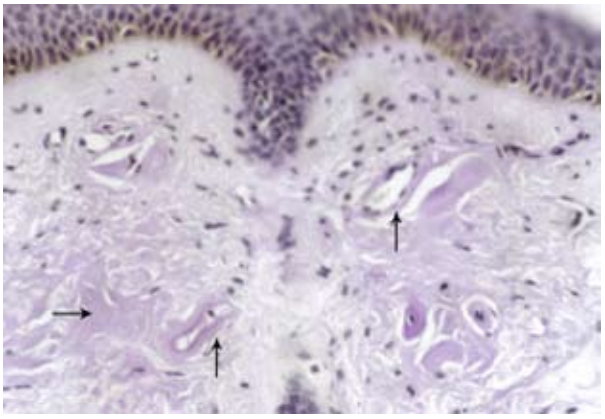

Figure 4 - Periodic-acid-Schiff positive diastase resistant hyaline deposits seen in the dermis (→) and around blood vessels (↑) in a section obtained from Case 2. Epidermis unremarkable (x 100).

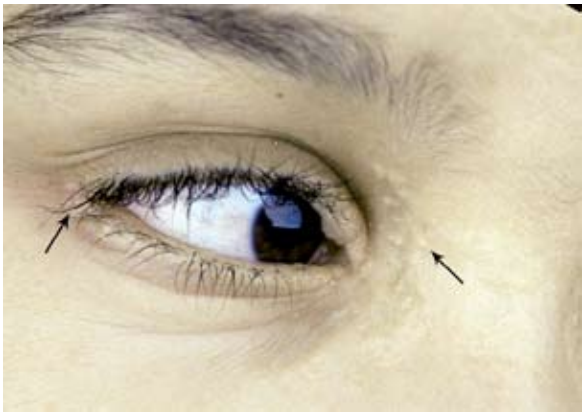

Figure 2 - The typical "beaded" papules present along the margins of the upper and lower eyelids (arrow) with partial loss of the lower eyelashes (Case 2).

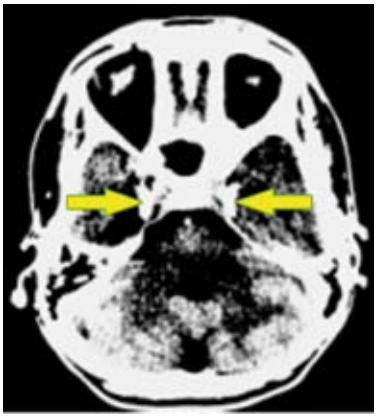

Figure 5 - Plain CT scan reveals the pathagnomonic bean shaped calcifications in the para sellar areas of the brain (Case 2).

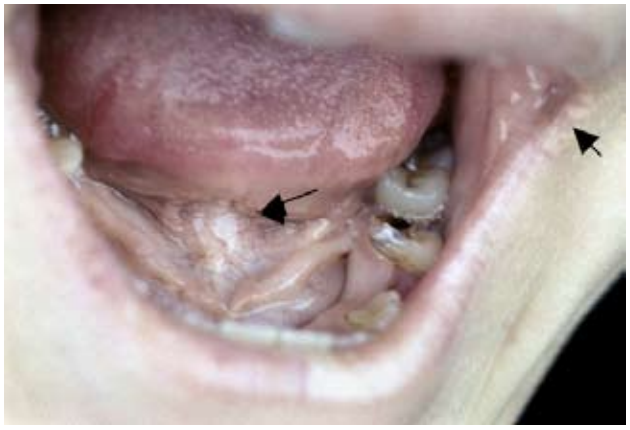

Figure 3 - Enlarged tongue with restricted movement and woody on palpation with deposits along the frenulum (arrow), angles of the mouth and lips (arrow). Aplasia and decay of teeth also noted (Case 1).

the pathognomonic beaded papules along the margins of the eyelids (moniliform blepharitis) in both siblings pointed out the diagnosis (**Figure 2**) (Case 2). Verrucous papules and nodules over the elbows bilaterally, and thickened infiltrated plaques over the labiae majora were present in the sister. Multiple hypopigmented macules not preceded by previous skin lesions were present over the shoulders and trunk in the brother. The oral mucosa, and lips in both siblings showed infiltration along with dental anomalies. The tongues were enlarged and hard on palpation with an inability to protrude the tongue beyond the lip margins. Dental anomalies were more obvious in the brother with loss of several upper and lower incisors and pre-molars with several carried teeth **Figure 3** (Case 1). Patchy areas of hair loss were present in the brother, in contrast to a generalized diffuse thinning

