

Bartonella Infection Presenting With Prolonged Fever in a Pediatric Renal Transplant Recipient

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Citation

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Abstract

Bartonella henselae infection is a common zoonosis acquired from cats. In immunocompetent individuals, it can present with a broad range of clinical symptoms including short lasting fever, regional lymphadenopathy, prolonged fever of unknown origin and hepatic or splenic granulomas. *Bartonella* infection in immunocompromised patients is more likely to present with a systemic illness. We describe an adolescent kidney transplant recipient who presented with prolonged fever without a focus fever of unknown origin caused by *Bartonella* infection. This case highlights the fact that *Bartonella henselae* infection must be considered in immunocompromised patients, including transplant recipients, with unexplained fever.

INTRODUCTION

Bartonella henselae infection is a common zoonosis transmitted by cats. Immunocompromised hosts tend to follow an atypical course with prolonged fever and systemic involvement. It may be difficult to differentiate from other causes of fever. Vigilant search for this infection is necessary to make a diagnosis.

CASE REPORT

A 16-year-old Caucasian female with history of fever for one week was admitted to the renal service. She complained of back and neck pain for three days prior to the onset of fever. The family recalled that the patient had a maximum temperature of 38.5°C at home. She had been given acetaminophen with limited antipyretic effects. Vomiting and loose stools developed one day before hospital admission.

The patient was born with complex cloacal anomalies and obstructive uropathy requiring multiple surgical procedures for her uro-genital malformations. She received a non-related live donor kidney transplant 19 months before this admission. At the time of transplantation, her cytomegalovirus (CMV) and Epstein Barr virus (EBV) antibodies were negative and positive respectively. The donor was positive for both CMV and EBV. The patient

received CMV immunoglobulin and valganciclovir prophylaxis after the transplant. She had never experienced a rejection episode. She had been admitted several times for lymphocele drainage before this admission. Her immunosuppression included prednisone 5 mg daily, mycophenolate mofetil 750 mg twice daily and tacrolimus 2.5 mg twice daily. She was also receiving cotrimoxazole at night for urinary tract infection prophylaxis due to the need for self-catheterization through a Mitrofanoff catheterizable stoma. She did not have any history of traveling to a foreign country. There were three adult cats and a dog in the household. She had also played with stray cats but she reported no recent bite or scratch by her cats. There was no other animal exposure or history of potential tick exposure.

Vital signs at time of admission were as follows: temperature 38.9°C, pulse 116 per minute, and blood pressure 113/69 mmHg. She weighed 47.4 kg and her height was 149.5 cm. On physical examination, she was mildly ill looking without signs of dehydration. No lymphadenopathy, rashes or skin lesions were detected. Her ear, nose and throat examinations were normal. She also had normal respiratory and cardiovascular examinations except for mild tachycardia. Abdominal examination showed no hepatomegaly, but her spleen was palpable 4 cm below the left costal margin. She had a Mitrofanoff catheterizable

stoma in her lower abdomen; this appeared normal.

She was empirically started on intravenous piperacillin sodium/tazobactam and itraconazole to cover for bacterial or fungal infection. Post-transplant lymphoproliferative disease was also considered and immunosuppression was decreased. Her EBV viral load by polymerase chain reaction (PCR) showed 150 to 15,999 copies/ml whole blood on day 2 of admission. This is a level that has not typically been associated with clinical disease in transplant patient. Ultrasound of her abdomen upon admission showed a small collection of fluid in the pelvis and a normal appearing renal allograft. It also revealed a normal appearing liver, a poorly visualized gallbladder, and an enlarged spleen with multiple hypoechoic lesions. Two days later, she had a MRI with contrast of her abdomen in order to search for other intra-abdominal pathology. Despite the fact that no lesion was found in the liver on the ultrasound, the MRI showed multiple enhancing nodules in the both the liver and spleen (Fig. 1).

