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CASE REPORT

A Case of Erythema Induratum of Bazin Necessitating Protracted Treatment for Complete Remission: Are We in Need of Disease-Specific Therapy Guidelines?

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ABSTRACT

Erythema induratum of Bazin (EIB) is a rare subcutaneous granulomatous disease that is considered to represent a form of tuberculin hypersensitivity. We present the case of a 74-year-old Bacillus Calmette–Guerin (BCG)-vaccinated female patient, who presented to our dermatology clinic with painful, erythematous purple nodules on the lower extremities. Clinical examination, histopathological analysis, a positive tuberculin skin test (TST) and interferon-gamma release assay (IGRA) supported the diagnosis of EIB. A standard six-month anti-tubercular therapy (ATT) led to improvement of the clinical presentation. However, after discontinuation of ATT, the clinical symptoms and sings relapsed and ATT had to be extended for a total of 10 months to achieve complete remission without relapse for 12 months. Given the lack of established treatment guidelines for the management of EIB, this case underscores the need for prolonged ATT for the effective management of this condition, which is guided by the relevant clinical picture and sometimes goes beyond standardized anti-tubercular treatment protocols.

Keywords: erythema induratum of Bazin, tuberculids, anti-tubercular therapy.

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INTRODUCTION

Exposure to *Mycobacterium tuberculosis* (*M. tuberculosis*) can lead to a variety of outcomes, including primary progressive disease, latent *M. tuberculosis* infection (LTBI), or the development of resistance to *M. tuberculosis* infection. The transition within these clinical presentations is determined by the interplay between bacterial virulence potential and host susceptibility factors, both of which remain under extensive investigation (1-3).

The frequency of extrapulmonary tuberculosis has increased in recent years, with reports indicating a rise from 16.4% to 22.4%. Within the spectrum of extrapulmonary tuberculosis, cutaneous tuberculosis (CTB) is rare, comprising 1.0% to 1.5% of all tuberculosis cases (4). On the other hand, tuberculids lie on the paucibacillary end of the CTB spectrum and some authors do not consider them 'true' CTB (5). Erythema induratum of Bazin (EIB) is a rare tuberculid that accounts for only 0.1% of *M. tuberculosis* manifestations (6). Due to its ability to mimic various skin dermatoses, EIB poses a major diagnostic challenge, especially in countries with a low incidence of tuberculosis. Furthermore, the absence of established treatment protocols leads to the empirical selection of treatment schemes.

Herein, we present a relevant case of EIB in a Bacillus Calmette–Guerin (BCG)-vaccinated patient who required a 10-month anti-tubercular therapy (ATT) to achieve sustained remission of the lesions. ❑

CASE REPORT

A 74-year-old woman presented with a four-month history of three painful ulcerated erythematous purple nodules on the lower limbs without lymphadenopathy (Figure 1A). She reported no systemic symptoms or local trauma and had BCG vaccination during childhood. The differential diagnosis included EIB, nodular vasculitis, erythema nodosum, inflammatory panniculitis, cutaneous lymphoma, cutaneous polyarteritis nodosa and lupus profundus. Histopathologic analysis of an incisional biopsy from the left calf showed a diffuse septolobular panniculitis, with granulomatous inflammation, vasculitis, focal necrosis and septal fibrosis (Figure 2A-B). Ziehl–Neelsen staining for acid-fast bacilli was negative as well as direct immunofluorescence for the presence of immunoglobulins or complement.

Laboratory tests revealed anemia [hemoglobin (Hb) 11.3 mg/dL, normal 11.8-17.8], elevated erythrocyte sedimentation rate (44 mm/h, normal<30) and C-reactive protein (17 mg/L, normal <6). Immunological, viral profile, tissue cultures and lesional tissue polymerase chain reaction (PCR) for *M. tuberculosis* was also negative. The Mantoux tuberculin skin test (TST) was strongly positive (21-mm skin induration at 48 hours). The interferon-gamma release assay (IGRA) yielded a positive result, supporting *M. tuberculosis* sensitization and ruling out BCG vaccination as a possible cause of the findings (7). Relevant to tuberculosis imaging procedures (chest X-ray, computed tomography) were also negative. Likewise, bronchoalveolar lavage and PCR of consecutive urine samples were also negative for *M. tuberculosis*.

