CASE REPORT

Not the usual suspect: a case of erythema induration of Bazin in an urban primary care clinic

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Frontline clinicians in the United States, especially those working in safety net hospitals or with immigrant populations, will likely see cutaneous tuberculosis given the tremendous burden of tuberculosis infection worldwide. The tuberculid is a subtype of cutaneous tuberculosis that poses a diagnostic challenge because organisms are not found in smears or cultures taken from the lesions. Tuberculid lesions can mimic erythema nodosum, thrombophlebitis, and cellulitis. We describe the case of a 57-year-old woman immigrant from China who presented with tender, subcutaneous nodules on her ankle and thigh in the setting of prior exposure to tuberculosis. We describe the clinical, pathophysiologic, and histopathologic features of tuberculids in order to raise awareness among primary care clinicians about this difficult to diagnose but readily treatable manifestation of tuberculosis.

Keywords: erythema induratum of Bazin; tuberculids; cutaneous tuberculosis; mycobacterial skin disease; primary care of vulnerable populations

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Cutaneous disease accounts for only 1–2% of cases of tuberculosis (1). However, since one-third of the world’s population is infected with Mycobacterium tuberculosis, frontline clinicians, especially those who work in safety net hospitals or serve immigrant populations, need to be familiar with the varied clinical presentations of cutaneous tuberculosis. Several classification systems exist for describing cutaneous tuberculosis. A widely used nomenclature is based on the route of inoculation: primary infection due to direct inoculation from an exogenous source (e.g., reseptor’s wart), secondary infection from an endogenous source (e.g., scrofuloderma), and cutaneous hypersensitivity reaction to antigen, presumably related to an extracutaneous focus of infection (2, 3). Lesions in this last category are referred to as tuberculids and are of four subtypes: lichen scrofulosorum, papulonecrotic tuberculid, nodular tuberculid, and erythema induratum of Bazin (EIB). The tuberculids can be particularly challenging to diagnose because M. tuberculosis organisms are not found in smears or cultures taken from the lesions. We present a case of tuberculids (subtype: EIB) to heighten awareness among primary care clinicians of its key features. In some parts of the world, EIB accounts for a significant proportion of cases of cutaneous tuberculosis had EIB (4). In South Africa, a review of 92 cases of cutaneous tuberculosis revealed 20 cases of EIB (5). However, EIB is rarely reported in the United States, suggesting possible underdiagnosis, particularly in communities with high numbers of immigrants from endemic countries. Including tuberculids in the differential diagnosis of characteristic chronic, non-healing skin lesions will avoid unnecessary suffering and societal cost, as these lesions often respond readily to antituberculosis chemotherapy.

Case report

A 57-year-old woman presented to our primary care clinic with tender, subcutaneous nodules on her right ankle and right thigh of 2 months duration. The lesions had begun as 1–2 mm reddish papules that progressed into 2–3 cm nodules. She denied insect bites, local trauma, or the use of new cosmetic products. Her medical history consisted of well-controlled asthma. Her only medication was inhaled albuterol. She had received a Bacille Calmette–Guerin vaccine during childhood. She had emigrated from China 20 years ago. Her husband had been successfully treated for pulmonary tuberculosis.
tuberculosis 30 years ago. She herself had never received a diagnosis of latent or active tuberculosis. She had no history of substance abuse.

Physical examination revealed three dusky, reddish, ill-defined, edematous subcutaneous nodules (2–3 cm) proximal to her right medial malleolus (Fig. 1). The lesions were slightly tender and cool to touch. There were subcentimeter lesions of similar appearance scattered along the medial right thigh. There was no lymphadenopathy. The remainder of the physical examination was normal.

