Costal osteomyelitis due to *Bartonella henselae* in a 10-year-old girl

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**Abstract.** *Bartonella henselae* is the bacterial agent responsible for cat scratch disease. This infection is frequently the cause of localized lymphadenitis in children. It is also sometimes responsible for endocarditis, encephalitis, hepatic peliosis and in rare cases osteomyelitis. We describe the second known case of unifocal thoracic osteomyelitis in a 10-year-old child.

1 Introduction

Cat scratch disease is the most common zoonotic disease, affecting children and young adults in 80% of cases (Mirouse et al., 2015). The first French cases were reported in 1950 by Robert Debré, who described the presence of spontaneously resolving adenopathies in the drainage area following cat scratches (Debre et al., 1950).

The so-called classic clinical form manifests itself as a single or single-site, unilateral, inflammatory, and sensitive lymphadenopathy. Atypical forms have been described with systemic expressions depending on the immune status of the host: examples include Parinaud’s oculo-glandular syndrome, hepato-splenic abscess, endocarditis and encephalitis etc. (Leclainche and Bourrillon, 1996; Carithers, 1985). *Bartonella* osteoarticular infections are rare, and in fact the prevalence of these bone manifestations lies between 0.2% and 0.3% (Hajjaji et al., 2007; Maman et al., 2007) and affects mostly children; 75% of cases are unifocal (Zellali et al., 2019), and the infection is usually localized in the spine (Zellali et al., 2019). The rib cage is rarely the site of such infections. There are a total of six cases of multifocal osteomyelitis with thoracic involvement and only one case of unifocal thoracic osteomyelitis in the literature.

Here, we report the second case of a child hospitalized for a suspected thoracic tumor that was finally found to be cat scratch disease, and we provide a review of the literature on osteoarticular *B. henselae* infections in the pediatric population.

2 Method

We consulted the PubMed database to perform the present literature review.

We included systematic reviews, journals and case reports published in English since the first case was found in 1952.

We retained only cases reported for children, so all patients older than 18 years were excluded from the study.

The terms used in the search database were as follows: cat scratch disease, bone, bone infection, bone joint infection, bartonella, bartonellosis.

3 Case study

A 10-year-old girl presented with fever, diarrhea and diffuse muscle pain. Treatment with non-steroidal anti-inflammatory drugs and paracetamol was initiated by the treating physician, but the symptoms persisted and the patient developed bone pain in the sacroiliac, left thigh and left costal areas. She was hospitalized on the 10th day of clinical evolution, in a context of altered general condition and a weight loss equivalent to −3.5% of total body weight. The clinical examina-
tion was unremarkable and did not reveal lymphadenopathy or hepato-splenomegaly. The first blood test showed white blood cells at 15.57 G/L, CRP of 150 mg/L and sterile blood cultures.

The thoracic–abdominal–pelvic CT scan showed moderate hepato-splenomegaly, a 20 × 23 mm left axillary ganglion (Fig. 1) and retro-pectoral lymph nodes larger than 1 cm. There were no abnormalities in the bone window. A technetium-99m bone scan revealed increased uptake in the left midrib.

Treatment with paracetamol and naproxen 10 mg/kg/d reduced the fever and allowed the patient to return home, and the diagnostic retained was then chronic aseptic osteomyelitis.

One month later, the child was again experiencing pain in the left costal area. Bioassay results showed hyperleukocytosis (10.7 G/L) and an elevated CRP level (37 mg/L). A new CT scan showed a single bone lesion on the anterior arch of the seventh left rib with a blown aspect and cortical lysis surrounded by a tissue sleeve. The lesion was 46 mm high, 64 mm deep and 34 mm wide, with a necrotic-looking tissue component (Fig. 2a).

The child was referred to the university hospital for a suspected chest tumor. A surgical biopsy of the middle arch of the left seventh rib was performed, and the intraoperative findings revealed a purulent fluid with false membranes, revealing a lytic lesion of the rib. Direct examination of pus after Gram staining found no bacteria. A few colonies of *Staphylococcus lugdunensis* were found after 6 days of culture. This result was considered as contamination of the sample taken by the surgeon.

