Open Forum Infectious Diseases

BRIEF REPORT

Serious and Atypical Presentations of *Bartonella henselae* Infection in Kidney Transplant Recipients

Feline Bos,[1] Bertrand Chauveau,[2,3] Jules Ruel,[1] Gabriel Fontant,[1] Elise Campistron,[1] Camille Meunier,[1] Frédéric Jambon,[1] Karine Moreau,[1] Yahsou Delmas,[1] Lionel Couzi,[1,3] Skander Korbi,[2] Manon Charrier,[1] Jean-François Viallard,[3,4] Léa Luciani,[5] Pierre Merville,[1,3] Estibaliz Lazaro,[3,4] and Hannah Kaminski[1,3]

[1]Department of Nephrology, Transplantation, Dialysis and Apheresis, Bordeaux University Hospital, Bordeaux, France, [2]Department of Pathology, Bordeaux University Hospital, Bordeaux, France, [3]Centre National de Recherche Scientifique Unité de Recherche Mixte 5164 ImmunoConcEpT, Bordeaux University, Bordeaux, France, [4]Department of Internal Medicine, Bordeaux University Hospital, Bordeaux, France, and [5]Centre National de Référence des Rickettsies, Coxiella et Bartonella Institut Hospitalo-Universitaire-Méditerranée Infection, Assistance Publique de Hôpitaux de Marseille, Marseille, France

This article describes 5 cases of bartonellosis with fever and atypical clinical presentations in kidney transplant recipients: thrombotic microangiopathies, recurrent hemophagocytosis, and immune reconstitution syndrome after treatment. The diagnosis, the pathological lesions, and treatments are described. Bartonellosis must be researched in solid organ transplant recipients with fever of undetermined origin.

Keywords. *Bartonella*; hemophagocytosis; immune reconstitution syndrome; solid organ transplant recipient; thrombotic microangiopathy.

Cat scratch disease is caused by an infection with *Bartonella henselae*, which are fastidious, gram-negative, facultative intracellular bacilli with a tropism for erythrocytes and endothelial tissue [1]. Cats are the main reservoir [2]. Transmission to humans is by scratching, biting, or rarely by a vector (cat fleas or ticks) [3].

In immunocompetent individuals, the typical clinical presentation consists of 1 or multiple inflammatory, sensitive, and sometimes suppurative adenopathies located in the drainage area of the inoculation site [4].

In immunocompromised patients, disseminated and atypical forms are more frequent, sometimes leading to a severe evolution. *Bartonella henselae* infection may manifest itself as fever of undetermined origin, endocarditis with negative blood culture, or angioproliferative lesions. *Bartonella* in immunocompromised patients is generally described as bacillary angiomatosis and hepatic and splenic peliosis. In solid organ transplant patients, disseminated forms account for two-thirds of cases [4, 5].

At Bordeaux University Hospital, we observed 5 severe cases of *B henselae* infection in kidney transplant recipients, within a year, with atypical clinical presentation and diagnosis.

CASE REPORTS

Characteristics of all patients and immunosuppressive regimens are summarized in Table 1, and biological features at admission are shown in Figure 1A.

Case 1

A 36-year-old woman received a kidney 3 years ago for an immunoglobulin A (IgA) nephropathy. She owned 1 young cat.

She was admitted for impaired kidney function and fever. Initial biological testing revealed anemia, thrombocytopenia, and thrombotic microangiopathy (TMA) stigmatas (elevated lactate dehydrogenase, collapsed haptoglobin, and schizocytes). The graft biopsy found glomerular and arteriolar TMA (Figure 1C). Plasma exchange was initiated in a possible infectious setting. The etiological search for TMA was normal and all microbiological documentation remained negative.

