Purpuric Lesions on the Leg

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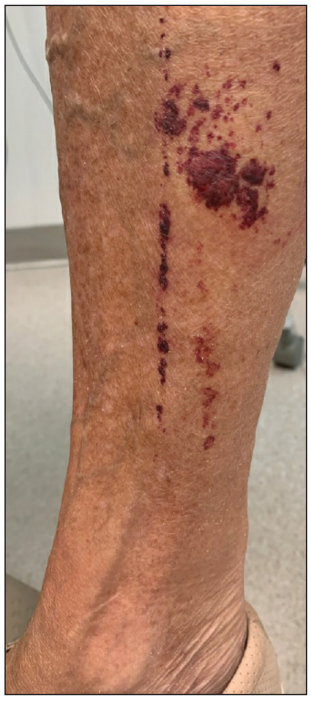

A 74-year-old woman who frequently traveled abroad presented to the dermatology department with retiform purpura of the lower leg along with gastrointestinal cramps, fatigue, and myalgia. The patient reported that the symptoms had started 10 days after returning from a recent trip to Africa.

WHAT'S YOUR **DIAGNOSIS?**

a. African tick bite fever
b. African trypanosomiasis (sleeping sickness)
c. chikungunya virus infection
d. dengue hemorrhagic fever
e. Zika virus infection

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THE **DIAGNOSIS:** Dengue Hemorrhagic Fever

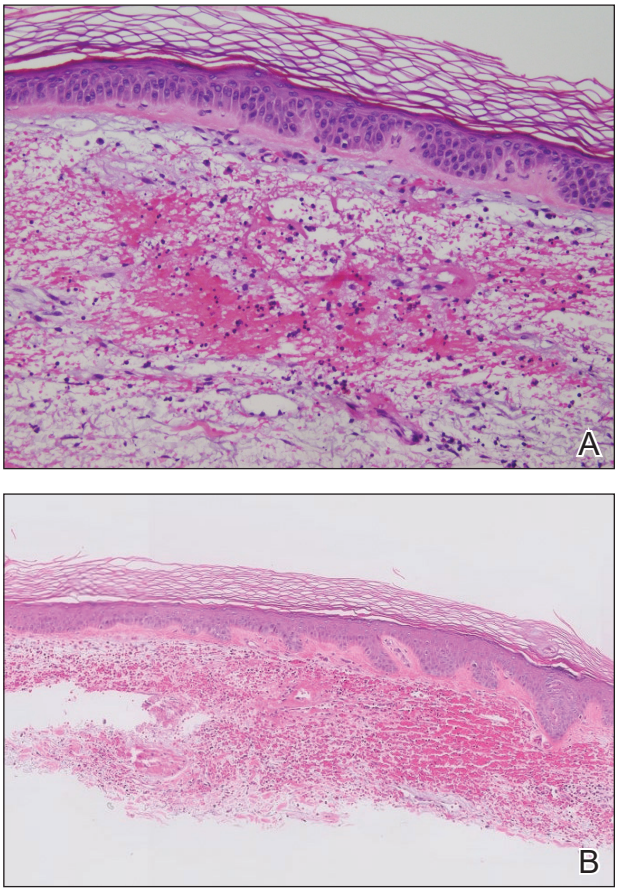
The retiform purpura observed in our patient was suggestive of a vasculitic, thrombotic, or embolic etiology. Dengue IgM serologic testing performed based on her extensive travel history and recent return from a dengue-endemic area was positive, indicating acute infection. A clinical diagnosis of dengue hemorrhagic fever (DHF) was made based on the hemorrhagic appearance of the lesion. Histopathology revealed leukocytoclastic vasculitis (Figure). Anti–double-stranded DNA, antideoxyribonuclease, C3 and C4, CH50 (total hemolytic complement), antineutrophil cytoplasmic antibodies, HIV, and hepatitis B virus tests were normal. Direct immunofluorescence was negative.

