DOI: http://dx.doi.org/10.3315/jdcr.2014.1168

Journal of Dermatological Case Reports

Two Egyptian cases of lipoid proteinosis successfully treated with acitretin

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Key words:

acitretin, blister, genodermatoses, hoarseness, lipoid proteinosis, pharynx, throat

Abstract

Background: Lipoid proteinosis (Urbach-Wiethe disease) is a rare progressive autosomal recessive disorder, characterized histologically by deposition of periodic acid Schiff-positive, diastase resistant, hyaline-like material into the skin, upper aerodigestive tract, and internal organs.

Main observation: We report two cases of lipoid proteinosis. A 2-year-old girl presented with vesiculobullous skin lesions on her face, trunk, extremities and scalp, inability to protrude the tongue and hoarseness of voice that appeared few months after birth. The other case is a 4-year-old girl, who presented with waxy papules on face and trunk, hoarseness of voice and enlarged lips and tongue. The lesions healed leaving pitted scars in both cases. Based on clinical, histopathological and laryngoscopy findings, lipoid proteinosis was diagnosed in both cases. Acitretin was started in a dose of 0.5 mg/kg/day in every child. Complete remission of cutaneous lesions and improvement of the hoarseness was observed after one year.

Conclusion: Acitretin may be benificial for treatment of mucosal and cutaneous lesions in lipoid proteinosis. (*J Dermatol Case Rep*. 2014; 8(1): 29-34)

Introduction

Lipoid proteinosis (Urbach-Wiethe disease) is a rare autosomal recessive genodermatosis. Classical clinical features include skin scarring, beaded eye lid papules, and laryngeal infiltration leading to hoarseness. The infiltrates in the tongue and its frenulum limit lingual movements and cause speech difficulties. Usually, the hoarse voice is present at birth or in early infancy, as the first disease manifestation.[1]

Diffuse skin infiltration and thickening with waxy texture gradually occurs, resulting in papules and chicken pox-like scars.[2] Lipoid proteinosis may also manifest with vesiculobullous lesions and oral ulcers.[3] Lesions involve primarily the face and extremities and rarely appear elsewhere.[1] Due to the rarity of lipoid proteinosis, a definite therapeutical approach is not established.

Case Reports

Case 1

A two-year-old girl, the first sibling of related parents, presented with progressive vesiculobullous skin lesions and hoarseness of voice few months after birth. Skin lesions were distributed on face, scalp, trunk and extremities and healed with atrophic scars (Fig. 1A). There was inability to protrude the tongue. The baby had average body weight (12 kg) and normal developmental milestones.

There was no history of seizures or visual disturbance and family history was irrelevant. Laboratory investigations including; complete blood count, serum glucose level, hepatic and renal function tests, porphyrin levels in serum, urine and stool were non contributary.

Patient underwent indirect laryngoscopy, on account of severe dysphonia, which showed thickening of the vocal cords and hyaline deposits in the larynx, oral cavity and oropharynx.

Evaluation of central nervous system (CNS) with magnetic resonance imaging (MRI) revealed no abnormality.

Skin biopsy from one representative lesion was taken after taking mother's consent. Light microscopic examination of hematoxylin and eosin (H and E)-stained sections showed massive deposits of homogeneous, eosinophilic, hyaline-like material at the dermal-epidermal junction, upper, mid and deep dermis (Fig. 2 A,B). This material was periodic acid Schiff positive and diastase resistant (PAS-D). It was deposited around blood vessels, pilosebaceous units, diffusely in dermis (Fig. 3, 4) and around intact and atrophic sweat glands (Fig. 3, 4).

Based on clinical, laryngoscopic and histopathological findings, the diagnosis of lipoid proteinosis was reached. Acitretin 0.5 mg/kg/day was prescribed with a total dose of 6 mg/day and patient was followed up every month. The drug dose was adjusted according to body weight in every follow-up visit.