Figure 1

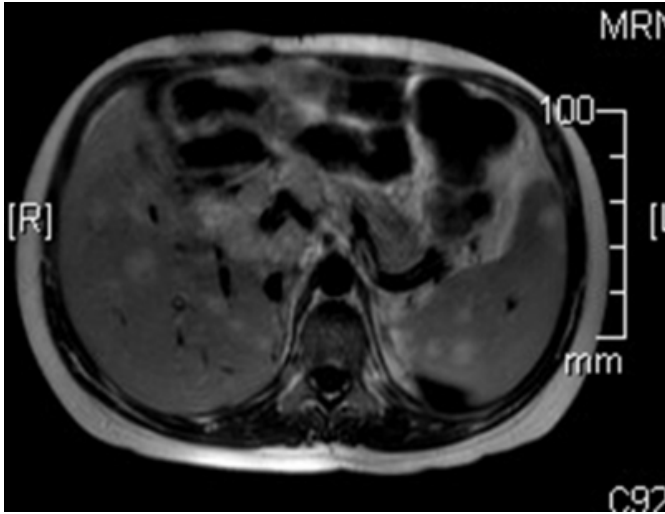
Table 1: Initial Laboratory results including sepsis work-up after admission. BUN= Blood Urea Nitrogen; AST= Aspartate transaminase; ALT= Alanine transaminase.

			Ref Range
White Blood Cell Count	3.4	10 ³ /mm ³	(5 – 13)
Hemoglobin	10.7	g/dL	(11 – 16)
Hematocrit	31.7	%	(33 – 48)
Platelet Count	118	10 ³ /mm ³	(140 – 450)
Sodium	140	mmol/L	(135 – 145)
Potassium	5.3	mmol/L	(3.5 – 5.0)
Chloride	111	mmol/L	(98 – 107)
Carbon Dioxide	19	mmol/L	(18 – 27)
BUN	27	mg/dL	(6 – 20)
Creatinine	2.0	mg/dL	(0 – 0.9)
Glucose	88	mg/dL	(60 – 115)
Calcium	8.7	mg/dL	(8.6 – 11.0)
Total Protein	6.2	g/dL	(6.3 – 8.6)
Albumin	3.2	g/dL	(3.7 – 5.6)
Total Bilirubin	0.2	mg/dL	(0.2 – 1.0)
AST	36	IU/L	(15 – 40)
ALT	27	IU/L	(2 – 15)
Alkaline Phosphatase	125	IU/L	(96 – 437)
C-reactive Protein	9.0	mg/dL	(0.3 – 0.9)
Tacrolimus Level	12.2	ng/ml	
Influenza A & B Antibody	negative		
Cytomegalovirus Culture	negative		
Blood Viral Culture	negative		
Blood Culture	negative		
Urine Culture	negative		
Stool Culture	No bacterial pathogen Positive <i>Enterovirus</i>		
Marrow <i>Mycobacterium</i> Culture	negative		
<i>Bartonella henselae</i> IgG	1:64		
<i>Bartonella henselae</i> IgM	<1:16		
<i>Bartonella quintana</i> IgG	<1:64		
<i>Bartonella quintana</i> IgM	<1:16		
Histoplasma Yeast Titer	<1:8		
Histoplasma Mycelial Titer	<1:8		
Blastomyces Titer	<1:8		
Coccidioides Antibody Titer	<1:2		

Table 1 depicts the patient's initial laboratory data including the results of her work-up for sepsis.

