Case Report

Refractory *Bartonella quintana* bacillary angiomatosis following chemotherapy for chronic lymphocytic leukaemia

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Bacillary angiomatosis is a well-recognized infection with cutaneous and systemic manifestations caused by *Bartonella henselae* or *B. quintana* and occurs in immunocompromised patients. We report a case of *B. quintana* bacillary angiomatosis following fludarabine-based chemotherapy for chronic lymphocytic leukaemia that was refractory to standard treatment and was complicated by lymphadenopathy and osteomyelitis.

Case report

A 66-year-old woman was admitted with several weeks of rapidly enlarging subcutaneous nodules and protuberant lesions involving her face, scalp, arms and torso. She had a 5-year history of chronic lymphocytic leukaemia (CLL), treated initially with chlorambucil monotherapy. Following relapse 4 years later, she received four cycles of fludarabine, cyclophosphamide and rituximab, as well as intravenous immunoglobulin for secondary hypogammaglobulinaemia. She also had a 1-year history of pure red cell aplasia managed with transfusions, cyclosporine and prednisolone, and a 1-year history of steroid-induced insulin-requiring diabetes mellitus. She was placed on trimethoprim–sulfamethoxazole three times weekly as prophylaxis against *Pneumocystis jiroveci* pneumonia. She also had mild intellectual disability from birth and migrated to Australia from Sicily in 1959. There was no history of cat exposures, homelessness, pediculosis or alcoholism.

On examination there were non-tender, non-pruritic subcutaneous nodules approximately 10 mm in diameter involving the dorsum of her hands, and polypoid protuberant angiomatous lesions ranging from 5 to 15 mm in diameter and 5–10 mm in thickness involving her face and scalp. There were also erythematous papules ranging from 2 to 5 mm in diameter involving her pharynx, shoulder and anterior tibial surface (Fig. 1).

Investigations revealed a white cell count of $5.8 \times 10^9 \text{ l}^{-1}$ and neutrophils $0.52 \times 10^9 \text{ l}^{-1}$, erythrocyte sedimentation rate of 42 mm h$^{-1}$ and C-reactive protein level of 37.5 mg l$^{-1}$. γ-Glutamyl transpeptidase was 92 IU l$^{-1}$ with normal serum transaminases, renal function and electrolytes. There was hypogammaglobulinaemia with IgG 3.4 g l$^{-1}$, IgA 0.1 g l$^{-1}$ and IgM 0.1 g l$^{-1}$, and serum protein electrophoresis demonstrated an IgG lambda band less than 2 g l$^{-1}$. HIV serology was negative and CD4 T-lymphocyte count was $444 \times 10^6 \text{ l}^{-1}$ (12%). γ-Interferon release assay was negative for tuberculosis. Chest X-ray was normal and abdominal ultrasound revealed cholelithiasis without evidence of cholecystitis and no other visceral changes.

Skin punch biopsy demonstrated lobular overgrowth of capillary-like blood vessels with oedema, and mixed acute and chronic inflammatory infiltrate with granuloma formation. Warthin–Starry silver stain demonstrated clumps of coccobacilli within the interstitium (Fig. 2). Initial serology for *Bartonella henselae* (immunofluorescence assay) was negative with IgG titre less than 1 : 128. *B. quintana* PCR was performed on a paraffin section of the skin punch biopsy using an in-house assay with primers published by Anderson et al. (1994), specifically CAT1 5′-GATTCAATTGGTTTGAAG-GAGGCT-3′ and CAT2 5′-TCACATCACCAGGAGTAT-TC-3′. A positive band was present in the neat sample only but it was too faint for further confirmation and was reported as equivocal for *B. henselae*.

