

## Case report

# Lupus erythematosus tumidus in childhood treated with antimalarials

*Lupus eritematoso tumidus en la infancia tratado con antimalárico*

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## Abstract

Lupus erythematosus tumidus is a rare dermatosis. It is considered a subtype of chronic cutaneous lupus erythematosus of uncertain pathogenesis, favorable prognosis and rare association with systemic lupus erythematosus. Clinically, it manifests as urticarial-like plaques in photo exposed areas, mainly affecting adults, being extremely rare in pediatric age. Herein, we present two cases of six and nine-year-old male patients with clinical and histological characteristics typical of lupus erythematosus tumidus and poor response to first-line treatment (topical, intralesional steroids and topical calcineurin inhibitors); therefore, it was decided to start systemic therapy with antimalarials, obtaining a very good response.

**Keywords:** Cutaneous lupus erythematosus; Skin abnormalities; Photosensitivity disorders; Child; Antimalarial drugs.

## Resumen

El lupus eritematoso tumidus es una dermatosis poco frecuente. Es considerada una variante del lupus eritematoso cutáneo crónico, de patogénesis incierta, pronóstico favorable y rara asociación con lupus eritematoso sistémico. Clínicamente, se manifiesta como placas de aspecto urticarial en zonas fotoexpuestas, que principalmente afectan a los adultos, siendo extremadamente rara en edad pediátrica. A continuación presentamos dos casos de pacientes de sexo masculino de seis y nueve años, con características clínicas e histológicas típicas de lupus eritematoso tumidus y poca respuesta al tratamiento de primera línea (esteroides tópicos, intralesionales e inhibidores de calcineurina tópica), por lo que se decidió iniciar manejo sistémico con antimalárico, obteniendo muy buena respuesta terapéutica.

**Palabras clave:** Lupus eritematoso cutáneo; Anomalías cutáneas; Trastornos por fotosensibilidad; Niño; Antimaláricos.

## Introduction

Lupus erythematosus tumidus is a variant of chronic cutaneous lupus erythematosus, which usually occurs in adulthood and is rarely associated with extracutaneous manifestations. It has its own clinical and histological features that allow it to be differentiated from other types of cutaneous lupus,

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such as a marked photosensitivity, spontaneous resolution without scarring, absence of alterations in the epidermal surface and more favorable prognosis than other subtypes of cutaneous lupus erythematosus (1-3).

In childhood, lupus occurs more frequently as systemic lupus erythematosus and, in the chronic cutaneous form, as discoid lupus erythematosus (5,6). Lupus erythematosus tumidus subtype has only been described in children in three cases (7). Treatment is based on topical glucocorticoids and photoprotection, similarly to adults, whereas the use of antimalarials is experimental, based on the favorable response that children with cutaneous lupus erythematosus have shown, even better than in adults; however, its employment is limited in childhood (4, 6, 11). The description of two pediatric patients with the disease is presented.

### Clinical case # 1

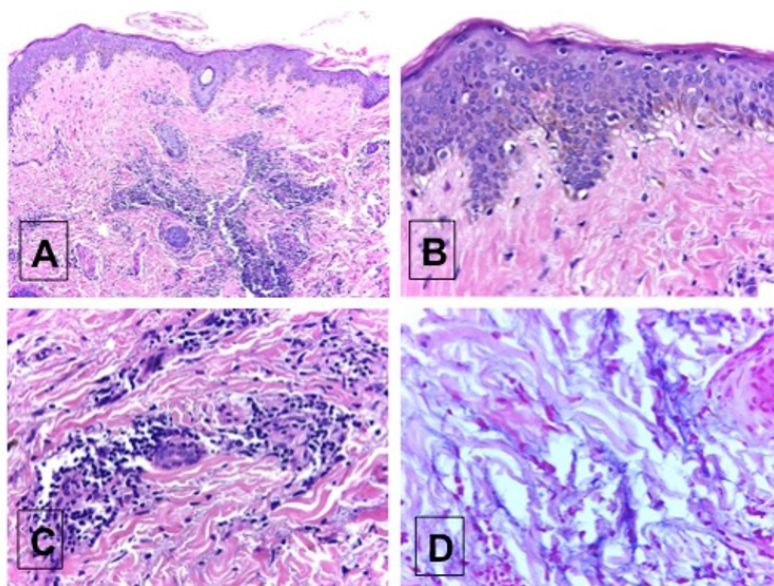
Nine-year-old male patient, with no significant personal or family history, who was taken to a dermatological consultation due to nine-month history of asymptomatic spots on the face, chest and arms. He did not report other skin lesions or systemic symptoms. Physical examination revealed multiple erythematous plaques from 1-4 cm in diameter, infiltrated, with well-defined borders, located on cheeks, preauricular region, left ear, upper limbs and anterior chest (photos 1 A-C). A diagnostic impression of cutaneous lupus erythematosus was performed, and a paraclinical profile was requested for autoimmune diseases, including antinuclear and anti-DNA antibodies, which were reported as negative.

