Use of pentoxifylline in lipoidoproteinosis or Urbach's disease: A case report.

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Abstract

Introduction: Lipoproteinosis, or Urbach's disease, Wiethe, is a genodermatosis of genetic origin with an autosomal recessive transmission pattern without sex predilection. It is characterized by varying degrees of intercellular deposits of hyaline material in the skin, mucous membranes, and internal organs, leading to infiltration and thickening of affected organs. The course is slow and benign.

Clinical case: The case of a 6-year-old girl who consulted for dry skin and hoarseness since she was two years old is presented. The clinical and histopathological diagnosis is made.

Evolution: Treatment with pentoxifylline was started, and a significant improvement in the lesions was observed after six months.

Conclusions: The efficacy and safety of pentoxifylline as a complementary therapy in pediatric patients diagnosed with lipoidoproteinosis are demonstrated.

Keywords:

MeSH: Lipoid Proteinosis of Urbach and Wiethe, Pentoxifylline, Dermatology, Child, Case Reports.

Introduction

Lipoidoproteinosis (LP) is a genodermatosis in which masses of PAS (periodic acid-Schiff)-positive hyaline-eosinophilic material are deposited in the skin, mucous membranes, brain tissue, and other organs. It is also known as hyalinosis of the skin and mucous membranes or Urbach-Wiethe disease. It is more common in people of European descent: descendants of German, Dutch, and Swiss immigrants. LP affects 1 in 300 inhabitants. The current incidence is still being determined; just over 400 cases are described in the bibliography. The age of patients at diagnosis ranges from 6 months to 60 years [1, 2].

In addition, the symptoms vary significantly among affected individuals, even within the same family. Usually, the disease begins in early childhood with a hoarse voice due to thickening of the vocal cords. Lesions and scars also appear on the skin, usually on the face and

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distal parts of the extremities. The skin can be easily damaged due to minor trauma or injury, leaving much additional blistering and scarring. Poor wound healing and scarring continue to increase as the patient ages, leaving the skin waxy. The skin is also often dehydrated and wrinkled. White or yellow infiltrates form on the lips, buccal mucosa, tonsils, uvula, epiglottis, and tongue frenulum. The diagnosis of LP is based on clinical findings and confirmed by histopathological examination [3-5].

This disease has a benign course, with lesions progressing to early adulthood without affecting life expectancy. Early diagnosis may justify a treatment that, although controversial, aims to reduce stigma and improve the quality of life of affected individuals. Currently, there is no effective treatment. Several molecules have been used with different results, such as D-penicillamine, dimethyl sulfoxide, and retinoids, for their inhibitory effect on collagen. Likewise, CO_2 laser, dermabrasion, and chemical peeling represent other therapeutic means for managing skin lesions [5, 6]. On the other hand, pentoxifylline has been reported in treating many skin diseases, such as venous leg ulcers, vasculopathy and vasculitis, leprosy, and pigmented purpuric dermatosis [7, 8]. However, there are few reports on the use and effectiveness of this drug in treating LP.

Clinical case

A 6-year-old female school patient from Coro, Falcón State, Venezuela. He went to the Pediatric Dermatology Service of the Pediatric Hospital in the company of her grandmother, who reported dry skin from age 2 with a tendency to fragility and poor wound healing at trauma sites, associated with a hoarse voice.

The daughter of nonconsanguineous parents was clinically healthy and had no personal or family pathological history. With two equally asymptomatic brothers. 24-year-old mother. A single preterm pregnancy at 32 weeks of gestation was removed due to premature rupture of the ovular membranes. She is not breathing or crying at birth and remains on noninvasive ventilatory support. Complementary feeding from 2 months of age. Severe malnutrition at six months of age. Weak cry from birth, evolving to dysphonia. At two years of age, isolated vesicle-type lesions were observed on the flexor surfaces of the extremities, with residual scarring.

