A 56-year-old man was referred to the transplantation infectious-disease clinic because of a low-grade fever and left axillary lymphadenopathy.

The patient had received a cadaveric kidney transplant five years earlier for polycystic kidney disease. He had been in his usual state of health until three weeks before the referral to the infectious-disease clinic, when he discovered palpable, tender lymph nodes in the left epitrochlear region and axilla. Ten days later a low-grade fever, dry cough, nasal congestion, and night sweats developed, for which trimethoprim–sulfamethoxazole was prescribed, without benefit. He was referred to a specialist in infectious diseases.

The patient did not have headache, sore throat, chest or abdominal pain, dyspnea, diarrhea, or dysuria. He had hypertension, gout, nephrolithiasis, gastroesophageal reflux disease, and prostate cancer, which had been treated with radiation therapy two years earlier. He was a policeman who worked in an office. He had not traveled outside of the United States recently. He had acquired a kitten several months earlier and recalled receiving multiple scratches on his hands when he played with it. His medications were cyclosporine (325 mg daily), mycophenolate mofetil (2 g daily), amlodipine, furosemide, colchicine, doxazosin, and pravastatin. Prednisone had been discontinued one year previously. He reported no allergies to medications.

The temperature was 36.0°C and the blood pressure 105/75 mm Hg.

On physical examination, the patient appeared well. The head, neck, lungs, heart, and abdomen were unremarkable. On the dorsum of the left hand was a single, violaceous nodule with a flat, necrotic eschar on top (Fig. 1); there was no erythema, fluctuance, pus, or other drainage, and there was no sinus tract. The patient said that this lesion had nearly healed, but that he had been scratching it and thought that this irritation prevented it from healing. There was a tender left epitrochlear lymph node, 2 cm by 2 cm, and a mass of matted, tender lymph nodes, 5 cm in diameter, in the left axilla. There was no lymphangitic streaking or cellulitis. The results of a complete blood count revealed no abnormalities (Table 1).

Additional laboratory studies were obtained, and clarithromycin (500 mg, twice a day) was prescribed. Within a day of starting treatment, the patient’s temperature rose to 39.4°C, and the fever was accompanied by shaking chills. He was admitted to the hospital. The temperature was 38.6°C, the pulse was 78 beats per minute, and the blood pressure was 100/60 mm Hg. The results of a physical examination were unchanged.
from those of the previous examination. A complete blood count, the levels of electrolytes, and the results of tests of renal and liver function were normal; the results of the laboratory studies are shown in Table 1.

A diagnostic procedure was performed.

**Differential Diagnosis**

**Dr. Jane E. Koehler:** This patient, who is immunocompromised because of a renal allograft, presented with left epitrochlear and axillary lymphadenopathy, low-grade fever, and a violaceous nodule with a necrotic eschar on the dorsum of the left hand. Although we do not know the duration of the hand lesion, the appearance is that of a chronic infection, and it is reasonable to assume that the hand lesion and the lymphadenopathy represent an infectious process with low-grade fever, night sweats, and other constitutional symptoms. The long duration of the lymphadenopathy makes a suppurrative process unlikely. The hand lesion could be a manifestation of a disseminated infectious process, but in the absence of any other cutaneous lesions, generalized lymphadenopathy, or evidence of involvement of other organs it probably indicates primary inoculation of the infectious agent on the left hand. The patient did not have nodular lymphangitis, a condition described by Kostman and DiNubile as “nodular subcutaneous swellings along the involved lymphatic glands.”

The differential diagnosis of a nodular cutaneous lesion with regional lymphadenopathy in this patient is quite broad (Table 2).

**Lymphocutaneous Infection in an Immunocompromised Patient**

A detailed history of travel, environmental exposures to pathogens, and contact with animals is essential for developing the differential diagnosis of lymphocutaneous infectious disease, as is evident from this case.

**Travel**

In the absence of recent international travel, cutaneous leishmaniasis or trypanosomiasis would be an unlikely diagnosis. A history of residency and travel within the United States would provide clues about an exposure to certain pathogens. Exposure to mycoses could occur during travel to areas where a mycosis is endemic, such as the southeastern or upper midwestern United States (Blastomyces dermatitidis), the Ohio River Valley (Histoplasma capsu-
latum), and the Southwest and the California Central Valley (Coccidioides immitis). Although recrudescent mycotic infections can develop in patients who are immunocompromised many years after they leave an endemic area, recurrent disease is frequently disseminated, causing multiple cutaneous nodules and generalized lymphadenopathy, rather than a single nodule and focal lymphadenopathy.\textsuperscript{2} Rhodococcus equi should be considered if the patient has had contact with horses or soil contaminated with horse manure, particularly in the southeastern United States. This bacterium can cause a primary nodular lesion of the arms or legs accompanied by ipsilateral adenopathy in patients who are immunocompromised.\textsuperscript{3} There is no mention of travel by this patient that could result in exposure to these pathogens, making them unlikely causes in this patient.

