Dermatology Reports

Dermatology Reports 2026; 18:10230
doi:10.4081/dr.2025.10230

Urbach-Wiethe syndrome: report of two clinical cases

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Abstract

Urbach-Wiethe syndrome, also known as lipoid proteinosis (LP), is a rare genodermatosis clinically characterized by mucocutaneous lesions, dysphonia with onset in early childhood, and, sometimes, neurological complications. Clinical signs, as well as the severity of the disease, are highly variable, while its course is usually slowly progressive. The typical primary sign is hoarse crying due to laryngeal infiltration at birth or during early childhood. Alterations of the skin and mucous membranes develop within the first two years of life. The skin lesions initially appear on the face and limbs and usually resolve by healing. Infiltration of the respiratory system can cause upper respiratory tract infections, hoarseness or aphonia, dysphagia, and even airway obstruction. Dystonia, epileptic seizures, and learning disorders may be observed in affected children. Treatment remains a major challenge as no standardized therapies exist, but oral acitretin appears to be effective in improving skin manifestations. We report two clinical cases of young women suffering from LP, presenting with dermatological, otorhinolaryngological, and neurological symptoms, currently referred to our Rare Cutaneous Syndrome Center at the Policlinico Umberto I in Rome (Italy).

Key words: lipoid proteinosis; case report; genodermatosis; extracellular matrix gene 1.

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Introduction

Urbach-Wiethe disease, also known as lipoid proteinosis (LP) or hyalinosis cutis et mucosae, is a rare autosomal recessive genodermatosis, first officially reported in 1929 by Erich Urbach and Camillo Wiethe. Since then, only about 400 cases have been described in the medical literature.[1] The disease is associated with a mutation in the *ECM1* gene (extracellular matrix protein 1) on chromosome 1, which histologically leads to the deposition of hyalin PAS-positive materials in the papillary and middle dermis as well as in blood vessel walls.[2]

The syndrome is characterized by dermatological, otolaryngological, psychiatric, and neurological symptoms. Typical clinical manifestations include a hoarse voice in early infancy, subsequent mucocutaneous lesions, bilateral amygdala calcifications, and beaded eyelid papules.

Here, we present two clinical cases of young Italian Caucasian women affected by Urbach-Wiethe disease.

Case Reports

Case 1

A 19-year-old female was referred to our Rare Cutaneous Syndrome Center due to dermatological lesions previously appeared at the age of 4. She was the only daughter of healthy consanguineous parents (second-degree cousins).

She did not present any disease manifestations at birth until the age of 2 weeks, when she developed gastroesophageal reflux with projectile vomiting, successfully treated with lansoprazole.

At five months, she developed hoarseness of voice, phonation difficulty with aphonia, and incapacity to speak well, although she did not have any respiratory problems. A laryngoscopy performed at the age of 2 revealed normal laryngeal mucosa with some infiltrated nodules on the posterior portion of the trachea and near the carina.

Dermatological manifestations began later with small, chickenpox-like scarred lesions on the face, knees, elbows, and the dorsal surfaces of the hands.

On our physical examination, she presented skin fragility with multiple atrophic acneiform scars on the face and neck (Figure 1). Verrucous hyperkeratosis was observed on the elbows, knees, shoulders, hands, and feet. Eyelid borders were erythematous and congested.

The tongue surface appeared irregular, devoid of papillae, and exhibited a cobblestone appearance, accompanied by ankyloglossia and a thickened frenulum.

She was started on oral acitretin treatment (25 mg once daily) for 6 months during the winter period, which led to an improvement in skin lesions, especially those on the face and neck (Figure 2). No significant side effects were observed, except for a slight increase in low-density lipoprotein (LDL) cholesterol levels, which did not require treatment discontinuation.

Brain MRI revealed bilateral and symmetric calcifications

localized in the mesial-temporal lobes, particularly involving the hippocampus. Furthermore, two hyperintense lesions were identified within the subcortical white matter of the frontal and posterior temporal lobes, consistent with nonspecific gliotic changes. Neurological symptoms, including generalized epilepsy, have been controlled with levetiracetam and lamotrigine.

The diagnosis was confirmed by mutation screening (sequencing test) of the *ECM1* gene, which reported a homozygous nonsense mutation c.727 C>T in exon 7. This mutation changes an arginine to a premature termination codon, p.Arg243X. Both parents appeared to be heterozygous carriers of the same alteration.

A biopsy taken from a cutaneous lesion on the right arm confirmed the diagnosis. Light microscopic examination revealed hyaline-like material deposits in the middle and papillary dermis, especially around blood vessels and within the collagen fibers. A perivascular lymphomonocytic infiltration was also described.

Case 2

A 28-year-old female presented to us for evaluation of several skin abnormalities first reported during her childhood. She had a history of LP, which was first diagnosed at the age of 6.

