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CASE AND RESEARCH LETTERS

Disseminated Cryptococcosis Presenting as Skin Nodules Resembling Erythema Nodosum

Nódulos cutáneos similares a eritema nodoso como manifestación de criptococosis diseminada

To the Editor:

We describe the case of an immunosuppressed kidney transplant patient diagnosed with disseminated cryptococcosis presenting as erythematous nodules resembling erythema nodosum on the lower limbs.

The patient, a 39-year-old woman, had kidney failure secondary to recurrence of immunoglobulin A nephropathy in 2 kidney transplants, and was receiving immunosuppressive therapy.

Two weeks earlier, she had started to experience generalized headache, with a single spike of fever (38ºC) and an episode of vomiting. She also had bilateral calf pain that had caused impaired limb function in the last 3 weeks. On physical examination, she appeared very weak, had low-grade fever, and was hemodynamically stable. The results of the neurological examination were normal. Inspection revealed the presence of 3 erythematous nodules on the anterior and lateral aspects of the left leg. The nodules were tender and resembled erythema nodosum (Figure 1).

Skin biopsy showed a dense inflammatory infiltrate predominated by polymorphonuclear neutrophils and lymphocytes in the reticular dermis and the hypodermis. Among these cells were multiple pale, round structures with central basophilia and an obvious capsule indicative of *Cryptococcus neoformans* spores (Figure 2). The structures were positive for staining with periodic acid-Schiff, methenamine silver, and mucicarmine (Figure 3). Given the suspicion of cryptococcosis, we performed a second skin biopsy and extracted a sample of cerebrospinal fluid (CSF). India ink staining was positive for the skin sample but negative for the CSF. Antifungal treatment with liposomal amphotericin B and 5-flucytosine was initiated to treat suspected disseminated cryptococcosis with meningeal involvement.

Laboratory tests showed leukocytosis (13 250/µL) and C-reactive protein values of 92 mg/L; the Mantoux test was negative. The chest radiograph and cranial computed tomography scan were normal, and fundoscopy revealed foci of chorioretinitis in the nasal quadrant of the left eye.

The suspected diagnosis of disseminated cryptococcus was confirmed by the isolation of *C neoformans* in 3 blood cultures and cultures of the skin biopsy sample and of the CSF.

Disseminated cryptococcosis is a systemic mycosis with a universal distribution that is caused by *C neoformans*. It mainly affects immunosuppressed patients with cell-mediated immune deficiency, and the major risk groups are patients with acquired immunodeficiency syndrome (AIDS) or who have undergone transplants. The portal of entry for the fungus is the respiratory tract, and from here it can spread to other organs via the blood.[1]

The central nervous system is the second most frequently affected organ (after the lungs). The clinical manifestations of the disease are diverse and vary from one patient to the next.[1,2]

The skin is the third most commonly affected organ; infection can be primary or appear as a manifestation of disseminated cryptococcosis. Skin involvement is seen in 10% to 20% of patients with disseminated cryptococcosis, and while lesions can occur on any part of the body, the head and neck are the most frequently affected sites. Although skin involvement tends to be a sign of disseminated infection, it is occasionally seen several months before other organs become affected. The lesions are nonspecific and have a range of presentations, including papules, vesicles, pustules, subcutaneous nodules that may become ulcerated, ulcers, cellulitis, and molluscum contagiosum–like lesions (the main form found in patients with AIDS). There have been very rare reports of necrotizing vasculitis, and lesions resembling herpes infection, pyoderma gangrenosum, or basal cell carcinoma.[2-4]

There have been previous descriptions of cases of nodules on the limbs and trunk, and even on the wing of the nose,[5-7] but we found no reports of lesions resembling erythema nodosum in our review of the literature.

Primary cutaneous cryptococcosis is very rare and presents with variable, nonspecific lesions[8]; it is identified by isolation of *C neoformans* in a skin biopsy or culture in the absence of disseminated disease.

