Bone marrow and skin granulomatosis in a patient with *Bartonella* infection

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This report describes a case of granulomatous inflammation, involving the bone marrow and skin, due to *Bartonella* infection in an immunocompetent patient. The clinical presentation included prolonged fever, pancytopenia, rash and hepatitis. *Bartonella* infection should thus be added to the growing list of entities that produce marrow granulomas and fever.

**Case report**

A 54-year-old white woman, with history of hypertension and stroke, was admitted to hospital because of fever, pancytopenia and impaired liver-function tests. Her illness began 2 weeks prior to admission, with fever, extreme weakness, nausea and vomiting, and abnormal liver function tests (bilirubin 4.5 IU, aspartate transaminase 331 units l⁻¹ and alanine transaminase 393 units l⁻¹). This presentation prompted the diagnosis of hepatitis. A pruritic maculopapular rash involving the face and upper extremities also appeared. Upon admission, physical examination disclosed the rash and mild right upper quadrant abdominal tenderness. Her lymph nodes, liver and spleen were not enlarged. Her medication included aspirin, atenolol and hydrochlorothiazide.

The transaminases gradually returned to normal, while gamma glutamyl transferase (GGT) remained elevated. Other laboratory abnormalities included hypoalbuminemia, hyper gammaglobulinaemia and pancytopenia (haemoglobin 9.2 g dl⁻¹; white blood cell count 4.21 × 10⁹ l⁻¹, 67.4 % neutrophils, 18.3 % lymphocytes, no eosinophilia; platelet count of 82 × 10⁹ l⁻¹). Abdominal ultrasonography was non-revealing.

Three sets of blood cultures were sterile; serological tests for hepatitis A, B and C viruses, cytomegalovirus and Epstein-Barr virus were negative, as was serology for HIV, *Brucella* and *Toxoplasma*. Anti-*Coxiella burnetii* IgG phase 2 antibodies titre was 1 : 100, with no change during convalescence.

Serological testing for *Bartonella*, using an enzyme immunoassay with *Bartonella henselae* antigens (Giladi et al., 2001; Metzkor-Cotter et al., 2003), demonstrated seroconversion of anti-*B. henselae* IgG antibodies and the presence of anti-*B. henselae* IgM antibodies, which disappeared by the seventh week of illness. This serological pattern was consistent with acute *Bartonella* infection (Table 1). Tests for anti-nuclear, anti-smooth muscle, anti-neutrophil cytoplasmic antibodies and rheumatoid factor were all negative.

A skin biopsy revealed interstitial granulomatous dermatitis, characterized by infiltration of histiocytes and lymphocytes distributed interstitially and in a palisaded array within the reticular dermis. A few neutrophils were scattered throughout the infiltrate. A bone marrow specimen revealed numerous epithelioid, non-necrotizing granulomas with a distinct doughnut-ring shape (Fig. 1). These ring granulomas exhibited a central lipid vacuole with a fibrinous outer ring and were composed of epithelioid histiocytes and giant cells, with admixed neutrophils and eosinophils. Gram, fungal, acid-fast and Warthin–Starry silver stains of both biopsy specimens were all negative. Bone marrow cultures were sterile. PCR failed to detect *Bartonella* or *C. burnetii* DNA in paraffin-embedded skin tissue as well as from fresh bone marrow tissue.

Treatment with doxycycline was withdrawn after 2 days because of gastrointestinal discomfort. Over the next 2 months the fever gradually decreased and GGT, as well as the blood count, slowly returned to normal. During 6 months of follow-up the patient remained well with normal blood count and liver function tests. The patient lived alone and owned numerous cats and kittens.

**Discussion**

Cat scratch disease (CSD) is a globally endemic zoonosis, transmitted to humans via domestic and stray cats. *B.
**henselae** is implicated as the causative pathogen (Rolain et al., 2003). The clinical spectrum of diseases attributed to *Bartonella* is rapidly expanding. Typical CSD presents with regional lymphadenopathy, often with a necrotizing granulomatous reaction, commonly preceded by an erythematous papule at the inoculation site. Atypical CSD occurs in up to 15% of cases and includes oculoglandular syndrome, fever of unknown origin, granulomatous hepatitis, atypical pneumonitis, osteomyelitis, splenic abscesses, endocarditis, breast mass, neurological syndromes (mainly encephalitis and neuroretinitis), erythema nodosum, arthropathy and various types of skin rashes (Anderson & Neuman, 1997; Daye et al., 1988; Giladi et al., 2001, 2005; Guptill et al., 2004). Our patient presented with fever and hepatitis with elevated alkaline phosphatase, GGT and mild hyperbilirubinemia, a pattern suggesting an infiltrative process, as might occur in granulomatous hepatitis.