Anatomo-pathological examination revealed granulomatous tissue, punctuated by small foci of necrosis surrounded by polymorphic inflammatory elements, rich in histiocytes and CD68+ macrophages around the foci. The periodic-acid–Schiff, Gram and Ziehl–Neelson stains were negative.

An interview with the girl’s parents revealed the presence of kittens in the home. Further tests including *Bartonella henselae* serology returned with an IgG titre of 1/1280 (IFI technique), for a positivity threshold of 1/320. *Bartonella henselae* polymerase chain reaction (PCR) on whole blood was negative and 16S PCR on biopsy tissue was positive for *Bartonella sp*.

Treatment with a combination of azithromycin and rifampicin for 6 weeks completely improved the symptoms: lasting apyrexia, disappearance of pain in a few days and a weight gain of 3 kg at mid-treatment.

The anti-*Bartonella* IgG titre at the end of treatment was 1/640, and the chest CT scan revealed that the peri-costal collection had resolved and there was a favorable evolution of the bone lesion (Fig. 2b).

Follow-up at 6 months from the end of treatment found the girl in good general condition with no recurrence of fever or pain.
| Year     | Authors                          | Sex/age | The bone        | Portions              | Lymphadenopathy | Fever | Serology | Antibiotics                  | Duration of therapy (day) |
|----------|----------------------------------|---------|-----------------|-----------------------|-----------------|-------|----------|----------------------------|----------------------------|
| 1954     | Adams and Hindman (1954)         | M/5y    | pelvic bone     | cervical/inguinal     | 38.1            | +     | Penicillin/doxycycline     | 9/15                       |
| 1959     | Collipp and Koch (1959)          | M/4y    | pelvic bone     | hip                    | cervical        | +     | Erythromycin/chloramphenicol | 15/10                      |
| 1969     | Carithers et al. (1969)          | F/6y    | Ve metatarsus    | axilla                | 38.1            | 38.4  | No treatment                  |                            |
| 1983     | Carithers et al. (1983)          | M/2y    | sternum         | cervical               | 38              | +     | Surgical treatment then cloxacillin | 14                        |
| 1985     | Johnson et al. (1985)            | M/18y   | rachis           | cervical               | 38              |       | Penicillin-M                  |                            |
| 1987     | Muszynski et al. (1987)          | M/2y    | frontal bone    | inguinal              | 38              |       | Penicillin-M                  |                            |
| 1987     | Welterbroek and Nimmo (1987)     | F/7y    | humerus          |                        |                 |       | Clindamycin                   |                            |
| 1989     | Shalom et al. (1989)             | M/11y   | L4               |                        |                 |       | Cefazolin                      | 14                        |
| 1990     | Karpin et al. (1990)             | F/6y    | T5               |                        |                 |       | Ceftriaxone                    | 15                        |
| 1990     | Cohen-Abbo et al. (1990)         | M/6y    | fronto-parietal bone /T12-L1 | cervical/inguinal | 40              | +     | Ceftriaxone/gentamicin       | 8/10                       |
| 1996     | Wakhovgel et al. (1996)          | M/9y    | rachis           | axillary               | 38.3            |       | Surgical treatment then oxacillin | 14                        |
| 1996     | Gallemore and Worley (1996)      | M/6y    | rachis           | retro-pharyngeal       | 40              | +     | Clindamycin/rifampicin       | 7/10                       |
| 1997     | Hopkin et al. (1997)             | M/6y    | L2               |                        |                 |       | Azithromycin                   |                            |
| 1999     | Berg et al. (1999)               | M/6y    | skull            | metacarpal-ophthalmal | 40              | +     | Surgical treatment then     | 18/28                      |
