In our review of the literature, we found many drugs described in association with EM (antibiotics, corticosteroids, nonsteroidal anti-inflammatory drugs), but there were few reports linking EM to topical treatments.\(^1\)\(^-\)\(^3\) We detected just 3 cases of EM associated with topical imiquimod, and none of the patients had Gorlin syndrome. Systemic absorption could explain why topical imiquimod causes EM, as the immunomodulatory effects of the drug could trigger a type III and/or IV hypersensitivity reaction, ultimately leading to EM. An intense local inflammatory reaction such as that experienced by our patient would probably favor this systemic absorption, predisposing patients to an EM-type skin eruption. Nonetheless, whether or not patients with Gorlin syndrome have an immune-based predisposition to EM remains to be confirmed.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References


S. Peña-López,\(^*\) O. Suárez-Magalena, B. Monteagudo, M. Cabanillas

Servicio de Dermatología, Complejo Hospitalario Universitario de Ferrol, Ferrol, A Coruña, España

\(^*\) Corresponding author.
E-mail address: Sandra.Pena.Lopez2@sergas.es (S. Peña-López).

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Treatment of Livedoid Vasculopathy With Rivaroxaban: A Potential Use of New Oral Anticoagulants for Dermatologists\(^\star\)

**Vasculopatía livedoide tratada con rivaroxabán. Potenciales usos de los nuevos anticoagulantes orales para el dermatólogo**

To the Editor:

Livedoid vasculopathy (LV) is a noninflammatory thrombotic disease that affects the small blood vessels of the skin and is characterized by livedo racemosa and painful skin ulcers on the lower extremities.\(^1\)\(^-\)\(^2\) We report 2 cases of LV in which treatment with rivaroxaban achieved a full and sustained response. We also review novel oral anticoagulants with potential applications in dermatology.

**Case Description 1**

A 53-year-old woman with no relevant past history presented with multiple skin ulcers on her feet. The ulcers were painful and had been present for 2 years. Physical examination revealed an ulcer measuring approximately 3 cm on the medial aspect of the left foot against a background of livedo racemosa and retiform purpura (Fig. 1A). The patient’s

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medical history and exploratory tests ruled out hypercoagulability, systemic inflammatory disease, and infection. In the evaluation of peripheral arterial disease, no alterations were observed in the ankle-brachial index or in the Doppler ultrasound scan. Skin biopsy showed fibrin clots in the dermal vessels, extravasated red blood cells, hyalinization of the vessel walls, and neovascularization consistent with LV. Treatment was initiated with acetylsalicylic acid 300 mg/d, intravenous alprostadil 60 µg/d, and subcutaneous enoxaparin 1 mg/kg/d. These treatments resulted in a mild reduction of pain and had almost no effect on ulcer healing. The patient was subsequently started on rivaroxaban 10 mg/d, which resulted in full resolution of pain after a week and healing of the ulcer at 3 months (Fig. 1B). Twelve months after initiation of treatment with rivaroxaban, the patient was free of pain and ulcers, although there were no changes to the livedo racemosa.

Case Description 2

A 55-year-old woman with no past history of interest presented with multiple painful cutaneous ulcers of 12 years’ duration on the lower legs. Physical examination revealed multiple ulcers, some measuring up to 10 cm, with a necrotic base and a livedo racemosa pattern extending up to the knees (Fig. 2A). Based on the patient’s medical history and tests, a secondary cause was ruled out. Skin biopsy findings were consistent with LV. The lesions were refractory to treatment with oral prednisone, hydroxychloroquine, acetylsalicylic acid, and pentoxifylline. Treatment with rivaroxaban 10 mg/d led to reversal of pain after 2 weeks and full resolution of ulcers by month 4 (Fig. 2B-D). After 9 months of treatment with rivaroxaban, the patient remained pain free and ulcer free. Similarly to the first case described, there were no changes to the livedo racemosa.

Figure 2 A, Cutaneous ulcers against a necrotic background on the legs. B-D, Progressive healing of ulcers after initiation of oral rivaroxaban.
LV can occur as a primary idiopathic condition or secondary to hypercoagulability states, e.g., presence of lupus anticoagulant, anticardiolipin, type I cryoglobulinemia, factor V Leiden mutation, protein C deficiency, hyperhomocysteinemia, and antithrombin III deficiency. It can also occur in association with systemic inflammatory diseases, such as systemic lupus erythematosus and rheumatoid arthritis. The hallmark clinical findings in LV are livedo racemosa, skin necrosis, and on occasions, noninflammatory vascular thrombosis. The characteristic scarring pattern left by ulcers in LV is known as atrophie blanche, which appears as a porcelain-white scar with red dots (prominent capillaries).