The extensive exposure to cats, the presence of granulomatous reaction and the seroconversion of anti-*B. henselae* IgG antibodies together with the short-lived anti-*B. henselae* IgM response, all support the diagnosis of CSD in our patient. The enzyme immunoassay used for serodiagnosis in this report has been shown to be highly specific for *Bartonella* infections (Gilad et al., 2003), and a large body of evidence supports the utility of this assay in the serodiagnosis of CSD (Ben-Ami et al., 2005; Chian et al., 2002; Gilad et al., 2003; Giladi et al., 2005; Landau et al., 1999; Metzkor-Cotter et al., 2003; Schattner et al., 2003). However, none of the serological assays currently available for the diagnosis of CSD is species-specific and therefore cannot distinguish between the numerous species of the genus *Bartonella* (e.g. *B. henselae, Bartonella quintana*). It is therefore more prudent to diagnose our patient as having *Bartonella* infection rather than CSD. The absence of *Bartonella* DNA within skin lesions and bone marrow, as demonstrated by the negative PCR results, may be attributed to the host response to the presence of *Bartonella* at other sites.

Prolonged fever accompanied by pancytopenia and bone marrow granulomas is a diagnostic challenge and the list of possible aetiologies includes: leishmaniasis, brucellosis, leprosy, miliary tuberculosis, *Mycobacterium avium* infection, Q fever, Epstein–Barr virus, cytomegalovirus, Hodgkin’s lymphoma, peripheral T-cell lymphoma and berylliosis (Metzkor-Cotter et al., 2003). Apparently *Bartonella* infection now can be added to this list.

Although bone marrow is rarely investigated in CSD or other *Bartonella* infections in immunocompetent patients, granulomatous involvement of the bone marrow with a resultant pancytopenia is probably extremely rare in this disease; to the best of our knowledge, this is the first report of bone marrow and skin granulomatosis in an immunocompetent patient with *Bartonella* infection. Except for rare cases of thrombocytopenic purpura and autoimmune haemolytic anaemia (Carithers, 1985; Van Audenhove et al., 2001), significant haematological manifestations have not been reported in CSD.

Distinctive bone marrow fibrin ring granulomas (so called doughnut granulomas), composed of an outer ring of epithelioid histiocytes around a central fat droplet, as noted in our patient, were thought to be pathognomonic for Q fever; however, in recent years the list of possible culprits has been expanded (Metzkor-Cotter et al., 2003), and *Bartonella* infection is another possible cause of these structures.

### Table 1. Enzyme immunoassay serological testing for *B. henselae* in a 54-year-old woman with bone marrow and skin granulomatosis

<table>
<thead>
<tr>
<th>No. of weeks after disease onset</th>
<th>Cut-off for positivity*</th>
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<tr>
<td></td>
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<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Anti- <em>B. henselae</em> IgM†</td>
<td>50</td>
</tr>
<tr>
<td>Anti- <em>B. henselae</em> IgG†</td>
<td>51</td>
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*Cut-off was calculated as the mean optical density reading + 3 SD of healthy controls, as previously described (Giladi et al., 2001).
†Serological results are presented as arbitrary units.

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**Fig. 1.** Bone marrow ring granulomas. Note the fibrinous outer ring.
Our patient lacked lymph node involvement; it is not clear why typical CSD presents with regional lymphadenopathy, whereas atypical CSD such as neurorretinitis and encephalitis often present without lymphadenopathy, and *Bartonella* endocarditis is not associated with lymphadenopathy at all. The enigma is even greater in immunocompromised patients where *B. henselae* and *B. quintana* may cause bacillary angiomatosis. Attempts to correlate clinical manifestations with various strains of *Bartonella* have failed, and no scientific explanation has been proposed for the different clinical manifestations of this multifaceted micro-organism.

The most common dermatological manifestation of CSD at the primary inoculation site consists of inflammatory infiltrate with numerous neutrophils and histiocytes. Interstitial granulomatous dermatitis has not been documented in any *Bartonella* infection. This condition has been associated hitherto only with arthritis, endemic mycosis and several drug reactions (Chian et al., 2002).

We conclude that bone marrow granulomas and granulomatous dermatitis should be added to the clinical syndromes that are caused by *Bartonella* infection.

References