The patient was treated initially with oral doxycycline 100 mg twice daily and given intravenous immunoglobulin for hypogammaglobulinaemia. After 7 weeks, there was no...
Despite dual therapy with doxycycline and clarithromycin for 3 weeks, she developed new lesions. A second skin punch biopsy was performed which again demonstrated small granulomata and there were features of cutaneous CLL. Serology for *B. henselae* was again negative with IgG titre less than 1:128. The same in-house PCR assay for *B. henselae* was performed on fresh tissue. Positive bands were detected in both neat and 1:100 dilution samples. Restriction endonuclease digestion with Tsp5091 for confirmation of PCR amplicons was performed; however, our patient’s specimen did not digest into 253 bp and 126 bp fragments as expected for *B. henselae*. As there was no commercially available assay in Australia for *B. quintana* PCR testing, sequencing was performed on the amplified product. Sequence analysis was performed with 346 nt at the 5’ end of the 16S rRNA gene, and a GenBank BLAST search (National Center for Biotechnology, Bethesda, MD, USA) was carried out. The patient’s isolate had 100% sequence similarity (346/346 nt) with *B. quintana* Toulouse strain with GenBank accession number BX897700 (data not shown) (Alsmark et al., 2004).

The patient was readmitted with fevers, lower limb cellulitis and widespread lymphadenopathy during week 8 of combination treatment with doxycycline and clarithromycin. Lymph node biopsy revealed granulomatous inflammation and evidence of cutaneous CLL. Stains and culture for acid-fast bacilli and fungi were negative, and Warthin–Starry staining was also negative. Blood and lymph node cultures for fastidious organisms were negative after 21 days. Mycobacterial and *B. henselae* PCR were negative in the lymph node. Repeat imaging of her chest and abdomen was normal. A transthoracic echocardiogram did not reveal any vegetations or structural valvular abnormalities. She was commenced on intravenous ceftriaxone in addition to doxycycline and clarithromycin, but continued to have fevers and developed new skin papular lesions.

Four weeks later, she developed unilateral swelling of her left second to fifth tarsometatarsal joints and lateral tarsal bones with an associated subcutaneous collection. There was scintigraphic and computed tomography evidence of osteomyelitis involving the proximal second to fifth metatarsals and the lateral and intermediate cuneiform bones. Fluid was aspirated but was culture-negative (including extended and mycobacterial culture). Cytology demonstrated numerous lymphocytes and many multinucleated giant histiocytes. Unfortunately, there was insufficient volume for PCR analysis, and the patient refused further aspiration. Given her failure to respond to ceftriaxone, doxycycline and clarithromycin, intravenous gentamicin was then added for presumed *Bartonella* osteomyelitis. Cyclosporine and prednisolone therapy for red cell aplasia were both ceased; her haemoglobin remained stable. She completed 6 weeks of gentamicin in total with an excellent clinical response in left foot swelling. She was switched to oral azithromycin plus rifampicin syrup for ongoing management. The cutaneous and
subcutaneous lesions were very slow to respond and she required 15 months of combination therapy for complete resolution.

Discussion

Bacillary angiomatosis was first reported in 1983 in an AIDS patient with atypical subcutaneous lesions responsive to oral erythromycin. Proliferation of endothelial cells and capillaries occurs, typically in the upper reticular dermis, in association with *B. henselae* or *B. quintana* infection. In a 5-year series between 1993 and 1998 in Marseille, France, the causative organism was *B. henselae* in 28% and *B. quintana* in 64% (La Scola & Raoult, 1999). Clinical manifestations may be cutaneous or disseminated. There is a diverse appearance of cutaneous and subcutaneous lesions including maculopapular eruptions, pendunculated or polypoid lesions, hyperkeratotic or indurated plaques, and nodules with or without ulceration. Atypical lesions can also occur, including those resembling Kaposi’s sarcoma and verruga peruana (Schwartz et al., 1997). Disseminated disease involves the liver, spleen, lymph nodes, gastrointestinal tract, bone, brain and other organs, and can occur without cutaneous lesions (Maurin et al., 1997; Margileth, 2000). Characteristic histopathological features have been found in these specimens (Koehler & Tappero, 1993). Disease, particularly disseminated disease, tends to occur in immunocompromised conditions such as HIV, CLL and solid organ transplantation (Bonatti et al., 2006).

Infection with *B. quintana* can also occur in immunocompetent hosts (Tappero et al., 1993), particularly cat owners, persons in overcrowded or homeless environments, injecting drug users and chronic alcoholics. There has been a paediatric case report of *B. quintana* encephalopathy complicated by Guillain–Barré syndrome and hydrocephalus in a healthy child (Mantadakis et al., 2007).