**Environmental Exposures to Pathogens**

Although the patient works in an office, we do not know whether he participates in outdoor activities that might result in exposure to pathogens associated with plants and soil, including nocardia, sporothrix, and filamentous fungi. *Sporothrix schenckii* is a thermally dimorphic fungus that is common in soil and on plant materials. Infection caused by sporothrix most frequently occurs after a traumatic injury and then contamination of the wound with the fungus, especially during gardening. Of the fungi that cause lymphocutaneous disease, *S. schenckii* would be the most likely to cause a cutaneous lesion like the one seen in this patient. However, sporothrix most often causes a nodular lymphangitis and only occasionally a lymphadenitis.

Nocardia species are ubiquitous saprophytic bacteria in soil and water. Cutaneous inoculation can result in lymphocutaneous nocardiosis.\textsuperscript{4} In the majority of patients who have received a transplant and who have cutaneous nocardiosis, there is disseminated disease, with involvement of other organs.\textsuperscript{5} Exposure to areas where pigeons nest or to soil containing bird guano is a risk factor for *Cryptococcus neoformans* infection, which is occasionally associated with a primary inoculation lesion on the arms or legs and a sporotrichoid lymphadenitis.\textsuperscript{6}

The patient’s history does not include any risk factors for mycobacterial disease. Lymphocutaneous disease can occur with nontuberculous mycobacteria, especially *Mycobacterium chelonae*, *M. fortuitum*, and *M. marinum*. *M. marinum* is more typically associated with nodular lymphadenitis, and there is no history in this case of contact with an aquarium, swimming pool, or other fresh or salt water. *Bacillus anthracis* is a cause of lymphocutaneous disease, and the lesion is often pruritic, with a central eschar, but often there are surrounding edema and vesicles.

**Table 2. Differential Diagnosis of Lymphocutaneous Infection in a Patient Who Is Immunocompromised (without International Travel).**

<table>
<thead>
<tr>
<th>Bacterial infections</th>
<th></th>
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<tbody>
<tr>
<td><em>Bartonella henselae</em> (cat scratch disease, bacillary angiomatosis)</td>
<td></td>
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<tr>
<td><em>Erysipelothrix rhusiopathiae</em></td>
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<tr>
<td><em>Francisella tularensis</em> (ulceroglandular tularemia)</td>
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<tr>
<td>Nocardia species</td>
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<tr>
<td><em>Bacillus anthracis</em> (cutaneous anthrax)</td>
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<tr>
<td><em>Rhodococcus equi</em></td>
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<tr>
<td><em>Yersinia pestis</em></td>
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<tr>
<td>Mycobacterial infections</td>
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<td><em>Mycobacterium tuberculosis</em></td>
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<tr>
<td>Nontuberculous mycobacteria</td>
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<tr>
<td><em>M. marinum</em></td>
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<tr>
<td><em>M. kansasi</em></td>
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<tr>
<td><em>M. abscessus</em></td>
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<tr>
<td><em>M. chelonae</em></td>
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<tr>
<td><em>M. fortuitum</em></td>
<td></td>
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<tr>
<td><em>M. haemophilum</em></td>
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<tr>
<td><em>M. avium</em> complex</td>
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<tr>
<td>Fungal infections</td>
<td></td>
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<tr>
<td><em>Sporothrix schenckii</em></td>
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<tr>
<td><em>Coccidioides immitis</em></td>
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<tr>
<td><em>Blastomyces dermatitidis</em></td>
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<td><em>Histoplasma capsulatum</em></td>
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<tr>
<td><em>Cryptococcus neoformans</em></td>
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<tr>
<td>Filamentous fungi</td>
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<tr>
<td>Viral infections</td>
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<tr>
<td><em>Parapoxvirus</em> (orf from goats or sheep, also called infectious eczema)</td>
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</tr>
<tr>
<td><em>Orthopoxvirus</em> (cowpox)</td>
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</tbody>
</table>

**Contact with Pets and Other Animals**

In recent years, the poxviruses have received prominent attention in the national news media because of concern about smallpox as an instrument of bioterrorism and the outbreak of monkeypox associated with pet prairie dogs. Two genera of poxviruses can cause a cutaneous lesion with regional lymphadenopathy in humans: orthopoxvirus (cowpox) and parapoxvirus (orf, or infectious eczema). The former is associated with contact with a cow, a
rodent, or a cat, and the latter with contact with a sheep or a goat. No history of contact with sheep or goats is mentioned for this patient; thus, orf is an unlikely diagnosis.