| 1999     | Kenet et al. (1999)              | M/9y    | pelvic bone      | cervical               | 40              |       | Azithromycin/clarithromycin   | 28                        |
| 1999     | LaRow et al. (1998)              | M/10y   | pubic/iliac crest| cervical               | 40              |       | Azithromycin                   | 14                        |
| 1999     | Ratner et al. (1998)             | F/8y    | iliac wing/sciatic | cervical/inguinal     | 40              | +     | Ciprofloxacin/ceftriaxime    | 42                        |
| 1999     | Hulbeso et al. (1999)            | F/10y   | L2               | cervical               | 40              |       | Ciprofloxacin/ceftriaxime    | 42                        |
| 1999     | Maccio et al. (1999)             | F/7y    | humerus          | cervical               | 40              | +     | Ciprofloxacin/ceftriaxime    | 10                        |
| 1999     | Robo et al. (1999)               | F/6y    | T9               | cervical               | 40              | +     | Ciprofloxacin/ceftriaxime    | 10                        |
| 2000     | Liap-Aduuvel et al. (2000)       | F/7,5y  | rib/rachis       | sub-mandibular/axillary | 40              |       | Ciprofloxacin/ceftriaxime    | 15                        |
| 2000     | Rues et al. (2000)               | F/7,2y  | rachis           | cervical               | 40              | +     | Ciprofloxacin/ceftriaxime    | 21                        |
| 2001     | Fretay et al. (2001)             | F/9y    | rib/rachis       | axillary/epithroclear  | 40              | +     | Azithromycin                   | 28                        |
| 2001     | Modi et al. (2001)               | F/9y    | pelvic bone      | cervical               | 40              | +     | Azithromycin                   | 14                        |
| 2002     | Del Santo et al. (2002)          | F/2y    | L4-L5            | cervical               | 40              | +     | Azithromycin                   | 28                        |
| 2002     | Pybis et al. (2002)              | F/6y    | femur            | retroperitoneal        | 40              | +     | Azithromycin                   | 28                        |
| 2003     | Mirakabz et al. (2003)           | M/6y    | orbital osteomyelitis | cervical               | 39.2            | +     | Azithromycin                   | 35                        |
| 2003     | Rolla et al. (2003)              | M/10y   | rachis           | axillary               | 39.8            |       | Azithromycin                   | 20                        |
| 2003     | Sakkellias et al. (2003)         | F/6y    | 10th rib         | cervical               | 39.8            |       | Azithromycin                   | 20                        |
| 2004     | Abdel-Haqq et al. (2004)         | F/5y    | T4-T5-T7         | cervical               | 39.8            |       | Azithromycin                   | 20                        |
| 2004     | Hipp et al. (2005)               | M/10y   | sacrum ilium     | femur                  | 39              | +     | Azithromycin                   | 35                        |
| 2004     | Hipp et al. (2005)               | F/9y    | sacrum/lumbar spine | cervical               | 39              | +     | Azithromycin                   | 20                        |
| 2006     | De Kort et al. (2006)            | F/9y    | cervical rachis  | cervical               | 39.6            | +     | Azithromycin                   | 99                        |
| 2006     | Vermeulen et al. (2006)          | F/9y    | cervical rachis  | cervical               | 39.6            | +     | Azithromycin                   | 21                        |
| 2007     | Hussain and Rutherford (2007)    | M/5y    | T9               | cervical, submandibular | 39              | +     | Azithromycin                   | 42                        |
| Year       | Authors                      | Sex/age | The bone          | Portions | Lymphadenopathy | Fever       | Serology | Antibiotics                  | Duration of therapy (day) |
|------------|------------------------------|---------|-------------------|----------|-----------------|-------------|----------|-------------------------------|---------------------------|
