Three Cases of Q Fever Osteomyelitis in Children and a Review of the Literature

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Q fever is a common zoonosis worldwide. Awareness of the disease and newer diagnostic modalities have resulted in increasing recognition of unusual manifestations. We report 3 cases of Q fever osteomyelitis in children and review the literature on 11 other reported cases. The cases demonstrate that Coxiella burnetii can cause granulomatous osteomyelitis that presents without systemic symptoms and frequently results in a chronic, relapsing, multifocal clinical course. Optimal selection and duration of antimicrobial therapy and methods of monitoring therapy are currently uncertain.

Q fever is a zoonosis caused by Coxiella burnetii, which has a worldwide distribution. Farm animals and pets are the main infection reservoirs, and acquisition by humans is usually via inhalation of contaminated aerosols. The clinical spectrum includes acute and chronic disease, which are distinguished on the basis of clinical expression, temporal course, and serological profile. Host factors are the most likely determination of disease chronicity [1, 2]. The most common manifestations of chronic Q fever include endocarditis, chronic vascular infections, osteoarticular infection, chronic hepatitis, pericarditis, and myocarditis. Q fever has rarely been reported in children, and there are only isolated reports of chronic infection [3]. We describe 3 patients with Q fever osteomyelitis and review cases of Q fever–attributed osteomyelitis that have been reported in the literature.

PATIENTS AND METHODS

Case Reports

Patient 1. A 4-year-old boy presented in May 1998 with a 2-year history of a cyst-like swelling on the dorsum of his right foot that was thought to have developed after a fall from a swing in an urban public park. A presumptive diagnosis of ganglion was made, until the cyst developed a purulent discharge. Surgical exploration revealed purulent fluid and soft-tissue and bone abscesses with multiple tracts and sinuses. Histologic examination revealed noncaseating granulomas and chronic inflammation. The results of stains and cultures for bacteria and fungi (including acid-fast bacilli) were negative. Results of Mantoux and serological tests and cultures for Bartonella, Brucella, Toxoplasma, and Histoplasma species were negative. A presumptive diagnosis of atypical mycobacterial infection was made. Empirical treatment with clarithromycin and cotrimoxazole was given for 7 weeks, with resolution of symptoms.

Three months later, in August 1998, patient 1 presented again with a 5-week history of a painful lesion on the chest wall. The lesion was excised, and histologic analysis again revealed a chronic abscess with noncaseating granulomas. In November 1998, he presented with back pain. MRI revealed a destructive lesion on T10 with extradural extension. There were no abnormal findings, such as an infected aneurysm, in adjacent blood vessels. Vertebral biopsy revealed a granulomatous inflammatory process with tight aggregates of histiocytes and open granulomas containing central necrosis and dystrophic calcification. A patchy lympho-
plasmocytic infiltrate was associated with these findings. Results of bacterial stains and cultures were again negative. Another 6-month regimen of clarithromycin and cotrimoxazole achieved symptomatic resolution.

Two years later, in January 2001, 5 years after onset of the first symptoms, patient 1 presented to the hospital with swelling of his left foot. Histological analysis revealed a necrotizing granulomatous inflammatory process involving soft tissue and navicular bone (figure 1). On this occasion, with information that patient 1 had lived on a dairy farm between 1 and 2 years of age, Q fever serological analysis was performed and showed a phase II complement fixation titer (CFT) of 1:128 and a phase I CFT of 1:256, and an indirect immunofluorescence (IFA) revealed an elevated anti–phase I and phase II IgG titer of 1:2560. No anti–phase I or phase II IgM or IgA antibodies were detected. Paraffin blocks of previously obtained foot and chest wall specimens underwent retrospective histologic analysis, and nucleic acid amplification by PCR revealed *C. burnetii*. Trans-thoracic echocardiographic findings were normal. Patient 1 commenced doxycycline and rifampicin therapy, and he remained free of symptoms for 1 year before developing a deep abscess on his right heel over a period of 6 weeks (figures 2 and 3).