A fluorodeoxyglucose positron emission tomography (FDG-PET) scan revealed a hypermetabolic lesion of the liver. A liver biopsy was performed and found an inflammatory infiltrate, foci of sinusoidal dilatation containing macrophages compatible with peliosis. *Bartonella henselae* polymerase chain reaction (PCR) was found positive in the liver, but not in renal parenchyma. *Bartonella* serology in serum was at first negative and became positive after 3 weeks, and then negative again. Doxycycline was administered as monotherapy for 4 months. Mycophenolic acid was stopped until *Bartonella* infection resolution. The evolution was favorable, but 2 months after the end of the antibiotic treatment, the patient had a recurrence of fever associated with inguinal lymphadenopathy and angiomatous papule of the calf [6]. The biopsy of the skin lesion suggested a bacillary angiomatosis. *Bartonella henselae* PCR was positive in the biopsy, confirming the recurrence (after a new cat scratch). Evolution was favorable with doxycycline treatment for 4 months (Figure 1B).

Case 2

A 75-year-old woman received a kidney graft 13 years ago for nephropathy of undetermined origin. She was admitted for fever, a skin injury to the wrist with axillary lymphadenopathy, and acute degradation of chronically impaired renal function. She owned a cat.

Received 14 December 2021; editorial decision 26 January 2022; accepted 3 February 2022; published online 5 February 2022.

Correspondence: Feline Bos, Department of Nephrology, Transplantation, Dialysis and Apheresis, Bordeaux University Hospital, Bordeaux, France (feline.bos@live.fr).

Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofac059

Table 1. Characteristics of Cases

Case	Age, y	Sex	Time to Tx, y	Immunosuppressive Regimen	Rejection	Clinical Presentation	Serology	Blood PCR	Tissue PCR	Treatment	Outcome
1	36	F	3	Tacrolimus, mycophenolic acid, prednisone 5 mg	No	TMA	Transitorily positive	Negative	Positive in liver	Doxycycline, 3 months	Recurrence
2	75	F	13	Tacrolimus, mycophenolic acid, prednisone 5 mg	Yes: chronic humoral rejection, 2012	TMA	Negative	Negative	Positive in skin and lymph node	Doxycycline and erythromycin, 4 months	Cure of infection, returned to hemodialysis
3	56	F	13	Tacrolimus, mycophenolic acid, prednisone 5 mg	Yes: chronic humoral rejection, 2021	TMA	Negative	Positive	Negative in renal parenchyma	Doxycycline and erythromycin, 3 months	Cure
4	54	M	2	Cyclosporin, prednisone 5 mg	No	Recurrent hemophagocytosis	Negative	Positive	Positive in liver	Long-term doxycycline	Clinical cure, persistence of *Bartonella henselae* in liver
5	78	M	17	Sirolimus, mycophenolic acid	No	Immune reconstitution syndrome after *Bartonella* infection	Negative	Negative	Positive in liver	Doxycycline 3 months	Cure

Abbreviations: F, female; M, male; PCR, polymerase chain reaction; TMA, thrombotic microangiopathy; Tx, transplantation; y, year.

Skin and lymph node biopsy were in favor of bacillary angiomatosis. Graft biopsy showed lesions of glomerular TMA. *Bartonella henselae* PCR was positive in the skin and node but negative in the kidney. *Bartonella* serology remained negative. A favorable infectious evolution was obtained with doxycycline and erythromycin treatment during 4 months for the bartonellosis. Her immunosuppressive regimen was not changed. The kidney function did not improve, and she returned to hemodialysis.

Case 3

A 56-year-old woman received a kidney graft 13 years ago for nephropathy of undetermined origin. She was admitted with fever, asthenia, and acute kidney failure associated with biological stigmatas of TMA.

She owned 4 cats and had scratches on her forearm with an axillar adenopathy. The *B henselae* PCR on blood was positive. The *Bartonella* serology was negative. Search for other causes of TMA was negative. A kidney graft biopsy was performed, which confirmed the TMA with multiple arteriolar thrombosis. The *Bartonella* PCR in renal parenchyma was negative. She was treated with doxycycline and erythromycin for 3 months with a regression of TMA stigmatas and improvement of kidney function. It was concluded to be *B henselae* infection linked to TMA. Her immunosuppressive regimen was not changed.

Case 4

A 54-year-old man received a kidney transplant 2 years earlier following anti-neutrophil cytoplasmic autoantibody vasculitis. He owned 2 cats.

