Iatrogenic Kaposi's Sarcoma Successfully Treated with Topical Timolol☆

Sarcoma de Kaposi iatrogénico tratado con éxito con timolol tópico

Dear Editor:

Kaposi's sarcoma (KS) is considered to be a slowly progressive multifocal tumor of the endothelial cells. Four clinical subtypes have been described: a) classic (in elderly Mediterranean men); b) endemic (in Africa); c) HIV-associated; and d) iatrogenic, which affects immunodepressed patients and recipients of organ transplants.1All the subtypes of KS have a common etiology: infection with human herpesvirus-8 (HHV-8), which may be considered to be a necessary though not sufficient condition for developing the disease. Other factors (genetic, hormonal, and environmental) are also necessary, together with immunosuppression. The latency period from infection to development of KS may vary depending on the clinical type.[1–3]

A 70-year-old woman was referred to our outpatient dermatology department with ahistory of primary hypothyroidism, partial epilepsy, myoclonic tremor, moderate cognitive deterioration, osteoporosis, bronchial asthma, and giant cell arteritis that had appeared a year earlier and was treated with prednisone, 7.5 mg/d and methotrexate, 10 mg/d. The patient complained of multiple purplish papules that caused discomfort, plaques, and dome-shaped nodules measuring between 0.4 and 0.5 cm distributed over the earlobes, cheeks, cervical, periumbilical, and sacral regions, and both members (Figs. 1 and 2).

Clinical examination revealed no enlarged lymph nodes or splenomegaly. Histology was compatible with KS. The histologic study revealed a tumor composed of fusiform cells with cytologic atypia demarcating the vascular spaces, with some mitotic figures (Fig. 3). Immune staining showed proliferative cells positive for CD31, CD34, and HHV-8. Immune staining of β-adrenergic receptors was positive for B2-AR. B2-ARP and B3-AR immune-staining techniques were not available. The blood count, globular sedimentation rate, coagulation profile, general biochemistry and full-body CT scan were normal. Serology for HIV was negative. Treatment with methotrexate was stopped and a combination of cryotherapy and imiquimod cream, 5% was instated with a good response after 10 weeks of uninterrupted treatment. Three months later, despite the reduced immunosuppression, small bluish-purple plaques appeared on the lower limbs and spread slowly over the middle part of the ankle and left foot (Fig. 3). All the lesions resolved completely after 16 weeks of treatment with timolol gel, 0.5% twice daily, and prednisone was reduced to 5 mg/d. No recurrences were observed after 6 months of follow-up. The patient used 2 30-mg containers and did not finish the second container. Local toxicity (allergic contact dermatitis) and systemic toxicity were monitored and no adverse effects were observed during treatment.

KS is an angioproliferative disease, first described by Moritz Kaposi in 1872. It is classified into 4 subtypes: classic, endemic, HIV-associated, and iatrogenic, with different courses and epidemiology, but with similar histology. The iatrogenic form of KS appears in patients who are immunodepressed due to organ transplant (particularly kidney transplants), chemotherapy, or rheumatologic disease.[4] In these cases, the disease usually appears a year after the first administration of the drugs. It has been reported with

