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LETTER TO THE EDITORS

Cutaneous tuberculosis mimicking erysipelas of the lower leg in a heart transplant recipient

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Opportunistic infections play a key role in the management of heart transplant recipients. Infections caused by mycobacterium tuberculosis (MTb) are rare, with a reported incidence of about 3% [1]. However, active tuberculosis is associated with a mortality of 31% [2]. Localized cutaneous infection is a rare manifestation of tuberculosis [3]. We present a case with localized cutaneous tuberculosis of the left leg, which was initially misdiagnosed as erysipelas.

A 59-year-old Caucasian male patient presented at our institution with an erythematous, hyperthermal, and doughy swelling of his left forefoot and pain in his upper ankle. Orthotopic heart transplantation because of ischemic cardiomyopathy had been performed 9 months ago. Red maculae and papules extended up to the left knee (Fig. 1a). The patient complained of local pain at rest and general exhaustion, with subfebrile temperatures not exceeding 38 °C. He had no history of tuberculosis and no previous Bacillus Calmette-Guérin (BCG) vaccination. MTb status of the donor is unknown. Before presenting at our department, his general practitioner had treated him with systemic cortisone (20 mg/day) because of suspected recurrent psoriasis vulgaris. White blood cell count ($9500/mm^3$) was within normal range and C-reactive protein (CRP) was slightly increased at 18 mg/l (normal range, <5 mg/l). The patient's maintenance immunosuppressive regimen consisted of cyclosporine (target trough level 200 ng/ml), mycophenolate mofetil (1500 mg b.i.d.), and prednisone (5 mg/day). As an induction regime antithymocyte globulin (ATG, 1.5 mg/kg) and methylprednisolone (1375 mg) had been used. Blood cultures for bacteria and serum polymerase chain reaction (PCR) testing for herpes simplex virus, varicella zoster virus, and cytomegalovirus were negative.

The dermatology consultant's suspected diagnosis was erysipelas; intravenous ampicillin therapy was recommended. Symptoms did not improve, and CRP levels increased up to 58 mg/l. Therefore, after 6 days, antibiotic therapy was switched from ampicillin to clindamycin. Concomitantly, bone infection was ruled out by x-ray and magnetic resonance tomography. Subcutaneous inflammation seen on the latter prompted us to perform skin biopsies from four affected sites. Histology revealed granulomatous inflammation showing histiocytes and multinucleated giant cells in all four samples, suggestive of tuberculosis. Ziehl-Neelsen staining showed no acid-fast bacteria. However, in two specimens, mycobacterium tuberculosis complex was confirmed by real-time PCR testing and analyses of melting curves (Qiagen Artus® Mycobac. diff. LC PCR Kit; Qiagen GmbH, Hilden, Germany). Further differentiation of the Mycobacterium tuberculosis complex into *Mycobacterium tuberculosis*, *M. africanum*, *M. bovis*, *M. microti*, or *M. pinnipedii* was not possible due to low bacterial load. Cultures for mycobacteria from two additional biopsies turned out negative. PCR testing for Leishmania, dermatophyte, Borrelia, herpes simplex virus, and Treponema were negative.

Therefore, a cutaneous manifestation of tuberculosis was diagnosed. An extensive search for other tuberculoid foci was initiated, including thoracic and abdominal computed tomography scans as well as blood and sputum cultures; all results were negative. The QuantiFERON test showed an indeterminate result. Anti-tuberculotic treatment was started using isionazid (300 mg/day), ethambutol (1600 mg/day), and pyrazinamide (2000 mg/day). The patient underwent close surveillance of cyclosporine trough levels and dose adjustment; no rejection episodes were detected. CRP levels normalized within 10 weeks. The cutaneous findings had markedly diminished after 10 weeks (Fig. 1b) and had disappeared by 6 months.

Generally, in solid organ recipients suffering from tuberculosis, 63% show lung involvement, 25% have a disseminated form of tuberculosis, and in 12% extrapulmonary infection has been reported [2]. Cutaneous tuberculosis is mostly a manifestation of systemic disease; therefore, other tuberculoid foci must be ruled out [4]. In the present case, imaging and microbiological testing excluded any systemic tuberculoid infection. The reported spectrum of skin lesions in cutaneous tuberculosis include erythemas, nodules, papules, ulcers, and, rarely, lesions mimicking bacterial cellulitis or erysipelas [3]. Except for ulcers, all these manifestations were seen in our patient.