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**Photo 1. Evolution of skin lesions.** A - C. Infiltrated erythematous-violaceous plaques, located on the cheeks and forearm. D - F. Evolution after three months of treatment.

A skin biopsy was carried out, in which epidermis with normal thickness was observed, vacuolization foci in basal lamina; in the dermis, superficial and deep lymphoplasmocytic perivascular and periadnexal inflammatory infiltrate was evidenced, extending to the subcutaneous cellular tissue, focally compromising fat lobules, with the presence of an interstitial filiform gray-blue material compatible with mucin (photo 2).



**Photo 2. Microphotography of skin face (HE).** A. Perivascular dermal infiltrate (4X). B-C. Epidermis with normal thickness and focal basal cell hydropic degeneration. Perivascular lymphocytic infiltrate accompanied by interstitial mucin deposits (10X and 40X). D. Alcian blue which highlights dermal mucin (400X).

Based on these clinical and histopathological findings, the diagnosis of lupus erythematosus tumidus was confirmed. The patient had been treated previously with topical tacrolimus, triconjugate, topical and systemic steroids (prednisone). Due to the lack of improvement, he consulted again and was restarted on topical treatment with methylprednisolone aceponate, continuing with topical tacrolimus; two intralesional infiltrations with triamcinolone were administered, and instructions regarding sunscreen protection were given.

Four months after first-line treatment initiation, he attends a control appointment and, due to the persistence of lesions, together with pediatric rheumatology and after assessment with ophthalmology, systemic therapy with chloroquine was started, at a dose of 4 mg/kg/day, obtaining adequate clinical response and tolerance. A slight elevation of transaminases that resolved spontaneously was the only side effect observed.

Three months after initiation of treatment with antimalarials, almost complete improvement of the lesions was attained.

Three months after initiation of treatment with antimalarials, almost complete improvement of the lesions was attained, without residual scars, only with the presence of non-infiltrated erythematosus macules in cheeks that, after 14 months of treatment, completely resolved.

## Clinical case # 2

Six-year-old male patient, with no significant personal or family history, who was evaluated by dermatology for a clinical picture of six months of evolution, consisting of erythematosus lesions, located initially in the inner canthus of the right eye, with posterior extension to the cheek. The patient described that with heat, the lesions increased in size and became more erythematous. He did not report additional lesions or symptoms.

He had previously consulted in another institution, where they undertook a skin biopsy whose report oriented towards a diagnosis of cutaneous lupus; periodic acid-Schiff, methenamine silver and Ziehl – Neelsen stainings were negative. The patient had received multiple treatments with topical and oral erythromycin, topical metronidazole, mometasone furoate and emollients, without evidence of recovery.

He was admitted with lab tests without alterations (antinuclear antibodies, rheumatoid factor, blood cell count, urinalysis and C-reactive protein).

On physical examination, at the level of the inner canthus of the right eye and on the right cheek, macules and erythematous plaques, conformed by confluent papules, without epidermal changes and with slight infiltration, were evidenced. No other lesions were observed in the rest of the skin ([photo 3](#)).

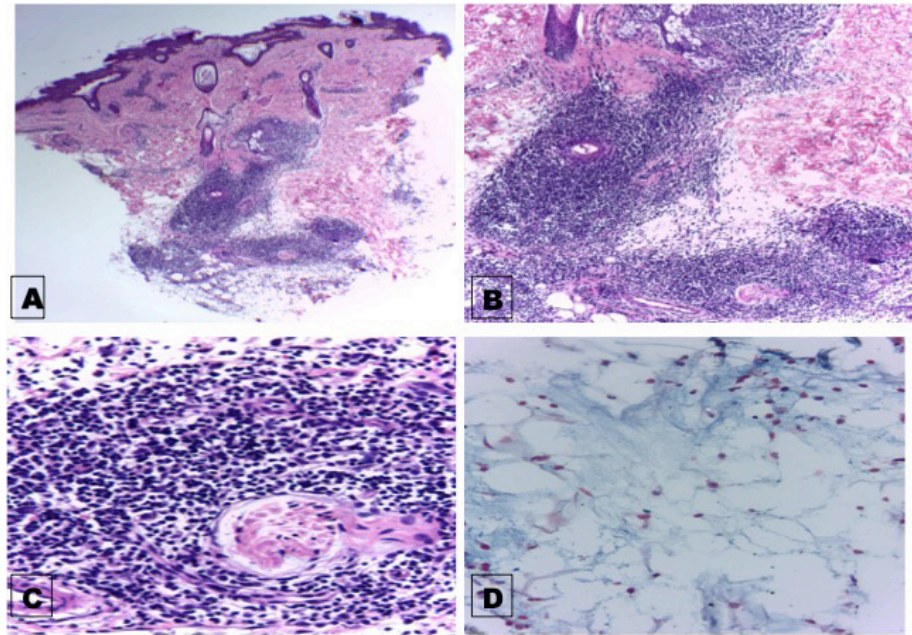
Treatment with chloroquine was initiated at a dose of 4 mg/kg/day, after assessment by ophthalmology, while photoprotection was continued. He attended control three months after the initiation of therapy with antimalarials, evidencing improvement and resolution of plaques and infiltrated erythematous papules.