Figure 2

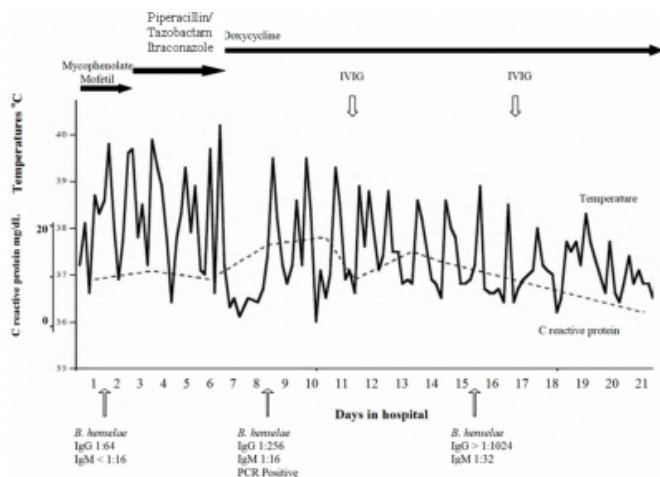
Figure 1: MRI of the abdomen showing multiple gadolinium enhanced nodules in liver and spleen.



Para-aortic lymphadenopathy was also noted. Bone marrow aspirate done after five days of admission showed normal cellularity and culture for Mycobacterium mycobacteria and fungus were subsequently negative. Doxycycline was started on day six of hospitalization when she was found to have an IgG antibody titer of 1:64 to Bartonella henselae (Fig. 2).

Figure 3

Figure 2: Fever, titers, C-reactive protein levels and treatments after hospitalization



The empirical antibiotics and anti-fungal agents were discontinued. A diagnosis of bartonellosis was confirmed when her Bartonella henselae PCR on whole blood (sent on day six of admission) was later reported to be positive (Real time PCR performed by Associated Regional and University Pathologists, Inc., Salt Lake City, Utah), and the repeat Bartonella henselae titers increased markedly (Fig. 2). Two

days after the patient was put on doxycycline, a single stool culture was positive for Enterovirus and she received two doses of intravenous immunoglobulin (IVIG). She developed non-oliguric renal failure with maximum creatinine of 4.9 mg/dL on day 11. This was felt to be due to elevated tacrolimus levels and to the ibuprofen she received in an attempt to control her high fever. She recovered with intravenous rehydration and adjustment of her tacrolimus dose. She also had a transient but rapid increase in her liver transaminases seven days after starting doxycycline; levels returned to normal without any treatment. MRI of her abdomen at that time showed marked resolution in the hepatic and splenic lesions. A repeat of the EBV PCR from blood on day 15 showed an increase of virus copies to 16,000 to 800,000 copies/ml blood. This level of viremia has been associated with an increased risk of having or developing EBV infection or EBV related lymphoproliferative disease. However, no further changes in her immunosuppression were made at this time. A subsequent EBV PCR two weeks after discharge was less than 150 copies/ml blood. Her fever came down gradually after the initiation of doxycycline and she was discharged from the hospital on day 21. At six month follow up after her illness, she has remained afebrile with normal liver function and a normal serum creatinine of 0.9 mg/dL.

DISCUSSION

Bartonella henselae was initially isolated in cat species in 1990, and cats remain the only known natural reservoir (1). Bartonellosis has broad clinical manifestations. It typically presents in immunocompetent individuals with low-grade fever, cutaneous papules and regional lymphadenopathy (2). Although bartonellosis is usually transient and benign in nature, systemic complications had have been reported in 5% to 14% of cases (2, 3). A review of the literature shows that complications such as Parinaud's oculoglandular syndrome, osteolytic lesions, encephalopathy, pneumonia, arthritis, transverse myelitis and necrotizing glomerulonephritis occur in rare circumstances (4, 5, 6, 7). Jacobs and Schutze (8) describe reported Bartonella henselae infection as to be the third most common infectious etiology of fever of unknown origin in children. Tsujino et al. have reported their experience with Bartonella infections in 127 immunocompetent children; they found that a lack of lymphadenopathy was associated with an increased likelihood of prolonged fever and systemic complications (9).