Three months later, all old lesions healed (Fig. 5 A-F). There was slight reduction in the appearance of new skin lesions. Six months following treatment initiation, the hoarseness and aphonic cry were partially improved, the tongue can be partially protruded (Fig. 6 A,B) and new skin lesions continued to decrease in number. Indirect laryngoscopy revealed decreased vocal cord thickening and decreased hyaline deposits in larynx, oral cavity and oropharynx. After one year follow up, no new lesions appeared and no further improvement in voice was noticed. During the follow-up period of acitretin therapy, control laboratory tests including complete blood count, liver and kidney function tests, serum electrolytes, and fasting lipid profiles of patient did not reveal any abnormalities.

Case 2

A 4-year-old girl, the second sibling of consanguineous parents, presented with progressive waxy skin papules that appeared since the age of 6 months and hoarseness of voice, manifested by weak cry, few months after birth. Skin lesions were distributed on face, trunk and extremities and healed with varioliform scars (Fig. 1B). Lips were hard to touch and there was inability to protrude the tongue with thickened frenulum. The patient has normal developmental milestones and average body weight (16 kg).

There was no history of seizures or visual disturbance and there was no affection of other family members. Laboratory investigations including; complete blood count, serum glucose level, hepatic and renal function tests, porphyrin levels in serum, urine and stool were all normal.

Indirect laryngoscopy was performed to investigate the cause of hoarseness. It showed thickening of the vocal cords and hyaline deposits in the larynx, oral cavity and oropharynx. Evaluation of CNS with MRI revealed no abnormality.

Skin biopsy from one representative papule was taken after taking mother's consent. Light microscopic examination of (H and E)-stained sections showed massive deposits of homogeneous, eosinophilic, hyaline-like material at the dermal-epidermal junction, upper, mid and deep dermis (Fig. 2 A,B). This material was positive periodic acid Schiff and diastase resistant (PAS-D) revealing the glycoprotein nature of the substance. It was deposited around blood vessels, pilosebaceous units, diffusely in dermis (Fig. 3, 4) and around intact and atrophic sweat glands (Fig. 3, 4).

Based on clinical, laryngoscopic and histopathological findings, the diagnosis of lipoid proteinosis was made. Acitretin 8 mg/day was prescribed and patient was followed up every month. The drug dose was adjusted according to body weight in every follow up visit.

After three months treatment, all old lesions healed with slight reduction in the appearance of new skin lesions. Six months following treatment initiation, the hoarseness and aphonic cry were partially improved and new lesions markedly decreased in number. The tongue partially decreased in size with improved protrusion. Indirect laryngoscopy showed improvement in vocal cord thickeness and decreased mucosal hyaline deposits. After one year follow up, no new lesions appeared at all but there was no further improvement in voice. Routine laboratory testing including hemogram, liver and renal function tests, electrolytes and lipogram were all normal during the treatment period. Emollients were sometimes used, when needed, to compat with acitretin-induced xerosis.