The majority of patients with Yersinia pestis have no cutaneous lesion; the bubo that characterizes plague is exquisitely tender and the progression of infection is rapid. Erysipelothrix rhusiopathiae is a gram-positive rod acquired through traumatic contact with fish, swine, and other vertebrates; the primary inoculation lesion is painful, is violaceous, and progresses to resemble cellulitis over a period of days.7

Francisella tularensis, the agent of tularemia, and Bartonella henselae, the bacterium that causes cat scratch disease, are the two bacterial species most likely to cause lymphocutaneous disease without nodular lymphangitis, as seen in this patient. Ulceroglandular tularemia occurs after a person has direct cutaneous contact with an infected animal, typically a rabbit (usually the arms are affected), or receives a bite from a tick or deerfly (usually on the legs). The cutaneous lesion begins as a papule and then usually forms an eschar and a raised border; regional lymphadenopathy then develops.8

The most common manifestation of cat scratch disease is axillary lymphadenopathy and an antecedent cutaneous inoculation lesion of the hand or arm.9 In the immunocompetent host, the site of B. henselae inoculation begins as a papule, then becomes vesicular, with the subsequent ulcer remaining for days to weeks. As with ulceroglandular tularemia, lymphadenopathy associated with cat scratch disease can involve a single node or a group of lymph nodes, can suppurate and drain, and can persist for many months. Nodular lymphangitis occurs rarely with ulceroglandular tularemia8 and it was not identified in patients with cat scratch disease in the largest published series.9 Systemic symptoms are more prominent with ulceroglandular tularemia than with cat scratch disease, but both conditions can cause low-grade fever and prolonged constitutional symptoms.

Zoonotic Pathogens Transmitted from Cats to Humans

The patient had recently acquired a kitten, from which he had received scratches on his hands. A number of infections can be transmitted from cats to humans (Table 3). Most of these infections can be ruled out by the presentation with lymphocutaneous disease. Pasteurella multocida causes a lesion at the site of inoculation (usually a cat bite), but the infection spreads rapidly, with cellulitis and purulent drainage developing within hours or a few days; the time course of the cutaneous lesion in the patient under discussion is not consistent with pasteurella infection.

The zoonotic pathogens most likely to cause the hand lesion and axillary lymphadenopathy in this patient are B. henselae, S. schenckii, F. tularensis, and orthopoxvirus (which causes cowpox, among other diseases). Cutaneous lesions occasionally develop in cats after environmental inoculation with S. schenckii; these sores can contain very large numbers of infectious organisms that can be transmitted readily to humans, even through intact skin.10 S. schenckii lesions in cats are usually identifiable, however, and there is no mention of any illness in this patient’s pet. Humans actually acquire cowpox more frequently from cats than from cows; it is believed that rodents are the main reservoir and that cats may become infected from feeding on rodents.11 Cats can directly transmit F. tularensis by biting or scratching a human after eating an infected animal,12 causing ulceroglandular tularemia. A kitten would be less likely to hunt and, therefore, be exposed to cowpox and F. tularensis than a mature cat. However, human exposure to a kitten is a risk factor for infection with B. henselae13 because, in comparison with adult cats, kittens are more likely to have bacteremia with B. henselae,14 have much higher bloodstream titers of B. henselae, and are more likely to scratch.

The patient was initially treated with trimethoprim–sulfamethoxazole, without improvement. Trimethoprim–sulfamethoxazole does not have efficacy against any of the most likely cat-related zoonoses that could have caused lymphocutaneous disease in this patient, including bartonella.15 After treatment with clarithromycin was begun, however, a high fever developed in the patient within 24 hours; this probably represents a Jarisch–Herxheimer reaction. This type of response to treatment with an efficacious antibiotic has been described in patients infected with either B. henselae16,17 or F. tularensis.8 However, clarithromycin would be considered an optimal treatment for B. henselae, but not F. tularensis, and this distinction further implicates B. henselae as the cause of this patient’s infection.