| 2007       | Kodama et al. (2007)         | F/11y   | T3 L4 L5 femur    |          |                 |             | IgG      | 1/1024 Azithromycin/doxycycline | 28                        |
| 2007       | Rozmanic et al. (2007)       | M/11y   | 8th rib, T8, iliac bone | inguinal |                 |             | IgG      | 1/8192 Azithromycin/rifampicin | 42                        |
| 2008       | Ridder-Schröter et al. (2008) | F/12y   | humerus           | axilla/epistroclear |            |             | IgG      | 1/1024 Clarithromycin then clindamycin/rifampicin | 10/11                      |
| 2009       | Tasher et al. (2009)         | M/5y    | C1-C4-C5 cervical, submandibular | |             |             | IgG      | 1/1024 Surgical treatment then Azithromycine/rifampicin |                      |
| 2010       | Kossiva et al. (2010)        | F/13y   | hip, acetabulum   | cervical |                 |             | IgG      | 1/1024 Ceftriaxone            | 10                        |
| 2011       | Boggs and Fisher (2011)      | M/11y   | cubitus           | +Azithromycin |               |             |         |                               | 21                        |
| 2012       | Al-Rahawan et al. (2012)     | M/7y    | T6-T8            |          |                 |             | IgG      | 1/512 Azithromycin            | 14                        |
| 2013       | Dusser et al. (2013)         | F/13y   | hip, sacrum, humerus, femur, tibia |          |                 |             | IgG      | 1/512 Azithromycin            | 28                        |
| 2015       | Lafenetre et al. (2015)      | F/13y   | T2 T3 L4 L5 femur | submandibular |         |             | IgG      | 1/10000 Cotrimoxazole/rifampicin | 21                        |
| 2015       | Knafl et al. (2015)          | M/18y   | T7 cervical       |          |                 |             | IgG      | 1/10000 Azithromycin/rifampicin | 21                        |
| 2015       | Mirouse et al. (2015)        | M/14y   | C1-C2 supracondylar |               | negative |             |         | Amoxicillin-clavulanic acid/ciprofloxacin | 90                        |
| 2016       | Dornbos et al. (2016)        | F/5y    | T8-T11 inguinal   |          |                 |             | IgG      | 1/128 Azithromycin then Doxycycline/rifampicin | 5/46/25                    |
| 2017       | Harry et al. (2017)          | F/9y    | sternum, rib, pelvis, hip |          |                 |             | IgG      | 1/512 Azithromycine | 28                        |
| 2017       | Harry et al. (2017)          | F/3y    | skull, eye socket, T4 T12 cervical | |             |             | IgG      | 1/1024 Azithromycine  | 28                        |
| 2017       | Rafferty et al. (2017)       | M/5y    | C7 T13           |          |                 |             | IgG      | 1/1024 Ciprofloxacin/rifampicin | 42                        |
| 2018       | Akbari et al. (2018)         | M/7y    | C2-C4 cervical    |          |                 |             | IgG      | 1/1024 Azithromycin/rifampicin | 42                        |
| 2018       | Aoki et al. (2018)           | F/2y    | pelvic bone, femur, cervical |          |                 |             | IgG      | 1/1024 |                               | 28                        |
| 2018       | Donà et al. (2018)           | F/12y   | temporo-parietal bone | cervical, submandibular |          |             |         | Azithromycin then Cotrimoxaxol/rifampicin | 15/84                     |
| 2018       | Karski et al. (2018)         | F/1.5y  | radius            |          |                 |             | IgG      | 1/320 Surgical treatment |                      |
| 2018       | Mathews et al. (2018)        | F/12y   | elbow, hip        |          |                 |             | IgG      | 1/1024 Azithromycin  | 42                        |
| 2018       | Rafee and English (2018)     | F/3y    | frontal bone, pre-auricular, inguinal | Azithromycin/rifampicin | |             |         |                               | 42                        |
| 2018       | Zellali et al. (2019)        | M/3y    | pelvic bone, S4–S5 inguinal |            |                 |             | IgG      | 1/1024 Cefamandol/azithromycin then Amoxicillin-clavulanic acid/rifampicin | 15/42                     |