**Photo 3.** A-B. Erythematous plaques and papules in inner canthus and right cheek. C-D. Evolution three months later

A review of the biopsies was requested by dermatopathology, which reported: "Epidermis of usual thickness, without atrophy, follicular plugging or changes in the interface. The main alterations were found in the middle and deep dermis, and even in the subcutaneous cellular tissue, observing moderate perivascular and periadnexal lymphoplasmocytic inflammatory infiltrate, accompanied by an increase in interstitial mucin in both dermis and adipose tissue. Alcian blue staining was performed, observing an increase in dermal mucin" ([photo 4](#)). With the histological findings, the diagnosis of lupus erythematosus tumidus was established.





**Photo 4. Microphotography of skin face (HE).** A), B) and C) Abundant perivascular, perianexial and perineural lymphoplasmocytic inflammatory infiltrate (4X, 10X and 40X). D) Alcian blue stain that highlights the dermal mucin (40x).

Treatment with chloroquine was initiated at a dose of 4 mg/kg/day, after assessment by ophthalmology, while photoprotection was continued. He attended control three months after the initiation of therapy with antimalarials, evidencing improvement and resolution of plaques and infiltrated erythematous papules, persisting only residual erythematous non-scarring macules.

Cutaneous lupus erythematosus in childhood is infrequent, and its most common presentation is discoid lupus erythematosus, associated with a higher probability of systemic disease than in adults.

## Discussion

Lupus erythematosus tumidus was first described by Erich Hoffman in 1909, in two patients who presented lesions on the face and other photo exposed areas, which manifested as raised, erythematous, oval and infiltrated plaques, without desquamation and evanescent when pressed (1).

According to the classification proposed by Guilliam, it is considered a variant of cutaneous lupus erythematosus (2); although some authors consider it a separate entity due to its differences with other subtypes of chronic cutaneous lupus erythematosus and classify it in another category called intermittent cutaneous lupus erythematosus (3,4).

Its exact incidence is unknown; it affects both sexes equally, and the age of onset is similar to that of discoid lupus erythematosus, approximately in the third and fourth decades of life (5). Cutaneous lupus erythematosus in childhood is infrequent, and its most common presentation is discoid lupus erythematosus, associated with a higher probability of systemic disease than in adults (6). Children rarely develop lupus erythematosus tumidus and appear to have a clinical and histopathological behavior similar to that of adults.

To date, only three children diagnosed with lupus erythematosus tumidus have been reported: two boys of eight and three-years-old and a five-year-old girl, with onset of lesions at nine months, two and three years of age, respectively (7). These patients were followed for six years after the onset of their illness; all three shared a common history of photosensitivity, negative immune profile and absence of systemic involve-

ment during follow-up. Two of the subjects had adequate response to topical steroid treatment and sunscreen use; whereas only one patient required treatment with antimalarials (chloroquine) due to lack of improvement with first-line therapy, with adequate response, as evidenced in the children described herein.

Clinically, lupus erythematosus tumidus is characterized by extreme photosensitivity and non-scarring lesions of benign course, described as single or multiple erythematous, violaceous, infiltrated or succulent papules or plaques, with well-defined edges, urticaria-like, with smooth or shiny surface. Unlike discoid lupus erythematosus, it does not present follicular plugging, desquamation or residual scar (8).

The lesions are located in exposed areas, respecting the inside of the arms, axillae and knuckles, and up to 16% can present in the lower limbs (5); they can also occur on the scalp, with a similar appearance to alopecia areata. There are descriptions in association with other skin lesions in cutaneous lupus erythematosus, being the discoid subtype the most frequent (up to 5%) and, most rarely, lupus panniculitis (6, 11).

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Photosensitivity is a very important trait, which explains recurrences during spring and summer; the lesions do not appear immediately after sun exposure, but in a latency period from 24 hours to several weeks (9).

Pathogenesis is not well known, although there are alternative theories to those mediated by antibodies that try to explain the marked photosensitivity, since this variety of lupus is not associated with positivity of antinuclear antibodies, such as anti-Ro or anti-La.

