contributed to this deterioration; the effect may have been more intense in this patient as she had underlying kidney disease (serum creatinine, 1.4 mg/dL). Dose adjustment and the falling blood levels coincided with the improvement in renal function.

In our patient, absorption of the topical preparation was high as it was applied to ulcers (absent stratum corneum) and to skin folds (occlusive dressing). The progressive fall in tacrolimus blood levels in our patient may be explained not only by the dose reduction (topical 0.03% tacrolimus), but also by the improvement in the lesions and in the barrier properties of the skin.

In summary, we have presented a case of systemic absorption of tacrolimus after topical application, with a deterioration of renal function (a common adverse effect of this drug). This coincided with the direct application of tacrolimus to ulcerated areas (altered skin barrier) and the use of occlusive dressings (skin folds and moist areas). Monitoring tacrolimus blood levels is recommended to avoid side effects associated with unexpectedly high concentrations, particularly in patients with underlying kidney disease. A rational regimen would be to monitor levels weekly for the first month and every 2 weeks or every month thereafter, and at any time that complications are detected.[7]

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Quinacrine: A Treatment Option That Should Not Be Overlooked☆

Quinacrina, un escalón terapéutico que no debemos obviar

To the Editor:

Quinacrine, or mepacrine as it is also known, is a synthetic quinine analog that was the drug of choice for malaria prevention during World War II.[1] It was during this period that its effectiveness in the treatment of connective tissue diseases became obvious, when many soldiers taking the drug to prevent malaria experienced improvements in the symptoms of lupus and rheumatoid arthritis. With the advent of hydroxychloroquine and chloroquine, both of which proved to be more effective antimalarial agents, quinacrine fell into disuse.

Clinical Cases

The patient, a 45-year-old woman (nonsmoker), had been diagnosed with cutaneous lupus erythematosus (CLE) when she was 38 years of age. Six years later her condition met the criteria for systemic lupus erythematosus (SLE). Clinically, her condition was characterized by photosensitivity, malar eruption, scattered erythematous papules (Fig. 1a), and aphthous mouth ulcers. Laboratory test results revealed chronic lymphocytopenia and a positive antinuclear antibody titer of 1:640. Despite treatment with several different topical and systemic agents (prednisone, hydroxychloroquine, methotrexate, and colchicine), the patient never achieved optimal control of the disease. Seven months ago, after quinacrine 100 mg/d was added to her treatment regimen (colchicine 1 mg/d and hydroxychloroquine 200 mg/d), the patient experienced marked

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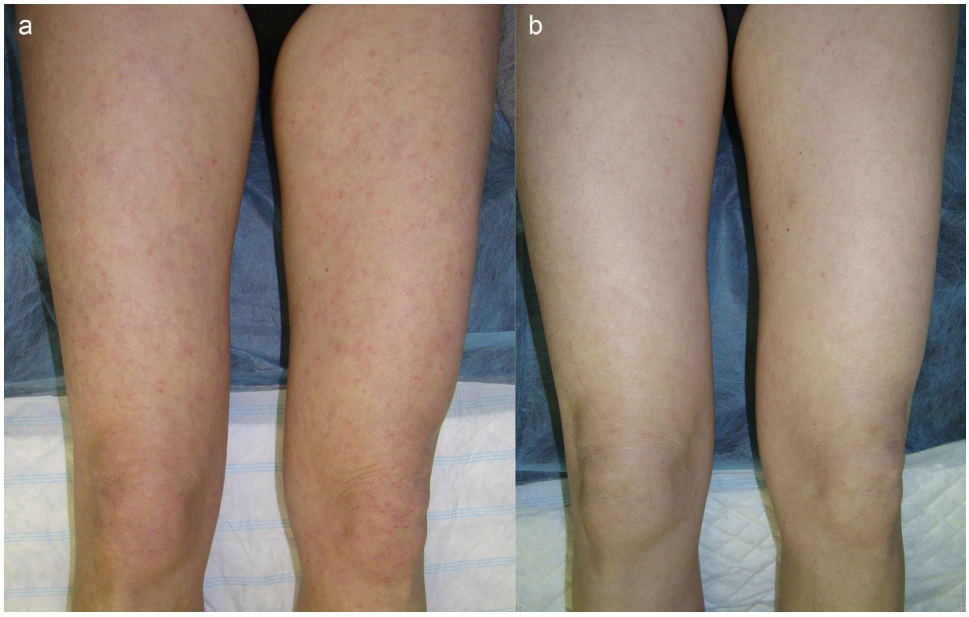

