Case Report

Lipoid proteinosis in Middle East and North Africa: A case report and literature review

Mohammed Alraddadi

Department of Internal Medicine, University of Tabuk, Tabuk, Kingdom of Saudi Arabia

Correspondence to: Mohammed Alraddadi, E-mail: moh_rad27@yahoo.com

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ABSTRACT

Lipoid proteinosis (LP) is a rare autosomal recessive genodermatosis characterized by the deposition of amorphous hyaline material in the skin, mucosa, and viscera. The classic manifestation is onset in infancy with a hoarse cry due to laryngeal infiltration. Skin and mucous membrane changes become apparent clinically, and the disease typically follows a slowly progressive, yet often benign, course. Virtually any organ may be involved, but visceral involvement rarely leads to clinically significant consequences. The aim of this study was to analyze the epidemiologic, genetic and clinical findings of reported cases in the Middle East and North Africa, reporting a case of LP to emphasize the occurrence of this condition in Saudi Arabia and to update information on latest development in diagnosis and management of LP. We review most of the cases reported in the Middle East and North Africa and analyze clinical signs and investigative findings, and we report a case with characteristic clinical and histological findings of LP. In the Middle East and North Africa, we found that the prevalence of LP is highest in Turkey with forty-eight reported cases. The reported cases in Saudi Arabia reached ten cases. In Iran, nine cases were reported, six of them belonging to two families. The fourth country in the prevalence of LP is Tunisia with five reported cases from the same family, followed by Kuwait with four reported cases. In our review of eighty-one cases reported in the literature, we found variable incidence of mucocutaneous lesions that include multiple depressed acneiform scars on the face and extremities (96.29%, 78 cases), beaded eyelid papules (86.41%, 70 cases), thickening of the skin (51.85%, 42 cases), verrucous plaques on the knee and elbow (37.03%, 30 cases), involvement of the tongue (55.55%, 45 cases), and thickening of the frenulum (48.14%, 39 cases). Although LP has a benign course, it can be a cause of morbidity in these patients. Thus, a detailed examination to determine the extent of involvement is important from time to time. The pathogenesis of LP is still an enigma, and the rarity of these cases makes them worthy of reporting to facilitate a better understanding of the disease.

KEY WORDS: Lipoid Proteinosis; Systematic Review; Case Report; Middle East; North Africa; Saudi Arabia

INTRODUCTION

Lipoid proteinosis (LP) is a very rare autosomal recessive genodermatoses whose true incidence is not known. It was first described by Siebenmann in 1908, and the first case series as lipoidosis cutis et mucosae was presented by a Viennese "dermatologist, Urbach and an otorhinolaryngologist, and Weithe in Later was renamed by Urbach in 1930 as "LP cutis *et al*.1929 mucosae."[1,2] It has been known by several terms such as "Urbach–Weithe disease," "lipoglycoproteinosis," "lipid proteinosis," and "hyalinosis cutis et mucosae."[3,4] Molecular genetic studies of LP patients have revealed that mutations in the ECM1 gene located on chromosome 1q21.2 are responsible for this disease. The ECM1 gene encodes the glycoprotein extracellular matrix protein.[5,6] The disease is characterized by deposits of hyaline-like Material in skin,

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mucosa, and viscera. The original designation, LP, refers to the histological features of the deposited material, which shows similarities to both lipid and protein, although no abnormalities in lipid metabolism have been identified.[7,8]

We will discuss eighty-one cases reported in the Middle East and North Africa and report a case with characteristic clinical and histological findings of LP in this article.

LITERATURE REVIEW

A systematic literature review for clinical studies and case reports of LP on the Cochrane, PubMed, and Embase databases was conducted with a focus on cases reported in the Middle East and North Africa. We found that the prevalence of LP is highest in Turkey with forty-eight reported cases. The reported cases in Saudi Arabia reached ten cases. In Iran, nine cases were reported, six of them belonging to two families. The fourth country in the prevalence of LP is Tunisia with five reported cases from the same family, followed by Kuwait with four reported cases [Table 1]. Male to Female Ratio was 1:1.25, with a mean age of seventeen years old, and positive history of consanguineous parents in forty-five patients [Table 2]. [1-44]

In our review of eighty-one cases reported in the Middle East and North Africa, we found variable incidence of mucocutaneous lesions that include multiple depressed acneiform scars on the face and extremities (96.29%, 78 cases), beaded eyelid papules (86.41%, 70 cases), thickening of the skin (51.85%, 42 cases), verrucous plaques on the knee and elbow (37.03%, 30 cases), involvement of the tongue (55.55%, 45 cases), and thickening of the frenulum (48.14%, 39 cases) [Table 3].