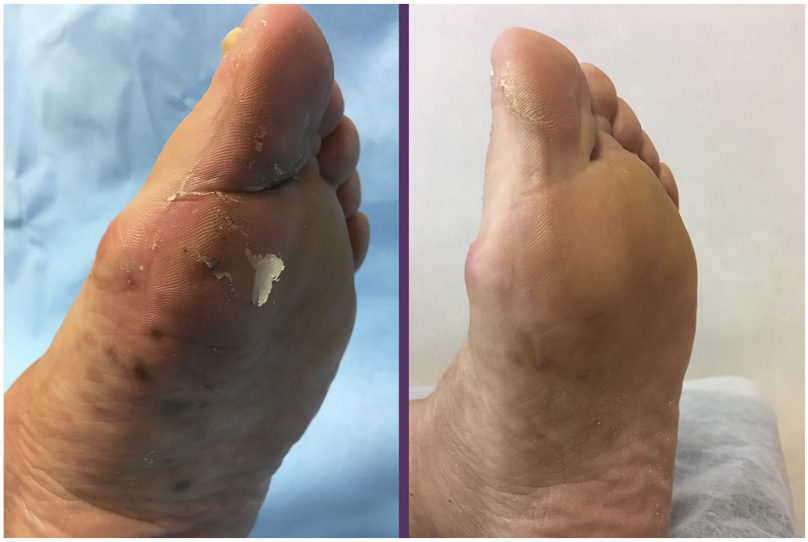

Figure 1 Multiple violaceous papules on the sole of the left foot, at the start and end of treatment.

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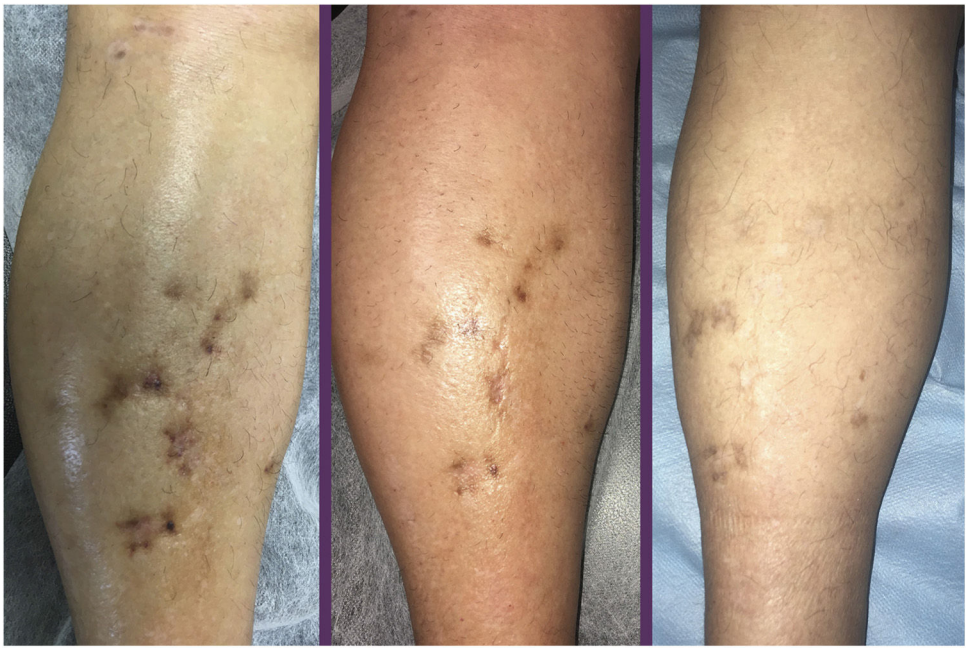

Figure 2 Evolution of the bluish papules and nodules on the right leg, before start of treatment with timolol gel, 0.5%, after 8 weeks, and after 3 months.

use of cyclosporin, oral corticosteroids, and other oral immunosuppressive agents.[4–6] The pathogenic mechanism involved is still unknown, but it is linked to the inhibition of TGF-β and reactivation of infection with HHV-8, which leads to the induction of angiogenesis. The lesions have a multifocal clinical presentation. The course is variable, from an indolent form, with cutaneous manifestations only, to a disseminated form with extension to the mucous membranes and visceral involvement. Where the disease is localized on the skin, various treatment options are available, such as local resection, cryosurgery, photodynamic therapy, laser, imiquimod, alitretinoin gel, or radiation therapy.[7,8] There is no cure and the objective of all these approaches is to manage the symptoms. If systemic dissemination appears, chemotherapy with liposomal doxorubicin is required.[7] KS that appears in patients with significant immunosuppression will resolve, in most cases, when the immunosuppressive therapy is changed, reduced, or stopped.