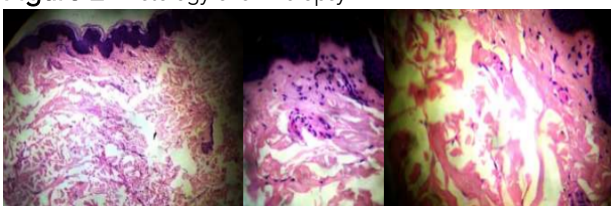
A patient with an aged face, Fitzpatrick III, is observed on physical examination. Generalized dermatosis is characterized by cutaneous xerosis and multiple yellowish micropapules that converge to form plaques with a rough surface predominantly on the posterior chest, extremities, and face, which alternate with excoriations/hematic scabs and atrophodermic-type scars at a previous site of trauma, respecting the genital area, buttocks, palms, and plantar region. In scalped skin, sparse hair and diffuse alopecia are evident.

A skin biopsy is performed, which is sent for histopathological study, which reports a cut of skin covered with intact epithelium. Moderate acanthosis. Preserved basal. The entire dermis is occupied and replaced by an amorphous, basophilic material with areas of hyalinosis. In the upper dermis, the presence of nuclear remains of a source to be specified is observed. Marked elastolysis throughout the dermis. Absence of pilosebaceous or sweating appendages. The findings linked to the clinical symptoms and evolution time require studying compatibility with URBACH DISEASE-LIPOID-PROTEINOSIS-CUTANEOUS AND MUCOUS HYALINOSIS.

With the histopathological diagnosis, general skin protection measures are indicated, and treatment with pentoxifylline at a rate of 400 mg orally is started. After six months of continuous use of pentoxifylline, without alterations in laboratory studies or side effects, it was decided to maintain the dose, evidencing improvement in skin lesions, pending completion of complementary studies such as neuroimaging and laryngoscopy studies.

Figure 1. Photographic evolution of the case

Figure 2. Histology of skin biopsy.



Discussion

LP was described in 1929 by doctors Erich Urbach, a dermatologist, and Camilo Wiethe, an otorhinolaryngologist, with the term lipoidosis cutis and mucosa. A decade after its description, Urbach suggests the name mucosal cutaneous hyalinosis. It is more common in people of European descent: descendants of German, Dutch, and Swiss immigrants. Just over 300 cases are described in the bibliography; the age of patients at diagnosis ranges from 6 months to 60 years. The molecular basis of LP was unknown until 2002, when it was shown that the genetic defect was located on the long arm of chromosome 1q21, the gene that encodes extracellular matrix protein-1 (extracellular matrix protein or ECM1). Loss-of-function mutations in the ECM1 gene cause lipoid proteinosis. This gene is composed of 11 exons; mutations can occur in any of them, and the most frequently compromised exons are 6 and 7 [9, 10].

The global function of the extracellular matrix is associated with angiogenesis, healing, proliferation, and differentiation of the basement membrane, which has a vital role in the fibroblasts of the dermis; in LP, it is reduced compared to normal fibroblasts. The ECM1 defect increases type IV collagen, resulting in deposits of abnormal hyaline material in the dermis and other tissues [11].

The clinical picture is determined by the degree of infiltration of hyaline material into the skin, mucous membranes, and internal organs. Generally, it begins to infiltrate the vocal cords and oral mucosa, manifesting with alterations in the tone of the voice or crying. Subsequently, there is infiltration in the skin; the infiltration on the edge of the eyelids is very characteristic: it presents small pearly papules, "moniliform blepharosis"; on elbows and knees, yellowish papules and warty-looking nodules are formed, as well as blisters that, when resolved, leave atrophic scars. Lesions that occur on the scalp leave scarring alopecia. In the oral cavity, dental abnormalities include aplasia or hypoplasia of the upper incisors, macroglossia with dental impressions on their lateral edges, and transient edema of the lips and tongue. In addition to the skin and mucous membranes, there may be infiltration in the central nervous system that causes calcifications at the level of the temporal lobes with manifestations that range from behavioral alterations such as memory alterations, schizophrenic behavior, and depression to convulsive crises [1- 3, 10, 11].