Bacterial and fungal infections, vasculitis, thrombophlebitis, erythema nodosum, and sarcoid were considered in the differential diagnosis. A complete blood count, basic serum chemistry, and erythrocyte sedimentation rate were normal. Serum complement levels and serologies for antineutrophil cytoplasmic antibodies, antineutrophil antibodies, and rheumatoid factor were normal. Antibodies to hepatitis B and C and HIV were negative. A plain film of the chest was normal. The excisional biopsy of one of the lesions revealed granulomas in the subcutaneous fat, surrounded by fibrosis and reactive changes (Fig. 2). At this point, cutaneous tuberculosis was suspected. An interferon gamma release assay was positive for \( M. \text{tuberculosis} \), signifying infection. However, mycobacterial staining and culture of tissue for acid-fast bacilli (AFB) were negative. Polymerase chain reaction (PCR) applied to the tissue failed to detect \( M. \text{tuberculosis} \) DNA. Bacterial and fungal cultures of tissue were also negative. A CT scan of the thorax to evaluate for occult pulmonary tuberculosis was normal.

We decided to treat the patient for presumptive cutaneous tuberculosis because of the histopathologic findings of granulomas in the setting of the patient’s immigration from an endemic area, history of exposure to active tuberculosis (spouse), and positive interferon gamma release assay. Eight weeks after beginning treatment with pyrazinamide, rifampin, ethambutol, and isoniazid, the lesions had completely resolved. The patient received a total of 9 months of treatment and has had no recurrence during 3 years of follow-up.

Discussion

Our patient was initially diagnosed clinically to have cellulitis due to either \( S. \text{aureus} \) or beta-hemolytic streptococci. Failure of clindamycin, histologic findings on skin biopsy, and negative cultures were needed to clarify the diagnosis. Cutaneous lesions that contain granulomas but from which \( M. \text{tuberculosis} \) organisms cannot be isolated, in the setting of sensitization to \( M. \text{tuberculosis} \) and with response to antituberculous therapy, is consistent with tuberculids. The EIB subtype of tuberculid typically presents as chronic, erythrocyanotic, indurated, and sometimes ulcerated nodules on the legs, without purulent drainage. The majority of cases are in women. The lesions are characteristically cool to touch, which helps to distinguish them from common bacterial infections. By appearance, the lesions can be easily confused with erythema nodosum. On skin biopsy, granuloma is found in the subcutaneous fat.

Tuberculids were first described in 1896 by Jean Durier in a case series of patients with cutaneous lesions.
who exhibited exceptionally intense cutaneous reactions to tuberculin (6). All had previously recovered from active tuberculosis. All available tests for identifying *M. tuberculosis* in the lesions were negative. Tuberculids are currently understood to be a cutaneous hypersensitivity reaction to *M. tuberculosis* antigen mediated by T-cell following hematogenous spread to skin from an extracutaneous site of past or current *M. tuberculosis* infection (7, 8). In a case series, 4 of 26 patients had a personal history of active tuberculosis, whereas 6 of 26 had a family member with active tuberculosis (7). Tuberculids occur almost exclusively in patients with intact immune systems, as manifested by a strong reaction to the tuberculin skin test; all 26 patients in a case series had >20 mm of induration at the injection site, and non-specific markers of inflammation such as the erythrocyte sedimentation rate may be increased (7). Despite the inability to directly visualize by stain or to culture *M. tuberculosis* in tuberculid lesions, the etiologic link between tuberculids and *M. tuberculosis* is supported by the fact that *M. tuberculosis* DNA has been recovered by PCR from tuberculid lesions (9, 10). In addition, tuberculid lesions frequently resolve concurrent with antituberculosis chemotherapy (11). The detection of *M. tuberculosis* DNA from biopsy specimens by PCR has been reported in 25–77% of patients with EIB (9, 11). The subtypes of tuberculids can be distinguished by means of histopathologic analysis; granulomas are seen at different depths within the cutaneous tissue (Table 1).

Patients diagnosed with tuberculids should be evaluated for a non-cutaneous focus of active tuberculosis infection. A review of 66 Japanese patients with tuberculids found that 30 had concurrent extracutaneous infection (14).

Much still needs to be learned about optimal treatment of tuberculids. If left untreated, lesions typically follow a chronic course, with eruptions several times per year (13). Lesions respond temporarily to antiinflammatory agents, such as steroids (15). Observational studies show that multidrug antituberculous therapy speeds up resolution of lesions and decreases recurrences (11). The World Health Organization recommends that cutaneous tuberculosis be treated no differently than pulmonary disease (16).

