Pathologic Quiz Case

A 17-Year-Old Renal Transplant Patient With Persistent Fever, Pancytopenia, and Axillary Lymphadenopathy

Ridas Juskevicius, MD; Cindy Vnencak-Jones, PhD

A 17-year-old adolescent boy with end-stage renal disease due to focal segmental glomerulosclerosis underwent a second kidney transplant because of the chronic rejection and loss of the first allograft that he had received 11 years previously. The patient was on several immunosuppressive drugs including FK506 and prednisone. Laboratory studies perioperatively demonstrated pancytopenia, and on the second postoperative day, the patient began to display temperature spikes that reached as high as 39°C. The postoperative graft function was excellent. On physical examination, the patient was found to have left axillary lymphadenopathy, which was later confirmed by computerized tomography scanning. Computerized tomography scanning did not demonstrate any other abnormalities. Results of aggressive workups for infectious disease, including blood and urine cultures, cytomegalovirus analysis, and polymerase chain reactions for parvovirus B-19, herpesviruses 6, 7, and 8, and hepatitis serologic studies, were negative. The patient continued to experience temperature spikes despite the discontinuation of some of the immunosuppressive drugs that initially were thought to be the cause of his persistent fever. A biopsy of the axillary lymph node was performed.

The excised lymph node measured 2 cm in its greatest dimension and showed a grossly unremarkable cut surface. A microscopic examination of the hematoxylin-eosin–stained sections demonstrated confluent nodular areas containing proliferation of the vessels of various sizes and shapes in the background of the intact lymph node architecture (Figures 1 and 2). The plump endothelial cells lining the lymphatic vessels showed variable size, abundant pale cytoplasm, and vesicular nuclei with occasionally prominent nucleoli. Many areas had solid clusters of the plump endothelial cells without visible vascular lumens (Figure 3). Rare mitotic figures, numerous neutrophils, and extravasated erythrocytes were present. Interstitial areas contained abundant amphophilic granular and amorphous material (Figure 3, insert) that, on Warthin-Starry–stained sections, showed the presence of the small rod-shaped structures consistent with bacilli. Granulomata were not present, and special acid-fast bacilli and Gomori methenamine silver stains were negative. DNA was extracted from ten 10-μm-thick sections of the paraffin-embedded lymph node, and varying amounts of template DNA were amplified in a multiplex polymerase chain reaction (tubes 1, 3, 5, and 7). One primer pair was specific for the 16S ribosomal RNA genes of *Bartonella henselae*, and a second primer pair, specific for exon 10 of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, was used as a quality control locus to verify successful amplification of patient DNA.[1,2] Control reactions included multiple negative controls interspersed between patient samples (tubes 2, 4, and 6), normal human DNA (tube 8), and *B henselae* DNA (tube 9). Amplicons were subjected to electrophoresis on a 2% agarose gel (Figure 4, bottom) and characterized using DNA marker fragments of known sizes (tube 10). Amplicons generated from the host *CFTR* gene are fragments 98 base pair (bp) in length, while those generated from *B henselae* DNA are 153 bp. The sensitivity and specificity of the assay was increased by Southern blotting and hybridization with a ^{32}P-labeled probe (Figure 4, top) specific for *B henselae*.[3]

What is your diagnosis?

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From the Department of Pathology, Vanderbilt University Medical Center, Nashville, Tenn.

Corresponding author: Cindy Vnencak-Jones, PhD, Department of Pathology, Vanderbilt University Medical Center, 4605 The Vanderbilt Clinic, Nashville, TN 37232 (e-mail: cindy.vnancak-jones@vanderbilt.edu).