B. Henselae as a Zoonotic Infection

B. henselae is 1 of 20 distinct bartonella species that have now been identified, 5 of which have been isolated from humans (B. henselae, B. quintana, B. bacilli-
Formis, B. vinsonii subspecies arupensis, and B. elizabethae. Mammalian hosts, each type infected with its own cognate bartonella species, now include deer, cows, rodents, wild cats, and many other mammals. Although humans are the apparent reservoir for B. quintana and B. bacilliformis, B. henselae is normally cultivated only from small-mammal reservoirs.

Cats in the United States frequently have bacteremia with B. henselae (reported in 41 percent of cats in the San Francisco Bay area), which is one of four species that have been isolated from cats: B. henselae, B. clarridgeiae, B. koehlerae, and B. bovis (formerly, B. weisii). In contrast, in certain regions of the world, cats are infected with B. clarridgeiae or B. henselae. In cats, the organisms reside within erythrocytes and appear not to cause serious illness. There may be differences in pathogenicity between B. henselae and B. clarridgeiae, because the latter has never been isolated from humans with cat scratch disease. It is, therefore, most probable that B. henselae was the Bartonella species causing lymphocutaneous disease in the patient under discussion.

In summary, I would favor a diagnosis of cat scratch disease in this transplant recipient who is immunocompromised and who has received multiple scratches from a newly acquired kitten, has systemic symptoms, and has chronic lymphocutaneous disease of the left arm without nodular lymphangitis. Culture of Bartonella species remains challenging, and biopsy of any suspicious lesions is the most efficient approach to rapid diagnosis. The diagnostic procedure of choice in this case is a biopsy of the hand lesion. Regardless of the suspicion of a particular pathogen, the biopsy specimen should be examined with special stains to identify mycobacterial and fungal pathogens, as well as with a Warthin–Starry silver stain to detect B. henselae, and cultured for a broad range of organisms, including mycobacteria, other bacteria, and fungi.

Serologic testing can be diagnostic, and serum samples from the patient at the time of the acute illness and also during convalescence (six weeks later) should be tested. However, the sensitivity of the currently available indirect fluorescence antibody test, as reported in a recent study, was 75 percent for patients who were immunocompromised — lower than the 82 to 95 percent sensitivity reported for patients who were immunocompetent.

Dr. Nancy Lee Harris (Pathology): Dr. Basgoz, would you review with us your thinking at the time of the diagnostic procedure?

Dr. Nesli Basgoz (Infectious Disease): I was asked to see this patient in the clinic for transplant recipients. He actually had not called attention to the hand lesion, but when I examined his skin and saw the nodule, I asked him about exposures. He mentioned the kitten immediately, saying that the kitten scratched him often when he was playing with it. So, number one on our list was B. henselae. I thought that a biopsy of the skin lesion would be the procedure of choice, but I initiated antibiotic therapy while the procedure was being scheduled and obtained blood for serologic testing. I also thought that the febrile episode after effective antibiotic therapy was initiated was probably a Jarisch–Herxheimer reaction.
**Clinical Diagnosis**

Cat scratch disease, with a primary cutaneous lesion and lymphadenopathy, in a renal-transplant recipient.

Jarisch–Herxheimer reaction after antibiotic therapy.

**Dr. Jane E. Koehler’s Diagnosis**

Cat scratch disease, with a primary cutaneous lesion and lymphadenopathy, in a renal-transplant patient.

Jarisch–Herxheimer reaction after antibiotic therapy.

**Pathological Discussion**

Dr. Lyn M. Duncan: The diagnostic procedure was excision of the cutaneous nodule. There was marked epidermal hyperplasia and a dense inflammatory infiltrate that involved both the superficial and the deep dermis and extended into the subcutis (Fig. 2A). The infiltrate contained neutrophils, histiocytes, and poorly formed granulomas. There were focal collections of neutrophils within the epidermis. Prominent vasculature, lymphocytes, and plasma cells were also present (Fig. 2B).

A periodic acid–Schiff stain with diastase and a Gomori’s methenamine silver stain revealed no fungi. The absence of organisms on these stains does not rule out a diagnosis of *S. schenckii*, because the organisms may be sparse in biopsy specimens of well-developed lesions. A Gram’s stain of the tissue (Brown and Hopps) and an acid-fast stain were negative, tending to rule out *F. tularensis* and mycobacterial infections, respectively. A Steiner stain was negative, but the Warthin–Starry stain revealed numerous clumped and solitary organisms that were consistent with bartonella (Fig. 2C). In our laboratory, the Steiner stain appears to be effective in staining borrelia and other treponemes, but not bartonella, whereas the Warthin–Starry stain shows intense staining of bartonella. The results of fungal, mycobacterial, and routine cultures were negative.