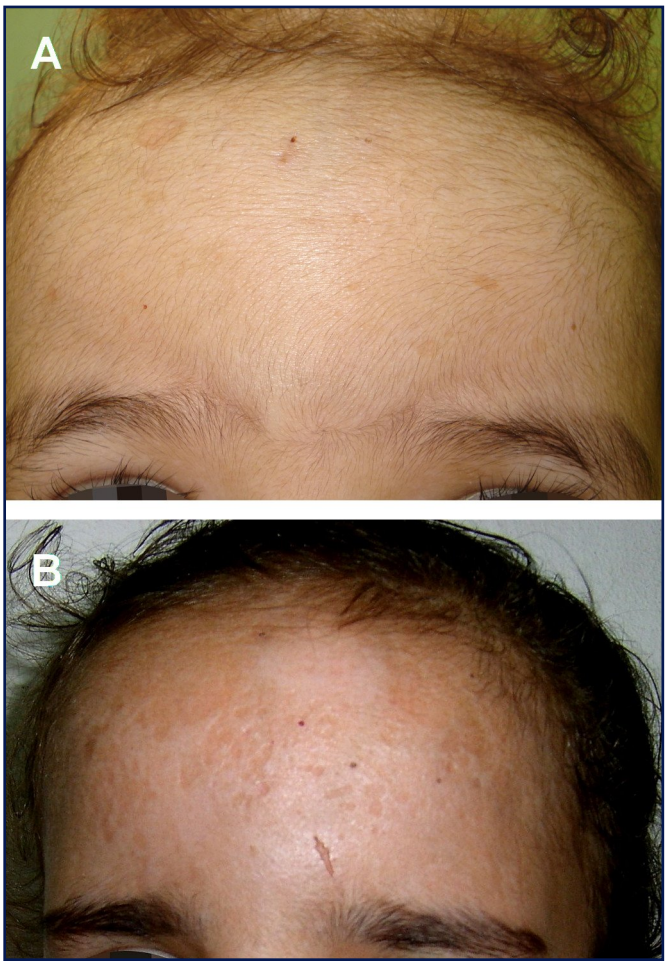

Figure 1

Atrophic scars on forehead of patient 1 (A) and in patient 2 (B).

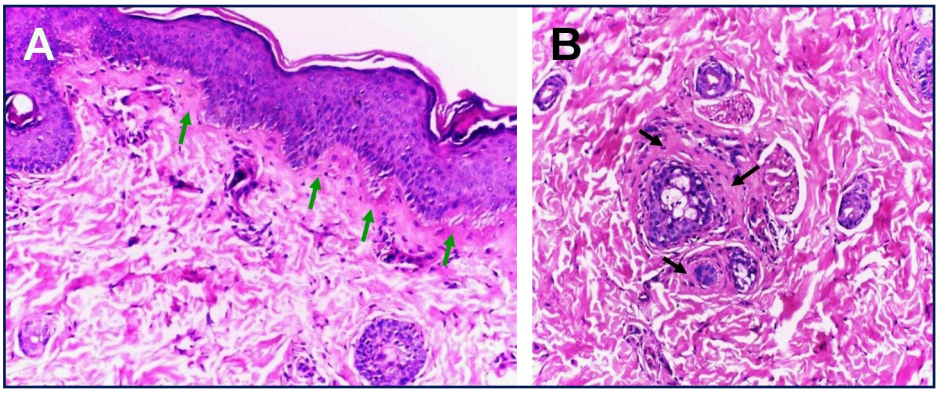

Figure 2

A) deposition of homogenous structurless eosinophilic material in dermo-epidermal junction (arrows) and dermis. B) the dermis displays the same deposits around the adnexal structures (arrows) and freely (H and E X200).

