Tuberculous Cellulitis: Diseases Behind Cellulitislike Erythema

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PRACTICE **POINTS**

- Most cases of cutaneous tuberculosis are not associated with pain; however, some cases of tuberculous cellulitis have pain and tenderness.
- Tuberculous cellulitis should always be included in the differential diagnosis of a cellulitislike rash if the skin lesion is not improved despite standard antibiotic therapy.

An 89-year-old man presented with an inflammatory erythematous plaque on the left thigh that closely mimicked cellulitis. Empiric therapies with ordinary antibiotics were not effective. A skin biopsy showed epithelioid cell granulomas throughout the dermis and subcutis. Ziehl-Neelsen stain revealed numerous acid-fast bacilli. Additionally, Mycobacterium tuberculosis *was isolated from a skin biopsy specimen as well as gastric fluid and sputum cultures. He was diagnosed with tuberculous cellulitis with pulmonary tuberculosis. Cellulitis is a common disease seen by dermatologists; however, sometimes other diseases may masquerade as this banal illness. Among them, cutaneous tuberculosis should be excluded because of its clinical significance. Most cases of cutaneous tuberculosis are symptom free, but tuberculous cellulitis is sometimes painful. Therefore, cutaneous tuberculosis should always be considered in the differential diagnosis of a cellulitislike rash if the lesions do not respond to ordinary antibiotic therapy, especially in countries with a high incidence of tuberculosis.*

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Local tender erythema is a typical manifestation of cellulitis, which is commonly seen by dermatologists; however, cutaneous manifestations of other diseases may bear resemblance to the more banal cellulitis. We present the case of a patient with tuberculous cellulitis, a rare variant of cutaneous tuberculosis.

Case Report

An 89-year-old man presented to a local primary care physician with a fever (temperature, 38°C). Infectious disease was suspected. Antibiotic therapy with oral cefaclor and intravenous cefotiam hydrochloride was started, but the patient's fever did not subside. Six days after initiation of treatment, he was referred to our dermatology department for evaluation of a painful erythematous rash on the left thigh that had suddenly appeared. The patient had a history of pulmonary tuberculosis 71 years prior. He also underwent surgical treatment of pancreatic cancer 14 years prior. Additionally, he had chronic kidney disease (CKD) and polymyalgia rheumatica, which was currently being treated with oral prednisolone 5 mg once daily.

Physical examination revealed a hot and tender erythematous plaque on the left thigh (Figure 1). The edge of the lesion was not well defined and there was no regional lymphadenopathy.

A complete blood cell count revealed anemia (white blood cell count, 8070/μL [reference range, 4000–9,000/μL]; neutrophils, 77.1%

[reference range, 44%–74%]; lymphocytes, 13.8% [reference range, 20%–50%]; hemoglobin, 9.3 g/dL [reference range, 13.0–17.0 g/dL]; and platelet count, $329\times10^3/\mu L$ [reference range, $150–400\times10^3/\mu L$]). The C-reactive protein level was 7.3 mg/dL (reference range, 0.08–0.3 mg/dL). The creatinine level was 2.93 mg/dL (reference range, 0.6–1.2 mg/dL). There were no signs of liver dysfunction.

A blood culture was negative. A purified protein derivative (tuberculin) skin test was negative (6×7 mm [reference range, ≤9 mm). A chest computed tomography (CT) scan showed small centrilobular nodules that had not changed in number or size since evaluation 3 months prior.

The antibiotics were changed to meropenem hydrate 0.5 g and clindamycin 300 mg twice daily for presumed bacterial cellulitis, then meropenem hydrate 1 g and clindamycin 600 mg daily, but there was still no improvement after about 1 week. Therefore, a skin biopsy was performed on the left thigh. The specimen showed epithelioid cell granulomas throughout the dermis and subcutis (Figure 2). Ziehl-Neelsen stain revealed numerous acid-fast bacilli (Figure 3). Polymerase chain reaction was positive for *Mycobacterium tuberculosis* in the skin

