

Disseminated Erythema Induratum in a Patient With a History of Tuberculosis

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PRACTICE POINTS

- Erythema induratum is an uncommon panniculitis attributed to a delayed-type hypersensitivity reaction, classically to *Mycobacterium tuberculosis*.
- The workup for such patients with exposure to both *M tuberculosis* and bacillus Calmette-Guérin should include IFN- γ release assays.
- Clinicians should be aware of the disseminated variant of erythema induratum and the laboratory testing needed to establish a cause and help direct treatment.

To the Editor:

Erythema induratum, also known as nodular vasculitis, is a panniculitis that usually affects the lower extremities in middle-aged women. Classically, it has been described as a delayed-type hypersensitivity reaction to *Mycobacterium tuberculosis*, also known as a tuberculid.^{1,2} Other infections, however, also have been implicated as causes of erythema induratum, including bacillus Calmette-Guérin (BCG), the attenuated form of *Mycobacterium bovis*, which commonly is used for tuberculosis vaccination. Medications also may cause erythema induratum. The characteristic distribution of the nodules on the posterior calves helps to distinguish erythema induratum from other panniculitides. A PubMed search of articles indexed for MEDLINE using the term *disseminated erythema induratum* revealed few case reports documenting nodules on the arms, thighs, or chest, and only 1 case report of disseminated erythema induratum.³⁻⁸ We

describe a rare combination of disseminated erythema induratum in a patient with remote exposure to tuberculosis and recent BCG exposure.

An 88-year-old woman presented for evaluation of violaceous, minimally tender, nonulcerated, subcutaneous nodules on the legs, arms, and trunk of several weeks' duration (Figure 1). She had a remote history of tuberculosis as a child, prior to the

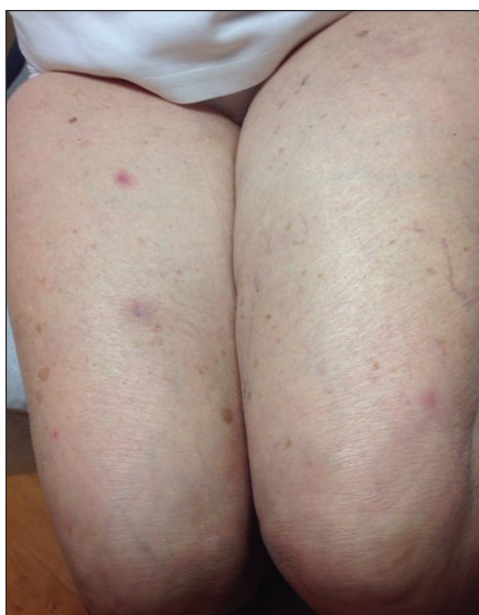


FIGURE 1. Disseminated erythema induratum in a patient with a history of tuberculosis. Violaceous, minimally tender, nonulcerated, subcutaneous nodules were present on the legs.

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advent of modern antituberculosis regimens. Her medical history also included hypertension, breast cancer treated with lymph node dissection, gastroesophageal reflux disease, and bladder cancer treated with intravesical BCG 10 years prior to the onset of the nodules. She reported minimal coughing and a 25-lb weight loss over the last year, but she denied night sweats, fever, or chills.

Workup included a biopsy, which showed a dense inflammatory infiltrate within the septae and lobules of the subcutaneous tissue (Figure 2A). Foci of necrosis were seen within the fat lobules (Figure 2B). The histologic diagnosis was erythema induratum. Tissue cultures for bacteria, fungi, and atypical mycobacteria were negative. *Mycobacterium tuberculosis* polymerase chain reaction (PCR) analysis also was negative. An IFN- γ release assay test was positive for infection with *M tuberculosis*, suggesting that the erythema induratum was due to tuberculosis rather than BCG exposure. A chest radiograph demonstrated a 22-mm nodule in the left lung (unchanged from a prior film) and a new 10-mm nodule in the left upper lobe.