There is evidence of reduced fibrinolytic and increased thrombin activity in the vessel walls in LV. This thrombotic microvascular state is a histopathologic feature of LV. A perivascular lymphocytic infiltrate may also be observed, but it is considered to be a secondary finding and does not cause vasculitis. The most novel, and effective, treatments for LV are thus anticoagulants rather than immunomodulatory drugs. Table 1 provides a list of these anticoagulants together with a summary of their potential applications and doses. Thanks to these new anticoagulants, dermatologists are now better positioned to manage microcirculatory thrombotic disorders, essentially because they eliminate the need for hematologic control. Rivaroxaban is a novel factor X inhibitor that has proven effective in different clinical cases and a phase II multicenter clinical trial. The 10-mg dose has been found to achieve rapid relief of ischemic pain and complete remission of ulcers.

There have also been recent success stories with the use of dabigatran 220 mg/d and apixaban 10 mg/d in patients with LV refractory to vasodilators and/or antiplatelet agents. It should be noted that the doses used for LV tend to be lower than those established for the approved indications of these new anticoagulants. Formulations containing lower doses are also commercially available (Table 1).

In conclusion, we have described 2 new cases of cutaneous ulcers due to LV that did not respond to treatment with vasodilators or antiplatelet agents but that were successfully treated with rivaroxaban. This anticoagulant resulted in rapid pain resolution and complete and lasting resolution of ulcers. Dermatologists should be familiar with the existence and use of these novel oral anticoagulants in view of their potential applications in thrombotic disorders of cutaneous microcirculation.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

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References
Mucocutaneous Leishmaniasis in Immunocompromised Patients: Report of 4 Cases in Spain

Leishmaniasis mucocutanea en pacientes inmunocomprometidos: reporte de 4 casos autóctonos

To the Editor:

Leishmaniasis is a disease caused by parasites of the *Leishmania* genus. Clinically, it can present as cutaneous leishmaniasis, mucocutaneous leishmaniasis, or visceral leishmaniasis. The disease is endemic in a number of Spain’s autonomous communities, namely, Madrid, Catalonia, Aragon, Castilla-la Mancha, Andalusia, Valencia, Extremadura, Murcia, and the Balearic Islands. In some communities it is a notifiable disease, although not all cases are reported. Clinical manifestations depend on the species of *Leishmania*, the inoculation site, and the host’s immune status. Immunosuppressed patients have a high risk of severe disease.

Between 1% and 10% of all cases of cutaneous leishmaniasis spread to the mucous membranes, and almost 90% of these are caused by *Leishmania braziliensis*, which is rare in our geographic area.

In a retrospective search of the database at our hospital, we identified 18 cases of cutaneous/mucocutaneous leishmaniasis (Table 1). The patients (9 males and 9 females) were aged between 9 and 84 years (mean age, 46 years) and the mean time to diagnosis was 10 months. Six of the 18 patients were immunocompromised for varying reasons (diabetes mellitus, congestive heart failure, liver transplantation, Crohn disease, psoriatic arthritis). Four of them had mucocutaneous leishmaniasis and none of them had been abroad recently.

**Case 1**

The first patient was a 59-year-old woman with systemic lupus erythematosus under treatment with methotrexate 15 mg/wk, hydroxychloroquine 400 mg/d, trimethoprim-sulfamethoxazole 160/800 mg 3 days a week, acenocoumarol, prednisone, and subcutaneous adalimumab 40 mg every 2 weeks. In the week preceding her visit, she had experienced deterioration in her general health and polyarthritis of the carpal bones and knees. Physical examination revealed thickening of the dorsum of the tongue, multiple ulcers on the palate, and erythematous-violaceous papular lesions on her fingers and palms. She was admitted to hospital. A gastric biopsy performed several weeks earlier showed inclusion bodies consistent with *Leishmania* parasites. Biopsy of the oral mucosa also showed microorganisms consistent with *Leishmania*. Empirical treatment was started with amphotericin 1 mg/kg/d on days 1-5, 10, 17, 24, 31, and 38. Adalimumab therapy was interrupted and the daily dose of prednisone was increased to 20 mg. The patient progressed favorably.

**Case 2**

The second patient was a 62-year-old man who had undergone liver transplantation and had a history of chronic kidney failure, gout, and chronic obstructive pulmonary disease. He was being treated with mycophenolate, tiotropium, and allopurinol, and presented with...