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CASE REPORT

# Cutaneous bacillary angiomatosis due to *Bartonella quintana* in a renal transplant recipient

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## Summary

Bacillary angiomatosis (BA) is a disorder of neovascular proliferation involving skin and other organs of immunosuppressed patients caused by *Bartonella* species. BA has been recognized in both immunocompetent and immunodeficient patients, mostly in human immunodeficiency virus (HIV)-infected persons, much more rare in those with other immunodeficiencies, including organ transplantation. Diagnosis is based on serologic analysis, culture and molecular biology [detection of *Bartonella* species deoxyribonucleic acid (DNA) in tissue biopsy extracts by real-time polymerase chain reaction (PCR)]. All immunosuppressed patients with BA should be treated with antibiotics because of potentially life-threatening course of the disease. We report the first case of cutaneous bacillary angiomatosis due to *Bartonella quintana* in renal transplant recipient. This presentation demonstrates that BA should be considered a differential diagnosis in immunocompromised patients presenting with fever and cutaneous angioma-like lesions.

## Introduction

Bacillary angiomatosis (BA) is a vascular proliferative disorder caused by species of the genus *Bartonella*, namely *Bartonella* (Rochalimaea) *henselae* (BH) and *Bartonella quintana* (BQ), which have the ability to produce angiogenic factors [1]. The disease usually manifests as cutaneous tumours, but may also involve other organs (lymph nodes, the gastrointestinal and respiratory tracts, the bone marrow, bones and brain) [2]. A related angioproliferative lesion of the liver and spleen is known as bacillary peliosis [3]. BA has been recognized in both immunocompetent and immunodeficient patients, mostly in human immunodeficiency virus (HIV)-infected persons [4], much more rare in those with other immunodeficiencies [5,6], including organ transplantation [2,7]. Diagnosis is based on serologic analysis, culture and molecular biology (detection of *Bartonella* species DNA in tissue biopsy extracts by PCR). All immunosuppressed patients with BA should be treated with antibiotics because of potentially life-threatening course of the disease. Bacteria of the genus *Bartonella* are susceptible to wide range of agents, including penicillins, cephalosporins, aminoglycosides, chloramphenicol, tetracyclines, macrolides, rifampicin, fluoroquinolones and co-trimoxazole [8]. In clinical practice, erythromycin is the drug of choice. Doxycycline can be given to patients intolerant to erythromycin [9].



 

## Case report

A 43-year-old Caucasian woman underwent a first renal transplantation from deceased donor in October 2012 because of chronic renal failure due to biopsy proven renal-limited form of ANCA-associated crescentic glomerulonephritis. Immunosuppression had consisted of two doses of basiliximab and standard dosages of tacrolimus, mycophenolate mofetil and prednisone. No antirejection therapy was applied during the post-transplant course. She had a stable, but decreased renal function (serum creatinine level 230 μmol/l). In February 2013, she presented with fever and diffuse multiple angioma-like lesions. Her current therapy included tacrolimus (7 mg/day), mycophenolate mofetil (1.5 g/day) and prednisone (15 mg/day). She was in contact with household dog breeding by her sister, but not with cat. Physical examination verified multiple erythematous skin nodules sized cca. 5 × 5 mm on legs, hands, trunk, breast and head, including ear lobes (Fig. 1). No other pathological clinical findings were revealed. The chest X-ray showed no abnormalities; abdominal sonography verified only hepatomegaly with steatosis, but no lesions. Her white blood count was 7900/mm$^3$ (80.4% neutrophils, 10.6% lymphocytes and 7.2% monocytes), haematocrit 26%, haemoglobin level 7.8 g/dl, platelet count 178 000/mm$^3$ and C-reactive protein 56.6 mg/dl. The stool, urine, throat sweb and blood cultures were negative as well as tissue biopsy cultures. Viral serology for HIV, hepatitis B virus (HBV), hepatitis C (HCV), Cytomegalovirus, Toxoplasma gondi, Toxocara canis, Mycoplasma, Chlamydia and Herpes zoster virus was negative, as well as an initial serology for *Bartonella henselae* and *Bartonella quintana* tested by indirect immunofluorescence assay (Bartonella IFA IgM and IgG, Focus Diagnostics, Cypress, CA, USA). This was positive after 4 weeks in the second blood specimen (IgM titre 1:20 a IgG titre 1:64). Detection of DNA of HCV, HBV, Aspergillus, Mycobacteria, parvovirus B19 and BK virus by PCR was negative. Two lesions – from abdomen and from right breast – were excided. Histological examination revealed a lesion containing a proliferation of blood vessels with prominent endothelium surrounded by a neutrophil-rich infiltrate. Endothelial cells expressed CD31 and CD34 antigens. These changes were consistent with the diagnosis of bacillary angiomatosis. The Warthin–Starry

