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

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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. Bartonella henselae, a Gram negative bacillus, is mainly involved as the causative agent. Large historical studies underline the low incidence of CSD in adults and the rarity of systemic manifestations, particularly bone lesions.  

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 pathophysiologic 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 $\chi^2$ 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.  

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%) ($p = 0.007$). 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) ($p < 0.001$). 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 vertebrae were most frequently affected followed by the lumbar and cervical spine.
Including one personal case, not published. Missing data, Presence of Elbow, knee, metacarpus, metatarsus, orbit, sacrum, tibia (each, n = 1). Arm, orbit, psoas (each, n = 1). Abscess or nodules (none, n = 1). Abscess drainage (none, n = 1). No special host factor was identified to explain extra-nodal spread of infection, as most of the patients reviewed here had no immunosuppressive condition. Young adults may be over-represented in this setting. Nevertheless, considering the reference population is predominately from the paediatric literature, adults may have been underestimated. Indeed recent data suggest that adults may account for up to 45% of patients with CSD.

The mode of bacterial spread to the bone is not always the subject of speculation by authors. In less than 40% of reviewed cases, a single bone lesion was contiguous or in the satellite area of an infected lymph node, which was more likely to be related to loco-regional lymphatic spread of infection. In all the remaining cases, haematogenous spread was implicated by the distance between nodal disease and the location of bone infection, multiple and separate bone lesions, or hepato-splenic abscesses. Also, we believe that primary osteomyelitis is the mechanism that might account for a majority of the reviewed cases. Both mechanisms were possible in some patients. It is

Bone involvement in CSD is a rare phenomenon. In Carithers’ report on a cohort of 1200 patients with CSD seen between 1955 and 1985, only sixty patients (5%) had systemic involvement, in whom two (0.17% of whole population) had bone infection. Margileth reported similar results: osteomyelitis was found in 5 out of 1852 patients (0.27%).

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noteworthy that the bone location was typically axial and joint involvement was rare. Indeed, although the vertebra was by far the most common site, discitis was rarely reported.

Although CSD has been recognized for decades, only with the recent application of molecular biology have the diagnostic criteria been clarified. PCR, scintigraphy or CT scan are useful to demonstrate evidence of bony involvement in the setting of CSD. Histology of lymph nodes show characteristic, but non-specific granulomatous lesions with central, sometimes stellate necrosis and neutrophils surrounded by palisading histiocytes. The Bartonella bacteria can be identified using the Warthin-Starry silver stain. Serological confirmation has now become the cornerstone of CSD diagnosis. Detection of antibodies against B. henselae by immunofluorescence assays or enzyme immuno-assay has high sensitivity (88%) and specificity (97%). False negative may be due to the absence of detectable antibodies, infection with a non-cross-reactive bacteria (i.e. B. clarridgeiae or Afipia felis) that are occasionally reported as CSD causative agents, or result from heterogeneous antigenicity among B. henselae species. PCR allows direct and specific detection of the bacteria in biopsied tissues or pus aspirates. Moreover PCR can differentiate Bartonella species. Nevertheless a negative PCR does not exclude the diagnosis, as infection with other bacteria is possible. Culture of B. henselae is difficult and less sensitive than PCR or serology.

Nodal CSD does not systematically require antibiotic therapy. However a prospective, placebo-controlled and randomised study demonstrated a clinical benefit (i.e. time to decreased lymph node size) in young patients with uncomplicated CSD treated with oral azithromycin for 5 days. Because of its rareness there is no evidence-based guidelines for treatment of disseminated CSD, particularly when there is bone involvement. Additionally, no clinical trial has ever addressed the possible role of antibiotics in the prevention of extra-nodal spread during the nodal phase of the disease. In a retrospective study of 268 patients with mild to severe CSD Margileth found successful antibiotic treatment of fever, general symptoms and limitation of the evolution of lymphadenopathy. The most effective antibiotics were (in decreasing efficacy): rifampin, ciprofloxacin, gentamicin, trimethoprim and sulfamethoxazole. Nevertheless only aminoglycosides have in vitro bactericidal activity. In our review it is noteworthy that patients received a variety of antibiotics, often monotherapy, most of which are considered to have poor activity on Bartonella and/or mild penetration in bone tissue. Moreover almost half of patients received a short course antibiotic therapy (less than 6 weeks) for the treatment of a bone infection. Nevertheless all patients had a similar good prognosis, whatever the treatment used. There were even four patients who received neither antibiotic therapy, nor surgery but went on to a complete recovery.

In conclusion, the presence of bone pain and fever during the course of nodal CSD should raise the possibility to the physician that bony spread has occurred, especially in young adults, even though systemic manifestations rarely occur. Serology, and ultimately PCR of peripheral node, are sufficient to confirm the diagnosis of CSD. Because Bartonella infection of the bone has a universally favourable prognosis, the physician should avoid invasive exploration in order to demonstrate the presence of Bartonella in bone, except in the cases where malignant disease or infection with other bacterial agent are suspected, or when surgical excision is required as a therapeutic option. Antibiotic therapy is probably sufficient for complete bone recovery but further studies are warranted to determine the best antibiotic combination and duration, if indeed a combination is necessary.

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References
