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REVIEW

Bone infection in cat-scratch disease: A review of the literature

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Review

Summary *Objective:* To describe the main features of bone infection associated with Cat-scratch disease (CSD).
Methods: We searched for articles indexed in the international literature databases by using the following key words: ''*Bartonella*'', ''bone'', ''cat-scratch'', ''osteomyelitis'' and ''osteolytic''.
Results: Cases of 47 patients were reviewed. The median age was 9 years, with an equal sex distribution. Bone pain and fever were the main symptoms. The presence of fever and increased age were more common in patients with bone infection than classically reported in uncomplicated (i.e. nodal) CSD. The vertebral column and pelvic girdle were the most common sites of infection. Radiological examination typically confirmed bone osteolysis. All patients recovered without complications or chronic infection, although they received a various combination antibiotic regimen and duration therapy. The mechanism by which infection might spread to the bone is via the haematogenous route, accounting for most of the disseminated cases and via the lymphatic route, for those with regional limited extension.
Conclusions: Bone infection is rare but should be considered when bone pain and fever are present in a patient with nodal CSD. The prognosis is good, whatever treatment is given. Thus bone biopsy should be recommended only in a difficult diagnostic setting, when other bacteria or malignant disease are suspected.

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Introduction

Cat-scratch disease (CSD) is a benign infection occurring mostly in childhood. Typically regional lymphadenopathy appears within a few weeks after a cat-scratch and heals spontaneously in a few weeks or months.[1] *Bartonella henselae*, a Gram negative bacillus, is mainly involved as the causative agent.[2,3] Large historical studies underline the low incidence of CSD in adults and the rarity of systemic manifestations, particularly bone lesions.[1,4–6]

Herein we review the literature of bone involvement during the course of CSD. We focus on clinical features, radiological findings, treatment and outcome. Finally we try to identify predisposing factors for dissemination of CSD to the bone.

Methods

We searched for articles indexed in the Cochrane Library, Embase, Medline and Pascal databases by using the following key words: ''*Bartonella*'', ''bone'', ''cat-scratch'', ''osteomyelitis'' and ''osteolytic''. No limits were set in our search concerning the time or language of publication. The references from the identified articles were also searched for relevant publications.

Cases of CSD-related bone infection were retained as follows: either when authors reported on a bone infection during the course of typical CSD (i.e. lymph node enlargement with positive *B. henselae* serology and/or isolation of the causative bacterial agent in the node using PCR assay or culture and/or, at least, a positive skin test) or when the causative agent of CSD was directly demonstrated (by PCR assay and/or culture and/or, at least, suggestive histological findings with positive Warthin-Starry silver stain) in a bone lesion in the absence of concomitant nodal disease. Bone involvement associated with bacillary angiomatosis (an AIDS related disease), was excluded, given that it belongs to a different pathophysiological entity and is more likely related to *Bartonella quintana*.

Clinical, biological, radiological and histopathological findings of patients with CSD-related bone infection were collected. Some clinical and demographic parameters were compared to those reported in large historical cohorts of patients with nodal CSD, in order to highlight signs that may suggest bony spread of the disease or conditions that may be associated with it.

For statistical analysis, categorical data from cases (patients reviewed herein) and controls (patients reported in large historical cohorts) were compared by either χ^2 test or Fisher's exact test according to the tested variables. Statistical analysis was carried out using SAS version 8.0 (SAS Inc., Cary, NC, USA). For all tests, $p < 0.05$ was considered to be statistically significant.

Results

One hundred and six articles were identified by the literature search. Sixty six articles were excluded because of insufficient clinical data on cases or because cases didn't meet the criteria of bone infection due to CSD (see Section 2). Finally, 40 articles reporting 47 cases of CSD-related bone infection (including one personal case, not published) were collected.[5,7–45] The main characteristics of these observations are summarised in Table 1.

Demographic and clinical characteristics

The median age of patients was 9 years (lower to upper quartiles = 5 to 14), with an equal sex distribution (M/F = 24/23). Adults (23%) were over-represented as compared to the general population in Carithers' study (10%) ($p = 0.007$).[1] Severe underlying diseases or debilitating host factors were uncommon: only two patients were potentially immunocompromised (HIV infection, $n = 1$; renal graft, $n = 1$). Patients typically complained of bone pain (89%) and fever (84%). Fever was significantly more frequent in our reviewed population than in non-systemic CSD (nearly 41% in Carithers' study) ($p < 0.001$).[1] Bone involvement in a single site accounted for 72% of cases. Vertebral localisation was by far the most common site of infection, followed by the pelvic girdle, chest wall and skull. Children and adults did not differ in terms of site of bone infection, visceral spread of infection or the presence of fever. In most of cases, CSD was suspected to be the cause of bone infection because of previous or concomitant typical nodal disease (68%). In some reports patients were investigated for pyrexia of unknown origin or for suspected malignant disease. In these cases a history of a scratch by a cat or kitten frequently helped to obtain the final diagnosis of CSD.

Diagnostic tools

Serological tests for *Bartonella henselae* were positive in 32/33 patients tested. A bone biopsy was performed in 13/47 patients, in whom the presence of the causative bacterial agent was proven by PCR in 5 cases (*Bartonella*, $n = 4$; *Afipia*, $n = 1$) or suggested by Warthin-Starry staining in 2 cases tested. Additionally *Bartonella* was found by PCR assay on node or pus aspirates in 5 and 4 cases respectively, and was suggested by Warthin-Starry staining on a node in 6 cases. There was no case reported where bacteria were not cultured from either blood or biopsied tissues. Overall, combining serology and PCR, *B. henselae* infection was demonstrated in 34 cases and *Afipia felis* in 1 case. Elevated C-reactive protein and erythrocyte sedimentation rate were common, but non-specific, findings.

All 47 patients had radiological and/or radionuclide bone scan abnormalities. Increased uptake of ^{99m}Tc or Gallium on radionuclide bone scan was the most common feature ($n = 27$) reported by authors, followed by osteolytic lesion(s) either on Computed tomography (CT) scan ($n = 16$), radiography ($n = 9$) or Magnetic resonance imaging (MRI) ($n = 6$). Other findings included bone signal abnormalities without osteolysis on MRI ($n = 11$), periosteal reaction ($n = 2$) or marginal sclerosis ($n = 1$) on radiography. In patients with multiple sites of bone infection it is noteworthy that either radionuclide bone scan and MRI frequently identified lesions that were not clinically relevant. With specific reference to the vertebral column, infection was reported at every anatomical site but predominately affected the vertebral body; the thoracic vertebra were most frequently affected followed by the lumbar and cervical spine (54, 38