Skin histopathology is important as the clinical diagnosis of cryptococcosis is difficult due to the nonspecific nature of the manifestations. Both conventional hematoxylin-

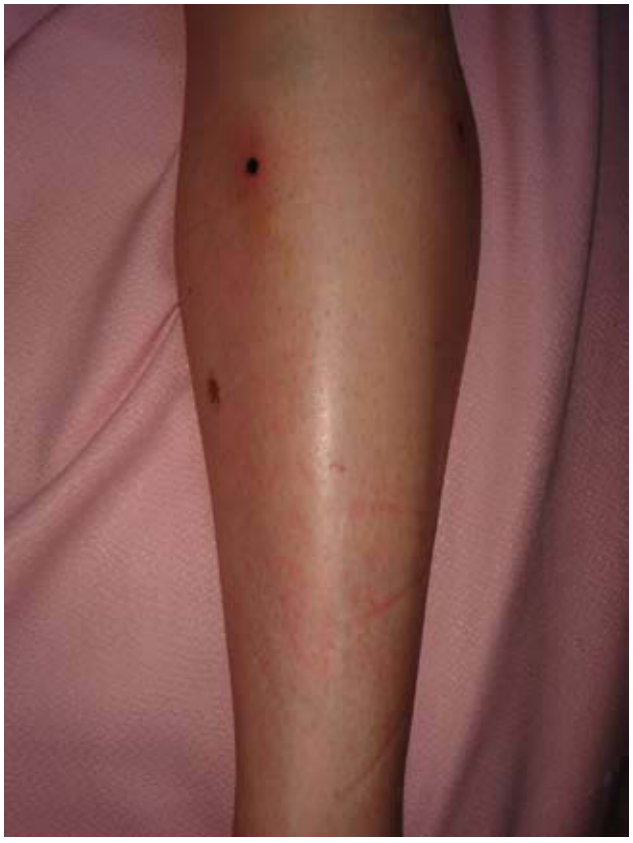

Figure 1 Clinical appearance of 2 subcutaneous nodules on the left leg after the skin biopsies.

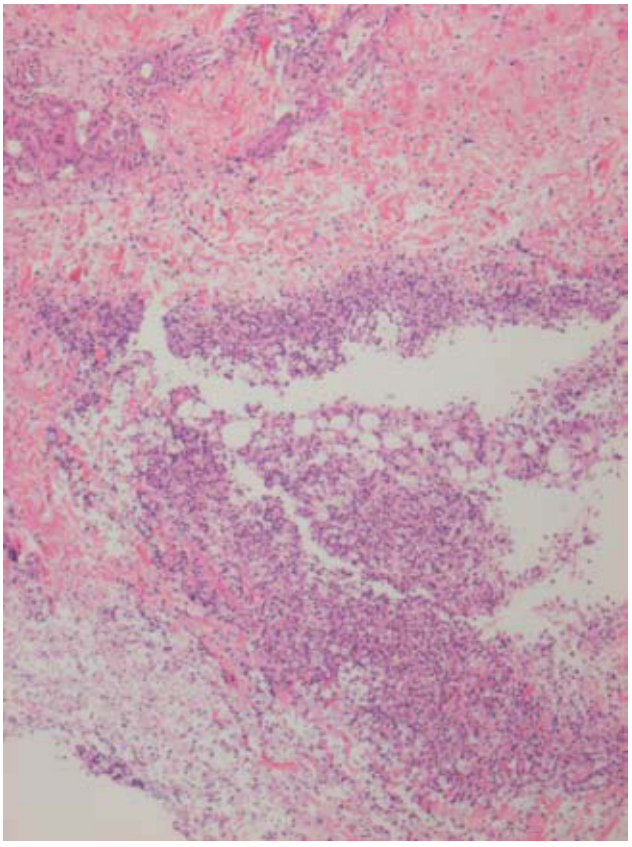

Figure 2 Histological image of a dense inflammatory infiltrate occupying the reticular dermis and the hypodermis, showing multiple pale, round structures with a hyperchromatic center (hematoxylin-eosin, original magnification ×100).

eosin staining and special staining techniques such as PAS, methenamine silver, and mucicarmine show spores indicative of cryptococcal infection.[1,6] As occurred in our patient, histological identification of cryptococci means that antifungal treatment can be initiated without having to wait for confirmation by fungal culture. Nonetheless, a definitive diagnosis can only be established when *C neoformans* is isolated in fungal cultures of a skin specimen.

Treatment consists of systemic liposomal amphotericin B plus 5-flucytosine, followed by maintenance therapy with fluconazol.[1] Surgical treatment of the lesions may be necessary in selected cases.

In summary, the appearance of skin lesions, even if nonspecific, in an immunosuppressed patient should raise a suspicion of fungal infection. Histological studies of skin lesions can lead to the early detection of certain deep fungal infections, particularly in at-risk patients.

