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Case Report

Use of Pentoxifylline in Lipoidoproteinosis or Urbach's Disease: Case Report

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Abstract:

Lipoidoproteinosis or Urbach's disease, is a genodermatosis with an autosomal recessive transmission pattern, without sex predilection. 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. Two cases are reported: a 6-year-old schoolgirl who consulted for dry skin and hoarseness since she was 2 years old; and a 13-year-old adolescent with similar symptoms. The clinical and histopathological diagnosis is made. Treatment with oral pentoxifylline was started, and a significant improvement of the lesions was observed after six months.

Keywords: lipoidoproteinosis; urbach wiethe; pentoxifylline

1.Introduction

Lipoidoproteinosis (LP) is a genodermatosis in which PAS (periodic acid-Schiff)-positive eosinophilic hyaline material is 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 most common in people of European ancestry: descendants of German, Dutch, and Swiss. It affects 1 in every 300 inhabitants, there are just over 400 cases described in the literature. The age of diagnosis varies from 6 months to 60 years old. [1,2]

Symptoms vary greatly. The disease usually begins in early childhood with dysphonia due to thickening of the vocal cords. Lesions and scars also appear on the skin, usually on the face and distal parts of the extremities; The skin can be easily damaged as a result of minor trauma or injury, leaving residual scars. Poor wound healing results in an aged appearance. White or yellow infiltrates develop on the lips, oral mucosa, tonsils, uvula, epiglottis and frenulum of the tongue. The diagnosis is based on clinical findings and is confirmed by histopathology [3,4,5].

This disease is benign with lesions progressing into early adulthood without affecting life. Early diagnosis may justify treatment that aims to reduce stigma and improve the lifestyle 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. [5.6.] On the other hand, pentoxifylline has been reported in the treatment of many skin diseases. [7,8]. However, there are currently few reports of the use and effectiveness of this drug in the treatment of LP.

2. CASE REPORT

2.1 Patient 1

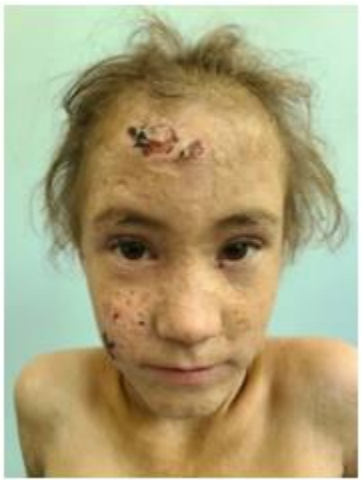
A 6-year-old female, from Coro, Falcón State, Venezuela, attends to the Pediatric Dermatology Service accompanied by grandmother who refers dry skin since 2 years of age with a tendency to fragility and poor healing of wounds at sites of trauma, associated with a hoarse voice.

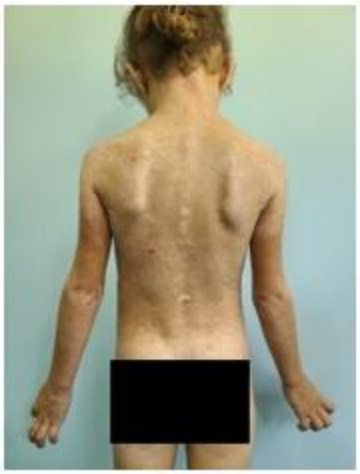
The patient is a daughter of non-consanguineous parents, clinically healthy and without personal or family pathological history. With 2 equally asymptomatic brothers. Within her perinatal history, she comes from a single preterm pregnancy of 32 weeks of gestation from a 24-year-old mother and is extracted due to premature rupture of ovular membranes. Also, she does not breathe or cry at birth and remains on non-invasive ventilatory support. During her development, she receives complementary feeding from 2 months of age and is diagnosed with severe malnutrition at 6 months. Weak cry from birth, evolving to dysphonia. At 2 years old, she begins with isolated vesicle-type lesions on the flexor surfaces of extremities with residual scarring that evolve over the years.

The physical examination revealed a Fitzpatrick III skin phototype and aged facie with a generalized dermatosis on the chest, extremities and face characterized by cutaneous xerosis, multiple yellowish micropapules that

converge to form plaques with a rough surface which alternate with excoriations and hematic scabs, and atrophic scars at the site of previous trauma. The genital area, gluteal area, palms and plantar region are not affected. Thinning hair and diffuse alopecia are evident on the scalp.

