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CASE REPORT

Disseminated *Bartonella* infection following liver transplantation*

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Summary

Bartonella henselae has not only been identified as the causative agent of cat scratch disease, but it is also associated with other significant infectious syndromes in the immunocompromized population. We describe two cases of *B. henselae* associated diseases in liver transplant recipients who both had contact with cats. The first recipient developed localized skin manifestation of bacillary angiomatosis in association with granulomatous hepatitis. He tested positive for Immunoglubulin G (IgG) antibodies against *B. henselae*. The second patient developed axillary lymphadenopathy, with biopsy showing necrotizing granulomatous inflammation and polymerase chain reaction studies were positive for *B. henselae* DNA. Her serology for bartonellosis showed a fourfold rise in antibody titers during her hospitalization. Both patients responded to treatment with Azithromycin in combination with Doxycycline. These were the only cases within a series of 467 consecutive liver transplants performed in 402 patients performed during a 4-year period. Although bartonellosis is a rare infection in liver transplantation recipients, it should always be included in the differential diagnosis of patients presenting with fever, central nervous system (CNS) symptoms, skin lesions, lymphadenopathy, and hepatitis especially if prior contact with cats is reported.

Introduction

Cat scratch disease is caused by *Bartonella henselae*, a small intracellular Gram-negative rod [1–3]. *Bartonella henselae* is one of the more common causes of human *Bartonella* infection [4,5]. Cat scratch disease, as its name implies, is a zoonotic infection, which results from transmission of *B. henselae* from feline reservoirs, to humans, by cat bites and scratches [6,7]. Recovered in culture of clinical specimen only within the past 15 years, *Bartonella* spp. have drawn attention because of a peculiar interaction with host defense by blocking T-cell reaction and the ability to transfer bacterial DNA to eukaryotic cells by virulence associated type IV secretion systems [8]. *Bartonella* causes a variety of disorders in humans including bacillary angiomatosis (BA), peliosis hepatis, meningitis, pneumonia, neuroretinitis, and culture negative endocarditis predominantly in the immunocompromized host. In addition, *Bartonella* can cause pseudocancerous lesions and might function as oncogenic microorganisms [9,10]. The most common initial presentation of bartonellosis is localized acute disease with typical skin lesions and lymphadenopathy. Immunosuppression seems to be the most important factor for disseminated disease [2]. Several case reports describe this disease in transplant recipients [11]. It has been emphasized that accurate diagnosis using serology, special staining or polymerase chain reaction (PCR) enables adequate treatment and favorable outcome. Newer macrolides, quinolones, and tetracycline have been most commonly used to treat cat scratch disease [12]. With lymphadenopathy being a common condition post-transplant, it is important to include cat scratch disease in the differential diagnosis in this population [13].

This article describes the clinical course of two patients who developed cat scratch disease following liver transplantation (LT).

Case report no. 1

A 51-year-old male 5-month status post-LT for end stage liver disease secondary to hepatitis C virus (HCV) was presented to the emergency room with a 2-week history of intense headache, fever up to 101 °F (38.3 °C), night sweats and two erythematous crusting nodular lesions of nearly 0.6 cm each in the lateral aspect below the left knee. A 1-cm nontender, firm, mobile, left inguinal node was found with normal overlying skin. The patient was in contact with a new kitten at home. His immunosuppression included mycophemal mufetil (MMF) and tacrolimus.

Results of his physical examination other than described above were unremarkable. Chest X ray showed mild enlargement of cardiac silhouette, bibasal subsegmental atelectasis, and small amount of right-sided pleural fluid tracking into minor fissures. Computer tomography (CT) scan and magnetic resonance imaging (MRI) of the head were normal. Laboratory studies showed a white blood cell count of 5 000/mm^3 with 68% neutrophils; a hematocrit of 25.5 and a platelet count of 64×10^9/mm^3 . The international normalization ratio was 1.1, alkaline phosphates was 286 IU/l, alorin amino transferase (AST) 66 IU/l, and asparbal amino transferase (ALT) 72 IU/l. Blood cultures were drawn and remained sterile for 7 days; cerebrospinal fluid culture studies were also negative. On hospital day 2, he was started on i.v. Ganciclovir for presumed cytomegalovirus (CMV) disease; however, CMV antigenemia assay remained negative. The hospital course was characterized by persistent headache, fever, photophobia, and malaise. A skin biopsy of the left leg nodular lesions revealed granulomatous inflammatory process compatible with *Bartonella*-associated BA (Fig. 1). Ganciclovir was discontinued and i.v. Azithromycin 500 mg daily was started on hospital day 4. The patient continued spiking fever as high as 40.5 °C (105 °F) and on hospital day 5 Doxycycline (100 mg oral twice daily) was added. On hospital day 6, the left inguinal node was excised and histology showed acute necrotizing lymphadenitis. Gram stain showed numerous white blood cells, but no organisms. Liver biopsy showed granulomatosis hepatitis with focal centrilobular necrosis. Polymerase chain reaction for *B. henselae/quintana* of the left inguinal node was negative. Serum indirect immunofluorescence assay for *Bartonella* serology showed *B. henselae* IgM <1:20 and IgG 1:256 and *Bartonella* quintana IgM <1:20 and IgG 1:512. The patient defervesced after 7 days and had full resolution of all symptoms and skin lesions. Doxycycline was stopped and he continued therapy with Azithromycin 500 mg daily for a total of 2 months. Repeat liver biopsy after six weeks revealed resolution of the granulomatous hepatitis and AST and ALT normalized. The patient is alive with a well functioning graft 5 years after this infectious episode.