A histopathological study of the skin confirmed the clinical diagnosis. Histologically, the tissue was stained with periodic acid-Schiff (PAS). With hematoxylin and eosin (H/E) staining, pale pink thickening is observed in the capillaries of the dermal papillae. Under the electron microscope, deposits of hyaline amorphous material are monitored around the walls of blood vessels and in fibroblasts, which show cytoplasmic inclusions containing electron-dense granular structures [12]. The evolution is chronic, and in the early years of development (childhood and adolescence), it is compatible with everyday life. Morbidity is conditioned by complications due to infiltration of the different organs, while mortality is associated with obstruction due to airway infiltration [11, 12].

The case presented relates to a patient with a history of dysphonia since childhood and extensive skin lesions characteristic of this pathology, facilitating the diagnosis. In this regard, it should be noted that not all

cases reported in the literature present varied and extensive dermatological involvement, particularly on the face and extremities, as in this patient [13]. This pathology is inherited with an autosomal recessive pattern; patients often have affected relatives or are children of consanguineous parents. This was not the case with our patient, nor was data collected on other family members with this condition. However, clinical findings may vary between affected individuals within a family or a given population, including neurologic abnormalities without cutaneous manifestations. Clinical variability between siblings carrying the same homozygous mutation indicates that genotype is not the only factor determining phenotype; genetic, epigenetic, or environmental factors probably play a role in the clinical expression of LP [14].

Topical and oral corticosteroids, chloroquine, etretinate, dimethyl sulfoxide, and D-penicillamine have been used for treatment, but the results have been variable, and the adverse effects are relevant. Adjuvant methods Fractionated $CO2_{laser}$. Recently, pentoxifylline has had good results with evident clinical improvement. Pentoxifylline is a synthetic derivative of the methylxanthine group, which, due to its pharmacological activity as a vasodilator and ability to reduce blood viscosity, was initially indicated in various diseases that evolved with obstructive processes at the vascular level. It has been found to stimulate adenosine receptors in red blood cells, leukocytes, and platelets, inhibit phosphodiesterase, and increase cyclic adenosine monophosphate or cAMP through tests and reported cases; there is more excellent knowledge of its anti-inflammatory and protective activity in the inflammatory processes generated in the vascular endothelium as well as at the tissue level, activity on fibroblasts and functions related to healing and collagen diseases, and the inhibition of the production and activity of tumor necrosis factor is considered its primary mechanism of action [8, 9].

In this case, the use of pentoxifylline after six months of treatment demonstrates the drug's clinical effectiveness in improving the skin lesions presented by the patient, highlighting that the prolonged administration of the drug did not have side effects in the patient. Currently, the patient is in good general condition, with satisfactory progress.

Conclusions

The importance of publicizing this clinical case is due not only to the fact that it is a rare disease but also to the extent that the literature review covered very few documented cases of the use of pentoxifylline as a treatment for this disease. , highlighting its effectiveness as evidenced by the evident clinical improvement of dermatological lesions.

Abbreviations

PCR: C-reactive protein.

Supplementary information

No supplementary materials are declared.

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Does not apply.

Author contributions

Jennifer Katherine Cañarte Mero: Conceptualization, Data Preservation, Fund-raising, Research, Resources, Software, Writing - original draft.

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Therapeutic procedures, laboratory studies, and images were part of the regular activities of the pediatric dermatology service and were not an additional cost to the patient. The researchers covered the administrative expenses of this research.

Availability of data and materials

The data sets generated and analyzed during the current study are not publicly available due to clinical case confidentiality.

Statements

Ethics committee approval and consent to participate

Not required for clinical cases.

Publication Consent

The authors have permission for publication from the patient's parents.

Conflicts of interest

The authors declare they have no conflicts of interest.

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