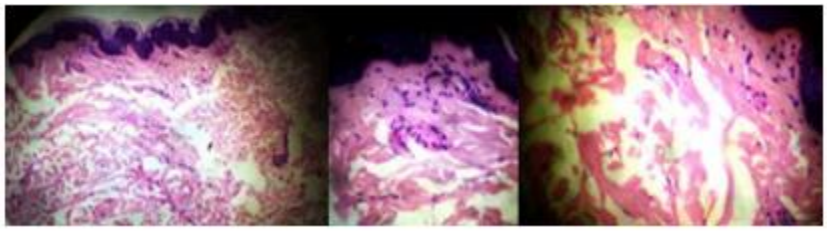
A skin biopsy was performed and sent for histopathological study which reported: Skin section covered with intact epithelium that shows moderate acanthosis and preserved basement membrane. The entire dermis shows elastosis and is occupied and replaced by an amorphous, basophilic material with areas of hyalinosis. Absence of pilo-sebaceous or sweat annexes. *(Figure 1A, 1B)*





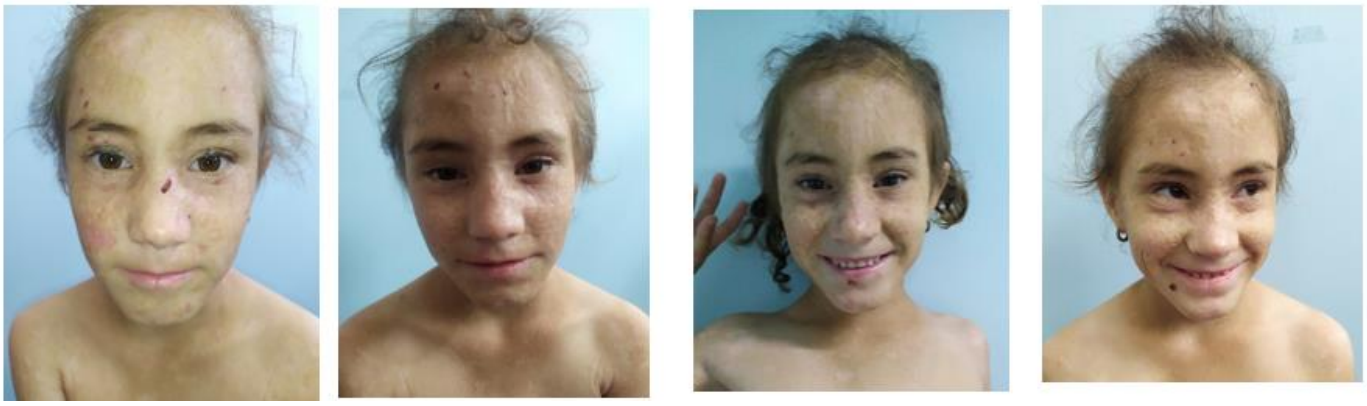
Patient 1: First consultation November 2022.

All these histopathological findings accompanied by the physical examination and time of evolution allowed us to guide the diagnosis of: URBACH DISEASE-LIPOID-PROTEINOSIS-MUCOUS CUTANEOUS HYALINOSIS (*Figure 2*).



Histopathological study patient 1 Hematoxylin/Eosin staining 10x vision.

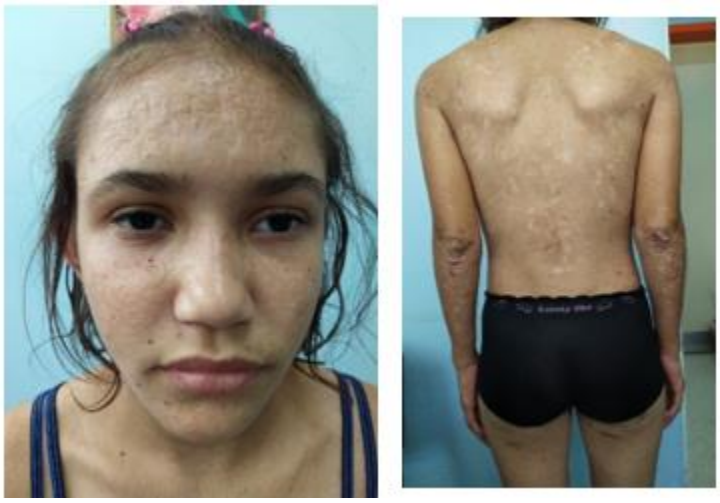
The therapeutic approach consisted of general skin protection measures and pharmacological treatment with 400mg of pentoxifylline orally (10 mg per kilogram of weight per day). After 6 months of continuous administration of pentoxifylline, improvement of the skin lesions was demonstrated, without alterations in laboratory studies or side effects. To date, the patient has been on treatment for more than 1 year, maintaining the same dose without side effects *(Figure 3A,3B,3C, 3D).*



Photographic evolution of the case. Patient 1: April 2023, September 2023, March 2024 June 2024

2.2 Paciente 2

The second case report is about a 13-year-old teenager from Maracaibo, Zulia state, Venezuela. With no family pathological history, symptoms began at 2 years of age characterized by dry skin, dysphonia and poor wound healing. (*Figure 4A,4B*). According to physical examination and histopathological findings, the diagnosis was similar to that of the first case, and it was decided to start oral pentoxifylline at a rate of 10 mg per kilogram of weight. Currently, the patient has received 4 months of treatment showing significant clinical improvement. (*Figure 5A, 5B*).