Figure 1 A. Erythematous papules on the lower limbs. B. Reduction in the number, intensity, and inflammation of the lesions 6 months after the addition of quinacrine 100 mg/d to the treatment regimen.

improvement in her skin lesions (Fig. 1b) and a decrease in the frequency and severity of disease flares. The only side effect was a slight yellowing of the skin and mucous membranes.

The second patient is a 35-year-old woman (smoker) with a history of chronic juvenile arthritis, who had been diagnosed with SLE at 26 years of age. She reported almost daily episodes of fever, frequent outbreaks of aphthous ulcers, arthritis, and vasculitis in the form of purpuric papules on the lower limbs (Fig. 2a). Laboratory test findings included a positive ANA value of 1:1280 and chronic leukopenia. The response to treatment with many different systemic agents (prednisone, hydroxychloroquine, methotrexate, sulfones, rituximab, belimumab, and thalidomide) was poor. Twelve months ago, quinacrine 100 mg/d was added to the basic treatment regimen of hydroxychloroquine 200 mg/d. Since then, the patient has experienced considerable improvement in her condition (Fig. 2b), with a significant decrease in the number of flares and no adverse effects.

The third case involves a 47-year-old woman (smoker) diagnosed 4 years ago with amyopathic dermatomyositis (negative ANA, negative anti-melanoma differentiation-associated gene 5, and negative transcriptional intermediary factor 1-γ). The salient clinical features in this case were photosensitivity, heliotrope erythema, and edematous erythematous plaques on the face (Fig. 3a), upper chest, elbows, and knees. The patient had undergone treatment

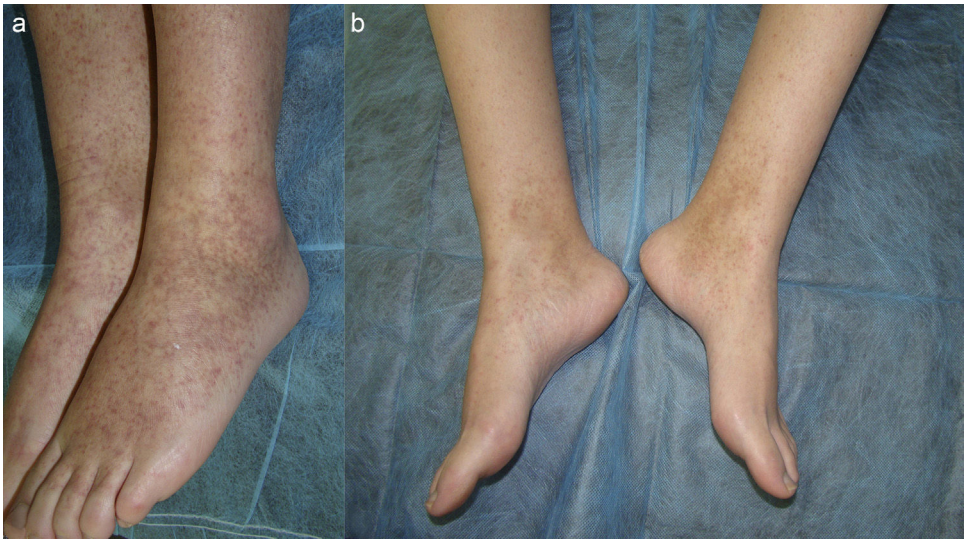

Figure 2 A. Purpuric papules on the lower limbs. B. Significant improvement after 3 months of quinacrine 100 mg/d.