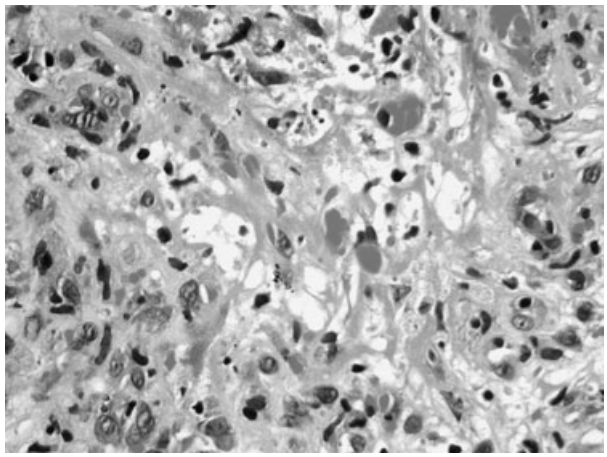

Figure 1 Cutaneous lesion with vascular proliferation, mixed inflammation and karyorrhexis consistent with bacillary angiomatosis (Hematoxylin and eosin, ×400).

Case report no. 2

A 62-year-old female 9-month after LT for end stage liver disease secondary to cryptogenic cirrhosis was admitted because of headache, fever up to 38.8 °C (102 °F), and progressive neck pain with rigors. Past medical history included type II diabetes mellitus, chronic renal insufficiency, and pulmonary tuberculosis that was appropriately treated with a full course of antituberculous therapy. The post-transplant course was complicated by tacrolimus-associated neurotoxicity requiring switch to Cyclosporine A (CsA). At the time of her admission, immunosuppression included CsA, MMF, and prednisone. She reported having contact with her grand daughter's kitten 2 months prior to the onset of symptoms. Physical examination was unremarkable except for right axillary lymphadenopathy. Chest films showed areas of parenchymal scarring at the right apex and base, but no evidence of active disease. Laboratory studies showed a white blood cell count 5 400/mm^3, the hematocrit was 26% and the platelet count was 112×10^9/mm^3 . International normalization ratio was 1.2, alkaline phosphate was 411 IU/l, AST was 25 IU/l, and ALT was 31 IU/l. Blood cultures, serum and cerebrospinal fluid (CSF) cryptococcal antigen, cerebrospinal fluid and chlamydia serology were all negative.

During hospitalization, the fever and headache persisted with development of progressive nausea and vomiting. On the second hospital day, she underwent

esophagogastroscopy, which was normal. She was started on i.v. ganciclovir for suspected CMV disease, but she remained febrile. CMV studies and biopsies from the upper endoscopy remained negative. On hospital day 8, she was started on Levofloxacin 500 mg daily and became afebrile with resolution of the nausea.. On hospital day 4, a chest radiograph showed change consistent with congestive heart failure, interstitial edema, and moderate size right pleural effusion. The bartonellosis serology at admission was negative, but repeat serology on hospital day 14 showed the presence of *B. henselae* IgG >1:1024 and *Bartonella* quintana IgG >1:1024 indicating fourfold rise in antibody titers. The right axillary node was biopsied on hospital day 11 and showed necrotizing granulomatous inflammation with features suggestive of cat's scratch disease (Fig. 2). Warthin–Starry stain and acid fast bacilli (ASB)-stain were negative from the right axillary lymph node, but PCR studies were positive for *B. henselae* DNA. The patient was discharged on hospital day 15 and continued on Levofloxacin with subsequent improvement of symptoms. Levofloxacin was discontinued and Azithromycin 500 mg daily was started. Therapy was continued for 6 months and the patient is currently alive with a well functioning liver graft 5 years following this infection.