Dengue virus is a single-stranded RNA virus transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes and is one of the most prevalent arthropod-borne viruses affecting humans today.[1,2] Infection with the dengue virus generally is seen in travelers visiting tropical regions of Africa, Mexico, South America, South and Central Asia, Southeast Asia, and the Caribbean.[1] The Table shows the global distribution of dengue serotypes from 2000 to 2014.[3,4] There are 4 serotypes of the dengue virus: DENV-1 to DENV-4. Infection with 1 strain elicits long-lasting immunity to that strain, but subsequent infection with another strain can result in severe DHF due to antibody cross-reaction.[1]

Dengue virus infection ranges from mildly symptomatic to a spectrum of increasingly severe conditions that comprise dengue fever (DF) and DHF, as well as dengue shock syndrome and brain stem hemorrhage, which may be fatal.[2,5] Dengue fever manifests as severe myalgia, fever, headache (usually retro-orbital), arthralgia, erythema, and rubelliform exanthema.[6] The frequency of skin eruptions in patients with DF varies with the virus strain and outbreaks.[7] The lesions initially develop with the onset of fever and manifest as flushing or erythematous mottling of the face, neck, and chest areas.[1,7] The morbilliform eruption develops 2 to 6 days after the onset of the fever, beginning on the trunk and spreading to the face and extremities.[1,7] The rash may become confluent with characteristic sparing of small round areas of normal skin described as white islands in a sea of red.[2] Verrucous papules on the ears also have been described and may resemble those seen in Cowden syndrome. In patients with prior infection with a different strain of the virus, hemorrhagic lesions may develop, including characteristic retiform purpura, a positive tourniquet test, and the appearance of petechiae on the lower legs. Pruritus and desquamation, especially on the palms and soles, may follow the termination of the eruption.[7]

The differential diagnosis of DF includes measles, rubella, enteroviruses, and influenza. Chikungunya and West Nile viruses in Asia and Africa and the O'nyong-nyong virus in Africa are also arboviruses that cause a clinical picture similar to DF but not DHF. Other diagnostic considerations include phases of scarlet fever, typhoid, malaria, leptospirosis, hepatitis A, and trypanosomal and rickettsial diseases.[7] The differential diagnosis of DHF includes antineutrophil cytoplasmic antibody–associated vasculitis, rheumatoid vasculitis, and bacterial septic vasculitis.

Acute clinical diagnosis of DF can be challenging because of the nonspecific symptoms that can be seen in almost every infectious disease. Clinical presentation assessment should be confirmed with laboratory testing.[6] Dengue virus infection usually is confirmed by the identification of viral genomic RNA, antigens, or the antibodies it elicits. Enzyme-linked immunosorbent assay–based serologic tests are cost-effective and easy to perform.[5] IgM antibodies



A, Histopathology of a biopsy from the right medial leg showed early leukocytoclastic vasculitis with karyorrhexis and red cell extravasation (H&E, original magnification ×200). B, Extensive erythrocyte extravasation and expended vessel walls with fibrin deposition also were seen (H&E, original magnification ×100).

Global Distribution of Dengue Serotypes (2000–2014)[3,4]

Continent	DENV-1	DENV-2	DENV-3	DENV-4
Africa				
Eastern	× (Sudan[a])	× (Kenya[a])	× (Mozambique[a])	
Central		× (Gabon[a])		
Northern				
Southern				
Western		× (Nigeria[a])		
Americas				
Caribbean	×	×		×
Central	×		×	×
North	×	×	×	×
South	×	×	×	×
Asia				
Central				
Eastern	×	×	×	×
Southeastern		×	×	×
Southern		×	×	×
Western	×		× (Saudi Arabia[a])	
Europe				
Eastern				
Northern				
Southern				
Western				
Oceania				
Australia and New Zealand			×	×
Melanesia		×		
Micronesia			×	
Polynesia	×			×

Abbreviation: DENV, dengue virus.

[a]Sporadic cases.