Cutaneous examination revealed skin thickening with some atrophic acneiform scars on the face and neck. Perimucosal xerosis, particularly around the lips and eyes, was described in association with mild hyperkeratosis of the elbows and knees. The skin's thickening and fragility tended to get worse over the years, with multiple erosions, especially on the fingers and toes (Figure 3). Flaws on the axillary and inguinal folds, foot cracks, and painful ulcerative lesions of the tongue were also observed. Multiple yellowish beaded papules were raised over the bilateral sides of the neck. However, her skin condition did not require systemic treatment, as it could be successfully managed through an appropriate topical therapy based on emollients and barrier repair creams (Figure 4).

These cutaneous lesions appeared during the first years of her life, when she also developed hoarseness of voice with severe dysphonia. A microlaryngoscopy was performed at the age of 8 to obtain a decortication of the true vocal cords. Moreover, exams carried out later showed small, nodular deposits on the larynx and an irregular left vocal fold with restricted movement, despite a normal glottal gap.

Her brain MRI disclosed several bilateral calcifications in the inferior mesial cerebral lobes, particularly involving the hippocampus region. As a result of these neuroimaging reports, she has been presenting a history of seizures since 2015, successfully treated with lamotrigine.

The diagnosis was supported by molecular analysis of the *ECM1* gene, which identified the R243X/542inSAA mutation, also found in heterozygosis in her parents.

Discussion and Conclusions

Urbach-Wiethe disease is a rare inherited disorder characterized by abnormal infiltration of PAS-positive hyaline materials into various organs and tissues. As described in our case reports, the disease is systemic and phenotypically heterogeneous, as it could manifest itself with variable clinical features that may include dermatological alterations, respiratory disorders, and neurological or neuropsychiatric involvement.

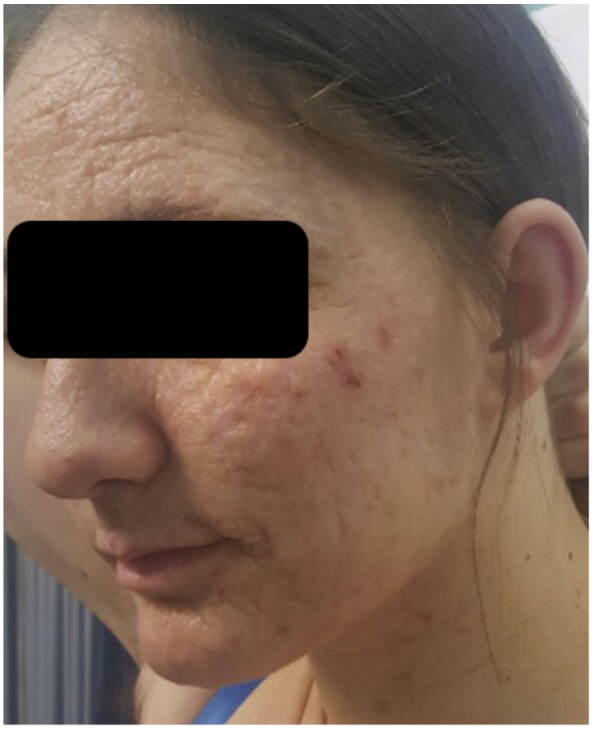

Figure 1. Skin manifestations in a patient suffering from lipoid proteinosis: involvement of the face with acneiform scars.

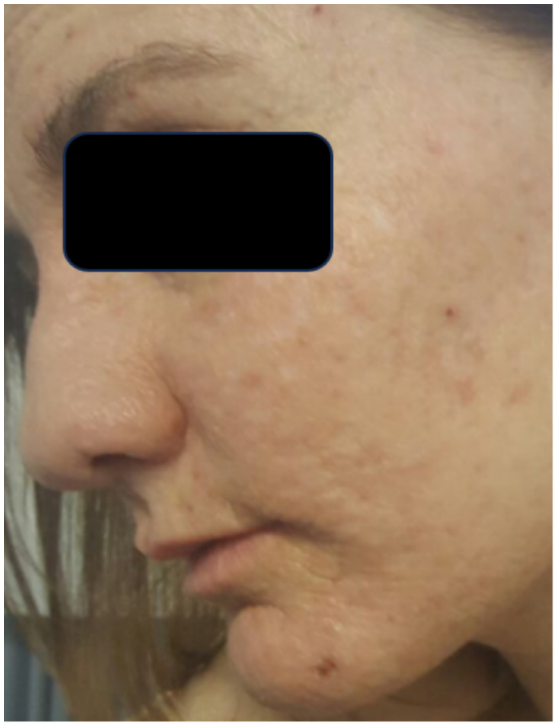

Figure 2. Clinical improvement of acneiform scars of the face after 6 months of therapy with acitretin 25 mg/day.