### Conclusions

Tuberculids are a form of cutaneous tuberculosis characterized by a hypersensitive reaction to the *M. tuberculosis* antigen. Patients are likely to present first to primary care clinicians with chronic skin lesions characteristic in appearance and distribution of one of the four subtypes of tuberculids. Lesions are characteristically cool to touch, which helps to distinguish them from clinical mimics, such as cellulitis. A purified protein derivative (PPD) or interferon gamma release assay test should be performed if risk factors for tuberculosis are present. Patients diagnosed with tuberculids should be thoroughly evaluated for a non-cutaneous focus of tuberculous infection. Tuberculids can be particularly challenging to diagnose because commonly *M. tuberculosis* cannot be detected by any method in lesions nor can extracutaneous disease always be found. The generally accepted criteria for making the diagnosis of tuberculids are a positive PPD or interferon gamma release assay, negative AFB stains and negative culture for *M. tuberculosis*, and resolution of lesions with antituberculous therapy (17). The prognosis of tuberculids is excellent with adequate antituberculous treatment.

### Disclosures

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### References

1. Kandola P, Meena LS. Extra-pulmonary tuberculosis: Overview, manifestations, diagnostic and treatment techniques. Adv Mater Rev 2014; 1(1): 13–19.
2. Jordaan HF, Schneider JW, Abdulla EA. Nodular tuberculid: A report of four patients. Pediatr Dermatol 2000; 17(3): 183–8.
3. Savin JA. Mycobacterial infections. In: Rook A, Wilkinson DS,.;. dermatology. 5th ed. Oxford: Blackwell; 1992, p. 1033–63.
4. Ho CK, Ho MH, Chong LY. Cutaneous tuberculosis in Hong Kong: An update. Hong Kong Med J 2006; 12(4): 272–7.
5. Visser AJ, Heyl T. Skin tuberculosis as seen at Gu-Ranikuwa Hospital. Clin Exp Dermatol 1993; 18(6): 507–15.
6. Darier MJ. Des “tuberculides” cutanées. Ann Dermatol Syph 1896; 7: 1431–6.
7. Rademaker M, Lowe DG, Munro DD. Erythema induratum (Bazin's disease). J Am Acad Dermatol 1988; 21(4 Pt 1): 740–5.
8. Cho KH, Lee DY, Kim CW. Erythema induratum of Bazin. Int J Dermatol 1996; 35(11): 802–8.
9. Baselga E, Margall N, Barnadas MA, Coll P, de Moragas JM. Detection of MTB DNA in lobular granulomatous panniculitis (erythema induratum–nodular vasculitis). Arch Dermatol 1997; 133(4): 457–62.
10. Victor T, Jordaan HF, Van Niekerk DJ, Louw M, Jordaan A, Van Helden PD. Papulonecrotic tuberculid. Identification of Mycobacterium tuberculosis DNA by polymerase chain reaction. Am J Dermatopathol 1992; 14(6): 491–5.
11. Schneider JW, Jordaan HF, Geiger DH, Victor T, Van Helden PD. Erythema induratum of Bazin: A clinicopathological study of 20 cases and detection of MTB DNA in skin lesions by polymerase chain reaction. Am J Dermatopathol 1995; 17(4): 350–6.
12. Frankel A, Penrose C, Emer J. Cutaneous tuberculosis, a practical case report and review for the dermatologist. J Clin Aesthet Dermatol 2009; 2(10): 19–27.
13. Mascaró JM Jr, Baselga E. Erythema induratum of Bazin. Dermatol Clin 2008; 26(4): 439–45.
14. Shimizu A, Takahashi A, Negishi I, Tamura A, Ishikawa O. The close association of Lymphadenitis tuberculosa and Erythema induratum of Bazin in Japanese patients. Dermatology 2003; 207(4): 426–7.
15. Förström L, Hannuksela M. Antituberculous treatment of erythema induratum Bazin. Acta Derm Venereol 1970; 50(2): 143–7.
16. World Health Organization (2010). Treatment of tuberculosis: Guidelines. 4th ed. Geneva: World Health Organization.
17. Sethuraman G, Ramesh V, Ramani M, Sharma VK. Skin tuberculosis in children: Learning from India. Dermatol Clin 2008; 26(2): 285–94.