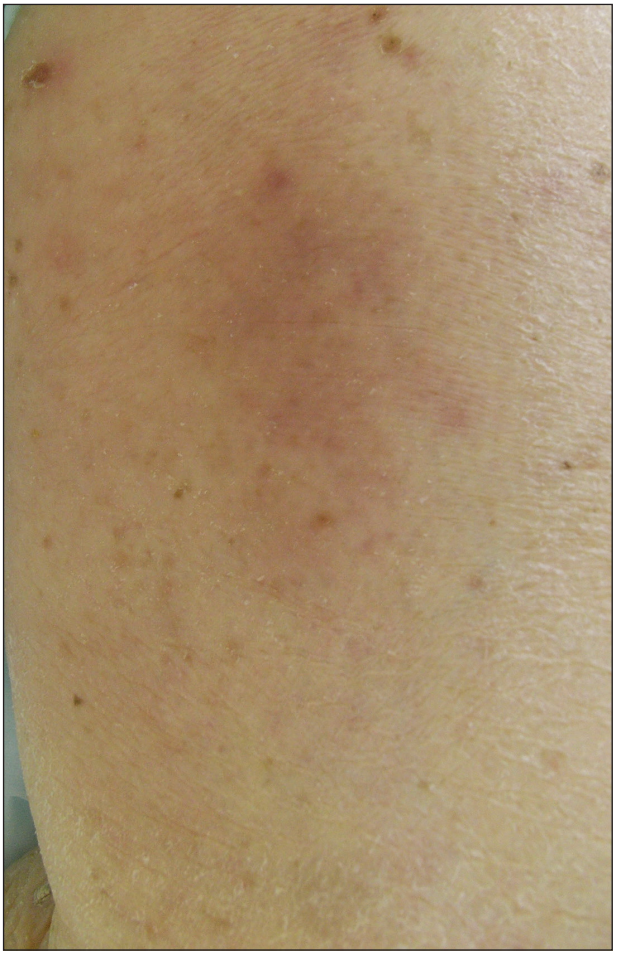

Figure 1. Tender erythematous plaque on the left thigh.

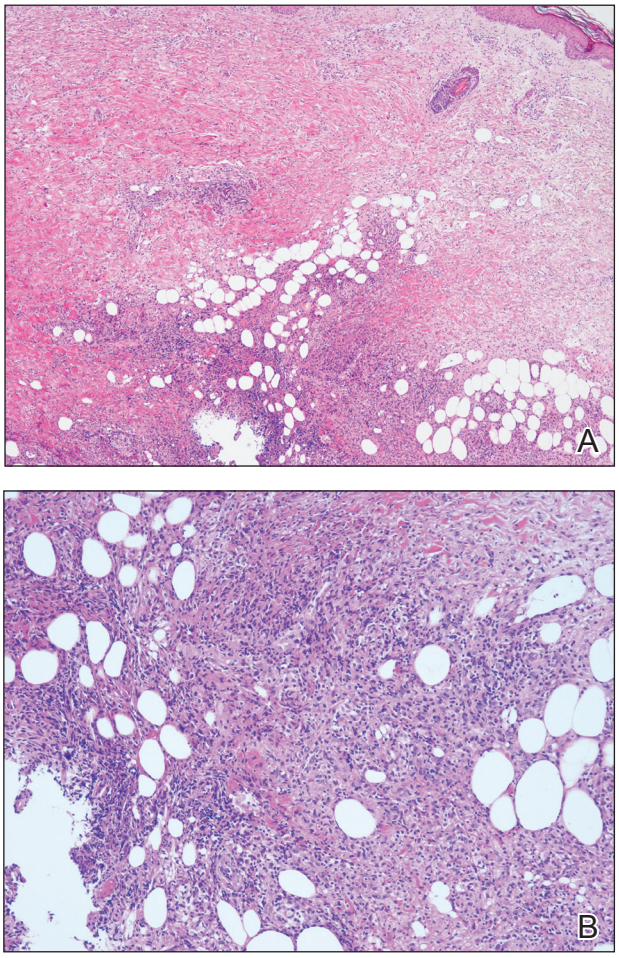

Figure 2. A skin biopsy specimen from an erythematous plaque on the left thigh showed diffuse infiltration of inflammatory cells through the dermis and subcutis (A) (H&E, original magnification ×40). Epithelioid cell granuloma involving the dermis and subcutis (B)(H&E, original magnification ×100).