Bartonella species cause three clinically and epidemiologically distinct processes that involve the skin: cat scratch disease, bacillary angiomatosis, and verruga peruana. The cutaneous lesions share the following histopathological findings: a granulomatous inflammation with neutrophils and plasma cells, epidermal hyperplasia, and vascular proliferation, with organisms present in the intercellular space. Of the lesions caused by *B. henselae*, bacillary angiomatosis is associated with a lobular vascular...

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**Figure 2. Biopsy Specimen of the Cutaneous Lesion.**

Epidermal hyperplasia is present at low magnification (Panel A), with an underlying dense inflammatory infiltrate that extends throughout the dermis and into the subcutis. At higher magnification, the inflammatory infiltrate (Panel B) is composed of histiocytes, lymphocytes, neutrophils, and plasma cells (Panels A and B, hematoxylin and eosin). Warthin–Starry silver staining (Panel C) shows clumped and solitary rods (black-stained organisms), consistent with bartonella species.
proliferation, whereas cat scratch disease typically causes granulomatous inflammation with neutrophils and less prominent vascularity. Peliosis, a lesion seen in the liver and spleen, resembles bacillary angiomatosis histologically.

Dr. Basgoz: Serum samples obtained at the time of the patient’s presentation and one month later were sent to the Centers for Disease Control and Prevention (CDC); the initial specimen had a titer of 1:31 (negative) and the later one had a titer of 1:8192 of antibodies to B. henselae and B. quintana. These results confirmed the diagnosis of bartonella infection.

Dr. Harris: Dr. Koehler, can you comment on the clinical spectrum and management of bartonella infection in patients who are immunocompromised?

Dr. Koehler: The majority of the cases of bartonella infections reported in transplant recipients have been in patients who received renal transplants, such as this patient. The severity and duration of bartonella infection increase with the degree of immunosuppression: patients with the acquired immunodeficiency syndrome and cardiac-transplant recipients almost always have bacillary angiomatosis, bacillary peliosis hepatitis, or both, whereas in renal-transplant recipients, who tend to have less immunosuppression, granulomatous disease develops, with a histopathological pattern similar to that in an immunocompetent host, but with more severe and disseminated infection — exactly the pattern seen in this patient.

This patient should be instructed to follow guidelines that have been drawn up for the prevention of opportunistic infections in patients who are infected with the human immunodeficiency virus; owning a pet cat is not proscribed, but avoidance of scratches, and prompt cleaning if scratches do occur, are important. Kittens are more likely to be bacteremic, more likely to have high levels of bacteremia, and more likely to scratch than adult cats. Eradication of flea infestation is critical to preventing transmission because contamination of cat claws or of a scratch wound with infected flea feces is a possible mechanism for infecting humans.

Although patients who are immunocompetent and who have cat scratch disease do not usually require antibiotic treatment, all patients who are immunocompromised and who have bartonella infection should be treated with antibiotic drugs. Since it takes four to six weeks to obtain serologic results from the CDC, the clinical suspicion of infection is sufficient for early treatment. A macrolide antibiotic (erythromycin, azithromycin, or clarithromycin) or doxycycline is the treatment of choice. Patients who are immunocompromised and who are treated for a short time (less than six weeks) frequently have relapses; the duration of treatment should be at least three months. A Jarisch–Herxheimer reaction can occur after the first several doses of antibiotics, as was observed in this patient.

Dr. Harris: Why do you not recommend treating cat scratch disease in patients who are immunocompetent?

Dr. Koehler: There is no compelling evidence that treatment reduces the duration of symptoms. Exposing people to antibiotics can increase emergence of resistant organisms. In most cases of suspected lymphadenitis associated with cat scratch disease, I would suggest performing an adequate fine-needle aspiration biopsy to rule out cancer, and to culture for mycobacterial and fungal infection, to be followed by observation, if these cultures are negative.

Dr. Harris: Dr. Basgoz, can you tell us how the patient is doing?

Dr. Basgoz: The patient’s fever resolved spontaneously, and antibiotic therapy was continued. In consultation with the transplant team, we gradually tapered his doses of immunosuppressive agents to about half the original dose. The patient was advised to treat the kitten for fleas and to avoid being scratched. By the end of a six-month course of treatment, the lymph nodes had resolved, and the cat had matured and stopped scratching him.

ANATOMICAL DIAGNOSIS

Bartonella henselae infection (cat scratch disease) in an immunocompromised host.

REFERENCES


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