He presented with recurrent hemophagocytosis episodes confirmed with medullar examinations: 3 during the last 6 months, without etiologic documentation. The episodes resolved with multiple etoposide administrations, broad-spectrum antibiotic treatment, and intensive care support.

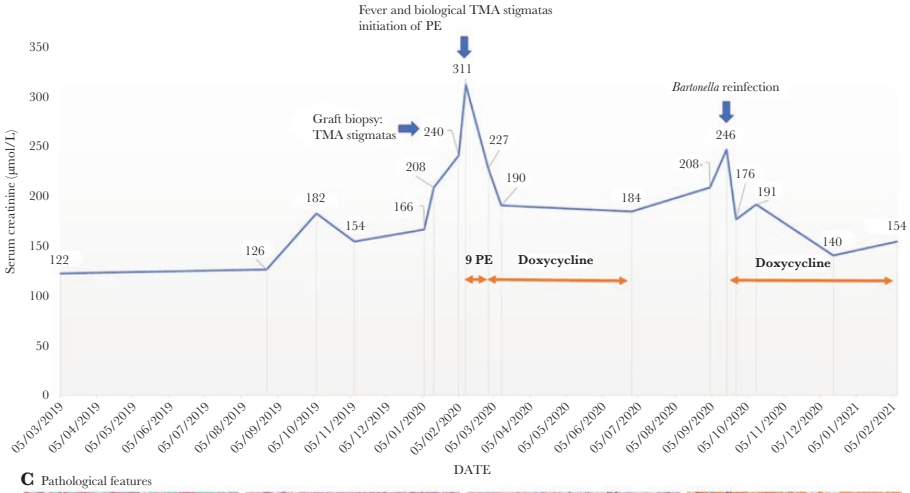
At the third episode, a liver biopsy was performed because he had unexplained chronic cholestasis associated with hepatic micronodules on the computed tomography (CT) scan. The liver biopsy found vascular lesions with dilatation of the sinusoids and marked regenerative nodular hyperplasia. Neutrophilic microabscesses were focally seen (Figure 1C), as well as clusters of bacilli (Figure 1C) in the sinusoids, stained by Warthin-Starry, suggestive of bacillary angiomatosis. The presence of Küpferian hyperplasia with hemophagocytosis confirmed the macrophagic activation syndrome (Figure 1C).

The diagnosis of bartonellosis was confirmed by a positive PCR in the liver tissues and blood. The *Bartonella* serology remained negative all along. Fever and inflammatory stigmatas evolved favorably with doxycycline for 4 months. No relapse occurred after *Bartonella* curative treatment. His immunosuppressive regimen was not changed.

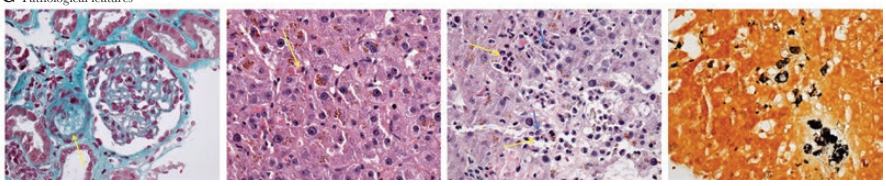
A Biological features

Marker (unit)	Case 1	Case 2	Case 3	Case 4	Case 5
Urea (mmol/L)	19.3	38.3	37.9	6.8	8.6
Creatinine (µmol/L)	311	374	333	143	76
GFR (mL/min) CKP-epi	15.9	9.7	12.8	47.8	59.2
Ferritin (ng/mL)	unknown	458	unknown	2147,7	789
CRP (mg/L)	76.4	79.5	240	96.9	94
Leukocytes (g/L)	3.7	2.6	4.85	3.1	4.7
Neutrophils (g/L)	2.91	2.08	3.97	2.9	unknown
Lymphocytes (g/L)	0.35	0.16	0.28	0.36	unknown
Hemoglobin (g/dL)	6.6	10.4	8.1	10	9.4
Platelets (g/L)	70	113	60	78	415

B Serum creatinine evolution after treatment in case 1



C Pathological features



Case 1:: Kidney allograft biopsy (Masson trichrome, original magnification ×400) showing mucoid intimal thickening with arteriolar occlusion next to an ischemic glomeruli

