Abscess-forming lymphadenopathy and osteomyelitis in children with *Bartonella henselae* infection

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*Bartonella henselae* is the agent of cat-scratch disease (CSD), a chronic lymphadenopathy among children and adolescents. A systemic infection is very rare and most of these cases are found in patients with immunodeficiency. Here, cases involving four children of 6–12 years of age are reported. Three of the children had an abscess-forming lymphadenopathy and surrounding myositis in the clavicular region of the upper arm. The diagnosis was made serologically and, in one case, using eubacterial universal PCR. One child was treated with erythromycin for 10 days, the second received cefotaxime and flucloxacillin for 14 days and the third child was not treated with antibiotics. The fourth child had a different course: a significantly elevated signal intensity affecting the complete humerus was found in magnetic resonance imaging, consistent with osteomyelitis. A lymph node abscess was also found in the axilla. Diagnosis was established by indirect fluorescence assay and lymph node biopsy. Antibiotic therapy using clarithromycin, clindamycin and rifampicin was gradually successful. Immunodeficiency was excluded. All described lesions healed without residues. In immunocompetent patients, infection affects skin and draining lymph nodes; however, prolonged fever of unknown origin as in the fourth patient indicated a systemic complication of CSD.

**Abbreviations:** CSD, cat-scratch disease; ESR, erythrocyte sedimentation rate; IFA, indirect fluorescence assay; MRI, magnetic resonance imaging.
and the diagnosis and treatment in immunocompetent children.

**Case reports**

**Case 1**

A 10-year-old girl presented with soft tissue swelling above the right clavicle that lasted 1 week. No trauma was noted. The girl had often played with cats and kittens. The family doctor admitted the girl with the presumed diagnosis of lymphoma. Fever, weight loss, sweating at night or elevated temperature was denied. Physical examination revealed a solid swelling on the right supraclavicular notch (diameter 4 cm), which was somewhat painful at palpation. There was no redness. On the right parasternal region small red papules were present where the kittens had scratched her. Further physical examination was normal. Ultrasound of the right supraclavicular region showed multiple enlarged lymph nodes without abscess formation. Blood tests, radiography of the thorax and abdominal ultrasound were unremarkable (Table 1). Serology for Epstein–Barr virus, cytomegalovirus and *Toxoplasma gondii* was negative. However, IgG antibodies to *B. henselae* were detected using an indirect fluorescence assay (IFA), as described previously by Kempf et al. (2001). The cut-off titre of this IFA has been determined at 1:100. Based on the presence of skin papules, regional lymphadenitis and positive serology, the diagnosis of *B. henselae*-associated lymphadenitis was made. The girl was treated successfully with erythromycin for 10 days.

**Case 2**

A 7-year-old girl was admitted because a painful red swelling had developed on the left infraclavicular region during the past week. She had subfebrile temperatures. Two small crusty papules were present on the left forearm. The family had two adult cats and scratches caused by the cats were reported. Further history was unremarkable. The physical examination showed a tender infraclavicular swelling with a diameter of 5 cm. In the left cervical region, small lymph nodes with diameters of up to 2 cm were palpable. Further physical examination was normal. Erythrocyte sedimentation rate (ESR) was accelerated (51 mm h⁻¹). Other blood tests and X-rays of the thorax and clavicle were normal (Table 1). The ultrasound showed a 3 × 3 × 2 cm structure of low signal intensity but high overall blood perfusion. A central area of 1.5 × 0.7 cm did not give a colour doppler signal consistent with abscess formation. Using magnetic resonance imaging (MRI), osteomyelitis of the clavicle was excluded, but the left M. pectoralis showed signal changes consistent with myositis. A fine-needle-aspiration of the lymph node was performed and pus was aspirated. Therefore, an antibiotic therapy using cefotaxime and flucloxacinillin was started empirically and was given for 2 weeks. Microbial aerobic and anaerobic cultures from blood and the aspirate, as well as mycobacterial cultures from the aspirate, were negative. However, *B. henselae* DNA was found in the aspirate using universal 16S rRNA gene amplification and sequencing, as described previously (Girschick et al., 1999, 2005). Thus, the diagnoses of *B. henselae*-associated lymphadenitis and myositis were made. As the symptoms had already improved significantly, no additional therapy was implemented after the PCR results had been obtained.

**Case 3**

A 6½-year-old girl was admitted to the hospital with an acute swelling of the left distal arm close to the elbow. Extension in the elbow joint was painful and limited. Two weeks earlier, a blunt trauma to this arm had been noticed. Fever, weight loss, night sweat or reduced appetite was denied. There was no swelling of lymph nodes elsewhere. There was a close contact with adult cats. Six months earlier, an abscess-forming skin lesion on the right knee (diameter of 1 cm) had been noted, which resolved spontaneously. Physical examination showed a tender swelling. Motion of the left elbow joint was impaired. Further physical examination was normal. Blood tests were normal, except for an ESR of 27 mm h⁻¹ (Table 1).