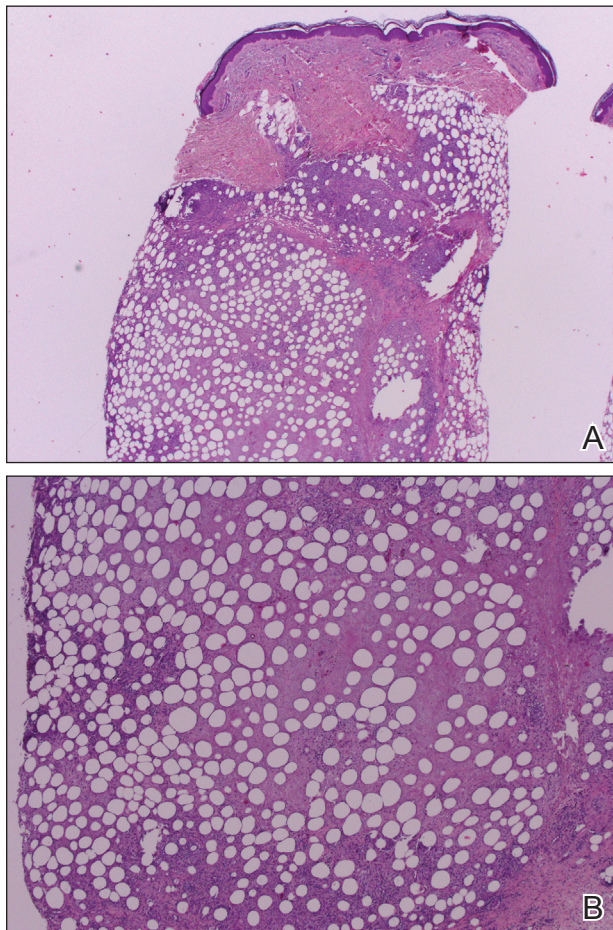


FIGURE 2. A, Histopathology showed septal and lobular panniculitis (H&E, original magnification $\times 20$). B, There was granulomatous inflammation with focal necrosis within lobular adipose tissue (H&E, original magnification $\times 40$).

The patient was referred to an infectious disease specialist who concurred that the erythema induratum and the new lung nodule likely represented a reactivation of tuberculosis. Sputum samples were found to be smear and culture negative for mycobacteria, but due to high clinical suspicion, she was started on a 4-drug tuberculosis regimen of isoniazid, rifampin, pyrazinamide, and ethambutol. Some lesions had started to improve prior to the institution of therapy; after initiation of treatment, all lesions resolved within 4 weeks of starting treatment without recurrence.

Erythema induratum was first described by Bazin⁹ in 1861. The disorder usually occurs in middle-aged women and is characterized by violaceous ulcerative plaques that classically present on the lower extremities, especially the calves. When the eruption occurs due to a nontuberculous etiology, the term *nodular vasculitis* is used.^{1,5} The distinction largely is historical, as most dermatologists today recognize erythema induratum and nodular vasculitis to be the same entity. Examples of nontuberculous causes include infections such as *Nocardia*, *Pseudomonas*, *Fusarium*, or other *Mycobacterium* species.¹⁰ Medications such as propylthiouracil also have been implicated.¹¹ The classification of erythema induratum as a tuberculid suggests that the nodules are a reaction pattern rather than a primary infection, though the term *tuberculid* may be imprecise. The differential diagnosis of violaceous nodules on the lower extremities and trunk is broad and includes erythema nodosum, cutaneous polyarteritis nodosa, pancreatic panniculitis, subcutaneous T-cell lymphoma, and lupus profundus.^{1,11,12}

Histologically, lesions classically demonstrate a mostly lobular panniculitis with varying degrees of septal fibrosis and focal necrosis. Neutrophils may predominate early, while adipocyte necrosis, epithelioid histiocytes, multinucleated giant cells, and lymphocytes may be found in older lesions. The presence of vasculitis as a requisite diagnostic criterion remains controversial.^{1,12}

The incidence of erythema induratum has decreased since multidrug tuberculosis treatment has become more widespread.³ Our case displayed the disseminated variant of erythema induratum, an even rarer clinical entity.⁸ Interestingly, our patient had a history of tuberculosis and exposure to BCG prior to the development of lesions. Case reports have documented erythema induratum after BCG exposure but less frequently than in cases associated with tuberculosis.^{3,13}

The use of BCG vaccines has necessitated the need for a more precise method of determining tuberculosis activity. The tuberculin skin test reacts positively with a history of BCG exposure, rendering it an inadequate test in a patient who is suspected of having an active or latent *M tuberculosis* infection.^{13,14} IFN- γ release assays are more specific in detecting latent or active tuberculosis than the tuberculin skin test. Such assays use early secretory antigenic target 6 and cultured filtrate

protein 10 as antigens to determine sensitization to *M tuberculosis*.^{13,15} These antigens are not produced by BCG or *Mycobacterium avium*; however, other mycobacteria such as *Mycobacterium marinum*, *Mycobacterium kansasii*, and some strains of *M bovis* produce the aforementioned antigens, and exposure to these microbes may be confounding.¹³ Importantly, positive IFN- γ release assay results also have been documented after BCG exposure but occur at a much lower frequency than for tuberculosis.¹⁵ Thus, the combination of the positive IFN- γ release assay and new chest radiograph nodule in our patient provided strong evidence of reactivated tuberculosis as the precipitating cause of her skin disease.