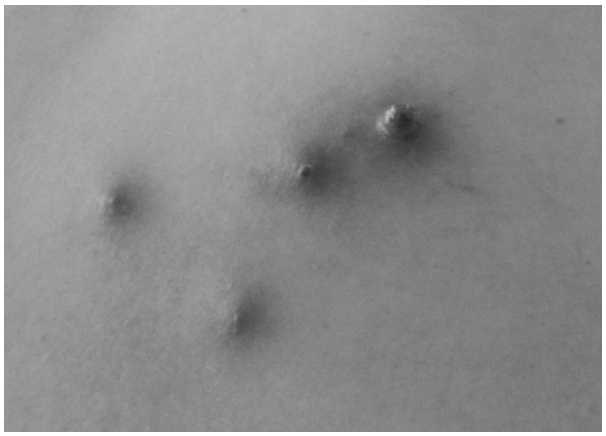

**Figure 1** Livid erythematous, angioma-like nodules before therapy.

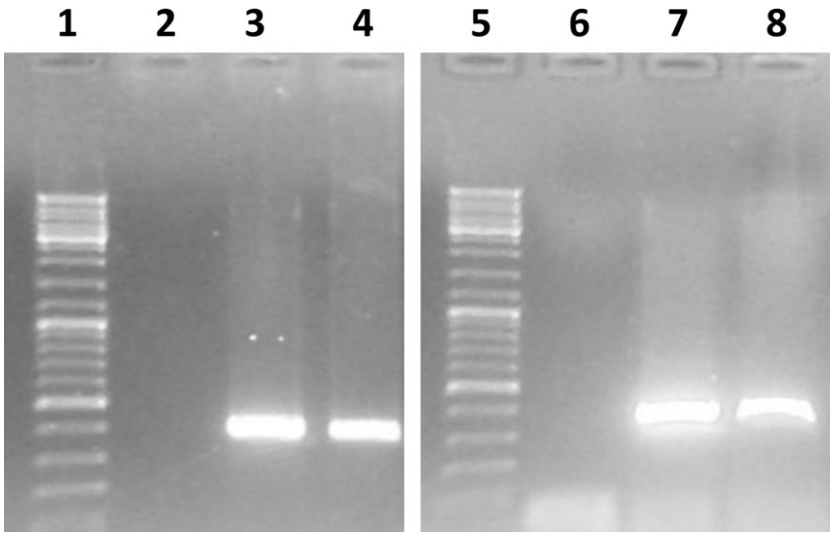


**Figure 2** Amplification of *ribC* (1–4) and *ftsZ* genes (5–8) of *B. quintana* from the patient skin biopsy. 1, 5 – 100 kb ladder; 2, 6 – negative controls; 3, 7 positive control amplicons of *B. quintana* (CIP 103739) *ribC* and *ftsZ,* respectively; 4, 8 – positive amplicons of *B. quintana* (CIP 103739) *ribC* and *ftsZ,* respectively, amplified from the patient skin biopsy.