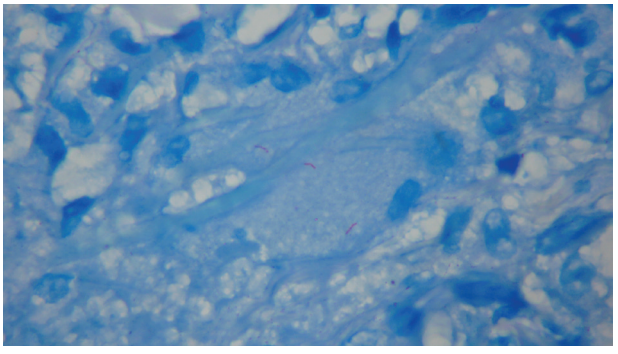

Figure 3. Ziehl-Neelsen stain revealed acid-fast bacilli (original magnification ×1000).

biopsy specimen and gastric fluid. Additionally, *M tuberculosis* was isolated from the skin biopsy specimen, gastric fluid, and sputum culture. After the series of treatments described above, a remarkable increase in nodule size and number was observed in a follow-up chest CT scan compared with the prior examination. These pulmonary lesions showed bronchogenic spread.

A diagnosis of tuberculous cellulitis with pulmonary tuberculosis was made. Treatment with isoniazid 200 mg once daily, rifampin 300 mg once daily, and ethambutol 500 mg once every other day was started; the dosages were reduced from the standard dose due to the patient's CKD.[1] Four days after initiation of these medications, the patient was transferred to a hospital specifically for the treatment of tuberculosis. Approximately 8 months after treatment with isoniazid, rifampin, and ethambutol, *M tuberculosis* could not be detected in the sputum and a chest CT revealed that the pulmonary lesions were remarkably improved. However, polymerase chain reaction of the skin biopsy specimen was still positive for *M tuberculosis*. It was determined that debridement

Table 1.

Differential Diagnosis of Cellulitislike Erythema

Diagnosis	Diagnostic Clues
Infectious Diseases	
Mycoses[3]	Culture, skin biopsy
Necrotizing fasciitis	CRP, CK, CT, MRI
Nontuberculous mycobacterial infection[4]	Culture, skin biopsy (Ziehl-Neelsen stain)
Tuberculous cellulitis[12-16]	Culture, skin biopsy (Ziehl-Neelsen stain)
Noninfectious Diseases	
Wells syndrome	Eosinophilia, skin biopsy (flame figure)
Thrombophlebitis	Edema on ankles, angiography, skin biopsy
Reactive angioendotheliomatosis[5]	Skin biopsy (CD31, factor VIII)
Cutaneous metastasis of primary malignancy[6]	PET-CT, skin biopsy
Subcutaneous panniculitislike T-cell lymphoma[7]	Skin biopsy, Southern blot analysis (T-cell receptor rearrangement)
Langerhans cell histiocytosis[8]	Electron microscope (Birbeck granules), skin biopsy (S100, CD1a)
Sweet syndrome[9]	High fever (temperature, >38.0°C), preceding infection, neutrophilia, skin biopsy
Adult-onset Still disease[10]	High spiking fever (temperature, ≥39.0°C), arthralgia, neutrophilia, ferritin test
Fixed drug eruption caused by acetaminophen[11]	Relapsing erythema with pigmentation

Abbreviations: CRP, C-reactive protein; CK, creatine kinase; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

of the skin lesion was needed, but the patient died from complications of deteriorating CKD 10 months after the initiation of the antituberculosis medications.

