Polyarthritis, neuropathy, and persistent violaceous plaques

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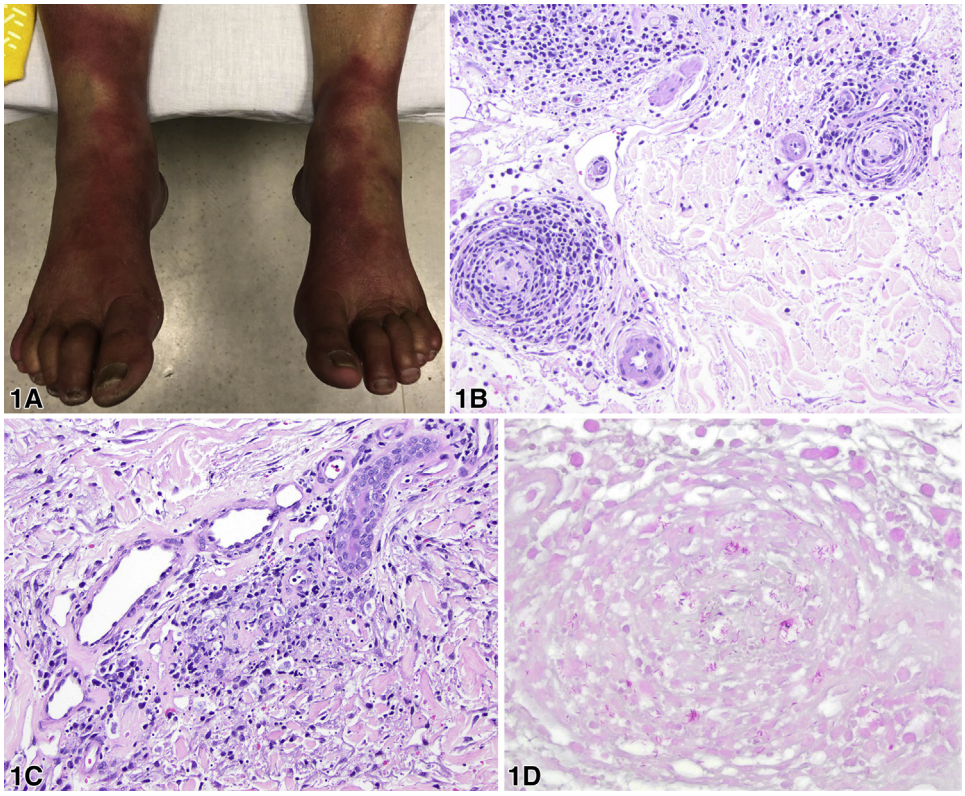

A 77-year-old woman from India presented with a rash of 2 months' duration, long-standing neuropathy in a stocking glove distribution, polyarthritis, and fever. The cutaneous eruption consisted of violaceous-to-erythematous patches, nodules, and plaques with associated edema, starting on the bilateral hands and feet and gradually spreading to the proximal limbs, trunk and face (Fig 1, *A*). The patient had lived in the United States for 2 decades and last visited India 2 years ago. Laboratory tests were remarkable for anti-nuclear antibody positivity, elevated C-reactive protein and erythrocyte sedimentation rate, and slightly decreased complement C3. Initial workup for an infection was negative. After initial improvement with a course of systemic corticosteroids, the rash worsened during steroid taper. Punch biopsies were performed (Fig 1, *B-D*).

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Question 1: What is the most likely diagnosis?

A. Cutaneous tuberculosis

B. Drug reaction

C. Erythema nodosum leprosum

D. Sweet syndrome

E. Tumid lupus erythematosus

Answer:

A. Cutaneous tuberculosis — Incorrect. There is clinical and histologic overlap of erythema nodosum leprosum with certain presentations of cutaneous tuberculosis (such as lupus vulgaris) and other infectious granulomatous diseases. However, the neural tropism of the acid-fast organisms—a highly characteristic feature of leprosy—and the prominent vasculitis make cutaneous tuberculosis less likely.

B. Drug-induced erythema nodosum — Incorrect. Drug reaction is a diagnosis of exclusion. Although hypersensitivity reactions to certain drugs can present with a clinical picture of erythema nodosum, the histopathologic features and the findings of organisms by Fite staining excludes a drug reaction.

C. Erythema nodosum leprosum (ENL) — Correct. Histopathology shows a superficial and deep perivascular, prominent perineural and interstitial infiltrate of lymphocytes, foamy histiocytes and plasma cells (Fig 1, *B*). Perivascular neutrophils, nuclear dust, and fibrin deposition are also present (Fig 1, *C*). Fite stain shows numerous acid-fast bacilli within histiocytes, within a nerve, and in endothelial cells (Fig 1, *D*). The diagnosis rendered was multibacillary leprosy with associated vasculitis, consistent with ENL. Subsequent polymerase chain reaction on the specimen was positive for *Mycobacterium leprae*.

D. Sweet syndrome — Incorrect. Sweet syndrome presents with tender, edematous, erythematous papules and nodules typically on the upper body. Prodromal fever and flu-like symptoms are common. An array of extracutaneous inflammatory manifestations can occur, especially of the joints and eyes. Microscopically, Sweet syndrome presents as a diffuse dermal neutrophilic infiltrate, which may extend into the subcutaneous fat, with papillary dermal edema and frequently an accompanying secondary leukocytoclastic vasculitis.[1]

E. Tumid lupus erythematosus (TLE) — Incorrect. In TLE, patients usually present with erythematous patches and plaques of sun-exposed areas of the upper body, neck, and face. Microscopically, dense perivascular and periadnexal lymphocytic infiltrates are seen with sparing of the papillary dermis and epidermis, along with mucin deposits in the reticular dermis.[2] The prominent mixed infiltrate (as opposed to lymphocytic), perineural tropism, and lack of dermal mucin deposition argue against TLE.