There is substantial evidence that Bartonella species are an important pathogens in immunocompromised individuals,

and Bartonella infection should be included in the differential diagnosis in organ transplant recipients with fever without a focus (4,8). Moreover, bartonellosis in patients receiving immunosuppressive therapy after organ transplantation may present in a more aggressive manner. Besides persistent bacteremia and unexplained fever, clinical manifestations may include generalized lymphadenopathy, peliosis hepatis, bacillary angiomatosis, pulmonary nodules, sternal abscess and cardiovascular shock. Acute renal allograft rejection has been reported in patients with bartonellosis after organ transplantation (10, 11, 12, 13, 14, 15).

Peliosis hepatis is a well-characterized, angiogenic lesion with invasion of endothelial cells by *Bartonella henselae* that has been well described in Bartonella infection in immunodeficient hosts (16). It requires a characteristic histological diagnosis with biopsy showing multiple blood-filled spaces in the liver. In our patient, although only splenomegaly was detected on clinical examination, the MRI showed multiple hypodense enhancing lesions in both the liver and spleen with para-aortic lymphadenopathy that were suggestive of lymphoproliferative disease or or infection visceral organ involvement. We were not able to differentiate the patient's hepatic lesions from granulomas since liver biopsy was not performed. It is also not possible to rule out EBV (PTLD) as a coinfection in this patient for the same reason. At the time of admission, concern about this entity led to a reduction in her immunosuppression. Quantitative PCR of her blood did not indicate a high risk for this condition at initial presentation although a subsequent increase in the amount of detectable virus two weeks later and the appearance of the visceral lesions on MRI might be suggestive of possible PTLD. The slow resolution of symptoms and the visceral lesions could have been the result of the reduction in immunosuppression. However, it seems more likely that her symptoms were secondary to systemic bartonellosis: she had significant recent exposure to cats in addition to rising titers against *B. henselae* and a positive blood PCR for *B. henselae* DNA.

As illustrated by our patient, Bartonella infection in immunosuppressed patients may be difficult to diagnose due to its non-specific clinical manifestations. A recent study from Israel indicated that anti-*Bartonella henselae* immunoglobulin M (IgM) antibodies remained positive for less than 3 months in most patients with Bartonella infection (17), and the presence of IgM antibodies against *Bartonella henselae* indicated an acute infection. Our patient had a more than four fold increase in the IgM titers, which was highly

suggestive of recent infection. Although she received IVIG for possible systemic Enterovirus infection (blood PCR for Enterovirus was negative), this should not have affected her Bartonella IgM titers. In addition, her Bartonella IgG titers increased from 1:64 to 1:256 before the administration of IVIG. The diagnosis of Bartonella infection was further confirmed by detection of *Bartonella henselae* DNA in blood by real time PCR.

Bartonella is susceptible to many antimicrobials in vitro, and anecdotal reports have indicated that ciprofloxacin, rifampicin and cotrimoxazole may all be effective treatments, but most investigators have observed no benefit with antibiotic treatment in immunocompetent hosts (17, 18, 19). The only published prospective double blinded, placebo-controlled treatment trial was reported by Bass et al. on the treatment of immunocompetent patients with uncomplicated cat scratch disease using azithromycin (18). No difference in the clinical outcomes was noted except that the rate and degree of initial reduction in lymphadenopathy was greater in treated patients. Although treatment is not usually recommended in immunocompetent patients, it is frequently necessary in immunocompromised patients since the clinical course of Bartonella infection may be much more prolonged and potentially life-threatening (13). There are still no accepted guidelines for treatment of Bartonella in immunocompromised hosts. As our patient had already been on cotrimoxazole prophylaxis when she developed this infection, the decision was made to use doxycycline rather than azithromycin to avoid interaction with tacrolimus. Although her febrile illness resolved slowly with the administration of doxycycline, it is unclear whether the resolution of her symptoms was due to the administration of doxycycline, a reduction of her immunosuppression or the natural course of her disease.

CONCLUSION

Bartonella infection should be included in the differential diagnosis in immunosuppressed patients with prolonged fever. Serology and direct detection for Bartonella DNA by real time PCR are helpful in confirming the diagnosis. Imaging studies of the liver and spleen should also be considered.

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