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**Table 1.** Clinical and diagnostic criteria of four patients suffering from CSD

<table>
<thead>
<tr>
<th>Patient</th>
<th>Contact with cats</th>
<th>Temperature (°C)</th>
<th>Skin lesions</th>
<th>Lymphadenitis Osteomyelitis</th>
<th>CRP (mg dl⁻¹)</th>
<th>Leukocytes (µl⁻¹)</th>
<th>ESR (mm h⁻¹)</th>
<th>Histology</th>
<th>Serology (IFA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>NE</td>
<td>+</td>
<td>+</td>
<td>NE</td>
<td>8000</td>
<td>9</td>
<td>NE</td>
<td>IgG+ (1 : 200)</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>NE</td>
<td>+</td>
<td>+</td>
<td>1.3</td>
<td>10 320</td>
<td>51</td>
<td>NE</td>
<td>ND (Bartonella-rRNA+)</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>NE</td>
<td>-</td>
<td>-</td>
<td>NE</td>
<td>7070</td>
<td>27</td>
<td>RA</td>
<td>IgG+ (1 : 256)</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>38.3</td>
<td>+</td>
<td>+</td>
<td>1.4</td>
<td>4380</td>
<td>101</td>
<td>RA</td>
<td>IgG+ (1 : 1024)</td>
</tr>
</tbody>
</table>
ultrasound showed a soft tissue mass and surrounding oedema consistent with myositis. A malignant disease could not be excluded. Therefore, a biopsy was performed. Histopathology revealed a reticuloendothelial, abscess-forming lymphadenitis. Subsequently, a positive IgG titre for *B. henselae* was documented (IFA) (Sander et al., 2001). The cut-off titre of this IFA has been determined at 1:64. The diagnoses of *B. henselae*-associated myositis and lymphadenitis were made. The girl was not treated with antibiotics because clinical severity was limited and spontaneous improvement was noted. A follow-up examination after 3 weeks showed further improvement, and another follow-up 3 months later was unremarkable.

**Case 4**

A 12-year-old girl was admitted with a swelling of the right upper arm that had been present for 3 weeks (Fig. 1). She had had a moderate fever for 7 days and had been coughing for 3 days. On the right parasternal rib-arc there were four small itchy red papules. On the dorsum of the right hand some cat scratches and another papule were noted. The family had several adult cats and a dog. Physical examination was otherwise normal, except for an elevated temperature of 38.3 °C. The ESR was 101 mm h⁻¹ and the C-reactive protein was 1.4 mg dl⁻¹. Additional blood tests were normal. The ultrasound of the right elbow notch showed multiple lymph nodes of low signal intensity with diameters of up to 2 cm. A conglomerate of enlarged lymph nodes (4 cm in diameter) in the right axilla was noted. In the biceps a diffuse increase of ultrasound signal intensity could be seen, suggesting local myositis. MRI was suggestive of osteomyelitis in the humerus: strong T2-weighted MRI using fat suppression technique (TIRM) revealed a significantly increased signal, and T1-weighted images before and after gadolinium showed a gadolinium enhancement in the humeral metaphysis and diaphysis (Fig. 2). Other diagnostics (echocardiography, ECG, radiography of the thorax, abdominal ultrasound) were normal. A biopsy of the axillary lymph nodes showed a reticuloendothelial, abscess-forming lymphadenitis (Fig. 3). Lymphoma or other malignancies were excluded. Blood cultures and cultures from biopsy tissue were negative for aerobic and anaerobic bacteria, mycobacteria and fungi. Infection by *B. henselae* was suspected based on the cat-scratch history and the presence of skin papules at scratch sites, in addition to lymphadenitis. However, initially no anti-*B. henselae* antibodies could be detected (IgG titre of below 1:32 in IFA; Sander et al., 2001). Seven days later, the antibody levels had still not risen. However, after another 18 days anti-*B. henselae* IgG antibodies were detected (titre of 1:1024, IFA). Therefore, the diagnosis of *B. henselae*-lymphadenitis with myositis and osteomyelitis was made. Interestingly, the mother of the patient was also positive for IgG antibodies against *B. henselae* (titre of 1:128, IFA). Therapy with clarithromycin for 10 days had been started initially, but the fever and inflammation did not disappear. The therapy was therefore changed to clindamycin and rifampicin. After 11 days, the symptoms

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**Fig. 1.** Clinical status of patient 4. This patient presented with painful reddish swelling of the right upper arm. Movement in the elbow joint was limited.