Discussion

Both of our cases showed that awareness of a possible *Bartonella* infection in the post-transplant setting followed by diagnosis and adequate treatment is associated with a good outcome. The clinical presentation for bartonellosis should be considered in patients with fever, malaise, lymphadenopathy, skin lesions, and an elevated alkaline phosphatase in the context of contact with a cat or kitten [14–19].

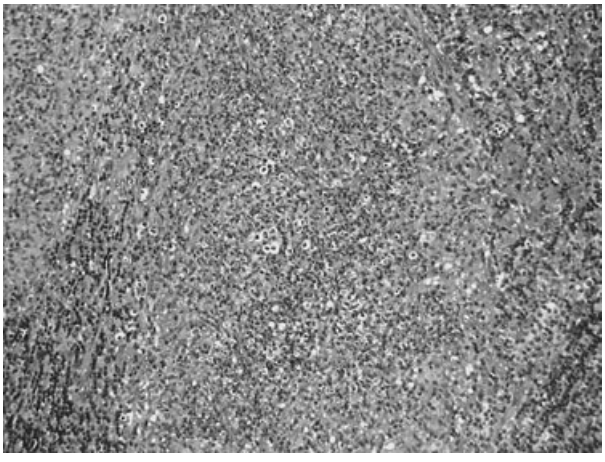

Figure 2 Lymph node biopsy: cat scratch disease with necrotizing granulomatous inflammation (Hematoxylin and eosin, ×100).

In the early 90s, the gram-negative bacterium *B. henselae* was first shown to be a causative agent of BA, peliosis hepatis, and bacteremia. Later studies have shown that this bacterium is involved in cat scratch disease [1]. Bacillary angiomatosis is a vascular-proliferative disorder and has been mostly reported in patients with acquired immune deficiency syndrome [2]. However, it has also been found in patients receiving immunosuppressive agents after bone marrow, renal, cardiac and liver transplants, as well as in immunocompetent patients [20–24]. Skin manifestations are the most common, but the bacillus may also be identified in bone, lymph nodes, central nervous system, bronchial mucosa, lung pleura, oral mucosa, spleen, and liver (bacillary peliosis hepatis).

Bacillary peliosis hepatis is a unique lesion composed of blood-filled spaces affecting the liver. Most cases of bacillary peliosis have been reported in HIV patients with AIDS, whereas granulomatous hepatitis is more common in immunocompetent patients. Both types of liver involvement have been described in transplant recipients [17,18]. Peliosis hepatis has also been described in association with tuberculosis, anabolic and androgenic steroids, malignant tumors, and immunosuppressive agents such as azathioprine and cyclosporine and can also involve other organs [25].

The diagnosis of *Bartonella* can be difficult as the presentation can obscure and the organism has been found to be able to escape immune defense [27–29]. The patient's clinical history is critical to make the diagnosis as *B. henselae* is associated with cat exposure [26].

Fever, high alkaline phosphatase and histopathologic findings consistent with BA in this clinical setting are of high predictive value for bartonellosis, which is similar to presentation in HIV-infected individuals. Koehler *et al.* showed that there is a significant potential for *Bartonella* infection in HIV patients presenting with fever and who are blood culture negative [30]. They also described the difficulties in making the diagnosis and the need for standardization of microbiology diagnostic techniques. Reported cases of bartonellosis in solid organ transplant recipients have shown that the most common sites of infection are lymph nodes, liver, spleen, and skin. New culture techniques and media have been described; however, their value in clinical settings has yet to be determined [31,32].

The current diagnostic methods were demonstrated in our cases. The serologic studies were diagnostic in both cases as titers of serologically immunofluorescent IgG antibody to *Bartonella* species ≥1:64 are considered positive evidence of infection. Obtaining histologic data was crucial to make the diagnosis in both cases. The liver biopsy in the first case demonstrated granulomatous hepatitis consistent with *Bartonella* infection. Lymph node

biopsies in both cases were consistent with *Bartonella* infection. Although the PCR of the lymph node was negative in the first case, it was positive in the second case helping to confirm the diagnosis. Polymerase chain reaction testing has been developed as a diagnostic tool [33] and appears to be a useful addition but a negative result should not exclude infection. The Warthin–Starry stain at least in one of these cases was not of diagnostic benefit.

Reported cases of disseminated *Bartonella* infection in transplant recipients have been seen to have excellent response to Azithromycin, erythromycin, and Doxycycline. When using macrolide antibiotics, drug interaction with calcineurin inhibitors must be considered [34].

In conclusion, with an expanding spectrum of pathogens associated with infections in immunocompromized individuals [35], *Bartonella henselae* disseminated infection should be considered in organ transplant recipients when they present with signs and symptoms consistent with generalized infection and a history of exposure to cats.

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