[b]Cases in North America mostly seen as local outbreaks in Florida, Texas, and Hawaii.

usually show cross-reactivity with platelets, but the antibody levels are not positively correlated with the severity of DF.[8] Primary infection with the dengue virus is characterized by the elevation of specific IgM levels that usually occurs 3 to 5 days after symptom onset and persists during the postfebrile stage (up to 30 to 60 days). In secondary infections, the IgM levels usually rise more slowly and reach a lower level than in primary infections.[9] For both primary and secondary infections, testing IgM levels after the febrile stage may be helpful with the laboratory diagnosis.

Currently, there is no antiviral drug available for dengue. Treatment of dengue infection is symptomatic and supportive.[2]

Dengue hemorrhagic fever is indicated by a rising hematocrit (≥20%) and a falling platelet count (>100,000/mm^3) accompanying clinical signs of hemorrhage. Treatment includes intravenous fluid replacement and careful clinical monitoring of hematocrit levels, platelet count, vitals, urine output, and other signs of shock.[5] For patients with a history of dengue infection, travel to areas with other serotypes is not recommended.

If any travel to a high-risk area is planned, country-specific travel recommendations and warnings should be reviewed from the Centers for Disease Control and Prevention's website (https://wwwnc.cdc.gov/travel/notices/level1/dengue-global). Use of an Environmental

Protection Agency–registered insect repellent to avoid mosquito bites and acetaminophen for managing symptoms is advised. During travel, staying in places with window and door screens and using a bed net during sleep are suggested. Long-sleeved shirts and long pants also are preferred. Travelers should see a health care provider if they have symptoms of dengue.[10]

African tick bite fever (ATBF) is caused by *Rickettsia africae* transmitted by *Amblyomma* ticks. Skin findings in ATBF include erythematous, firm, tender papules with central eschars consistent with the feeding patterns of ticks.[11] Histopathology of ATBF usually includes fibrinoid necrosis of vessels in the dermis with a perivascular inflammatory infiltrate and coagulation necrosis of the surrounding dermis consistent with eschar formation.[12] The lack of an eschar weighs against this diagnosis.

African trypanosomiasis (also known as sleeping sickness) is caused by protozoa transmitted by the tsetse fly. A chancrelike, circumscribed, rubbery, indurated red or violaceous nodule measuring 2 to 5 cm in diameter often develops as the earliest cutaneous sign of the disease.[13] Nonspecific histopathologic findings, such as infiltration of lymphocytes and macrophages and proliferation of endothelial cells and fibroblasts, may be observed.[14] Extravascular parasites have been noted in skin biopsies.[15] In later stages, skin lesions called trypanids may be observed as macular, papular, annular, targetoid, purpuric, and erythematous lesions, and histopathologic findings consistent with vasculitis also may be seen.[13]

Chikungunya virus infection is an acute-onset, mosquito-borne viral disease. Skin manifestations may start with nonspecific, generalized, morbilliform, maculopapular rashes coinciding with fever, which also may be seen initially with DHF. Skin hyperpigmentation, mostly centrofacial and involving the nose (chik sign); purpuric and ecchymotic lesions over the trunk and flexors of limbs in adults, often surmounted by subepidermal bullae and lesions resembling toxic epidermal necrolysis; and nonhealing ulcers in the genital and groin areas are common skin manifestations of chikungunya infection.[16] Intraepithelial splitting with acantholysis and perivascular lymphohistiocytic infiltration may be observed in the histopathology of blistering lesions, which are not consistent with DHF.[17]

Zika virus infection is caused by an arbovirus within the Flaviviridae family, which also includes the dengue virus. Initial mucocutaneous findings of the Zika virus include nonspecific diffuse maculopapular eruptions. The eruption generally spares the palms and soles; however, various manifestations including involvement of the palms and soles have been reported.[18] The morbilliform eruption begins on the face and extends to the trunk and extremities. Mild hemorrhagic manifestations, including petechiae and bleeding gums, may be observed. Distinguishing between dengue and Zika virus infection relies on the severity of symptoms and laboratory tests, including polymerase chain reaction or IgM antibody testing.[19] The other conditions listed do not produce hemorrhagic fever.

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