Clinical manifestations and epidemiology may also differ depending on the species of *Bartonella* infection. In HIV-positive patients, *B. henselae* was associated with lymphadenopathy, hepatosplenic peliosis and cat ownership, whereas *B. quintana* was associated with subcutaneous and soft tissue lesions, lytic bone lesions and lice infestation (Mohle-Boetani et al., 1996; Koehler et al., 1997). The vector for *B. quintana* is the human body louse, with hosts found in cats, dogs and monkeys (Chomel et al., 2006).

Differential clinical diagnosis of cutaneous bacillary angiomatosis includes Kaposi’s sarcoma, pyogenic granuloma, angiosarcoma and verruga peruana (*Bartonella bacilliformis*). Microbiological diagnosis can be difficult due to the fastidious nature of organism in culture (which may take up to 15–45 days) (Gasquet et al., 1998); however, silver staining may be positive. Serology may be unreliable in immunocompromised patients due to lack of antibody response (Maurin & Raoult, 1998), particularly in the context of hypogammaglobulinaemia. Cross-reactivity may also occur with *Coxiella burnetti* (La Scola & Raoult, 1996). *Bartonella* species are highly susceptible to macrolides, doxycycline, rifampicin and gentamicin (Rolain et al., 2000; Dörbecker et al., 2006). Treatment recommendations for bacillary angiomatosis usually include oral macrolides or doxycycline for 3 months (Rolain et al., 2004). A prolonged duration is required to prevent frequent relapse (Maurin & Raoult, 1996). Macrolides are potentially superior due to their antiangiogenic effects (Foucault et al., 2006; Meghari et al., 2006). Other antibiotic regimes are employed for other manifestations of *Bartonella* infection, for example chronic bacteremia, endocarditis, cat-scratch disease and Carrion’s disease. Treatment of chronic *Bartonella* bacteremia or endocarditis is combination therapy with intravenous gentamicin 3 mg kg⁻¹ daily for 14 days and doxycycline 100 mg twice daily for 4 weeks (bacteraemia) (Foucault et al., 2003; Rolain et al., 2004) or 6 weeks (endocarditis) (Raoult et al., 2003).

The seroprevalence of *B. henselae* and *B. quintana* in healthy populations has been estimated at 9–30% (Sander et al., 1998; Tea et al., 2003; Vermeulen et al., 2007) and 15%, respectively (Tea et al., 2003). Seroprevalence of *B. henselae* was 38% in asymptomatic Italian stray cats (Fabbri et al., 2004) and up to 50% in North American cats (Maurin & Raoult, 1998). In a study of *B. henselae* infection in HIV patients with cat contacts, four out of five human–cat pairs had closely related PFGE patterns, which suggested human infection was caused by cat contact (Chang et al., 2002). Seroprevalence of *B. quintana* in homeless patients in Marseilles was 30% (Brouqui et al., 1999).

There are three case reports of bacillary angiomatosis in CLL. All cases had complete resolution of skin lesions with oral treatment: 4 weeks of clarithromycin (Milde et al., 1994), 6 weeks of erythromycin (Török et al., 1994) and 6 weeks of doxycycline (Petersen et al., 2008). Our case differs from the above series with inadequate response to standard first-line treatment, the need for intravenous antibiotics, the presence of multifocal disease, and the extended duration of antimicrobials required for complete clinical response. Most patients with disseminated bacillary angiomatosis are bacteremic (Maurin & Raoult, 1998); however, we were unable to demonstrate this in our case. Infection with *B. quintana* is uncommon in Australia. There have been three cases of *B. quintana* endocarditis reported recently in Australia with unique strains (Woolley et al., 2007), and one recent case of *B. quintana* bacteremia occurred in an immigrant from Spain (Rathbone et al., 1996).

The degree of immunosuppression in our patient likely contributed to the chronicity and severity of disease. Fludarabine is known to cause profound and lasting immunosuppression, with a rapid reduction in T-cell subsets. Lymphopenia and lymphocyte dysfunction can persist for 1–2 years after treatment. Some fludarabine-treated patients have experienced overwhelming polymicrobial infections similar to HIV-positive patients with a similar spectrum of disease including fungi, viruses, mycobacteria, *P. jiroveci* and listeriosis (Chapel & Bunch,
fludarabine, especially when cutaneous lesions occur.

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References