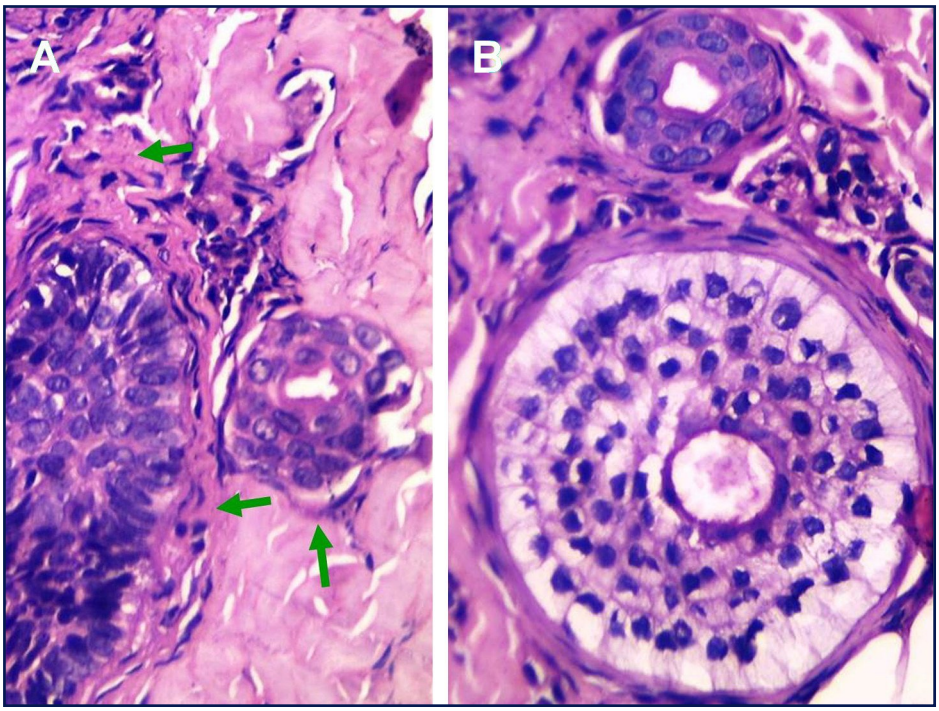

Figure 3

PAS positive, diastase resistant material is deposited around hair follicle and intact eccrine sweat glands (A and B) (PAS X400).

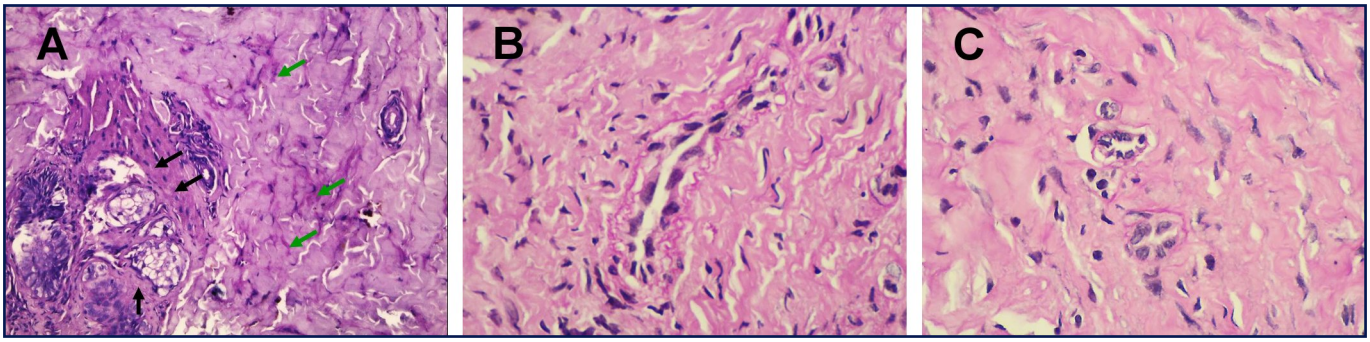

Figure 4

PAS positive, diastase resistant material is deposited A) around sebaceous glands (Black arrows) and freely in dermis (green arrows), B) around blood vessels and C) atrophic eccrine sweat glands (PAS X400).

