CASE REPORT

Vesiculobullous eruption revealing lipoid proteinosis: A potential diagnostic pitfall.
A case report and a brief review

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Abstract
We describe a new case of lipoid proteinosis (LP) in a child and discuss its different clinical presentations, especially in its early erosive stage, as well as its prognosis and therapy. A 3.5-year-old healthy girl presented with a chronic and recurrent vesiculobullous skin eruption since early childhood. She had developed hoarseness of the voice during the first few months of life. Cutaneous examination revealed the presence of multiple non-pruritic tense vesicles and erosions on a non-erythematous base on her face, hands and elbows with a waxy thickening of the skin on her face. Histologic examination confirmed the diagnosis of LP. The patient was then regularly followed in our department for therapy for her disease.

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1. Introduction

Lipoid proteinosis (LP), also referred to as Urbach–Wiethe disease, lipoglycoproteinosis and hyalinosis cutis et mucosae [1], is a very rare, autosomal recessive and inherited genodermatosis (OMIM 247100). It is a poorly understood disease that commonly affects the mucosae and skin. Cutaneous manifestations in LP are constant and characteristic, but they are frequently misdiagnosed at their early erosive vesicular stage, which can mimic many other diseases. Herein we describe a 3.5-year-old female patient with this uncommon disease, which was revealed by a vesiculobullous eruption.

2. Case report

A female child aged 3.5 years old was referred to our department for a chronic and recurrent vesiculobullous skin eruption since early childhood. She was born to consanguineous parents originating from the northwest of Tunisia
with no history of other affected family members. The patient had developed hoarseness of the voice during the first few months of life. At the age of one year old, she started to develop recurrent erosions and blisters located on her face, hands, elbows and knees without photosensitivity. No medical advice had been sought during this time. An examination revealed the presence of multiple non-pruritic tense vesicles and erosions on a non-erythematous base on her face, hands and elbows (Figs. 1 and 2). She also had a diffuse and firm waxy thickening of the skin on her face with multiple varioliform and acneiform scars. The lesions were located on acneogenic and non-acneogenic regions of the skin. The examination of her nails and hair was normal. She had an eversion of her lower lip with multiple carious teeth (Fig. 3). The intraoral examination did not show any infiltrated plaques in the oral cavity. The patient underwent laryngoscopy on account of her dysphonia, which showed thickening of the epiglottis and the aryepiglottic folds. She had no history of frontal headaches, seizures or visual disturbances. Her ophthalmologic, neurological and psychiatric examinations were normal. Routine haematological and biochemical investigations were within normal limits. Skin swab cultures were negative. Results from a porphyrin screen were normal for uroporphyrins and coproporphyrins in the urine and faeces. Protoporphyrins in the erythrocytes were also normal. The clinical features were highly suggestive of lipoid proteinosis. Light microscopic examination of a biopsy of an intact vesicle revealed a subepidermal blister with extensive deposits of homogeneous hyaline-like material in the upper dermis that reacted strongly with the periodic acid–Schiff (PAS) stain. Deposits were also found in the dermis between collagen bundles and near blood vessels (Fig. 4). Direct immunofluorescence of the perilesional skin was negative. Hence, a diagnosis of LP was assessed. The patient was then regularly followed in our department for therapy for her disease.

3. Discussion

Lipoid proteinosis, or Urbach–Wiethe disease, was first described by the dermatologist E. Urbach and the otolaryngologist C. Wiethe in 1929 [2]. It is a rare and recessively inherited disorder that is characterized by the deposition of hyaline material into the skin, oral cavity and larynx. It occurs with equal frequency in both males and females [3]. Approximately 300 cases of LP have been reported in the literature, predominantly in people of European ancestry. Few cases have been reported from patients originating from North Africa, especially in Tunisia, where only 11 cases have been reported [4].
The exact pathogenesis is unknown, but LP can be the result of either a lysosomal storage disorder, as suggested by Bauer et al, who demonstrated the presence of inclusions within the fibroblasts [5], or from a disturbance in collagen synthesis. Other authors have suspected that a metabolic deficiency in the degradation pathway of glycolipids or sphingolipids could lead to the storage of ceramide or more complex lipids [6].

Recent studies have shown that LP is the result of the reduced expression of the extracellular-matrix-protein (ECM1) gene mapped to chromosome 1 in fibroblasts. This discovery improves diagnostic accuracy and makes carrier screening and DNA based prenatal diagnosis of LP feasible [7].