**Fig. 2.** Diagnostic MRI of patient 4. (a) Strong T2-weighted MRI using fat suppression technique (TIRM) of the right upper arm revealed a significantly increased signal in the humerus, consistent with osteomyelitis. (b and c), T1-weighted image before (b) and after (c) gadolinium enhancement, showing a gadolinium enhancement of the humeral metaphysis and diaphysis.
Neurological symptoms including neuritis of the optic nerve, encephalitis, polyneuritis or cerebral stroke have been noted up to 6 weeks after lymphadenopathy had appeared (Gerber et al., 2002; Puligheddu et al., 2004; Rocha et al., 2004). There are only a few case reports on patients with B. henselae-associated osteomyelitis (Ledina et al., 2004; Prybis et al., 2002; Woestyn et al., 2003), including children (Robson et al., 1999; Abdel-Haq et al., 2005). In immunodeficient people, B. henselae causes a vasoproliferative process called bacillary angiomatosis (Koehler et al., 1997). The reason why patient 4 suffered from the rare manifestation of B. henselae-associated osteomyelitis is unclear. The affected child’s immune system appeared to be competent. CSD appears to be a disease of childhood and adolescence: 80% of patients are below 21 years of age. In contrast, Ridder et al. (2002) found a median age of 33.9 years (range 4–89 years) in a study of 61 CSD patients. Infections caused by B. henselae have been reported worldwide. Cats and in particular young kittens are the typical reservoir. B. henselae is transmitted from cats to humans predominantly by cat scratches or bites. Fifty-seven (Ridder et al., 2002) to 90% (Lamps & Scott, 2004) of patients had proven contact with cats. No transmission from person to person has been described. However, familial outbreaks due to contact with the same animal have been reported, similar to that in family no. 4. Cat fleas, which represent the main vector for transmission of B. henselae among cats, may function as additional vectors for the transmission to humans. Infection of dogs or monkeys appears to be possible (Lamps & Scott, 2004).

B. henselae is a facultative intracellular bacterium with a tropism for endothelial cells, which are entered by means of endocytosis (Lamps & Scott, 2004; Rolain et al., 2004). The pathogen can persist in erythrocytes and therefore remains in the bloodstream (Rolain et al., 2004). Mändle et al. (2005) showed that infection of human CD34+ progenitor cells with B. henselae results in the intraerythrocytic presence of the pathogen.

Diagnosis is made by clinical examination and serology. Metzkor-Cotter et al. (2003) showed that there is no particular association between the bartonella-specific antibody titre and the type and severity of the clinical manifestation. In 98 patients with CSD, they showed that IgM-seropositivity lasts for about 3 months, using an enzyme immunoassay. Patients can remain seropositive for IgG for more than 2 years after infection (Metzkor-Cotter et al., 2003). In a retrospective study with 508 unselected children and adolescents without any clinical signs and symptoms of CSD, Massei et al. (2004) showed that there was a high seroprevalence of bartonella-specific antibodies, supporting the hypothesis that B. henselae infection is often asymptomatic in young children and resolves spontaneously in most cases. As in Case 1 in this study, CSD may be clinically indistinguishable from lymphoma. Thus, biopsy is often necessary to establish a definite diagnosis. However, isolation of B. henselae from biopsy tissue or

**Discussion**

In 75% of patients the course of CSD is without complications; less than 50% of patients have fever (Massei et al., 2005). However, in 6% of infections, B. henselae causes an oculo-glandular syndrome that affects conjunctiva and preauricular lymph nodes (Lamps & Scott, 2004). Hepatosplenic (Daybell et al., 2004; Pelton et al., 2006), cardiopulmonal (Bookman et al., 2004) and renal (Liao et al., 2006) involvements have been described.
blood culture is often unsuccessful. PCR-based genetic analysis may be helpful during the first 6 weeks of infection (Hansmann et al., 2005). We used a universal eubacterial PCR approach to amplify ribosomal genes in patient 2 (Girschick et al., 1999).

Therapy for \( B. \) henselae infections is still controversial. At the moment it is not clear whether an antibiotic therapy in immunocompetent patients with CSD has any advantage over no therapy. The current recommendation for mild to moderately ill immunocompetent patients is to 'wait and see' after the diagnosis has been confirmed (Rolain et al., 2004; Koehler & Duncan, 2005). Supportive analgesic and anti-inflammatory treatment may be useful. If antibiotic therapy is necessary (i.e. in patients with very large lymph nodes or complicated disease), erythromycin, clarithromycin or azithromycin have been used successfully (Bass et al., 1998). A combination of rifampicin and doxycycline can be used as an alternative regimen (Rolain et al., 2004). The latter combination has been used successfully in complicated CSD, and in patients with neuroretinitis or central nervous system disease (Rolain et al., 2004).

References


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