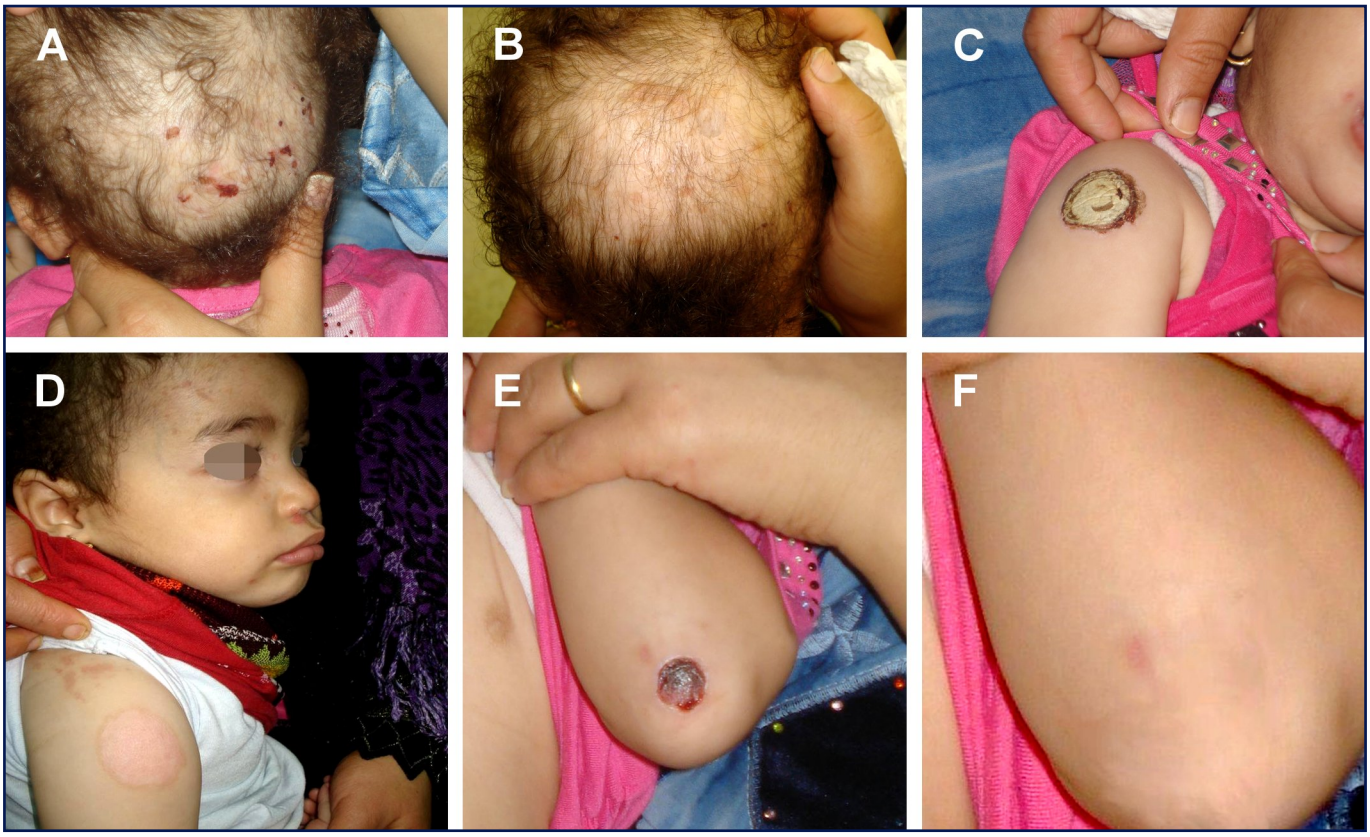

Figure 5

A, B) ruptured vesiculobullous lesions on the scalp that completely healed following acitretin therapy. C, D) ulcerated crusted lesion that healed after acitretin therapy. E, F) ulcerated lesion over the elbow that resolved after acitretin therapy.