Case 4:: Liver biopsy (HES, original magnification ×400), displaying hemophagocytosis (arrow)

Case 4:: Liver biopsy (HES, original magnification ×400), showing sinusoidal dilatation with neutrophils (yellow) and macrophages (blue)

Case 4:: Liver biopsy (Warthin-Starry, original magnification ×400), showing positive stains compatible with bacilli accumulation

Figure 1. *A*, Biological features. *B*, Creatinine evolution in case 1. *C*, Pathological features. Abbreviations: CKD-epi, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; GFR, glomerular filtration rate; HES, hematoxylin-eosin saffron; PE, plasma exchange; TMA, thrombotic microangiopathy.

During follow-up, a liver biopsy was performed for chronic biological liver disorders and found a positive *Bartonella* PCR. Doxycycline was reintroduced and is still ongoing.

Case 5

A 78-year-old man received a graft 17 years earlier following an IgA nephropathy. He owned 1 cat. He was referred for fever, diarrhea, and anicteric cholestasis. The FDG-PET scan found a hypodense and hypermetabolic hepatic lesion associated with multiple retroperitoneal adenopathies. The liver biopsy showed fibro-inflammatory areas with the presence of epithelioid and gigantocellular granulomas with central suppurated necrosis, compatible with bartonellosis. This was confirmed by a *B henselae*–positive PCR in the biopsy. The serology remained negative.

Treatment with doxycycline was introduced. He had a recrudescence of fever and biological inflammatory syndrome. Infectious samples returned all negative and no new antibiotics were introduced. A CT scan showed the appearance of a pulmonary miliary with multiple bilateral micronodules.

The diagnosis of immune reconstitution syndrome after the introduction of treatment for *Bartonella* was evoked. Rapamycin was replaced by cyclosporin A for 1 month. Prednisolone was increased at 20 mg/day for 2 weeks, with withdrawal at 1 month. The evolution was favorable.

DISCUSSION

The diagnosis of 5 patients with bartonellosis in <1 year was unusual for our center, which performs about 200 kidney

transplants per year. We made a statement to the Regional Health Agency (Agence régionale de santé) to see if there was an explanation for this resurgence of cases. This revealed an increase in the percentage of positive serologies from 5.7% in 2019 to 9.2% in 2020. As all patients had a cat, a major risk for bartonellosis, contact with cats should be examined for every patient with fever of unknown origin. This could also be an indirect consequence of the lockdown phase of coronavirus disease 2019, which strengthens the bond between individuals and their companion [7].

It is well known that there is a wide range of clinical presentations in immunocompromised patients who have *B henselae* infections. In this series of 5 bartonellosis cases, all patients presented with fever of unknown origin, 3 with evocative skin lesions, and 2 with adenopathy. In 3 patients, the clinical presentation was poor but severe with TMA or hemophagocytosis. *Bartonella* is a very rare cause of TMA but was found in 3 of our 5 described kidney transplant recipients. According to current knowledge on the pathophysiology of *Bartonella* infection, the vascular endothelium is probably the main niche that supports the bacterial proliferation [1]. The transendothelial migration of lymphocytes is promoted by *Bartonella*, which upregulates the NF-κB pathway [1]. The resultant inflammatory reaction could help bacteria to form vascular tumors through the production of cytokines and vasoproliferative factors [1]. It could also induce endothelial damage, by a proinflammatory context and by activating the complement pathway, similar to the Shiga toxin–producing *Escherichia coli*–associated hemolytic uremic syndrome [8, 9]. As previously described, *Bartonella* species partially escape complement activation by a modified lipopolysaccharide chain, but it is possible that immunocompromised hosts have higher bacterial load and complement activation occurs anyway [10]. We also noticed a case of immune reconstruction syndrome after antibiotic initiation. This complication has been described in organ transplant patients with granulomatous infections (tuberculosis, atypical mycobacteria) but not with bartonellosis [11, 12].

