Fever and malaise associated with a painful papule on the ankle

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A 29-year-old woman with no significant past medical history presented with malaise, fever, headache, inguinal lymphadenopathy, and a painful lesion on her ankle (Figures 1 and 2). Other pertinent findings on cutaneous examination included faint blanching 2- to 3-mm macules on her trunk. There were no oral lesions and no signs of embolic

phenomena. One week prior to presentation she had returned from a South African safari. All appropriate immunizations and prophylactic medications (i.e., antimalarial prophylaxis) were obtained before her trip.

What is the diagnosis, and what is the treatment of choice?

Figure 1. At presentation: hemorrhagic papule with central necrosis.

Figure 2. Four days later: hemorrhagic papulovesicle with central necrosis accompanied by satellite hemorrhagic papules.

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DIAGNOSIS: Tick bite fever (TBF).

DISCUSSION

This patient had an imported skin disease, most likely due to *Rickettsia africae*, that she contracted while in South Africa on safari (Table 1) (1). Rickettsiae are gram-negative coccobacillary bacteria that are strict intracellular parasites. Rickettsiae are most commonly associated with spotted fever infections (Table 2). In South Africa, TBF is commonly attributed to *Rickettsia africae*, *R. conorii*, and *R. mongolotimonae* (2). The disease is usually seen in white temporary workers or tourists (hunters and campers in rural areas) in endemic areas such as South Africa or the Mediterranean basin. The parasite, which lives in the salivary glands of arthropods, is introduced into the human host during a hematophagous tick bite. In South Africa, the most common tick vector for TBF is *Amblyomma hebraeum*. Rickettsiae introduced into the host at the inoculation site invade the endothelium, divide by binary fusion, and spread from cell to cell via the lymphatics to infect distant endothelial cells. In response, cytotoxic CD8+ T lymphocytes

Table 2. Common spotted fever infections	
Infection	<i>Rickettsia</i> species
Rocky Mountain spotted fever	<i>R. rickettsii</i>
Mediterranean spotted fever (boutonneuse fever)	<i>R. conorii</i>
Rickettsialpox	<i>R. akari</i>
African tick bite fever	<i>R. africae</i>

are directed against rickettsiae-infected endothelial cells. Acting in concert with the proinflammatory cytokines tumor necrosis factor alpha and interferon-gamma, these T lymphocytes are critical for clearing the host of the infection (3).

Clinical course

The incubation period for TBF is approximately 6 to 10 days. Initially, patients complain of flulike symptoms, including fever and headaches (4). A *tache noire*—a small, painless black eschar with a halo of erythema—often develops at the

Table 1. Common imported dermatologic diseases

Disease	Organism	Vector	Region	Diagnosis	Clinical picture
Cutaneous larva migrans	Cat or dog hook-worm larvae	—	Any; especially beaches of Caribbean islands	Clinical	Migrating erythematous pruritic serpiginous lesions, most often on the buttocks and feet
Dengue fever	Arbovirus	Mosquito (<i>Aedes aegypti</i>)	Southeast Asia	Culture or detection of the virus in blood by polymerase chain reaction or serologic studies	High fever, headache, backache, retroorbital pain, transient morbilliform or scarlatiniform eruption which may be followed by a generalized erythematous eruption with islands of sparing. Hemorrhagic complications leading to death are possible in up to 15% of patients.
Leishmaniasis	<i>Leishmania</i> spp. (protozoa)	Sandfly	Old World: Middle East, Mediterranean, India New World: Guatemala, Yucatan, Brazil	Monoclonal antibody immunoperoxidase stain, cultures, or histologic specimens with Giemsa stains	Old World infections usually have shorter incubation periods and a shorter, less destructive course. New World infections usually have longer incubation periods, are more destructive, and have possible mucocutaneous involvement (i.e., midline nasal destruction—espundia).
Loiasis	<i>Loa loa</i> (microfilarial nematode)	Fly (<i>Chrysops</i>)	West and Central Africa	Demonstration of microfilariae in blood or positive filarial serology by immunofluorescence or ELISA	“Calabar swellings,” or painful subcutaneous swelling involving fingers, breasts, or eyes (lids or conjunctiva). Patients may describe tingling or movement of adult worms at these sites.
Onchocerciasis	<i>Onchocerca volvulus</i> (microfilarial nematode)	Black fly	Central/South America, Middle East, Africa	Skin snip demonstrates microfilariae, or positive filarial immunofluorescence or ELISA (60%–90%)	Three distinct cutaneous phases: 1. Pruritic papular eruption 2. Lichenified dyschromic lesions 3. Subcutaneous nodules Other symptoms: lymphadenopathy; blindness in 5%
African tick bite fever	<i>Rickettsia africae</i> and <i>R. mongolotimonae</i>	Tick	South Africa and Mediterranean basin	Serology and DNA probes	Tache noire, often with small satellite lesions; fever; headache; arthralgias; and uncommonly a maculopapular rash
Mediterranean spotted fever (boutonneuse fever)	<i>R. conorii</i>	Tick	Mediterranean basin (endemic in southern Europe and northern Africa)	Serology and DNA probes	Tache noire followed by fever, headache, neck ache, and a widespread maculopapular rash