Clinically, the first sign of LP is a hoarseness of the voice due to vocal infiltration, which remains throughout the patient’s life. Cutaneous lesions appear shortly afterwards, usually during the first two years of life. They occur in two overlapping stages. The first stage is represented by vesicles, bullae and haemorrhagic crusts that appear spontaneously and resolve with scar formation. In the second stage, diffuse thickening of the skin occurs along with the development of yellowish and waxy infiltrated papules and nodules on the face because of the increasing deposition of hyaline material in the skin [8,9]. Hyperkeratotic or verrucous lesions resembling xanthoma may be seen on the elbows, knees and buttoks. The infiltration of the eyelids gives rise to a beaded appearance, also called moniliform blepharitis, which is characteristic of the disease. This feature was absent in our patient because of her young age [6]. Scalp involvement may lead to hair loss [7]. Nail dystrophy with haemorrhagic blisters on the wrists, fingers and nailbed is a common finding [1]. The mucosae of the pharynx, tongue, soft palate, tonsils and lips are also infiltrated and this may lead to respiratory difficulty [3]. Curious teeth and poor dental hygiene are frequently seen in LP and may result from dryness of the mouth associated with the infiltration and obstruction of the parotid duct by hyaline material [6].

Extracutaneous features may include epilepsy, mental retardation, memory loss, schizophrenic behavior and neuropsychiatric abnormalities, sometimes in association with calcifications in the temporal lobes or hippocampi, which were absent in our patient (Fig. 5) [6,3]. Hyaline deposits have also been described in the conjunctiva, cornea, trabeculum and retina. Corneal opacities or secondary glaucoma due to infiltration in the trabeculum may appear later [1].

The diagnosis is confirmed by histopathological findings that show extensive deposits of homogeneous hyaline-like material in the upper dermis that reacts strongly with the PAS stain. Hyaline deposits are also found in the dermis between collagen bundles surrounding blood vessels and around sweat glands. The hyaline material is eosinophilic, PAS+ and diastase-resistant, indicating the presence of glycoproteins [1].

Vesiculobullous eruptions represent the early erosive stage of LP and can mimic many other diseases. Thus, LP is rarely diagnosed at the early stages. In fact, the recurrent vesicles and erosions in LP could mimic other infectious processes, such as impetigo. LP could even mimic other childhood blistering dermatoses, such as epidermolysis bullosae, when the blistering is severe and diffuse [10].
The condition most closely resembling LP is erythropoietic protoporphyria (EP). It displays similar skin symptoms, but without oral lesions. Increased values of protoporphyrins in erythrocytes in EP are the key for differentiation. Clinical differentiation can be achieved by the absence of photosensitivity and the presence of skin lesions in non-sun-exposed areas in LP [1,12,13]. Histologically, EP has a deposition of PAS positive material that is less dense around blood vessels and never occurs around sweat coils [6]. The disease could be easily differentiated from xanthomatosis, amyloidosis, papular mucinosis and colloid milia, especially in consideration of the histological findings [9,13].

Regarding treatment, there is no effective and clear-cut treatment regimen for LP [1]. Usually, treatment for this disease is unsatisfactory and has been helpful in only limited cases [12]. Sustained benefits were reported in only a limited number of patients. Wong and Lin reported a remarkable response with dimethyl sulfoxide therapy in one patient [14], which they attributed to its solvent properties and its ability to dissolve collagen. Limited success has been found with oral steroids, chloroquine phosphate and etretinate [15]. Facial lesions have been treated successfully by dermabrasion, chemical peeling, blepharoplasty and a CO2 laser. Kaya et al even suggested D penicillamine as a promising agent, even at low doses, for the treatment of LP because of its ability to temporarily relieve symptoms [15]. A recent study conducted in Turkey reported that treatment with acitretin in 10 patients affected with lipid proteinosis was quite effective [16].

Currently, the identification of the EC1M mutation in LP provides a basis for the development of more rational forms of treatment, including trials of recombinant EC1M protein and the development of somatic gene therapy for the skin and respiratory mucosa [7].

This condition may compromise quality of life due to its disfiguring scars and multisystemic involvement and especially because of neurological impairment and respiratory obstruction [1]. However, LP usually follows a benign and slow progressive course. Finally, the course of the disease and the therapeutic possibilities are still being debated.

4. Conclusion

In summary, the lesson to draw from our case is that LP is rare and can easily be misdiagnosed. The diagnosis is easy when combining the early onset of hoarseness and characteristic cutaneous manifestations with evidence of dermal hyaline deposition. LP should be considered in the differential diagnosis of vesiculobullous lesions in children. In these patients, long-term follow-up and a detailed examination to determine the extent of involvement should be performed.

Conflict of interest
None.

References

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