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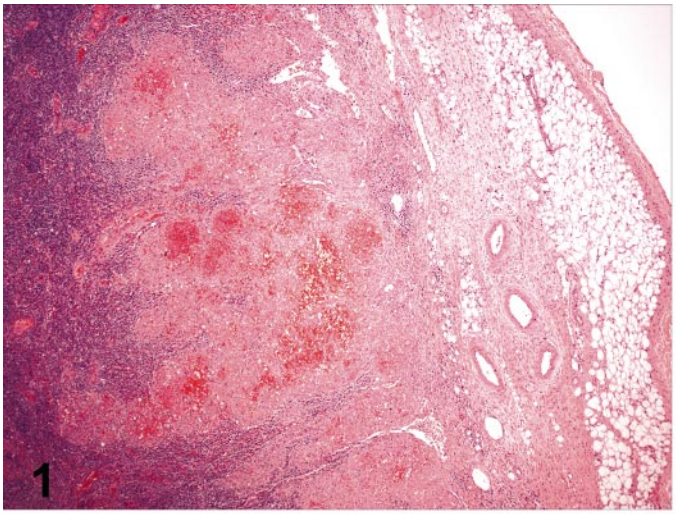

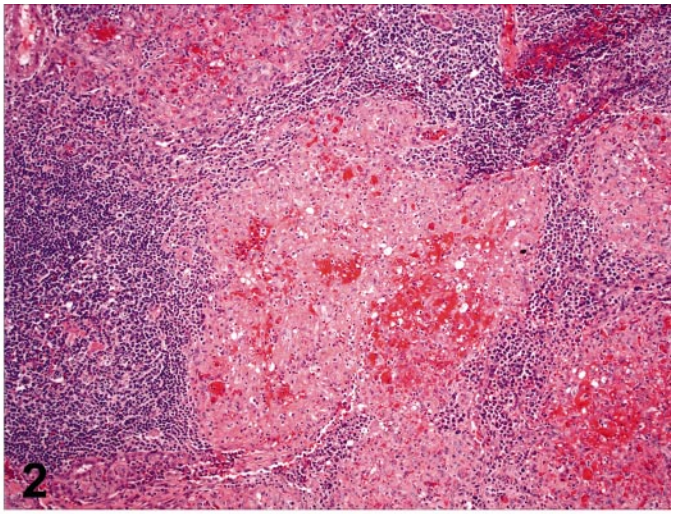

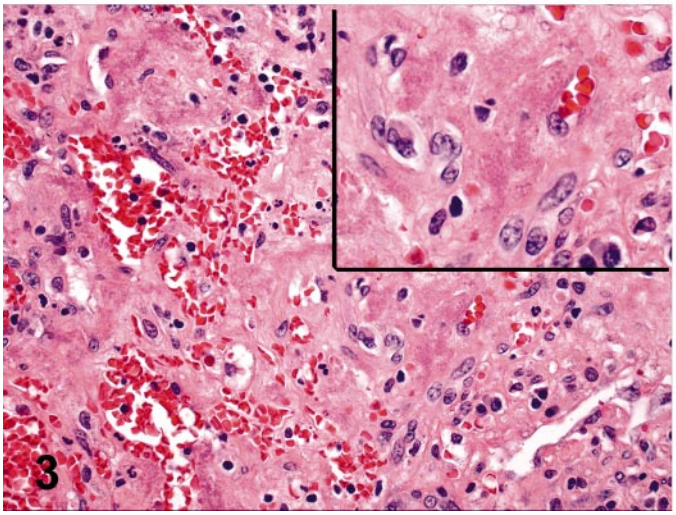

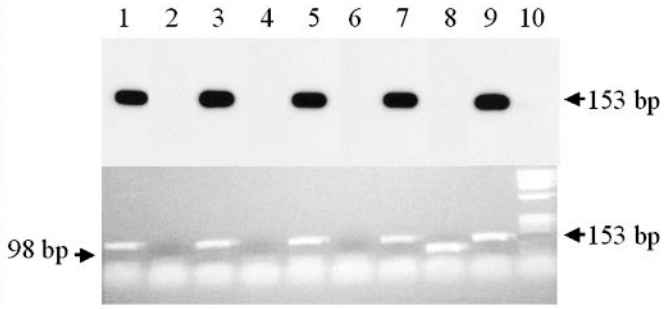

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Pathologic Diagnosis: Bacillary Angiomatosis of the Lymph Node in the Renal Transplant Recipient