of the hair in the sister. Systemic, neurological, and ophthalmologic examinations were unremarkable. Initial laryngoscopy carried out one year prior to the referral revealed congested hypertrophied vocal cords but mobile with air escape in the boy sibling, and the anterior 1/3 of left vocal cord was reported to be edematous and polypoidal but freely mobile in the sister. Both patients had hypertrophied vestibular bands. Routine laboratory, biochemical and protein electrophoresis screens were normal. Histological examination of the representative skin lesions from the face and trunk of both siblings showed a deposition of periodic acid-Schiff (PAS) positive hyaline deposits throughout the dermis primarily around the dermal blood vessels and sweat glands. The deposits were diastase resistant and stained negative with Congo red **Figure 4** (Case 2). Chest x-ray revealed no abnormality. Cranial computed tomography (CT) scanning revealed the pathognomic bilateral bean-shaped calcifications within the hippocampus in both patients **Figure 5** (Case 2). Electroencephalogram (EEG) findings included a generalized but non-specific disturbance of cerebral activity and infrequent generalized epileptic discharges predominantly in the right tempero-occipital region in both patients. Neuro imaging, barium swallow, and laryngeal CT scanning were scheduled but both patients failed to return for their appointments or follow up.

Discussion. Lipoid proteinosis first described in 1929 is a rare AR inherited disorder characterized by the infiltration of a hyaline-like material in the skin, larynx, brain and other internal organs.[1] Since then, approximately 300 cases have been reported in the literature.[2] Although seen worldwide, there seems to be a higher occurrence amongst people of European origin, including South African descendents of German or Dutch immigrants.[4] More recently, the condition has been found to be occurring more frequently in countries where consanguinity is common.[4] The occurrence in siblings is very rare.[3] Saudi cases[5,6] as well as those from other Gulf countries[7] have been reported in the literature. The reported siblings are Saudi and born to a consanguineous marriage, the parents being first degree cousins. The occurrence in the 2 siblings, a boy and a girl, amongst 8 other siblings supports the recessive inheritance. The cause of this AR disorder has now been established with the recent discovery of the underlying molecular defect. In 2002, Hamada et al[4] mapped this disorder to a locus on chromosome 1q21 and pathogenic mutations were identified in ECM1 gene, which encodes for the glycoprotein extracellular matrix protein 1. The function of ECM1 is still unclear, although an important role in skin physiology and homeostasis has been hypothesized.[4] The findings of Chan et al[8] indicate the clinical relevance of this gene to skin adhesion, epidermal differentiation, wound healing, scarring, skin ageing, angiogenesis/angiopathy and basement membrane physiology, as well as defining the molecular basis of this inherited disorder.[8] The principal function of ECM1 is its acting as a "biological glue" in the dermis by binding to key components of dermal ground substance and hence, regulating the bioactivity of many matrix components or influencing signalling associated with stromal responses.[9] The recent discovery and identification of mutations in ECM1 gene can now improve diagnostic accuracy, make carrier screening feasible, and DNA-based prenatal diagnosis of LP can be made.[4] The earliest and most consistent clinical sign of the disease is hoarseness usually presenting at birth with a hoarse or weak cry, but may present later in life, and usually progresses with age. Both siblings presented at birth with a hoarse and weak cry. Physicians, general practitioners, and otolaryngologists not familiar with this disease may mistake the laryngeal symptoms, and findings for more common diseases such as chronic laryngitis, Singer's nodules or polyps especially in the absence of skin lesions.[10] Both patients were diagnosed as chronic laryngitis early in childhood, and as vocal cord hypertrophy, and polyposis in the brother and sister, respectively, for several years prior to their referral to the dermatology clinic. This disease is easily overlooked, and it is possible that it occurs more frequently than the reported 300 cases.

In addition to infiltration of the larynx and pharynx, other mucosal findings include thickening of the tongue, becoming firm and woody with restriction of mobility and speech impediment. Involvement of the gingivae, xerostomia, and various dental anomalies have been previously reported.[11] Infiltration of the oral mucosa, tongues, frenula, and lips was observed in the 2 patients in addition to dental anomalies and caries. Skin lesions usually develop during the first 2 years of life however, may appear later. They consist of papules and hemorrhagic vesicles and crusts that heal with "ice pick" acneiform scars or waxy papules, nodules or plaques that may coalesce to result in diffuse thickening of the skin. These lesions are primarily distributed on the face, extremities, and rarely elsewhere, including neck, axillae, trunk and genitalia. Scalp involvement may lead to loss of hair. All the typical skin lesions were observed in both siblings and were noted to appear at 2 years of age in both. The classic and most characteristic sign is the "string of beads' appearance of papules along the eyelid margins (moniliform blepharosis), and is found in two thirds of patients.[1] This sign pointed out the diagnosis in both patients. However, the hypopigmented macules on the trunk of the boy sibling was not previously reported. Though deposition of hyaline material in the conjunctiva, cornea, trabeculum and retina (Bruch's membrane), have