One hypothesis considered a cellular origin of lupus erythematosus tumidus, which involves plasmacytoid dendritic cells and type I interferon ( $\alpha$  and  $\beta$ ). Interferon  $\alpha$ , together with interferon  $\gamma$  produced by T lymphocytes, induces the production of chemokines (CXCL 9, 10 and 11) by epithelial cells, fibroblasts and keratinocytes, which amplifies the inflammatory response, attracting more T lymphocytes and plasmacytoid dendritic cells. The activation of the latter could have its origin in cellular apoptosis produced by ultraviolet radiation, with the consequent exposure of autologous DNA, which leads to the formation of immunocomplexes and the production of type I interferon (10).

Clinical suspicion is the first step for the diagnosis, based on the presence of non-scarring plaques with an edematous aspect, well-defined edges and a bright surface, usually without changes in the surface. Histopathological confirmation is always required; immunofluorescence is usually negative, and the association with systemic manifestations of lupus disease is exceptional (5, 11, 13).

The characteristic histopathological findings are: a perivascular and periadnexal lymphocytic infiltrate in middle and superficial dermis, as well as interstitial mucin deposition, even at a higher concentration and frequency compared to other types of lupus, which can be demonstrated with colloidal iron or Alcian blue stainings (1, 7, 9, 13). There is absence of epidermal changes, although vacuolar degeneration of basal membrane has been reported between 16-46% of cases, as well as follicular plugging, hyperkeratosis or epidermal atrophy (9, 12).

Immunohistochemistry is not a reliable diagnostic method, although it has proven positivity for CD31 T lymphocytes, where predominance of CD4 over CD8 T lymphocytes in a 3: 1 ratio is present (13).

In general, the autoimmune study is negative, but positivity for antinuclear antibodies has been reported between 4-20 % of patients, and for anti-Ro antibodies in up to 5 % (13). The rest of the antibodies evaluated in case series have been negative.

Differential diagnoses that must be taken into consideration include: discoid lupus erythematosus, subacute cutaneous lupus erythematosus, polymorphic light eruption, Jessner lymphocytic infiltration, facial granuloma and pseudolymphoma (9,14,15).

The approach to cutaneous lesions due to lupus erythematosus tumidus is similar in children and adults, being of paramount importance rigorous photoprotection and education to the whole family regarding the use of chemical sunscreen protection in adequate quantity and frequency, use of protective clothing, avoiding sun exposure during hours of intense radiation (6). Topical steroids are the cornerstone of treatment, and antimalarials should be used when there is no response to first-line management (4, 6, 16); these medications are not commonly used in pediatric patients due to the difficulty of ensuring an exact dose calculated based on weight, as it differs from standard drug presentations.

The use of antimalarials and their effectiveness in the treatment of cutaneous lupus erythematosus (acute, subacute and chronic) has been widely known since 1951. This disease is the only dermatological indication approved by the *Food and Drug Administration* (FDA).

Concerning their mechanism of action, it is accepted that they act through various routes and have immunomodulator, anti-inflammatory and antiproliferative properties, with an additional photoprotective effect whose mechanism is not completely understood. However, two hypotheses have been considered: in the first place, antimalarials possess a "screen effect", absorbing certain sunlight wavelengths; and secondly, they inhibit the response to keratinocytes triggered by exposure to sunlight by apoptosis induction and can improve the natural photoprotection of the epidermis through the induction of *c-jun* protein transcription (17).

It has been described that therapy for chronic lupus erythematosus with chloroquine in children is more satisfactory with a prompt response compared to adults (18). Intralesional steroids are indicated mainly in adults, since in children they are poorly tolerated due to pain (6).

Regarding the clinical course of this condition, once the lesion has developed, it can persist in the same place or disappear spontaneously, without scarring or pigmentation, even if there is a recurrence. A more favorable prognosis is considered than in those with other forms of cutaneous lupus erythematosus. The association with systemic lupus erythematosus is rare and, usually, does not recur after a suitable local or systemic treatment (1, 9,19).

## Conclusion

Lupus erythematosus tumidus is considered an affection of exceptional presentation in childhood. Aspects such as marked photosensitivity, tendency to recur, lack of autoantibody positivity and manifestations of systemic lupus erythematosus, in addition

Aspects such as marked photosensitivity, tendency to recur, lack of autoantibody positivity and manifestations of systemic lupus erythematosus, in addition to its clinical and histological features, differentiate it from other classes of cutaneous lupus erythematosus.

to its clinical and histological features, differentiate it from other classes of cutaneous lupus erythematosus. It is important to recognize these characteristics to make a proper diagnosis and initiate a specific therapy. Lupus tumidus treatment is of great importance, since the relapse and persistence of lesions can affect quality of life.

### **Conflict of interests**

The authors do not declare.

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