Cutaneous Alternariosis in a Heart Transplant Recipient

Alternariosis cutánea múltiple en un paciente receptor de trasplante cardiaco

To the Editor:

Alternaria is a dematiaceous (pigmented) fungus found in the atmosphere and is pathogenic to plants. It is an opportunistic fungus and usually infects immunocompromised patients.[1,2] We describe the case of a heart transplant recipient with cutaneous alternariosis due to infection with *Alternaria* species who developed multiple lesions on the upper and lower limbs.

The patient was a 63-year-old man from a rural area whose hobby was gathering snails. He had received a heart transplant 6 months earlier and had been receiving mycophenolate mofetil (500 mg/12 h), tacrolimus (1.5 mg/24 h), and prednisone (15 mg/24 h) since transplantation, in addition to his usual antihypertensive and lipid-lowering medication and gastric protection.

He was referred to the dermatology department by his regular cardiologist due to multiple nodular lesions on the upper and lower limbs that had appeared several weeks earlier. The patient reported no other systemic symptoms.

Physical examination revealed multiple, hard, erythematous-violaceous nodules of different sizes on both the upper (Figure 1A) and lower (Figure 1B) limbs, some of them ulcerated with an overlying crust.

A skin biopsy was taken from one of these lesions for histopathological and microbiological studies. Histopathological study revealed a hyperplastic epidermis with crater-like invaginations, with a keratotic center and pseudoepitheliomatous hyperplasia. In the dermis there was an inflammatory infiltrate composed of histiocytes, some of them multinucleated giant cells which, focally, were seen to contain round encapsulated bodies with a fungus-like appearance (Figure 2A). These giant cells formed granulomas with central abscesses. Silver methenamine staining demonstrated these round bodies in greater detail, showing peripheral enhancement (Figure 2B).

Tissue culture on Sabouraud agar showed that the fungal structures observed were of the genus *Alternaria*, but the species could not be identified.

A chest radiograph, requested to rule out lung involvement, was normal, as was the blood test (complete blood count and general biochemistry).

The patient was treated with oral itraconazole (200 mg/d for 6 months) and topical ketoconazole cream (twice daily for the same period). At the same time, the patient received 12 sessions of cryotherapy (one session every 2 weeks) beginning 1 month after starting the oral and topical therapy. At the present time the patient is asymptomatic, with no active lesions. Only some hypopigmented and hyperpigmented scars at some of the sites treated with cryotherapy remain (Figure 3).

Cutaneous alternariosis can no longer be considered an uncommon fungal infection. A recent review of the literature found 89 cases that met both the microbiological and histopathological criteria for this entity.[3] Most of the patients affected are immunocompromised; transplant recipients in particular form a group in which this infection has increased considerably.[2,4]

It is believed that the disease can be acquired in one of 2 ways: the most common is by direct inoculation from plants, although some cases have been reported of infection by inhalation of fungal conidia with subsequent systemic spread, mainly affecting the lungs, paranasal sinuses, or brain.[1] Our patient was infected by direct inoculation from plants, as his hobby is gathering snails, for which purpose he wears a short-sleeved T-shirt and shorts.

Clinically, the lesions usually present as isolated nodules, plaques, or ulcers; multiple lesions, as in our patient, are rare.[3] The lesions can persist for years.

Histopathology shows a granulomatous infiltrate in the dermis with the presence of multinucleated giant cells and fungal hyphae that can be visualized with hematoxylin-