Proof of cutaneous tuberculosis is a diagnostic challenge because of the low bacterial load [5]. The diagnosis

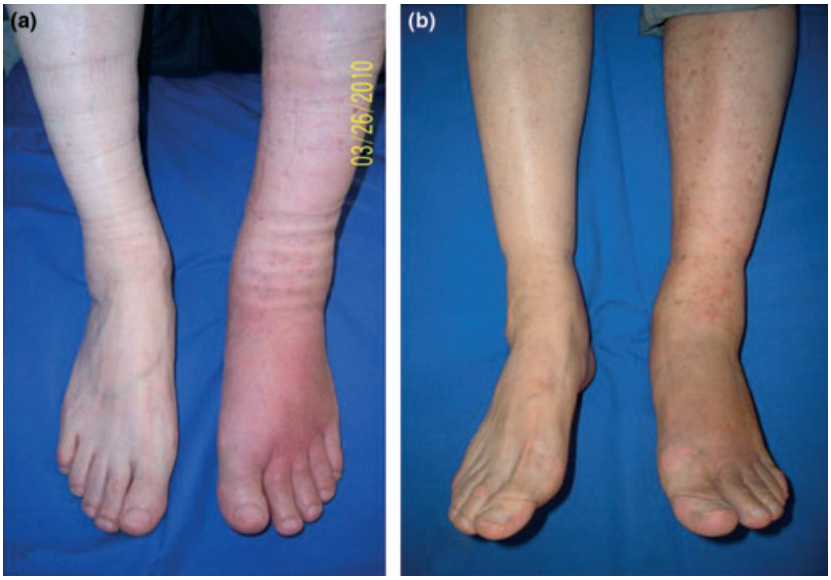

Figure 1 (a) Cutaneous findings before anti-tuberculotic treatment: erythematous, hyperthermal, and doughy swelling of left forefoot, with red maculae and papules on lower leg. Scar from saphenectomy on left leg due to prior coronary-artery bypass grafting. (b) Cutaneous findings after 10 weeks of anti-tuberculotic treatment: erythematous, doughy swelling, and cutaneous findings markedly diminished.

is generally based on the correlation of clinical and histopathologic findings [4]. Real-time PCR has proven to be a sensitive and specific test in patients with cutaneous tuberculosis and allows the differentiation between the mycobacterium tuberculosis complex and nontuberculous mycobacteria (NTM) [6,7]. Sensitivity is reported at 88% and specificity at 83% [6]. PCR-based TBc diagnostics in skin infections has been shown to predict response to anti-tuberculotic treatment better than diagnostics based on culture, immunohistochemistry, and acid-fast bacilli smears [6]. Therefore, PCR diagnostic is a valuable supplement to the standard TBc examinations of cultures and acid-fast bacilli smears [4]. In our patient, PCR was the decisive diagnostic tool, after clinical and histopathological suspicion of cutaneous TBc.

The treatment of choice for cutaneous tuberculosis is medical therapy. For all possible tuberculosis specimens in our patient (*M. tuberculosis*, *M. africanum*, *M. bovis*, *M. microti*, or *M. pinnipedi*), the anti-tuberculotic treatment is the same. Generally, a quadruple regimen of rifampicin, isionazid, pyrazinamide, and ethambutol or streptomycin, is recommended for 2 months, followed by a dual therapy of rifampicin and isionazid for 4 months [4]. In patients receiving calcineurin inhibitor (CNI) based immunosuppression, rifampicin should be used with caution. Close drug-level monitoring is mandatory due to known drug interactions: rifampicin induces the P-450 cytochrome activity and therefore markedly decreases CNI levels, with an associated risk of consecutive acute graft rejection [2,8]. This is why rifampicin was not used in our patient. We started treatment with a triple regimen of isionazid, ethambutol, and pyrazinamide; as the patient responded favorably, this regimen was continued without adding a fourth anti-tuberculotic drug.

In general, isolated cutaneous manifestations of mycobacteria are extremely rare [3]. In a review article on NTM infections in immunosuppressed patients, four cases of local cutaneous infections have been described in heart transplant recipients [9]. Anecdotally, disseminated forms with cutaneous infection of typical mycobacterium tuberculosis complex have also been reported [3,10].

In conclusion, cutaneous lesions in immunocompromised patients that do not resolve under standard therapy should be biopsied for further pathogen detection and histological examination to provide the correct diagnosis. Tuberculosis should always be considered as a differential diagnosis.

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