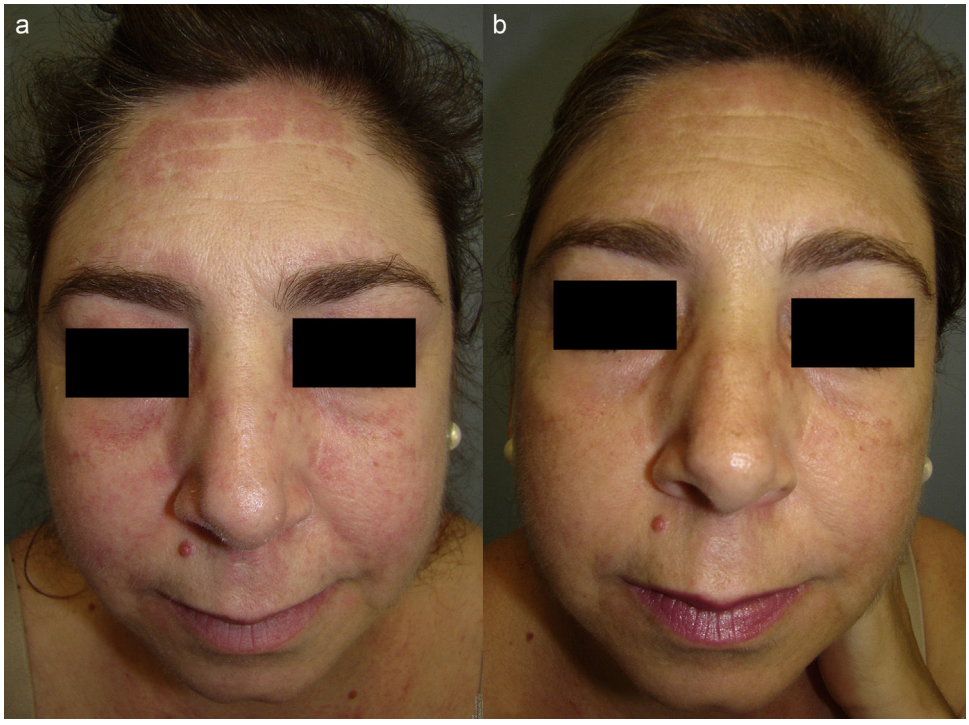

Figure 3 A. Heliotrope erythema and infiltrated pink plaques on the forehead, cheeks, and nasolabial folds. B. Significant improvement 6 months after the addition of quinacrine 100 mg/d to the regimen.

with several systemic drugs (prednisone, methotrexate, azathioprine, and rituximab) with little improvement. Since she started a combination regimen of hydroxychloroquine 400 mg/d, prednisone 5 mg/d, and quinacrine 100 mg/d some 7 months ago, the patient has experienced marked improvement in her skin lesions (Fig. 3b), with no adverse effects.

Discussion

The usefulness of antimalarial agents in the treatment of connective tissue disorders has been amply demonstrated and the treatment of lupus is the setting in which the most evidence has been accumulated.[2] The evidence shows that, in patients with lupus, antimalarial therapy not only reduces the number of disease flares and improves skin symptoms, but also improves glucose control and lipid profiles, has a potent antithrombotic effect, and is useful in the treatment and prevention of nephritis.[3,4] Thus, antimalarial therapy significantly reduces the mortality of patients with different forms of lupus. However, the use of hydroxychloroquine and chloroquine, the 2 best known and most often prescribed antimalarial agents is limited by certain drawbacks, including a lack of response to single-drug therapy and an association with retinal abnormalities. Owing to its chemical structure, quinacrine offers certain advantages over its analogs and can therefore prove very useful in certain cases. Several studies have demonstrated its effectiveness in combination with its analogs and reported good response rates in patients with refractory lupus[5–9] or dermatomyositis.[10]

It is also important to highlight that quinacrine has no ocular toxicity, making it a suitable alternative for patients with retinopathy who are candidates for antimalarial therapy. The use of quinacrine has also recently been proposed as a way to reduce the accumulated dose of hydroxychloroquine and chloroquine in patients with lupus on long-term antimalarial therapy.[2] The daily recommended dose of quinacrine is 100 mg, and the drug is available in this dosage.[1] However, quinacrine can only be acquired in Spain by requesting it as a foreign medication. The cost, while higher than that of chloroquine and hydroxychloroquine, is significantly less than that of other drugs used to treat connective tissue disorders (in our cases, belimumab and rituximab). The possible adverse effects of treatment with quinacrine include the appearance of a yellowish discoloration of the skin and mucous membranes, which resolves when treatment is withdrawn, and the risk of aplastic anemia, which is rare and usually preceded by a lichenoid eruption. Follow-up of patients on quinacrine should include quarterly laboratory testing and annual ophthalmological examinations.[7] Hypersensitivity to the active ingredient is the main contraindication for this drug; however, physicians should also bear in mind that quinacrine can exacerbate psychoses, myasthenia gravis, and psoriasis.