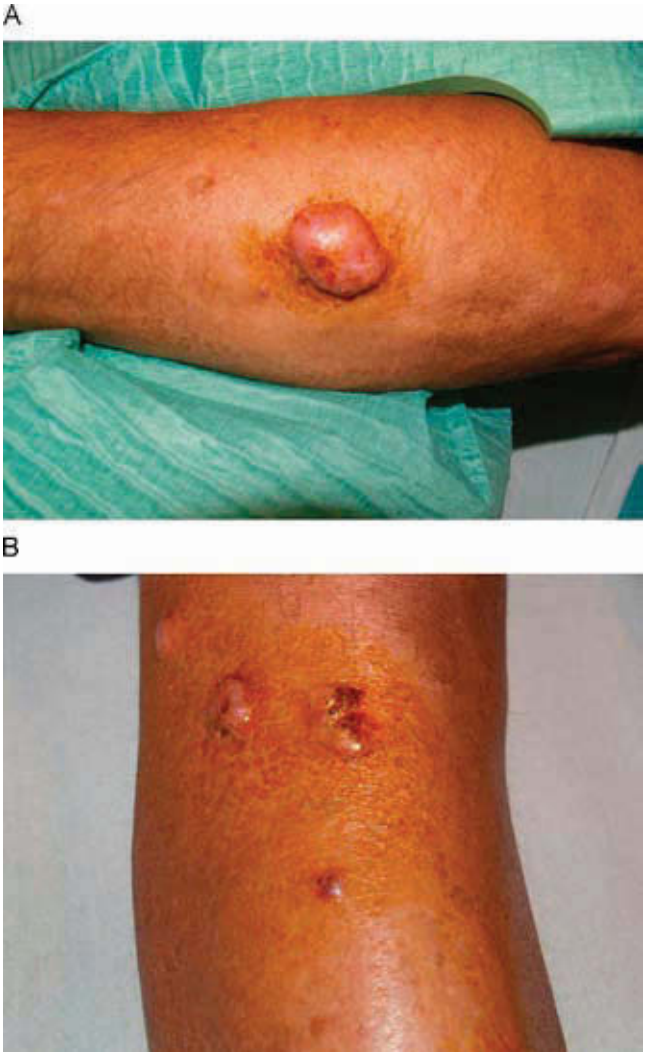

Figure 1 A, Hard, erythematous-violaceous tumor on the left forearm. B, Papules and nodules with an ulcerated, crusted surface on the anterior aspect of the left leg.

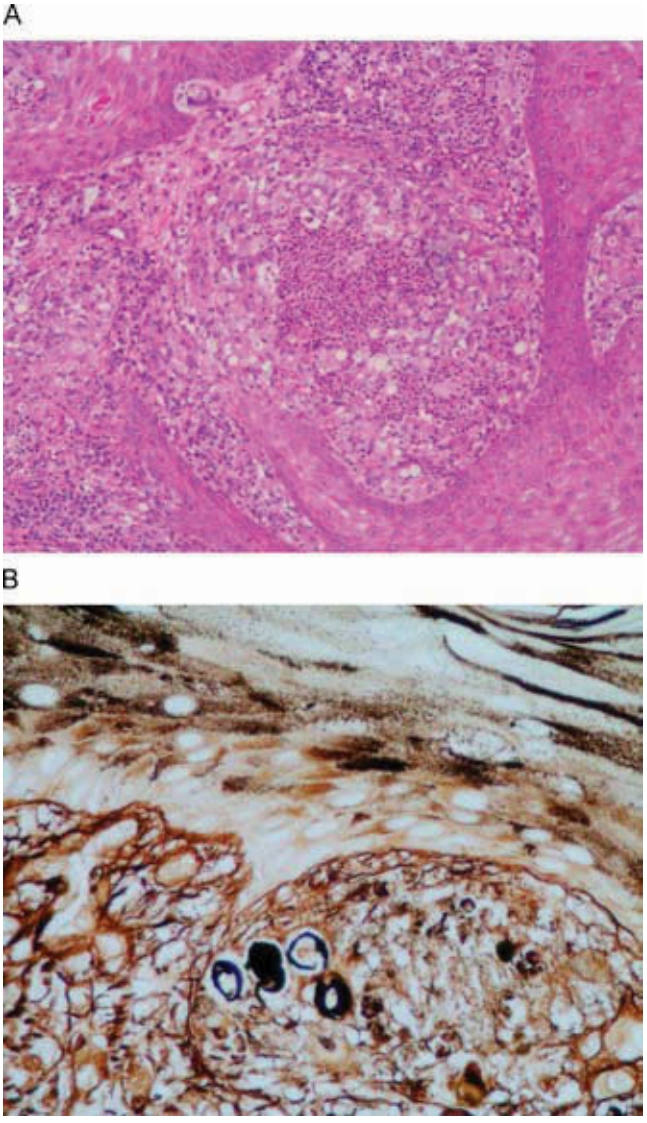

Figure 2 A, Pseudoepitheliomatous epidermal hyperplasia; inflammatory granulomatous infiltrate with central abscess formation within the dermis (hematoxylin-eosin, original magnification ×100). B, Round bodies with peripheral enhancement (silver methenamine, original magnification ×200).

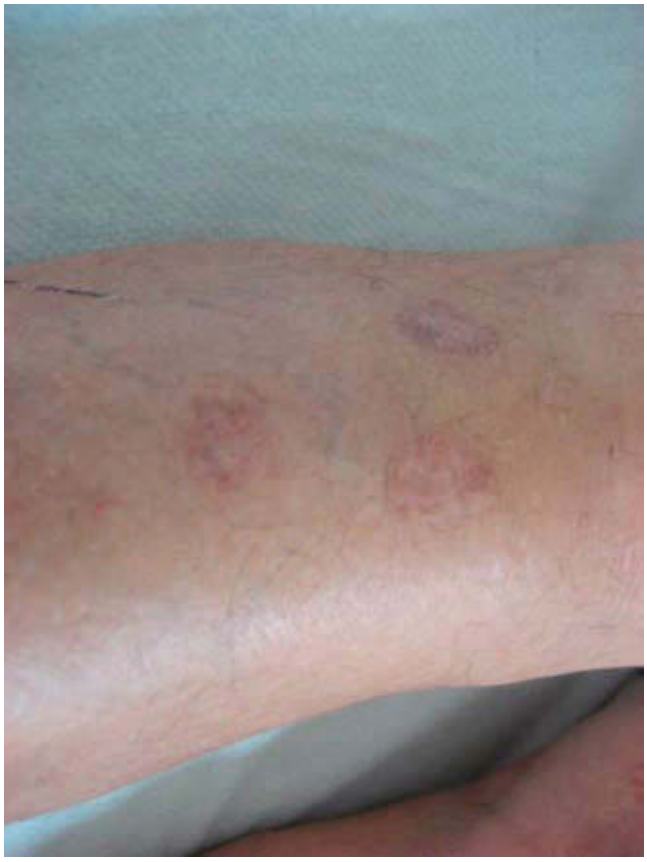

Figure 3 Residual scars at the site of lesions treated with cryotherapy.