**Table 1.** Bacillary angiomatosis in solid organ transplant recipients.

| Age (years) | Sex | Graft | Delay postgraft | Contamination | IS | Acute rejection | Clinical presentation | Histological diagnosis | Culture | PCR | Serologic tests | Treatment/ outcome | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | M | Kidney | 6 years | Kitten contact | Pred MMF Cy | 0 | Internal LD Fever | BA (axillary LN) WSS (+) | NA | BH in axillary LN | BH IgG 1024 | 9 days doxycycline+ 3 month azithromycin Recovery | Rostand *et al.* [17] |
| 9 | F | Heart | 33 month | Kitten contact | Tac Sirolimus | 0 | Lesions of liver, spleen, LD, emesis, weight loss | BA (cervical LN) WSS (−) Immunohistochemistry (+) | CSF (−) BM (−) | BH in cervical LN | BH IgG negative initially 1 month later BH IgG 128 | 3 month azithromycin + 1 month ciprofloxacin Recovery | Rostand *et al.* [17] |
| 16 | M | Kidney | 72 month | Kitten contact | Pred MMF Tac | 2 | 3 nodules R forearm and both hands Fever, hepatosplenomegaly | BA (skin) | NP | BH in skin lesion | BH/BQ (−) | 3 month ciprofloxacin, then 4 month erythromycin Relapse 1 month later | Moulin *et al.* [2] |
| 17 | M | Kidney | Days | NA | Pred Tac + NA | NA | L axillary LD Fever | BA (axillary LN) WSS (+) | Blood (−) | BH in axillary LN | NA | NA | Juskevicius *et al.* [22] |
| 19 | F | Kidney | 11 years | Owner of 2 cats, cat scratch | Pred MMF Tac | 3 | LD Fever, myalgia, arthralgia Recurrence 8 month later: LD | Initial:GD (LN) Recurrence: WSS (+) (LN) | Blood (−) LN (+) | BH in LN BQ (−) | BH/BQ (−) | Initial: 5 days azithromycin Recurrence: 1 month gentamicin + 6 month azithromycin | Rheault *et al.* [21] |
| 24 | M | Kidney | 12 month | Cat scratch | Pred MMF Cy | 1 | Nodule L nipple Fever, splenomegaly | BA (skin, lung, bone marrow) WSS (+) skin | Blood (−) | NP | NP | 6 month erythromycin Cessation of IS Recovery | Cline *et al.* [18] |
| 26 | F | Kidney | 11 month | Cat contact | Pred MMF Cy | 1 | Nodule L index finger Fever, myalgias, weight loss, multiple L axillary LD, pancytopenia | BA (axillary node) WSS (+) | Blood (−) | NP | BH/BQ (−) 3 weeks later IgG BH/ BQ >1024 | Levofloxacin MMF cessation Recovery | Patel *et al.* [19] |
| 38 | F | Heart | 5 years | Owner of cat, cat scratch on calf | Pred AZA Cy | Several | Liver and spleen lesions Fever, headache, myalgias, emesis | BA (liver and spleen lesions) WSS (+) ELMI (+) | Blood (−) CSF (−) | NP | NP | 8 weeks erythromycin Recovery | Kemper *et al.* [20] |
| **43** | **F** | **Kidney** | **4 month** | **Dog contact, no cat** | **Pred MMF Tac** | **0** | **Multiple skin nodules, whole body Fever** | **BA (skin) WSS (+) skin** | **Blood (−) Skin (−)** | **BQ in skin lesion** | **BH/BQ initially (−) 4 weeks later IgG BH/ BQ 64** | **3 month doxycycline, then 3 month clarithromycin Recovery** | **Present report** |



 

**Table 1.** continued

| Age (years) | Sex | Graft | Delay postgraft | Contamination | IS | Acute rejection | Clinical presentation | Histological diagnosis | Culture | PCR | Serologic tests | Treatment/ outcome | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 44 | F | Kidney | 5 years | NA | Pred AZA | NA | Lesions in liver and spleen, internal LD Fever, chills, pancytopenia | BA (liver and spleen) WSS (+) liver and spleen | Blood (−) Spleen (+) Liver (−) BM (−) | BH (WB) in spleen, liver | NP | 4 weeks erythromycin | Slater *et al.* [3] |
| 51 | M | Liver | 5 month | Kitten contact | MMF Tac | NA | 2 nodules L knee Fever, headache, photophobia, L inguinal LD | BA (skin) Granulomatous hepatitis and lymphadenitis | Blood (−) CSF (−) | Skin:NP LN: (−) | BH IgG 256 BQ IgG 512 | 2 month azithromycin Recovery | Bonatti *et al.* [16] |
| 56 | M | Kidney | 2 years | NA | Pred MMF Cy | NA | 3 nodules L hand Fever, pancytopenia | BA (skin) WSS (+) skin | Blood (−) | BH in skin lesion | NP | Ciprofloxacin IS cessation Recovery | Grabas *et al.* [23] |
| 58 | M | Kidney | 30 month | Trauma with branch | Pred MMF Cy | 0 | Scalp nodule Fever, cough, multiple neck LD, weight loss | BA (skin) WSS (+) skin | Blood (−) | BH in skin lesion | BH IgG 200 BQ IgG 400 | 3 month clarithromycin Recovery | Moulin *et al.* [2] |
| 60 | M | Kidney | 34 month | Owner of 3 cats | Pred MMF Tac | 2 | Penile nodule Fever, inguinal and abdominal LD, splenomegaly | BA (skin) | Blood (−) Skin (−) | BH in skin and inguinal LN | BH/BQ (−) | 6 weeks ceftriaxone Relapse 2 month later | Moulin *et al.* [2] |

AZA, azathioprine; BA, bacillary angiomatosis; BH, *Bartonella henselae*; BM, bone marrow; BQ, *Bartonella quintana;* CSF, cerebrospinal fluid; Cy, cyclosporine; GD, granulomatous disease; IgG, immunoglobulin-G; IS, immunosuppressive treatment; L, left; LD, lymphadenopathy; LN, lymph node; MMF: mycophenolate mofetil; NA, not available; NP, not performed; PCR, polymerase chain reaction; Pred, prednisone; R, right; Tac, tacrolimus; WB, western blot; WSS, Warthin–Starry stain.
Bold lines is the present case.

histochemical stain showed rod-like bacteria within the lesion and PCR on DNA extracted from the skin biopsy specimen verified presence of BQ specific *ribC* [10] and *ftsZ* [11] genes confirming the diagnosis of bacillary angiomatosis (Fig. 2). The patient was initially given co-amoxicillin 1.2 g twice daily intravenously. Based on biopsy, antibiotic therapy was changed to oral doxycycline at dose of 100 mg twice daily. Fever resolved after 1 week of this treatment and skin lesions began diminishing. She continued this medication for a total of 3 months, but because of persisting some skin lesions, the therapy was prolonged and switched to oral clarithromycin 250 mg twice daily (dose reduction because of renal insufficiency). By reason of drug interactions, the dosage of tacrolimus was adjusted according the blood levels. The therapy with clarithromycin was discontinued after 3 months when skin lesions had disappeared. From then, the patient is doing well.