Patient 2: First Consultation September 2023

Photographic evolution of the case. Patient 2: Control March 2024, June 2024.

3. Discussion

LP was described in 1929 by dermatologist Erich Urbach and otorhinolaryngologist Camilo Wiethe, with the term lipoidosis cutis y mucosas. A decade after its description, Urbach suggested the name Cutaneous Mucous Hyalinosis. There are just over 300 cases described in the bibliography. The age of patients at the time of diagnosis varies 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 the extracellular matrix protein-1 (Extracellular Matrix Protein or ECM1). Mutations cause a loss of function in the ECM1 gene leading to lipoidoproteinosis. This gene is made up of 11 exons, the mutation can occur in any of them but the most frequently compromised 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 an important role in fibroblasts of the dermis. The ECM1 defect generates an increase in type IV collagen, resulting in deposits of abnormal hyaline material in the dermis and other tissues. [11.]

Clinical findings are determined by the degree of infiltration of hyaline material into the skin, mucous membranes, and internal organs. Generally, the infiltration begins in the vocal cords and oral mucosa, manifesting with alterations in the tone of the voice or crying. Subsequently, an infiltration occurs in the skin that shows very characteristic small pearl-shaped papules on the edge of the eyelids called “moniliform blepharosis”; yellowish papules and nodules with a warty appearance also appear on elbows and knees, as well as blisters that leave atrophic scars when they resolve. Lesions that occur on the scalp leave scarring alopecia. In the oral cavity, dental anomalies occur such as aplasia or hypoplasia of the upper incisors, macroglossia with dental impressions on their lateral edges, and 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 ranging from behavioral alterations such as memory disorders, schizophrenic behavior and depression to seizures. [10,11.]

The diagnosis includes the findings on physical examination and is confirmed by histopathological study of the skin. Histologically, the tissue is stained with Periodic Acid Schiff (PAS). With Hematoxylin and Eosin (H/E) staining, a pale pink thickening is observed in the capillaries of the dermal

papillae. Under the electron microscope, deposition of amorphous hyaline material is observed around the walls of blood vessels and fibroblasts, showing cytoplasmic inclusions containing granular electron-donous structures.[11]. The evolution is chronic and in the first years of development (childhood and adolescence) it is compatible with a normal life. Morbidity is conditioned by complications due to infiltration of different organs, while mortality is associated with obstruction due to airway infiltration.[12.]

The reported cases present a patient of school-aged and adolescent with a history of dysphonia since childhood and skin lesions characteristic of this pathology, which facilitated the diagnosis. In this regard, it should be noted that not all the cases reported in the literature show varied and extensive dermatological involvement, particularly on the face and extremities.[13]. This pathology is inherited with an autosomal recessive pattern, patients often have affected relatives, this was not the case of our patients, nor are data collected on other family members who have this condition. However, signs and symptoms may vary among affected individuals within a family or population, including the presence of neurological abnormalities in the absence of cutaneous manifestations. The clinical variability between siblings carrying the same homozygous mutation indicates that the genotype is not the only factor that determines the phenotype. Genetic, epigenetic and environmental factors likely play a role in the clinical expression of LP. [14].

Regarding pharmacological therapy, topical and oral corticosteroids, chloroquine, etretinate, dimethyl sulfoxide and D-penicillamine have been used, but the results have been variable, and the adverse effects are evident. Likewise, adjuvant methods such as fractional CO2 laser have been described as a treatment for this disease. Recently, the use of pentoxifylline has shown great 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 cause vascular obstructive processes. This drug stimulates adenosine receptors on red blood cells, leukocytes and platelets; inhibits phosphodiesterase and increases cyclic adenosine monophosphate or cAMP. There is greater knowledge of its anti-inflammatory and protective activity in inflammatory processes generated in vascular endothelium and tissue. It also has effects on fibroblasts and events related to healing and collagen diseases, due to its inhibitory action on the production and activity of tumor necrosis factor. [8,9]. In this case, the use of Pentoxifylline, after 6 months of treatment, demonstrates the clinical effectiveness of the medication in improving the skin lesions presented by the patient, highlighting that the prolonged administration of the medication has had no side effects in the patient. Currently, the patients are in great general condition, with satisfactory progress.

CONCLUSIONS

The importance of making these two clinical cases known is that it is a rare disease and there are very few documented cases of the use of Pentoxifylline as a treatment for this disease, highlighting its effectiveness evidenced by the clinical improvement of dermatological lesions.

Declaration of Conflict of Interest

The authors declare not to have any interest conflicts.

Informed Concent

Representatives of minors were informed about Pentoxifylline oral treatment and authorized the publication of photographs for educational purposes.

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