Table 1. Continued
4 Discussion

The diagnosis of osteoarticular infections in children is difficult. The incidence of all these infections is low, estimated to be between 7.1 and 22 per 100,000 population (Mitha et al., 2015; Grammatico-Guillon et al., 2013), and they can affect all parts of the skeleton even if they are predominately found in the lower limbs: 75%–80% of cases (Vial and Chiavassa-Gandois, 2012). The main bacteria that cause these infections are group B streptococcus in children under 3 months of age, Kingellakingae between 6 months and 4 years of age, and Staphylococcus aureus at all ages (Ferroni et al., 2013).

The main differential diagnosis for rapidly progressing bone disease is a neoplastic process (Massei et al., 2000).

Cat scratch disease affects an estimated 40,000 people worldwide, with 80% of cases occurring in people under 18 years of age (Mirouse et al., 2015). The prevalence of osteomyelitis in Bartonella henselae varies between 0.2% and 0.3% (Hajjaji et al., 2007; Maman et al., 2007). Spinal injury is the most common manifestation (42% of cases) and multifocal injury is seen in 25% of cases (Zellali et al., 2019).

Our review of the literature identified 62 cases of B. henselae osteomyelitis in children published since 1954; only 7 cases included costal involvement (Table 1). The typical clinical picture is a child under 10 years of age with fever, cervical polyadenopathy and an average weight loss of 4.5 kg (Table 1). The scratch of a cat was observed in 20 out of 62 cases without necessarily being in the territory of the adenopathy (Table 1). Rare musculoskeletal manifestations (Maman et al., 2007) were reported for 30 out of 62 children, of which 20% were arthralgia.

Biological examinations did not provide enough data to suggest a particular diagnosis: leukocytes were higher than 10 G/L for 21 out of 62 children. Non-discriminating inflammatory syndrome was generally found, with average CRP median of 20 mg/L (<5–111 mg/mL).

Standard radiology was performed for 17 children, focusing on the painful segment. Osteolysis was sometimes found and in some cases associated with sclerosis or even a periosteal reaction within an infiltration of the surrounding soft tissues (Carithers, 1983; Johnson et al., 1985; Mazur-Melewska et al., 2015; Rohr et al., 2012). CT scans (performed on 25 children) confirmed bone destruction. MRI (31 children) was mostly used to evaluate the extent of lesions and whether they involved the bone marrow, adjacent tissues and the nervous system. Bone scintigraphy (23 children) offered the advantage of mapping the body, which revealed foci at a distance from the osteoarticular apparatus or detected abscesses on the liver and/or spleen in 15 out of 23 and 11 out of 23 children respectively. The potential of the PET scan has not yet been evaluated in this context.

Serology and molecular biology (polymerase chain reaction) techniques were used on tissue samples for microbiological diagnosis (Dusser et al., 2013; Hansmann et al., 2005). A total of 46 children were seropositive, and the anti-Bartonella IgG titre was greater than 1/512 for 26 of them. Only two children tested negative. Bartonella PCR was performed on 17 tissue samples and was positive on all samples; there were no false negatives in this series. The sensitivity of PCR analyses is estimated at 60%–75%, with high specificity allowing species diagnosis between Bartonella (Hansmann et al., 2005; Ratner et al., 1998; Eglantin et al., 2008).

Due to the rarity of osteoarticular forms of cat scratch disease, there are no defined antibiotic protocols. Macrolides were used for 52.0% of children, 22 of whom received azithromycin. Beta-lactam antibiotics were also used in 34.8% of children, fluoroquinolones in 7.6% and doxycycline in 6%.

When dual therapy was initiated (42.6% of children), rifampicin was associated in 29.0% and aminoglycosides in 13.6%. Other combinations were either with Fosfomycin, chloramphenicol or cotrimoxazole.

In our case, the choice of antibiotic therapy (azithromycin and rifampicin) was motivated by their low minimal inhibitory concentrations reported in the literature (azithromycin 0.006–0.015 mg/mL, rifampicin 0.03–0.06 mg/mL), but also by their intracellular activity (Rolain et al., 2004; Bass et al., 1998).

The median duration of antibiotic therapy is 22 d (5–99 d). Only 2 children (3.2%) did not receive antibiotics, and 4 (6.4%) laminectomy surgeries were performed.

5 Conclusions

Bartonella osteoarticular infections are rare in children, but should nonetheless be considered when a quickly progressing bone lesion is observed, a fortiori if there are signs of infection and there has been contact with animals, especially cats. Bartonella henselae serology should be carried out systematically in these cases, and close collaboration with the bacteriology laboratory should make it feasible to obtain a prompt diagnosis.

Ethical statement. Consent was received from the patient prior to submission for publication.

Data availability. No data sets were used in this article.

Author contributions. ASR, CD, PC, QB, CA and CB cared for the child, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final paper as submitted and agree to be accountable for all aspects of the work.

Competing interests. The authors declare that they have no conflict of interest.
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