Comment

Cellulitis is a suppurative inflammation involving the subcutis.[2] Local tender erythema, malaise, chills, and fever may be present at the onset. Cellulitis is commonly seen by dermatologists, and it is well known that other infectious diseases such as necrotizing fasciitis, cutaneous and subcutaneous mycoses,[3] and nontuberculous mycobacterial infections[4] sometimes present as cellulitislike skin lesions. Moreover, noninfectious diseases, such as Wells syndrome, thrombophlebitis, reactive angioendotheliomatosis,[5] cutaneous metastasis of a primary malignancy,[6] subcutaneous panniculitislike T-cell lymphoma,[7] Langerhans cell histiocytosis,[8] Sweet syndrome,[9] adult-onset Still disease,[10] and fixed drug eruption caused by acetaminophen[11] should be excluded. These differential diagnoses and diagnostic clues of cellulitislike erythema are summarized in Table 1.[3-16]

Cutaneous tuberculosis presenting as cellulitis, so-called tuberculous cellulitis, also is characterized as a clinical mimicker of cellulitis. On the other hand, histologically, it has features of cutaneous tuberculosis (eg, necrotic granuloma).[12,14,15] Tuberculous cellulitis is rare and therefore may often be misdiagnosed even in highly endemic areas. We summarized the clinical information of 5 well-documented cases of tuberculous cellulitis along with the current case in Table 2.[12-16] All of these cases had an associated disease and involved patients who were currently taking oral corticosteroids. If a patient undergoing immunosuppressive therapy develops cellulitislike erythema, tuberculous cellulitis should be considered in the differential diagnosis.

Cutaneous tuberculosis generally is classified into 4 types according to the mechanism of disease acquisition: (1) inoculation from an exogenous source, (2) endogenous cutaneous spread contiguously or

Table 2.

Clinical Characteristics of Tuberculous Cellulitis

Reference	Age, y	Sex	Distribution	Pain	Associated Disease	Immunosuppressive Therapy
Lee et al[12]	63	F	Abdomen	+	Arthralgia, diabetes mellitus	Oral corticosteroids
Kim et al[13]	47	F	Right axilla	+	Dermatomyositis, gastric cancer	PSL 15 mg daily
Chin et al[14]	28	F	Left leg	+	SLE	PSL 40 mg daily, cyclophosphamide 100 mg daily
Seyahi et al[15]	37	M	Left elbow, left calf and foot	NR	CKD (following renal transplantation), chronic hepatitis due to HBV infection	Methylprednisolone 8 mg daily, azathioprine 100 mg daily
Kato et al[16]	86	F	Left leg	–	Myasthenia gravis	PSL 15 mg every other day
Current case	89	M	Left thigh	+	CKD, polymyalgia rheumatica, pancreatic cancer	PSL 5 mg daily

Abbreviations: F, female; PSL, prednisolone; SLE, systemic lupus erythematosus; M, male; NR, not reported; CKD, chronic kidney disease; HBV, hepatitis B virus.

by autoinoculation, (3) hematogenous spread to the skin, and (4) tuberculids. In our case, it was suspected that the cellulitislike erythema may have been caused by hematogenous spread from pulmonary tuberculosis. Considering that negative reactions to purified protein derivative (tuberculin) skin tests often are observed in cases of miliary tuberculosis (widespread dissemination of M *tuberculosis* to 2 or more organs via hematogenous spread), we suspected that our patient could proceed to miliary tuberculosis; in fact, a case was reported in which miliary tuberculosis emerged approximately 3 weeks after the onset of erythema,[13] as observed in the present case. Therefore, erythema in the setting of tuberculosis may be a predictor of miliary tuberculosis. The types of cutaneous lesions caused by tuberculosis infection also are dependent on multiple host factors.[2] Cutaneous tuberculosis with an atypical clinical appearance has become more common because of the increasing number of immunocompromised patients.[17]

In addition, most cases of cutaneous tuberculosis are not associated with pain. Generally, tuberculous cellulitis also causes nontender erythematous plaques or nodules.[2] However, in some cases of tuberculous cellulitis, including our case, tender skin lesions have been reported.[12-14] Therefore, this symptom is not a sensitive factor for differential diagnosis.

We suggest that tuberculous cellulitis should always be included in the differential diagnosis of a cellulitislike rash with or without pain if the skin lesion is not improved despite antibiotic therapy.

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