eosin stain or, better, with Grocott's methenamine silver stain. In addition to this visualization of *Alternaria* species, infection must be confirmed by fungal culture. Alternaria colonies generally grow rapidly on Sabouraud dextrose agar, and have an olive green or blackish gray color.[5]

Treatment for this infection is still controversial. Many antifungal drugs have been used with varying results. Resistance to griseofulvin and 5-fluorocytosine has been reported.[6] Amphotericin B and miconazole have been used successfully.[7] More recent studies have focused on the use of oral itraconazole because of its lower toxicity and simple regimen, although the dose and duration of treatment have not yet been established. In some cases, surgery has been used as an adjuvant to oral therapy.[4]

In our patient we opted for treatment with oral itraconazole and topical ketoconazole. We decided to add cryotherapy for the most resistant lesions, which responded well to the treatment, although we found no reference in the literature to the use of this therapy.

In conclusion, we would like to stress the importance of taking into account opportunistic infections such as our patient's. Not many years ago they were considered exceptional, today this is no longer the case, due to the increased use of immunosuppressants.[9] We would also like to emphasize the peculiarity of this case, both because this infection is uncommon and because the patient presented multiple lesions.

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Gingival Hyperplasia Secondary to Everolimus Therapy

Hiperplasia gingival secundaria a everolimus

To the Editor:

We present the case of a 34 year-old woman with type 1 diabetes with onset 20 years earlier who consulted for thickening of the gums. The patient had a history of diabetic retinopathy and nephropathy that led to a kidney transplant 3 years ago. Graft function was normal at the time of presentation. Other relevant history included hypertension, migraine, and surgery for a pituitary adenoma 10 years earlier. She reported intolerance to enalapril and mycophenolate-mofetil and she was therefore being treated with injectable insulin, tacrolimus, calcitriol, pantoprazole, and everolimus. The patient had noted progressive thickening of the gums, erosive lesions on the oral mucosa and on the borders of the lips, and intense halitosis following introduction of the everolimus treatment 4 months prior to the present consultation (the other treatments had been employed for several years). She consulted as the condition was causing her considerable discomfort. Examination revealed gingival hyperplasia predominantly of the maxillary gingiva (Figure), accompanied by ulceration of the lips and gums. Severe pyorrhea was also observed.

A diagnosis of gingival hyperplasia secondary to everolimus therapy was made on the basis of the clear temporal relationship reported by the patient. Withdrawal of the drug was not considered appropriate as the kidney transplant was well controlled by the agent, meaning the only recommendation made was for rigorous oral hygiene and regular dental check-ups.

Drug-induced gingival hyperplasia is an adverse drug reaction of unknown etiology that could be related to changes in calcium metabolism and other local factors. The drugs most commonly associated with the condition include anticonvulsants, immunosuppressants, and calcium antagonists.[1,2]

In 1939, phenytoin was the first drug to be associated with the disorder and it is still the most common associated anticonvulsant. Ciclosporin[3] stands out in the literature as the leading immunosuppressant related to the condition and nifedipine is the most commonly cited calcium antagonist.[4]

Gingival hyperplasia tends to appear a few months after starting treatment with the drug, and in general

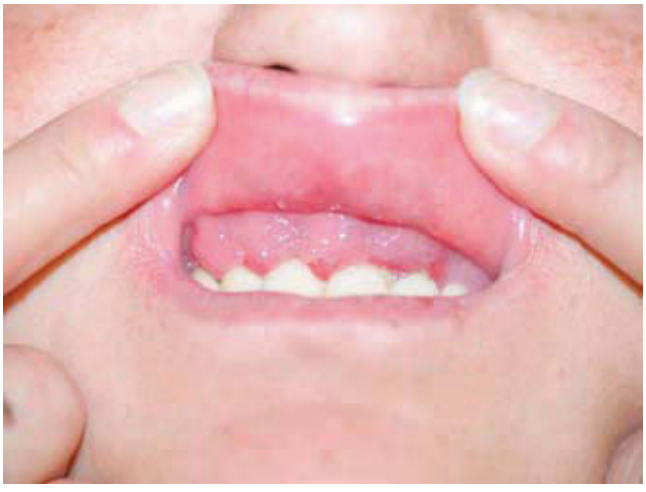

Figure Marked maxillary gingival hyperplasia. Erosions on the lips and gums.