## Discussion

We present the first case of bacillary angiomatosis caused by BQ in a renal transplant recipient. BA is a rare infection of the skin and other organs caused by *Bartonella* species. It mostly affects HIV-infected people and much more rarely those with other immunodeficiencies (oncology patients, particularly in chronic lymphatic leukaemia), including organ transplantation, but it can also affect immunocompetent people. It was first reported in 1983 in an AIDS patient [12], but infectious diseases caused by *Bartonella* spp. have been described for more than 1000 years [13]. First case of BA in renal transplant recipient was discovered in 1992 [3].

The causative organism of BA in different case series was found to be BH in 28% and 53%, respectively, and BQ in 64% and 47%, respectively [14,15]. BQ infection in bacillary angiomatosis is associated with homelessness, low socioeconomic status and exposure to lice [14]. Other clinical features of BQ are chronic bacteraemia, endocarditis and lymphadenopathy. In our patient, there was no history of cat exposure, homelessness, pediculosis or alcoholism, and no visceral impair was discovered.

Until now, 13 BA cases have been reported in organ transplant recipients, mostly after kidney transplantation. Only seven patients had skin involvement [2, 3, 16–23]. See Table 1. All these cases were caused by *Bartonella* species. However, not all cases were adequately documented bacteriologically. In only nine cases, the diagnosis was confirmed by detection of *Bartonella* DNA in biopsy extract by PCR technique. The others were verified by an increase of antibody titres (two cases) or by clinical and pathological findings, including the Warthin–Starry stain. However, serology may be unreliable in immunocompromised patients due to lack of antibody response. They can be initially negative and become positive after 2–4 weeks [16,19]. In addition, cross-reactions between the different *Bartonella* spp. exist, as in most cases serological tests are positive for both BH and BQ. According to the literature, our case is the first documented description of bacillary angiomatosis caused by BQ in a renal transplant recipient in the literature. The diagnosis was based on the histopathological findings, including the Warthin–Starry staining, and it was validated by detection of BQ DNA in skin nodules by PCR. Serology was initially negative, after 4 weeks then positive.

Skin lesions of BA are located in various body areas. They appear as erythematous or violaceous papules or nodules, which may be crusted or ulcerated. Their number is generally low in organ transplant recipients, in contrast with HIV-infected patients who have multiple lesions [2], but there can exist exceptions, as in our patient. Cutaneous lesions may mimic Kaposi sarcoma, pyogenic granuloma and angioma [19]. The pathologic findings with PCR detection of *Bartonella* DNA in biopsy extracts are crucial for diagnosis of BA. Histological findings consist of a lobular proliferation of small blood vessels lined by plump endothelial cells. A mixed cell infiltrate of neutrophils, histiocytes and lymphocytes is present [2].

Current treatment regimens for *Bartonella* infections rely mostly on expert opinion and antimicrobial susceptibility data. Recent systemic review and meta-analysis of treatment outcomes of human bartonellosis [9] showed erythromycin might be better than other antibiotics for BA, but with no statistically significant difference from doxycycline. Treatment should last at least 3 months to avoid relapses. We preferred doxycycline as an initial treatment because of inaccessibility of oral erythromycin in our country. In view of persistence of some skin lesions, the therapy was switched to oral clarithromycin 250 mg twice daily. Disadvantage of macrolides is their interaction with calcineurin inhibitors, requiring adaptation dosages of tacrolimus or cyclosporine according to blood levels, as in the case of our patient.

## Conclusion

To our knowledge, we present the first case of bacillary angiomatosis caused by *Bartonella quintana* in a renal transplant recipient, as well as the first case of bacillary angiomatosis in a renal transplant recipient in the Czech Republic. In conclusion, bacillary angiomatosis should be considered a differential diagnosis in immunocompromised patients presenting with fever and cutaneous angioma-like lesions. Identifying *Bartonella quintana* or *Bartonella henselae* as the causative organism often requires multiple diagnostic studies.


 

## Authorship

JO: wrote the article and took care of patient. PF: performed histopathological examination. OM and JT: performed serologic tests and molecular detection. JS: performed skin biopsy. MH, AK and KZ: took care of patient. KK and JZ: revised and approved the article.

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