Bacillary angiomatosis of the lymph node can be defined as a tumorlike proliferation of the small blood vessels and is one of the manifestations of infection by *B henselae*.[4] *Bartonella henselae* is a small, curved, motile gram-negative bacillus that is difficult to culture and frequently requires molecular methods for identification and speciation. The reservoir of *B henselae* is a domestic cat and cat flea, and the organism is transmitted to humans by direct contact with the cat that has long-term bacteremia. Cat fleas can transmit *B henselae* between cats, but transmission to humans by fleas from cats has not been proven.[5] *Bartonella quintana* is a related organism that causes trench fever, which is characterized by cycling fever and is transmitted among humans by the human body louse. An infection by *B quintana* can also manifest as vasoproliferative lesions histologically indistinguishable from the lesions of bacillary angiomatosis caused by *B henselae*. However, the distribution of the lesions may be influenced by different species of *Bartonella*; subcutaneous and bone involvement is strongly associated with *B quintana*, with lymph node involvement being almost exclusively associated with *B henselae*.[4,5]

It appears that the status of the host immune system is a critical determinant of the clinical and pathologic manifestation of the *B henselae* infection. In the immunocompetent host, it manifests as cat scratch disease with prolonged regional lymphadenopathy that, histologically, is characterized by necrotizing granulomata. Also, otherwise healthy cat scratch disease patients do not have a significant bacteremic phase. Recurrent fever with bacteremia and bacillary angiomatosis as a manifestation of *B henselae* infection almost exclusively occurs in human immunodeficiency virus–infected/acquired immunodeficiency syndrome patients, typically with CD4 lymphocyte counts less than 100 cells/mm^3. Only rare cases have been reported in immunosuppressed transplant recipients and cancer chemotherapy patients.[5]

Bacillary angiomatosis is a potentially systemic disease with wide range of documented tissue involvement (brain, lymph node, bone marrow, skeletal muscle, conjunctiva, and mucosal surfaces of the gastrointestinal and respiratory tract). Skin involvement is the most frequent and is best described occurring as single or multiple lesions. Involvement of the liver and spleen can manifest as bacillary peliosis.

Pathologic findings in most tissues are similar and consist of the proliferation of small vessels lined by plump endothelial cells that demonstrate variable atypia in the background of mucinous and fibrotic stroma. This stroma contains variable numbers of neutrophils and aggregates of bacteria that, on hematoxylin-eosin–stained tissue sections, have the appearance of purple-to-amphophilic granular clusters.[5,6]

The main differential diagnosis to consider is Kaposi sarcoma, which morphologically may resemble bacillary angiomatosis and also occurs in immunocompromised individuals, especially human immunodeficiency virus–positive persons. The vessels in Kaposi sarcoma are cleft-like, the endothelial cells are spindled shaped, and there are no aggregates of bacteria present.

It is not entirely clear why an infection by the same species of *Bartonella* causes different clinical and histopathologic manifestations between immunocompetent and immunosuppressed patients. These differences cannot be explained solely by differences in the status of the host immune system. The difference in virulence among the pathogenetic genotypes of *B henselae* and their geographic distribution may play a role, but this remains to be proven. Also, it has been proposed that a specific *Bartonella* factor causing endothelial proliferation is expressed or activated in persons with defective cellular immunity.[5]

This case illustrates the utility of confirming the presence of *B henselae* in formalin-fixed, paraffin-embedded tissue. The production of significant amounts of 153-bp amplicons visualized on the ethidium bromide–stained gel (Figure 4, bottom) specific to *B henselae* DNA from the patient specimen (Figure 4, top) correlates with the abundant amphophilic granular and amorphous material seen on hematoxylin-eosin–stained sections (Figure 3). Early diagnosis of bacillary angiomatosis is essential, since effective antibiotic therapy including erythromycin, azithromycin, or doxycycline is available, and unrecognized disease may lead to a fatal outcome.[7,8]

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