The provisional diagnosis of EIB was made and the patient was initiated on the standard six-month weight-based oral anti-tubercular therapy (ATT), consisting of two months isoniazid 300 mg o.d. with vitamin B_6 25 mg o.d. supplementation, rifampin 600 mg o.d., ethambutol 1.2 g o.d. and pyrazinamide 1.5 g o.d., followed by four months of isoniazid 300 mg o.d. with vitamin B_6 25 mg o.d. and rifampin 600 mg o.d.

A significant improvement was observed within one month of ATT. At the end of the six-month therapy, the skin lesions, excepting the nodule on the left calf, had healed, leaving atrophic scars and post-inflammatory hyperpigmentation. Despite the development of ulceration on this nodule (Figure 1B), we followed the guidelines (8, 9) and the ATT was discontinued. The patient returned after one month with recurring pain in this residual nodule and enlargement (Figure 1C). Therapy (rifampicin 600 mg o.d. and isoniazid 300 mg o.d.) was resumed for additional four months (10 months in total), during which the above-mentioned nodule gradually regressed and healed, leaving post-inflammatory hyperpigmentation (Figure 1D). No adverse events were observed during treatment. No signs of recurrence were noted at the 12-month follow-up. ❑

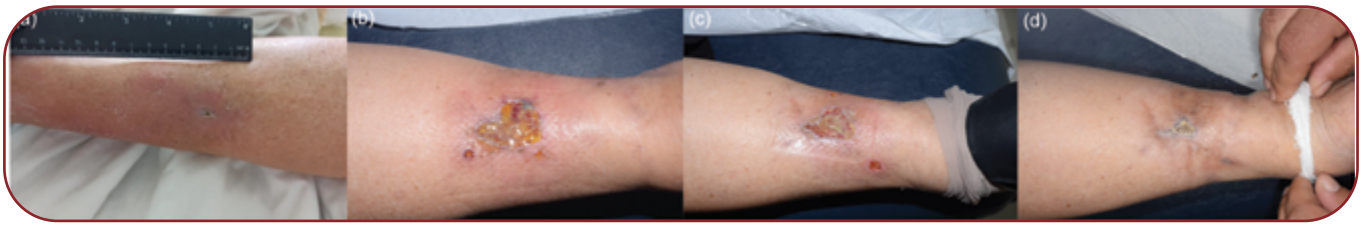

FIGURE 1. Well-demarcated purple, indurated, painful 3x3 cm nodule on the posterior aspect of the distal third of the left leg. A) Clinical image on day 1; B) Clinical image after six-month antitubercular therapy – the nodule on the left calf progressed to ulcer; C) One month without antitubercular therapy – the ulcerated nodule increased in size and became painful; D) The patient continued antitubercular therapy (rifampicin and isoniazid) for four more months, during which the nodule gradually regressed and healed, leaving post-inflammatory hyperpigmentation.

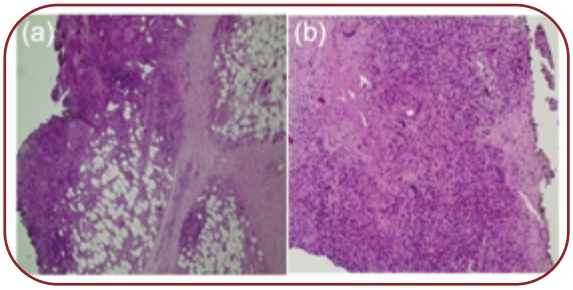

FIGURE 2. Histopathologic analysis of an incisional biopsy from the left calf. A) Septolobular panniculitis with thickened septae (H&E X40); B) Granulomas with multinucleated Langhans giant cells (H&E X100)

DISCUSSION

The herein presented case of EIB draws attention to the rapid relapse of symptoms and signs of EIB within one month after discontinuation of the antituberculosis treatment, which necessitated the extension of medication beyond the time recommended in current guidelines (8, 9).

The present case underscores the need to further explore the pathobiological background of EIB within the spectrum of tuberculids, that are currently not considered as true manifestations of cutaneous tuberculosis (CTB), but rather as a diverse collection of clinical conditions resulting from an exaggerated host response to degenerated dead bacilli or antigenic components of *M. tuberculosis* (10-12). Therefore, they are typically observed in individuals with strong cell-mediated immunity, as indicated by positive tuberculin skin and IGRA test (10). Likewise, EIB is considered to represent a cutaneous delayed hypersensitivity reaction to *M. tuberculosis* antigens in patients with strong cell-mediated anti-*M. tuberculosis* immunity (6, 11, 13-15).