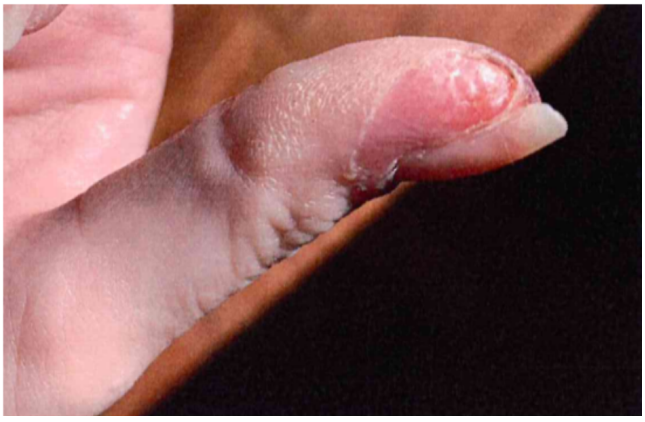

Figure 3. Skin manifestations in a patient suffering from lipoid proteinosis: involvement of fingers with skin fragility and multiple erosions before topical therapy.

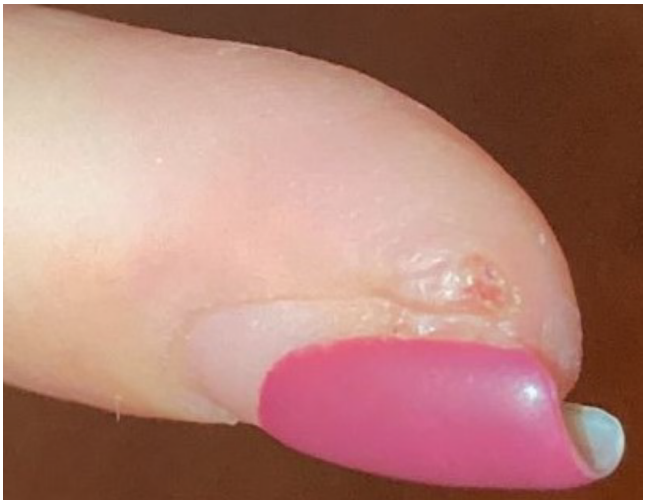

Figure 4. Clinical improvement after topical therapy based on emollients and barrier repair creams.

The most suggestive and earliest clinical hallmark of LP is a hoarse cry or voice due to laryngeal infiltration, developing soon after birth or later in childhood.

Cutaneous changes usually appear during the first years of life and consist of small, yellowish, infiltrated papules on the face and body, acneiform scars, and generalized skin thickening. Nodules or verrucous hyperkeratosis also occur, particularly in regions exposed to mechanical trauma, such as the elbows, knees, or extremities.[3] Mucosal changes in the mouth, pharynx, tongue, and lips are a typical trait. The presence of yellow-brown, beaded papules along the eyelids, the well-known moniliform blepharitis, is characteristic of the disease.

As shown in our cases, neurological abnormalities become evident with epilepsy or seizures during infancy and generally may be associated with bilateral brain calcifications in the temporal lobes or amygdala. Other findings include behavioral or learning difficulties and, less commonly, intracerebral hemorrhage.[4]

The genetic alteration of LP has been identified as a loss-of-function mutation in the gene encoding extracellular matrix protein 1 (*ECM1*), mapped on chromosome 1q21.2. Four gene splicing variants are currently known, but *ECM1a* seems to be the most biologically relevant.[5]

The *ECM1* gene encodes a multifunctional soluble glycoprotein involved in endochondral bone formation, angiogenesis, and tumor growth. It also interacts with several extracellular proteins to maintain skin homeostasis and regulate the integrity of the epidermal barrier. *ECM1* may act as a dermal "glue", influencing the proliferation and differentiation of keratinocytes.[6]

Histologically, LP is characterized by the extracellular deposition of hyaline materials in the papillary and middle dermis, around blood vessels and sweat glands; this leads to the disruption and dysregulation of the basement membrane.[7]

The exact etiology of the disease remains unknown. Despite its progressive and chronic course, prognosis is generally good, and treatment is not often needed. No effective therapy is currently available; however, as observed in our case (Case 1), oral treatment with acitretin may reduce the deposition of hyaline material and could be considered to improve skin lesions. The most crucial goal remains symptomatic management, and a multidisciplinary approach should be considered according to the single clinical case.[8]

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Received: 18 December 2024; Accepted: 10 March 2025.

Contributions: Ilaria Demofonte: writing, data curation, review and editing; Emanuele Miraglia: data curation; Sandra Giustini: review and editing, validation, supervision; Giovanni Pellacani: supervision. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: no ethical committee approval was required for this case report by the Department because this article does not contain any studies with human participants or animals. All patients included in this manuscript have provided written informed consent for their participation.

Consent for publication: the patients gave their written consent to use their personal data for the publication of this case report and any accompanying images.

Availability of data and materials: data supporting this study's findings are available on request from the corresponding author. However, due to privacy or ethical restrictions, the data are not publicly available.

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