Timolol is a nonselective β-adrenergic antagonist that exhibits antiangiogenic effects on topical administration for superficial infantile hemangioma. Its mechanism of action is not fully understood. The hypothesis has been suggested that beta blockers produce three consecutive steps (vasoconstriction, inhibition of proangiogenic signals, and induction of apoptosis of the endothelial cells) that lead to the regression of the hemangioma. By extrapolation to other proliferative vascular diseases, it has become an emerging alternative for localized KS (Table 1).[9,10] No differences exist in the response rate of iatrogenic KS treated with timolol between immunocompetent and immunosuppressed

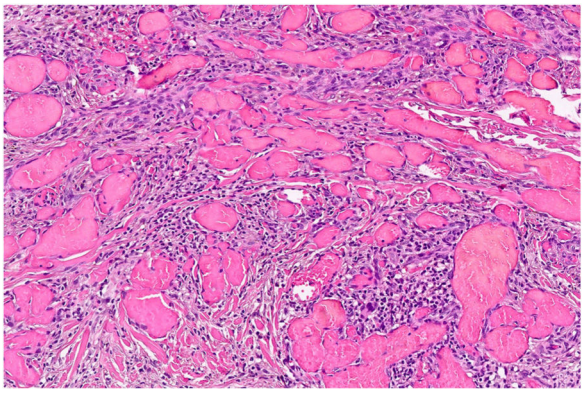

Figure 3 Proliferation of fusiform endothelial cells forming vascular spaces (hematoxylin–eosin, ×20).

patients. The main advantages of this treatment are the cost, ease of administration, and minimal adverse effects. Response time varies between 5 and 24 weeks (possibly related to the size of the lesion or lesions). Once the lesion has resolved, close vigilance is required, as only 2 of the 9 cases published in the literature have a follow-up period of more than 18 months.

This case highlights the therapeutic challenge posed by iatrogenic KS. Reduction or elimination of immunosuppression does not always lead to resolution of KS and local treatment with topical timolol may be an effective, painless, simple, and economic option.

Table 1 Clinical Characteristics of Patients with Kaposi's Sarcoma Treated With Topical Timolol.

Patient	Age, y	Sex	Area Involved	Clinical Type	Size, cm	Associated Disease	Time to Remission, mo	Follow-Up, mo
1	52	M	Left leg	Plaque	9 × 4	None	5	10
2	70	F	Left foot	Plaque	14 × 62.5 × 2.5	Hypertension	5	9
3	65	M	Right leg	Plaque	12 × 5	None	4	6
4	45	M	Right arm	Plaque	11 × 4	HIV-TB	6	4
5	78	M	Right foot	Nodular	NA	None	12	22
6	94	F	Right leg	Nodular	NA	None	12	20
7	89	M	Both feet	Nodular	NA	Hypertension	12	5
8	83	M	Right hand	Nodular	NA	None	18	4
9	71	M	Penis	Nodular	NA	None	24	10

Abbreviations: M indicates male; F, female; NA, not available; TB, tuberculosis; HIV, human immunodeficiency virus.

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When a Gin And Tonic Can Mean Trouble: Fixed Drug Eruption Due to Quinine☆

Cuando tomarse un gin-tonic se convierte en una mala experiencia: exantema fijo medicamentoso por quinina

To the Editor:

A fixed drug eruption (FDE) may be caused by different drugs, especially NSAIDs, paracetamol, and antibiotics. In recent years, cases due to the quinine in tonic water have been reported. We report a case of FDE caused by quinine after drinking a gin and tonic and we review the cases published to date. We analyze the current legislation on the amount of quinine allowed in drinks and the differences between the different brands sold in Spain.

A 32-year-old woman visited our department with repeated outbreaks of erythematous-violaceous lesions with irregular, edematous margins in the perioral region, the 5th finger of the left hand, and the lateral surface of the right hand, compatible with FDE (Fig. 1). The patient occasionally took diclofenac and metamizole but did not improve. On examining the patient's full medical history, we discovered that the lesions coincided with the consumption of gin and tonic; quinine was therefore suspected.

A skin-patch test performed with Schweppes® tonic water was negative, and epicutaneous tests with the tonic, with quinine in petrolatum at 20%, and in aqueous solution at 1%, were also negative after 48 and 96 h. An oral provocation test was positive, with appearance of the lesions a few hours

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