ELISA indicates enzyme-linked immunosorbent assay.

site of inoculation, but up to 50% of cases lack this lesion. A maculopapular or papulovesicular rash may be present (5, 6), and regional lymphadenopathy is often seen. In many cases, the untreated infection resolves spontaneously after 1 to 2 weeks.

Differential diagnosis

In South Africa the two most common types of TBF are African TBF and Mediterranean spotted fever. Typically, African TBF is a milder disease that is oftentimes self-limited and requires no therapy. Clinically, nonspecific flulike symptoms (fever, chills, and headache) along with myalgias are common. On skin examination, a tache noire is found at the inoculation site. In some cases, multiple eschars are found, which is virtually pathognomonic for African TBF. Rarely, a maculopapular rash may be present adjacent to the tache noire.

Mediterranean spotted fever, the second most common rickettsiosis in South Africa, is usually more severe, with a fatality rate of up to 5% among untreated patients. Clinically, fevers, myalgias, neck stiffness, and a maculopapular rash are common. Typically, skin examination reveals only one inoculation site, and in some cases dark red necrotic spots may appear on the arms and legs. Systemic involvement may be characterized by renal failure, liver dysfunction, and central nervous system alterations (mental confusion, vision loss, coma).

For the correct diagnosis, it is important to know the country or region where the patient has traveled. In the USA, for example, Rocky Mountain spotted fever (caused by *R. rickettsii*) is characterized by fever, rash, and multiorgan involvement; if left untreated, the mortality rate is 20% to 25%. In Rocky Mountain spotted fever, a tache noire is rare, and the initial cutaneous manifestation is erythematous macules, which first appear at the wrists and ankles and subsequently spread centripetally.

Diagnostic tests

Patient history is crucial in the diagnosis of TBF. Serologically, spotted fever infections, including TBF, show a positive Weil-Felix reaction (7). Routine skin biopsies have limited value for diagnosis since the organisms are too small to visualize; however, technological advances such as specific rickettsial monoclonal antibodies allow for more rapid and accurate diagnosis using direct immunofluorescence or immunoenzyme techniques.

Diagnosis is usually made by obtaining serial serum titers (10 to 14 days apart) for specific rickettsial organisms or by using polymerase chain reaction amplification to detect rickettsial DNA (8, 9).

Treatment

Early empiric therapy with tetracycline is the standard of care for any case considered consistent with a spotted fever infection while confirmatory laboratory results are pending. While many cases of African TBF resolve spontaneously, treatment with 100 mg doxycycline orally twice daily for 2 weeks is recommended. For pregnant women and children, chloramphenicol is the treatment of choice. Sulfa drugs are contraindicated.

Prevention

More than 80% of spotted fever infections occur in the summer or early autumn. Attention to season and region of travel may help prevent rickettsial infections. Additionally, patients living in endemic areas must be warned about inadvertent exposure to rickettsial organisms via their domestic animals, such as dogs and cats, which may harbor tick vectors. Furthermore, the repellent diethyltoluamide (DEET) has been shown to be effective in preventing tick bites; however, repeat applications are required.

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