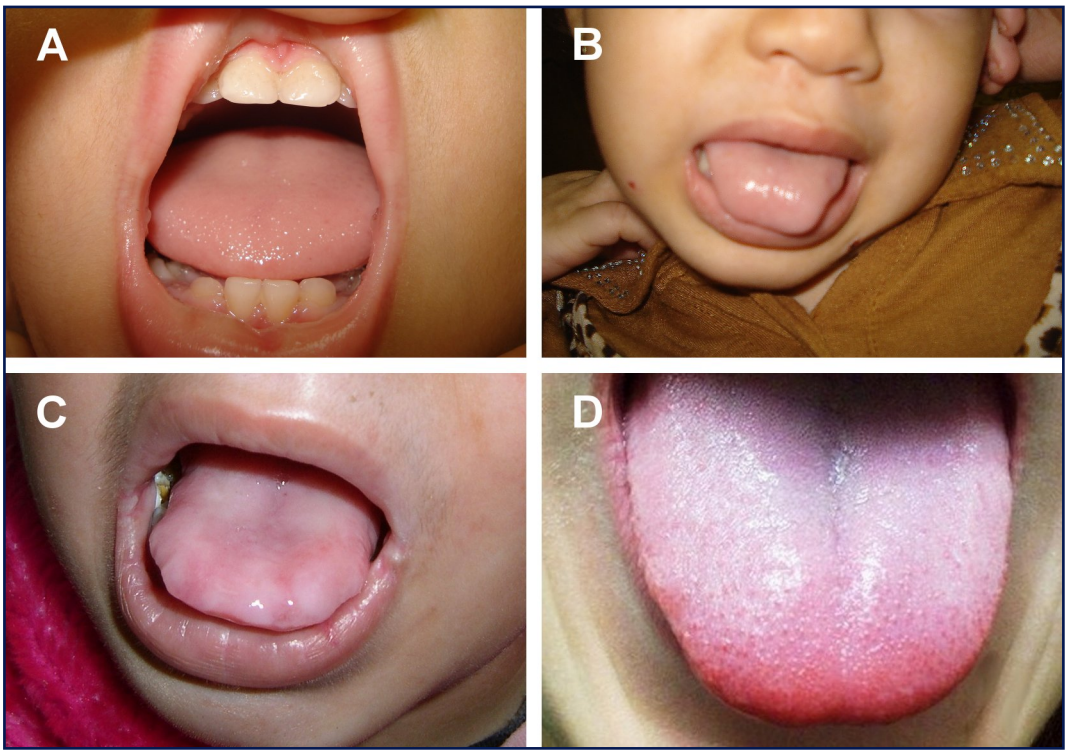

Figure 6

A, B) Improved tongue protrusion in case 1 after 6 months of treatment. C, D) Reduction in tongue size and improved protrusion in case 2.

Discussion

Lipoid proteinosis is a rare, autosomal recessive disease. The main clinicopathological features comprise skin and mucous membrane infiltration and scarring with deposition of hyaline material.[2] This disease can affect extracutaneous tissues, such as CNS. CNS involvement can usually be observed in the form of calcified spots in the temporal lobes or hippocampus amygdala. Epileptic seizures are reported in about 25% of lipoid proteinosis patients but correlation between seizures and intracranial calcifications was not established.[4]

The prognosis is, nonetheless, relatively good despite the progressive nature of the disease until early adulthood.[1]

Lipoid proteinosis is characterized, histologically, by deposits of PAS-positive, diastase resistant, homogenous, non-clefted, hyaline-like, material in the dermoepidermal junction and all levels of the dermis. This pale eosinophilic material is initially localized around blood vessels, eccrine sweat glands and pilosebaceous units. In advanced lesions, the deposits around blood vessels may have an 'onion-skin' appearance. There is also progressive atrophy of secretory sweat glands associated with increasing hyaline deposition. PAS-positive material in lipoid proteinosis is differentiated from amyloid by its negative or weak staining with Congo red stain. In erythropoetic protoporphyria, the deposits are more limited in distribution, being perivascular only, and the sweat glands are not involved.[5]

Hyaline deposition may also occur in mucous membranes, and internal organs.[6] Immunohistochemistry revealed widespread presence of type III and IV collagen in the hyaline material.[7]

The disorder has been shown to result from loss-of-function mutations in the extracellular matrix protein 1 (ECM1) gene on chromosome 1q21.[4] ECM1 has been reported to stimulate proliferation of blood vessel endothelial cells, to promote angiogenesis, and to be involved in the control of epidermal differentiation.[8] ECM1 is a secreted glycoprotein that binds to perlecan, the major heparan sulphate proteoglycan of the basement membrane, as well as to growth factors and fibrillar proteins. Thus, ECM1 may act as a "biological glue" in the dermis, helping to regulate basement membrane and interstitial collagen fibril macro-assembly and growth factor binding.[9]

Therefore, loss of ECM1 within the dermis may have profound effects on dermal homeostasis, leading to the clinical features of skin infiltration and scarring. Meanwhile, lack of ECM1 within the epidermis may alter the normal pattern of keratinocyte maturation and differentiation and give rise to the clinical features of warty hyperkeratosis.[8]

Because of the potential for causing unsightly scars, lipoid proteinosis should be treated as soon as possible to enable a normal psychosocial development.[1]

Due to the rarity of disease, the available treatment for lipoid proteinosis is quite limited and there are no large case

Table 1. Reported cases of lipoid proteinosis treated with acitretin and their response to treatment.