Because of the complexity of the management of connective tissue diseases, we consider it opportune to underscore the importance of being aware of this alternative treatment option, which can prove very useful in clinical practice.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Concomitant Pyoderma Gangrenosum and Erythema Nodosum in a Patient With Ulcerative Colitis

Pioderma gangrenoso concomitante y eritema nudoso en paciente con colitis ulcerosa

Dear Editor,

A 40-year-old woman was admitted to our hospital with a painful ulcer on her leg and fever of over 38 °C. She had been diagnosed with ulcerative colitis (UC) 14 years earlier and was on treatment with mesalazine, 3600 mg/d, and prednisolone at doses of up to 40 mg/d. Infliximab, 5 mg/kg, plus azathioprine, 50 mg/d, had been added to her treatment a year prior to admission and had been administered 8 times in total. The patient also reported atopic dermatitis since childhood. One week prior to admission she experienced painful erythema of sudden onset on the lower leg; the lesion became ulcerated 4 days later. She denied any history of trauma or bruising.

Physical examination revealed a very tender ulcer measuring 3 cm × 1.5 cm on the left lower leg (Fig. 1A). The ulcer had irregular, elevated borders with edema. Laboratory tests revealed a white blood cell count of 7100 cells/μL, with 67% neutrophils, and elevation of C-reactive protein levels (9.15 mg/dL) and of the erythrocyte sedimentation rate (39 mm/h). Serum levels of interleukin (IL) 8 were extremely high (1860 pg/mL). Bacterial culture was sterile. A biopsy taken from the border of the ulcer showed a diffuse neutrophil infiltrate in the dermis and subcutaneous adipose tissue (Fig. 1B and C). On the second day of hospitalization, the patient developed tender erythema on both her lower legs and on her right thigh. Physical examination revealed a number of poorly defined, indurated, pale pink-erythematous papules measuring 1 cm × 1 cm on the right knee (Fig. 1D) and on both lower legs. On histology, a neutrophilic infiltrate was observed in the subcutaneous adipose tissue (most intense in the septa) (Fig. 1E). The ulcer had reepithelialized completely 2 months after starting treatment with systemic prednisolone, 25 mg/d. The prednisolone dose was then gradually tapered to complete withdrawal 5 months later, with no relapse of the pyoderma gangrenosum (PG). Both infliximab and azathioprine were continued throughout the course of steroid treatment.

PG and erythema nodosum (EN) are skin lesions associated with UC.[1] In general, such manifestations appear to be related to activity of the intestinal disease; however, some patients develop skin lesions despite remission of their bowel condition. Our patient developed a deep ulcer on her lower leg, followed by painful erythematous subcutaneous nodules at an interval of several days, despite control of her intestinal disease. To date, counting our patient, only 5 five cases of concomitant PG and EN have been reported.[2,3] The details of these patients, all women aged between 19 and 49 years, are summarized in Table 1. One patient had Crohn disease, the other 4 had UC. Skin symptoms appeared simultaneously with an exacerbation of the intestinal disease in all cases except in our patient. Arthritis was observed in 1 case. Systemic steroids were used in 4 cases, with an adequate response, and 1 case was successfully treated using tacrolimus and granulocytapheresis.[3] Very rarely, PG can be induced by tumor necrosis factor (TNF) inhibitors[4]; however, we ruled out the possibility of biologics-induced PG in our patient because the administration of infliximab to control her intestinal symptoms after the onset of her PG and EN did not exacerbate either the skin or the joint manifestations. Furthermore, azathioprine was continued throughout the course of steroid treatment,