been described[12] no ophthalmic findings were observed in the 2 siblings. In contrast to reports of widespread visceral involvement,[13] the 2 siblings showed no evidence of such involvement. Histologically, LP is characterized by the extensive deposition of amphorous eosinophilic material around capillaries, sweat glands, hair follicles, arrector pili muscles, and in the papillary dermis. The hyaline material is PAS positive but diastase resistant.[1] The skin biopsy specimen from both patients demonstrated the characteristic histological findings. Perhaps, the most characteristic radiological findings are the bean-shaped intracranial calcifications in the temporal lobe and often seen after the age of 10 years and may be associated with epilepsy, memory loss, schizophrenic behavior, and intellectual impairment.[3,14,15] The pathognomonic calcifications within the hippocampus in the 2 siblings confirmed the diagnosis of LP. Although infrequent generalized epileptic discharges in the right tempero-occipital region were observed in the EEG of both patients, seizures were denied in both. However, a bizarre hyperactive and disinhibited type of behavior similar to what was previously reported[3] was observed in the brother during admission. Currently, there is no effective therapy for LP. The recent advances on the molecular basis of LP and development of recombinant protein for ECM1 may be of therapeutic value and suggest a possible future treatment for patients with this disorder.[4,9] Generally, life expectancy is normal.[1]

In conclusion, general practitioners as well as otolaryngologists should have knowledge, and be aware of the presentation of this rare disorder, otherwise, the diagnosis can be missed. In a country such as Saudi Arabia, and other countries where consanguineous marriages are frequent, the likelihood of offsprings afflicted with this disorder is high, therefore, it is important that the parents of affected children be counseled about the risks of having other affected off-springs. The recent identification of mutations in ECM1 gene can now improve diagnostic accuracy and carrier screening and DNA-based prenatal diagnosis of LP can now be made.

Acknowledgment. *The author would like to thank Dr. Fatma Shammasi for her contribution with patient management.*

References

1. Black MM. Lipoid proteinosis. In: Rook A, Wilkinson DS, Ebling FJG, editors. Textbook of Dermatology. 5th ed. Oxford (UK): Blackwell Scientific Publications; 1993. p. 2347-2348.
2. Hofer P. Urbach-Wiethe disease (lipoglyco-proteinosis; lipoid proteinosis; hyalinosis cutis et mucosae, a review. ***Acta Derm Venereol*** Suppl (Stockh) 1973; 53: 1-52.
3. Rahalkar MD, Kelkar AB, Gharpuray MB, Patwardhan NG. Lipoid Proteinosis. ***Ind J Radiol Imag*** 2001; 11: 85-87.
4. Hamada T, McLean WH, Ramsey M, Ashton GH, 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: 833-840.
5. Nanda A, AlSaleh QA, Al-Sabah H, Ali AM, Anim JT. Lipoid proteinosis: report of four siblings and brief review of the literature. ***Pediatr Dermatol*** 2001; 18: 21-26.
6. Al-Bitar Y, Samadani A. Lipoid proteinosis in two brothers with multiple organ involvement from Saudi Arabia. ***Int J Dermatol*** 2004; 43: 360-361.
7. Galadari I, Al-Kuwaiti R. Lipoid proteinosis: a case report. ***Int J Dermatol*** 2004; 43: 368-370.
8. Chan I, Liu L, Hamada T, Sethuraman G, McGrath J. The molecular basis of lipoid proteinosis: mutations in extracellular matrix protein 1. ***Exp Dermatol*** 2007; 16: 881-890.
9. Chan I. The role of extracellular matrix protein 1 in human skin. ***Clin Exp Dermatol*** 2004 ; 29 :52-56.
10. Oz F, Kalekoglu N, Karakullukcu B, Ozturk O, Oz B. Lipoid proteinosis of larynx. ***J Laryng Otol*** 2002; 116: 736-739.
11. Hofer P, Bergenholtz A. Oral manifestations in Urbach--Wiethe disease (lipoglycoproteinosis; lipoid proteinosis; hyalinosis cutis et mucosae). ***Odontol Revy*** 1975; 26: 39-57.
12. Francois J, Bacskulin J. Follmann P. Manifestations oculaires du syndrome d' Urbach Wiethe. ***Ophthalmologica*** 1968; 155: 433-438.
13. Caplan RM. Visceral involvement in lipoid proteinosis. ***Arch Dermatol*** 1967; 95: 149-155.
14. Aroni K, Lazaris AC, Papadimitriou K, Paraskevakou H, Davaris PS. Lipoid proteinosis of the oral mucosa: case report and review of the literature. ***Pathol Res Pract*** 1998; 194: 855-859.
15. Emsley RA, Paster L. Lipoid proteinosis presenting with neuropsychiatric manifestations. ***J Neurol Neurosurg Psychiatry*** 1985; 48: 1290-1292.