All the patients were suffering hoarseness of voice, the variable occurrence of other extracutaneous features including Laryngeal thickening (32.94%, 28 cases), neurologic symptoms (20%, 17 cases), and CT brain findings (12.94%, 11 cases) [Table 4].

Table 1: Demographic distribution of LP in Middle East and North Africa

Country	Number of cases (%)
Turkey	48 (59.25)
Saudi Arabia	10 (12.34)
Iran	9 (11.11)
Tunisia	5 (6.17)
Kuwait	4 (4.94)
Lebanon	3 (3.70)
Egypt	2 (2.47)
Libya	1 (1.23)
Total	81 (100.00)

CASE REPORT

A 47-year-old Saudi male patient presented to the dermatology clinic with skin lesions over both axillae, elbows, knees, and along eyelid margins since infancy, associated with the history of hoarseness of voice noticed by his parents at the age of two months as a weak cry then become apparent hoarseness at the end of 1st year. He also has multiple asymptomatic skin papules that had begun to develop when the patient reached the age of three years. His skin was easily damaged by minor trauma, leading to the development of bulla that healed leaving scars. Multiple skin-colored to yellowish papules on his face and along the margins of the upper and lower eyelids in the characteristic pattern of beads on a string [Figure 1]; multiple hyperkeratotic verrucous plaques on the dorsum of the hands, elbows, and knees [Figure 2]; waxy papules and plaques on the axillae [Figure 3]; oral mucosa was rigid and labial mucosa had become nodular and thickened, and the range of motion of the tongue was severely affected

Table 2: Basic information of LP patients

Nationality	Gender	*n*	Age (years)	Consanguineous parents
			Mean±SD	
Turkey	Male	23	19±12.09	11
	Female	25	18.84±10.59	16
	Total	48	18.92±11.21	27
Saudi Arabia	Male	5	17.6±10.97	5
	Female	5	15.2±3.11	3
	Total	10	16.4±7.71	8
Iran	Male	3	18.67±8.02	3
	Female	6	21.33±5.96	2
	Total	9	20.44±6.33	5
Tunisia	Male	2	16.5±2.12	0
	Female	3	7.33±5.51	0
	Total	5	11±6.44	0
Kuwait	Male	2	7.5±2.12	0
	Female	2	1.75±1.06	0
	Total	4	4.63±3.59	0
Lebanon	Male	0	-	0
	Female	3	17.67±8.51	3
	Total	3	17.67±8.51	3
Egypt	Male	0	-	0
	Female	1	2	1
	Total	1	2	1
Libya	Male	1	10	1
	Female	0	-	0
	Total	1	10	1
Total	Male	36	17.75±10.88	20
	Female	45	16.79±9.88	25
	Total	81	17.22±10.29	45

SD: Standard deviation

Table 3: Percentage of mucocutaneous features in reviewed patients

Mucocutaneous features	Number of patients (%)
Acneiform scars	78(96.29)
Beaded eyelid papules	70(86.41)
Thickening of the skin	42(51.85)
Verrucous plaques on the knees and elbows	30(37.03)
Thickening of the tongue	45(55.55)
Thickening of the frenulum	39(48.14)

Table 4: Percentage of extracutaneous features in reviewed patients

Extracutaneous features	Number of patients (%)
Hoarseness	81(100)
Laryngeal thickening	28(34.56)
Neurologic symptoms	17(20.98)
CT brain scan finding	11(13.58)

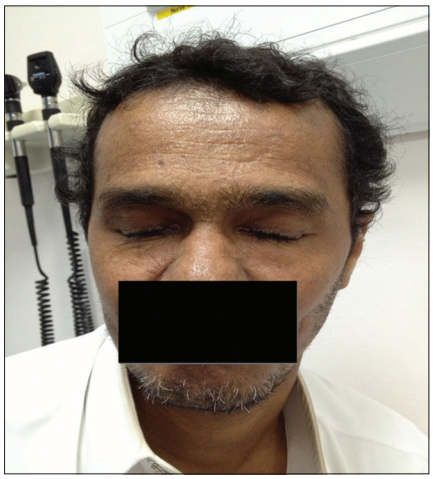

Figure 1: Facial tiny skin-colored to yellowish papules, and pearly papules on the eyelids

secondary to infiltration of the frenulum with missing all teeth in the upper jaw and 5 molars in the lower jaw [Figure 4]; The hair and nails were normal. The patient's psychomotor development was normal. An X-ray of the skull did not reveal brain calcifications. Hematological and biochemical examinations showed no abnormalities. The patient did not display any neurological symptoms or abnormalities on clinical examination. His parents are consanguineous (first-degree relatives), family history was positive for similar clinical features in a younger sister. Hematoxylin and Eosin stain and periodic acid Schiff (PAS) Stain of a skin biopsy were positive for deposits of hyaline material [Figures 5 and 6]; Verhoeff stain revealed the degeneration of elastic fibers. Thus, the patient was diagnosed with LP.