Question 2: This patient's clinical presentation of leprosy is best described as:

A. Lepromatous leprosy

B. Lucio phenomenon

C. Tuberculoid leprosy

D. Type 1 lepra reaction

E. Type 2 lepra reaction

Answer:

A. Lepromatous leprosy — Incorrect. Lepromatous lesions, which develop in patients with little resistance to the bacteria, are poorly demarcated and present as diffuse macules, papules, plaques and nodules. Biopsies exhibit diffuse dermal infiltration by macrophages, and acid-fast staining will demonstrate large numbers of organisms (multibacillary lesions).[3]

B. Lucio phenomenon — Incorrect. The Lucio phenomenon is a rare, life-threating lepra reaction. It occurs primarily in Mexico and Central America in patients with untreated or undertreated leprosy and presents with irregularly shaped, angulated purpuric patches and plaques that ulcerate. The histologic findings are similar to ENL, but thrombosis of blood vessels may also be observed.[4]

C. Tuberculoid leprosy — Incorrect. Tuberculoid and borderline lesions are well-demarcated, erythematous, hypopigmented plaques, which may ulcerate. Affected areas develop sensory and motor neuropathy. Biopsies show well-developed granulomatous inflammation following a nerve, and acid-fast staining reveals very sparse organisms (paucibacillary lesions).[3]

D. Type 1 lepra reaction — Incorrect. Type 1 lepra reactions occur in patients with tuberculoid and borderline lesions and are due to changes in T-cell reactivity to *M. leprae* antigens, evoking a Th1-type (interferon gamma and tumor necrosis factor [TNF]-alpha mediated) T-cell immune response.[3] Existing lesions become painful, erythematous, edematous, and may ulcerate. Affected areas may develop

sensory and motor neuropathy. Biopsies of lesions show well-developed granulomatous perineural inflammation and edema.[5]

E. Type 2 lepra reaction — Correct. ENL is a type 2 lepra reaction, which affects patients with lepromatous lesions. It is mediated by a combination of immune complex deposition as well as a cell-mediated immune response, resulting in increased levels of cytokines such as TNF-alpha. Patients rapidly develop new tender, erythematous, nodular lesions, often with fever and malaise. ENL is characterized by an intense, mixed inflammatory infiltrate in the dermis and subcutaneous fat with acute vasculitis, and organisms can be seen in endothelial cells.[5]

Question 3: Which of these drugs provides rapid control of symptoms in severe ENL?

A. Apremilast

B. Clofazimine

C. Etanercept

D. Ibuprofen

E. Thalidomide

Answer:

A. Apremilast — Incorrect. Apremilast is a phosphodiesterase-4 (PDE4) inhibitor used in the treatment of psoriasis. PDE4 inhibitors hold promise for use in ENL, but data from currently ongoing studies are still limited.[6]

B. Clofazimine — Incorrect. Clofazimine is a component of the antimicrobial regimen used to treat leprosy termed multiple drug therapy (MDT), consisting of rifampin, dapsone, and clofazimine. Clofazimine has some anti-inflammatory effects, and its inclusion in the MDT regimen may reduce the incidence of ENL.[3] However, it has a slow (weeks) onset of effect and does not provide rapid relief of symptoms in severe ENL.[5,6]

C. Etanercept — Incorrect. TNF inhibitors such as etanercept have been used in exceptional cases of refractory, severe ENL with some success.[5,6] However, this circumstance is uncommon, and randomized controlled trials to support routine use are needed.

D. Ibuprofen — Incorrect. Mild ENL can be managed with analgesics, including ibuprofen. Ibuprofen is inferior to thalidomide, clofazimine, and corticosteroids in the treatment of severe ENL.[6]

E. Thalidomide — Correct. While prednisone has an important role during the initial treatment of severe ENL, potential serious side effects limit its long-term use. Thalidomide is an effective alternative and gives rapid symptom control, likely exerting anti-inflammatory effects through inhibition of TNF-alpha. It is also the mainstay of long-term control of chronic and recurrent ENL as a steroid-sparing therapy.[6]

Abbreviations used:

ENL: erythema nodosum leprosum
MDT: multidrug therapy
PDE4: phosphodiesterase-4
TLE: tumid lupus erythematosus
TNF: tumor necrosis factor

Conflicts of interest

None disclosed.

REFERENCES

1. Cohen PR, Kurzrock R. Sweet's syndrome revisited: a review of disease concepts. *Int J Dermatol*. 2003;42:761-778.
2. Kuhn A, Richter-Hintz D, Oslislo C, Ruzicka T, Megahed M, Lehmann P. Lupus erythematosus tumidus—a neglected subset of cutaneous Lupus erythematosus: report of 40 cases. *Arch Dermatol*. 2000;136:1033-1041.
3. Britton WJ, Lockwood DNJ. Leprosy. *Lancet*. 2004;363:1209-1219.
4. Vargas-Ocampo F. Diffuse leprosy of Lucio and Latapí: a histologic study. *Lepr Rev*. 2007;78:248-260.
5. White C, Franco-Paredes C. Leprosy in the 21st century. *Clin Microbiol Rev*. 2015;28:80-94.
6. World Health Organization. *Leprosy: Management of Reactions and Prevention of Disabilities. Technical Guidance*. New Delhi: World Health Organization, Regional Office for South-East Asia; 2017:21-24.