Ref No	Age / Gender	Clinical features	Year, Authors	Response
19	3 years, female	- Erosive and vesiculobullous lesions and varioloid scars on face, neck, upper limbs and trunk; - Severe hoarseness and aphonic cry since birth; - Pebbly lips and tongue.	Toosi and Ehsani, 2009	- After 6 months: the hoarseness and aphonic cry was partially improved, but new cutaneous lesions were still present. - One year later, hoarseness was significantly improved, with slight reduction in the appearance of new skin lesions.
20	- Patient 1: 37 years, male - Patient 2: 39 years, male	- Hoarseness and beaded eyelid papules; - Thickened frenulum; - Hyperkeratotic plaques and infiltrated warty papules and nodules.	Akoglu *et al.* 2011	- After 11 months: some regression and softening of skin lesions were achieved in the 2 cases. - After 1.5 year treatment: minimal regression of hoarseness in patient 1 and no effect on hoarseness in patient 2 who underwent laryngoscopic curettage for laryngeal nodules.
21	21 years, female	- Waxy texture of face, glossy, infiltrated, yellow papules, and plaques on forehead and cheeks. - Beaded papules on the margins of the upper eyebrows. - Extensive atrophic scars, on face, shoulders, around elbows, and on the back of hands. - Yellow infiltrated plaques on the hard palate, tongue, and the floor of mouth. - Past history of weak cry during infancy and hoarseness since birth.	Gunduz *et al.* 2012	- After 6 months: the cutaneous plaques have become less indurated with significant improvement of the hoarseness. - The patient was lost for one year after and when returned, all her cutaneous lesions were still present and improvement of the hoarseness was deteriorated.

series to evaluate the therapeutic options. Remarkable clearance of skin and laryngeal lesions was reported in a case treated with oral dimethylsulfoxide[10] but no improvement was observed in three others.[11] Beneficial effects with etretinate have been reported in one patient.[12] Kaya *et al*. have treated a girl with D-penicillamine for 2 years and obtained good results.[13] Carbon dioxide laser surgery has been proposed for the treatment of affected vocal cords[14] and eyelid papules.[15]

It has been claimed that retinoids used *in vivo* modulate the metabolism of the connective tissue matrix of basement membrane. Etretinate, free acid of etretinate and 13-cis-retinoic acid (RA), reduce type IV collagen synthesis *in vitro*.[16] The proliferation and activity of cultured fibroblast cells and type III collagen synthesis are inhibited as the concentration of retinoids are increased in the medium.[17]

Acitretin may be superior to etretinate in decreasing the deposited collagen. Acitretin may decrease the deposition of hyaline material in dermis.[18] Therefore, we choose acitretin for treatment of our cases.

Toosi and Ehsani reported a case of lipoid proteinosis treated with acitretin that resulted in improvement of voice but had no effect on skin lesions.[19] Akoglu and colleagues reported softening of skin lesions in two lipoid proteinosis patients from the same family.[20] Gunduz *et al*. reported a case of lipoid proteinosis in 21-year-old female that showed marked improvement of hoarseness but no effect on her cutaneous lesions was noted[21] (Table 1). Therefore to our knowledge, our report might be the first one that demonstrated a possible role for acitretin for the treatment of both cutaneous and mucosal lipoid proteinosis lesions.

Conclusions

It is clear that no firm conclusion can be made based on two studied cases, but due to the rarity of the disease, performing large case series seems impracticable. Therefore, from authors' experience, acitretin may be helpful for lipoid proteinosis patients, for both cutaneous and mucosal lesions, an observation that requires further research.

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