The relationship between tuberculosis and EIB has been previously debated as *M. tuberculosis* was rarely cultured and isolated from tuberculid lesions, mainly due to the low bacteria load and the host's robust immune response (7, 16). However, detection of *M. tuberculosis* DNA in skin lesions of EIB patients by PCR suggests the tuberculous aetiology of EIB (7, 16, 17). It is noteworthy that our patient was BCG vaccinated in the past, albeit several years prior to the appearance of the lesions. Although some cases of erythema induratum have been reported after BCG exposure, they are less common than cases associated with tuberculosis (18-20). To rule out the possibility of BCG-induced erythema induratum or a false positive cross -reaction of the TST due to BCG vaccination, an IGRA was conducted, which revealed sensitization to *M. tuberculosis* rather than BCG exposure (7).

Currently, there are no established criteria for the treatment of EIB. The available ATT evidence on the treatment of EIB comes primarily from observational studies conducted in countries with a high incidence of tuberculosis, often with inadequate clinical surveillance. The long duration of standard tuberculosis treatment and the associated healthcare costs and likelihood of ATT-induced adverse events, further complicate decision making regarding the appropriate treatment (8). A retrospective analysis of 21 cases of Bazin's erythema induratum over an 11-year period found that clinical improvement or complete resolution of EIB was achieved in 76% of cases with ATT. The median duration of treatment was six months, with a range of five to nine months (8). Treatment discontinuation of EIB due to severe adverse effects, single or two-drug ATT, low patient's compliance, lost to follow-up and possible drug resistance may contribute to

ATT non response or relapse. Erythema induratum of Bazin may require longer treatment protocols especially if recurrence occurs (21). Recurrence of EIB may be related to several factors. These include the persistence of an extracutaneous dormant source that has not been completely eradicated, or the persistence of antigens even after treatment. In addition, the combination of obesity and local hemodynamic conditions, such as impaired blood flow in the lower limbs, may create circumstances that favor reactivation of EIB lesions (5). To address these features of EIB some authors suggest prolonging treatment with isoniazid for up to two years (10,11). This was also evident in our case with the rapid relapse of EIB after premature discontinuation of treatment and the need to extend therapy beyond the standard protocol suggested for the treatment of active tuberculosis.

The diagnosis of EIB and its association with TB is based on exclusion criteria and is supported by the clinical features of the lesions, histopathological findings, evidence of *M. tuberculosis* infection and response to ATT (16, 22, 23). However, failure to detect *M tuberculosis* by PCR does not exclude the diagnosis of EIB. A false negative PCR test may be due to insufficient target DNA or technical problems such as diminished PCR amplification (7, 16). Of note, a positive *M. tuberculosis* DNA from a biopsy sample varies between 25% and 77% (4, 24). In the present case, no *M. tuberculosis* DNA was detected in lesional skin tissue, bronchial lavage and urine samples. However, the diagnosis was supported by the typical skin lesions, the characteristic histopathological findings, the strongly positive TST and IGRA results as well as the rapid and favorable response to targeted therapy (13, 16, 22, 23, 25, 26). The rapid relapse of symptoms after discontinuation therapy and the response after resumption of anti-tuberculosis therapy also are in favor of the suggested diagnosis. ❑

CONCLUSION

The presented case underscores the need for disease specific guidelines pertaining to EIB that also accommodate the complex pathophysiology that underlies this condition. EIB represents a cutaneous delayed hypersensitivity reaction to *M. tuberculosis* antigens and lies within the spectrum of tuberculids, a diverse collection of clinical conditions resulting from an exaggerated host response to degenerated dead bacilli or antigenic components of *M. tuberculosis*. Presently, the rapid relapse of symptoms and signs of EIB within one month after discontinuation of the ATT dictated the extension of treatment beyond the timeline recommended in current guidelines.

As in our case the diagnosis is not always evident and *M. tuberculosis* cannot always be detected by PCR. This fact in conjunction with the absence of established treatment guidelines challenges the application of optimal treatment plans. This could constitute a burden to patients and physicians in areas with low tuberculosis prevalence, as the herein presented case. ❑

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