In our experience, the best way to diagnose *Bartonella* infection is to perform a tissue biopsy for a 100% sensitive PCR. Even if there are mild biological liver abnormalities, a liver biopsy is useful to have the diagnosis of bartonellosis. In some patients, a blood PCR for *B henselae* has been found positive (40%) [13]. The serology in immunocompromised patients has a very low sensitivity; it was negative in 4 patients and transitorily positive in 1 patient. A blood PCR should rapidly be performed in case of fever in immunocompromised patients, even in atypical clinical presentations. The sensitivity is low and does not rule out the diagnosis if negative, but it helps to have a quick diagnosis and prevent an invasive procedure, especially in case of TMA with severe thrombocytopenia.

The final challenge for immunocompromised patients is the duration of treatment, as there are no guidelines. For 1 patient, reinfection was identified, for another, chronic liver damage persisted and he is still treated with antibiotics. The duration of treatment varies from 5 days to 12 months among transplant recipients, and most reports do not relapse despite shorter treatment durations. However, in patients who relapse, lifelong treatment may need to be considered if the patient does not relinquish their cat.

In summary, bartonellosis is a nonexceptional cause of fever of unknown origin in transplant patients and may be responsible for atypical presentations and serious complications [13]. The transplant and infectious disease physicians should be aware of this diagnosis.

Notes

Patient consent. All of the data concerning the medical history of these patients were collected from the digital database of our institution: the RAN database (Commission Nationale de l'informatique et des Libertés final agreement, decision 2009-413, number 1357154, 2 July 2009). All patients gave their written consent for the use of their data for medical research. This study was approved by the institutional review board (reference number CERBDX-2021-50).

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Dehio C. *Bartonella*—host-cell interactions and vascular tumour formation. Nat Rev Microbiol **2005**; 3:621–31.
2. Chomel BB, Boulouis H-J, Maruyama S, Breitschwerdt EB. *Bartonella* spp. in pets and effect on human health. Emerg Infect Dis **2006**; 12:389–94.
3. Kaiser PO, Riess T, O'Rourke F, Linke D, Kempf VAJ. *Bartonella* spp.: throwing light on uncommon human infections. Int J Med Microbiol **2011**; 301:7–15.
4. Psarros G, Riddell J, Gandhi T, Kauffman CA, Cinti SK. *Bartonella henselae* infections in solid organ transplant recipients: report of 5 cases and review of the literature. Medicine (Baltim) **2012**; 91:111–21.
5. Pischel L, Radcliffe C, Vilchez GA, Charifa A, Zhang X-C, Grant M. Bartonellosis in transplant recipients: a retrospective single center experience. World J Transplant **2021**; 11:244–53.
6. Ilyas M, Maganty N, Ginsberg Z, Sharma A. Skin infections due to bacteria in solid organ transplant recipients: a review. Dermatology **2017**; 233:358–65.
7. Kogan LR, Currin-McCulloch J, Bussolari C, Packman W, Erdman P. The psychosocial influence of companion animals on positive and negative affect during the COVID-19 pandemic. Animals **2021**; 11:2084.
8. Travert B, Rafat C, Mariani P, et al. Shiga toxin–associated hemolytic uremic syndrome: specificities of adult patients and implications for critical care management. Toxins **2021**; 13:306.
9. Mele C, Remuzzi G, Noris M. Hemolytic uremic syndrome. Semin Immunopathol **2014**; 36:399–420.
10. Deng H, Pang Q, Zhao B, Vayssier-Taussat M. Molecular mechanisms of *Bartonella* and mammalian erythrocyte interactions: a review. Front Cell Infect Microbiol **2018**; 8:431.
11. Sun H-Y, Singh N. Opportunistic infection-associated immune reconstitution syndrome in transplant recipients. Clin Infect Dis **2011**; 53:168–76.
12. DallaPiazza M, Akiyama MJ. The first report of *Bartonella quintana* immune reconstitution inflammatory syndrome complicated by Jarisch-Herxheimer reaction. J Int Assoc Provid AIDS Care **2017**; 16:321–3.
13. Luciani L, El Baroudi Y, Prudent E, Raoult D, Fournier P-E. *Bartonella* infections diagnosed in the French reference center, 2014–2019, and focus on infections in the immunocompromised. Eur J Clin Microbiol Infect Dis **2021**; 40:2407–10.