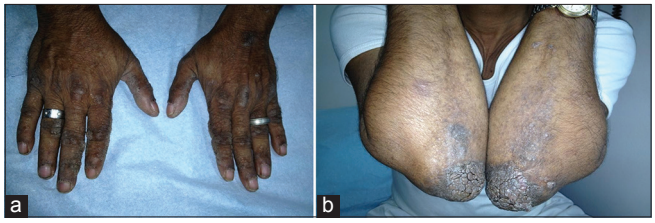

Figure 2: Warty plaques over the dorsal aspect of the hands (a) and elbows (b)

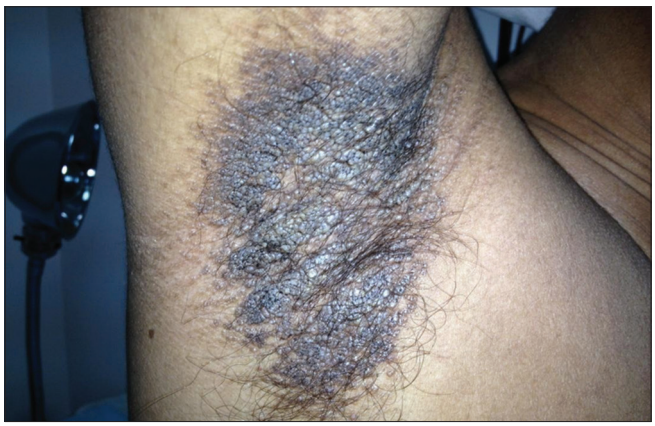

Figure 3: Waxy papules and plaques on the axillae

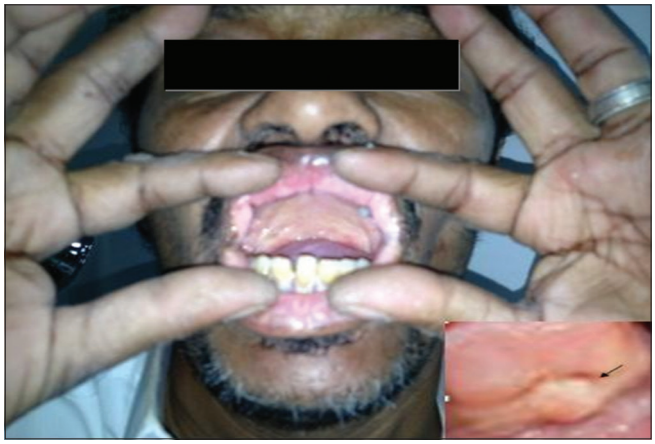

Figure 4: Missing teeth in the upper jaw, tongue involvement, with infiltration of the frenulum (insert)

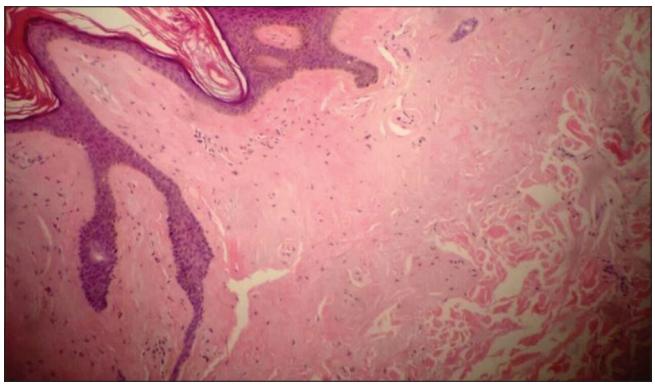

Figure 5: Skin biopsy shows mild papillomatosis with papillary and superficial dermal deposition of homogeneous pink material Hematoxylin and Eosin