Despite her negative PCR study, our patient's presentation remains consistent with the diagnosis of disseminated erythema induratum.^{13,15} The value of PCR studies in establishing the diagnosis remains to be determined. Case reports have described positive PCR results detecting *M tuberculosis* in panniculitic nodules, suggesting that trace amounts of the organism are present in lesional tissue despite the negative culture result and immunostains.¹ Tuberculid reactions, including lichen scrofulosorum, papulonecrotic tuberculid, and erythema induratum, historically are defined by the lack of positive cultures and immunostains, making positive PCR results difficult to reconcile pathophysiologically.^{1,13} Therefore, use of the term *tuberculid* altogether as a descriptor for pathogenesis of this disease may need to be avoided.¹⁶ Postulated explanations for the relationship of tuberculid diseases and negative cultures and immunostains include the presence of a small number of bacilli that escape routine laboratory detection, early destruction of organisms, or a reaction to circulating *M tuberculosis* fragments.² Regardless, until the pathophysiology of erythema induratum has been fully elucidated, the value of PCR remains unclear.

Disseminated erythema induratum, an exceptionally rare variant of panniculitis, may be seen in patients with a remote history of *M tuberculosis* exposure and/or recent therapeutic BCG exposure. It is imperative to rule out active tuberculosis, especially in elderly patients whose disease predated the advent of modern antituberculosis therapy. Using an IFN- γ release assay in addition

to chest radiographs and other clinical stigmata allows differentiation of the etiology of erythema induratum in those patients with tuberculosis who also were treated with BCG.

REFERENCES

- Mascaro JM, Basalga E. Erythema induratum of Bazin. *Dermatol Clin*. 2008;28:439-445.
- Lighter J, Tse DB, Li Y, et al. Erythema induratum of Bazin in a child: evidence for a cell-mediated hyper-response to *Mycobacterium tuberculosis*. *Pediatr Infect Dis J*. 2009;28:326-328.
- Inoue T, Fukumoto T, Ansai S, et al. Erythema induratum of Bazin in an infant after bacilli Calmette-Guerin vaccination. *J Dermatol*. 2006;33:268-272.
- Degonda Halter M, Nebiker P, Hug B, et al. Atypical erythema induratum Bazin with tuberculous osteomyelitis. *Internist*. 2006;47:853-856.
- Gilchrist H, Patterson JW. Erythema nodosum and erythema induratum (nodular vasculitis): diagnosis and management. *Dermatol Ther*. 2010;23:320-327.
- Sharma S, Sehgal VN, Bhattacharya SN, et al. Clinicopathologic spectrum of cutaneous tuberculosis: a retrospective analysis of 165 Indians. *Am J Dermatopathol*. 2015;37:444-450.
- Sethuraman G, Ramesh V. Cutaneous tuberculosis in children. *Pediatr Dermatol*. 2013;30:7-16.
- Teramura K, Fujimoto N, Nakanishi G, et al. Disseminated erythema induratum of Bazin. *Eur J Dermatol*. 2014;24:697-698.
- Bazin E. *Extrait des Leçons Théoriques et Cliniques sur le Scrofula*. 2nd ed. Paris, France: Delhaye; 1861.
- Campbell SM, Winkelmann RR, Sammons DL. Erythema induratum caused by *Mycobacterium chelonae* in an immunocompetent patient. *J Clin Aesthet Dermatol*. 2013;6:38-40.
- Patterson JW. Panniculitis. In: Bologna JL, Jorizzo J, Rapini RP, et al, eds. *Dermatology*. Barcelona, Spain: Mosby Elsevier; 2012:1641-1662.
- Segura S, Pujol R, Trinitade F, et al. Vasculitis in erythema induratum of Bazin: a histopathologic study of 101 biopsy specimens from 86 patients. *J Am Acad Dermatol*. 2008;59:839-851.
- Vera-Kellet C, Peters L, Elwood K, et al. Usefulness of interferon- γ release assays in the diagnosis of erythema induratum. *Arch Dermatol*. 2011;147:949-952.
- Prajapati V, Steed M, Grewal P, et al. Erythema induratum: case series illustrating the utility of the interferon- γ release assay in determining the association with tuberculosis. *J Cutan Med Surg*. 2013;17:S6-S11.
- Sim JH, Whang KU. Application of the QuantiFERON-Gold TB test in erythema induratum. *J Dermatolog Treat*. 2014;25:260-263.
- Wiebels D, Turnbull K, Steinkraus V, et al. Erythema induratum Bazin. "tuberculid" or tuberculosis? [in German]. *Hautarzt*. 2007;58:237-240.