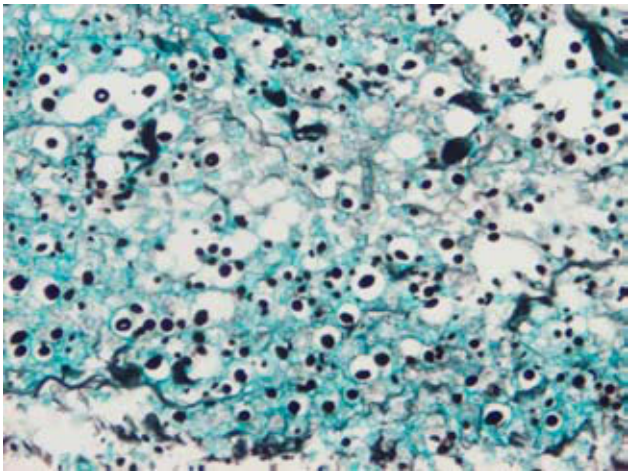

Figure 3 Histological image of cryptococcus spores (silver stain, original magnification ×400).

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Rosacea Triggered by a Vitamin B Complex Supplement

Rosácea desencadenada por un complejo vitamínico del grupo B

To the Editor:

Rosacea is a chronic inflammatory skin condition that preferentially affects the central area of the face. It is characterized by transient episodes of erythema and inflammatory lesions, mostly in the form of papules and pustules. The underlying pathophysiological mechanisms are not known for certain, but it has been postulated that the main mechanisms might be certain vascular disorders and immune responses to infestation by diverse microorganisms, including *Demodex folliculorum*.[1] Rosacea has multiple triggers, including food, emotional states, climate, the application of cosmetic and therapeutic products, and the use of certain systemic drugs.

We describe the case of a 38-year-old woman who consulted for an outbreak of edematous, erythematous papules and plaques and isolated pustules on both cheeks. The lesions had appeared approximately 2 weeks earlier.

The patient had no history of acneiform lesions and reported that she was not taking any regular medication and had not recently been exposed to the sun or applied cosmetics or creams to her face. She did, however, mention that the lesions had appeared 5 days after starting a vitamin B complex supplement (vitamins B_{12} [1 g/d], B_6 [500 mg/d], and B_1 [500 mg/d]) to treat neuropathic pain.

Because the lesions were highly suggestive of rosacea, it was decided not to perform a skin biopsy or request additional tests. The vitamin complex was withdrawn and treatment with sun protection and topical metronidazole was initiated; the lesions improved progressively and resolved completely within 3 weeks. No other outbreaks occurred in the months that followed.

A range of drugs can induce or exacerbate rosacea or acneiform lesions. The best known of these are corticosteroids, especially fluorinated steroids administered topically, orally, or by inhalation.[2] Our review of the literature revealed other drugs that can, albeit less frequently, cause rosacea-like eruptions. Among them, amiodarone[3], oral parabens,[4] acetazolamide,[5] amineptine (an antidepressant),[6] phosphodiesterase-5 inhibitors,[3] and several vitamin B derivatives.[7-10]

Various mechanisms have been linked to rosacea-like eruptions, although most of them involve nitric oxide and prostaglandins.

Specifically, it has been postulated that nitric oxide released following the administration of certain drugs such as phosphodiesterase-5 inhibitors (used to treat impotence) could cause vascular alterations and induce rosacea in genetically predisposed individuals.[3] Another theory is that irritation of the follicular epithelium due to a prolonged, high level of excretion of the responsible drugs (such as those mentioned above) could trigger an inflammatory response.[7]

Vitamin B_3 (niacin) can cause skin flushing, an adverse effect that may limit the use of this vitamin B derivative. Flushing has been associated with the daily ingestion of high doses of B_3.[10] Several studies conducted in rats have shown a dose-dependent increase in vascular permeability in rats treated intradermally with nicotinamide (a co-enzyme containing vitamin B_3) and its metabolite N-methylnicotinamide; the mechanism was believed to involve nitric oxide and prostaglandins.[8]

Vitamins B_2 (riboflavin), B_6 (pyridoxine), and B_{12} (cyanocobalamin) can exacerbate acne vulgaris or trigger an outbreak of acneiform lesions. Vitamin B–induced rosacea is more common in women than in men. It tends to present as disseminated papules and pustules on the face (above all on the forehead and cheeks), although it can also affect the upper part of the chest.[7]

There have also been reports of rosacea fulminans following the administration of vitamin B derivatives; in most of the cases, the reactions were dose-dependent.[7]