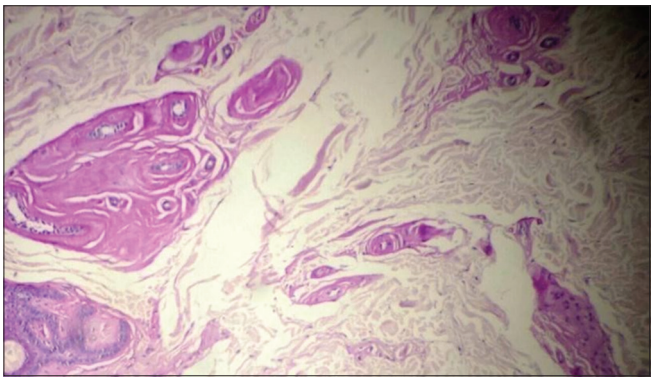

Figure 6: Deposition of periodic acid Schiff (PAS) positive hyaline material in the papillary dermis (PAS)

DISCUSSION

Hyalinosis cutis et mucosae, also named LP or Urbach–Wiethe disease, is a very rare disorder of autosomal recessive inheritance. Molecular genetic studies of LP patients have revealed that mutations in the ECM1 gene located on chromosome 1q21.2 are responsible for this disease. The ECM1 gene encodes the glycoprotein extracellular matrix protein. It is a storage disease that is probably related to the impairment of fibroblast and endothelial cells. It affects both genders sexes equally. Heterozygous carriers are usually asymptomatic.

One of the most remarkable clinical features of LP is hoarseness, caused by infiltration of the vocal cords. This is usually the first symptom in the most that appear during infancy. The laryngeal changes may rarely be a cause of life-threatening symptoms as respiratory insufficiency. Skin lesions may appear during the first two years of life and occur in two stages. The first consists of pustules, bullae, and hemorrhagic crusts of the skin, mouth, and throat. The skin lesions resolve with pock-like or acneiform scarring, usually on the face and distal extremities. In the second stage, deposits increase in the dermis, and the skin becomes thickened, yellowed, and waxy. Papules, plaques, and nodules take place primarily not only on the face but also on the axillae and on the scrotum. Beaded papules along the eyelid margins are characteristic findings. Verrucous lesions may occur on the extensor surfaces of the extremities, especially the elbow and the hands, usually after frictional trauma. Infiltration of the posterior tongue and frenulum may result in restricted mobility to the extent of causing speech difficulties. In addition to alopecia, dental anomalies and recurrent parotitis can occur.[24-28]

Neurologic manifestations may include seizures, behavioral changes, learning difficulties, and rage attacks. A pathognomonic finding of LP is bilateral intracranial bean-shaped calcifications within the temporal lobe or hippocampus-amygdala complex.[29-34]

LP is characterized histologically by disruption/duplication of the basement membrane of vessels and widespread deposition of eosinophilic hyaline material in the dermis. This material is PAS-positive, but diastase-resistant. Deposits can also surround hair follicles, sebaceous glands, and rarely arrector pili muscles. In addition, dermal fibroblasts demonstrate characteristic cytoplasmic vacuole formation.[35-40]

LP has no effective treatment so far. Due to the rarity of LP, there are no large case series to evaluate the therapeutic options. Anecdotal good results have been reported with oral dimethyl sulfoxide (DMSO),[45] D-penicillamine,[28] etretinate,[46] and acitretin,[47,48] and carbon dioxide laser surgery have been proposed in the treatment of affected vocal cords and eyelid papules.[49] However, there are also reports of limited success or unsatisfactory results with some of these medications. Experience with acitretin in LP patients is limited and conflicting results have been reported. Retinoids are proposed to modulate the metabolism of the basement membrane. Hein *et al*. reported the inhibitory effects of Vitamin A derivatives on collagen production. Through this inhibitory effect, acitretin may decrease the deposition of hyaline material in the dermis and restore the basement membrane. This inhibitory effect was the underlying rationale for the choice of acitretin. Dermabrasion and chemical peeling applications are tried for skin lesions, but these methods could provoke hyaline material deposition. Blepharoplasty and carbon dioxide laser surgery have improved beaded eyelid papules. Carbon dioxide laser surgery, microlaryngoscopy, and dissection of the vocal cords were performed in some cases.[50]

CONCLUSIONS

LP is a rare autosomal recessive genodermatosis characterized by the deposition of amorphous hyaline material in the skin, mucosa, and viscera. Although LP has a benign course, it can be a cause of morbidity in these patients. Thus, a detailed examination to determine the extent of involvement is important from time to time. The pathogenesis of LP is still an enigma, and the rarity of these cases makes them worthy of reporting to facilitate a better understanding of the disease.

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