The abscess was drained, and histological examination confirmed chronic inflammation with granulomata. Culture results were negative. Therapy was switched to oral ciprofloxacin (500 mg b.i.d.), but healing did not occur, and reexploration with extensive bone curettage was necessary 4 months later. Therapy was then switched to doxycycline (100 mg once daily) and hydroxychloroquine (200 mg once daily). Patient 1 has remained healthy for 13 months.

Patient 1 was apyrexial without systemic symptoms at every presentation to the hospital. On each occasion, the WBC count, serum C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR) were normal. Immunoglobulin levels, complement levels, T cell counts, and lymphocyte subsets were normal on successive occasions. Three years after commencing therapy, his anti–phase I IgG titer remains unchanged, at 1:2560. The hydroxychloroquine dosage has been increased (to 300 mg once daily), and hydroxychloroquine levels have increased from 386 to 897 μg/L. The dosage will be increased at a later date. More-recent measurements of doxycycline levels are pending.

**Patient 2.** A 7-year-old boy presented to the hospital with typical features associated with uncomplicated acute osteomyelitis of the left tibia. Flucloxacillin-cephalexin treatment was given for 6 weeks. Slow healing occurred over a period of 3 months. Patient 2 presented again 7 months later, in January 2002, with a lesion in the distal right radius. Neither presentation was associated with systemic symptoms, fever, neutrophil leukocytosis, or increased inflammatory markers. Histological analysis revealed multiple noncaseating granulomata and lymphocytic inflammatory cell infiltrate. Cultures for bacteria and fungi, including atypical mycobacteria, were negative. Additional history revealed that patient 2 lived on a small cattle farm and that his father had recently acquired acute Q fever. There was no history of drinking unpasteurized milk. Q fever serological testing showed a phase II CFT of 1:16, a phase I CFT of 1:128, an anti–phase I IgG titer of 1:10,240, and an anti–phase I IgA titer of >1:640. PCR of paraffin sections of both tibia and radius specimens were negative for *C. burnetii*. Nevertheless, a diagnosis of chronic relapsing multifocal osteomyelitis (CRMO) secondary to Q fever was made, and treat-
ment was commenced with trimethoprim-sulfamethoxazole and doxycycline, resulting in healing of the radial lesion.

Four months later, in May 2002, patient 2 developed recurrent osteomyelitis in his right shoulder. Rifampicin was added to the trimethoprim-sulfamethoxazole and doxycycline regimen, but this combination was poorly tolerated, resulting in worsening behavioral difficulties. Therapy was changed to ciprofloxacin alone. There have been no further recurrences for 18 months.

Immunological testing has since revealed normal immunoglobulin levels, complement levels, and neutrophil function. At the time of writing, 2 years after diagnosis, the serological status of patient 2 remains unchanged.

**Patient 3.** A 3-year-old boy presented to the hospital with a 3-week history of pain and swelling of the left wrist. He was afebrile. Pharyngitis had preceded the presentation by 1 week. Patient 3 had had a 3-week episode of buttock lesions 4 months earlier. He lived on a horse and cattle property in rural southeast Queensland. There was no history of drinking unpasteurized milk. A physical examination revealed tenderness of the left wrist. Plain radiography revealed a lytic lesion at the distal end of the left radius. The WBC count, ESR, and CRP level were normal. Debridement and histological analysis of the radial lesion revealed fragments of bone and a suppurative noncaseating granulomatous inflammatory process characterized by collections of neutrophils with surrounding histiocytes, epithelioid granuloma, and occasional multinucleate giant cells. Results of cultures of the operative specimens were negative. Results of serological analysis for *Brucella* species was negative. Q fever serological analysis revealed an anti–phase II IgG titer of 1:5120 and an anti–phase I IgG titer of 1:10,240. The anti–phase I IgA titer was also elevated (≥1:640), and the phase I CFT was >1:128. PCR was positive for *C. burnetii*, with confirmation by sequencing of the DNA product. Patient 3 was treated with rifampicin and ciprofloxacin for 7 months and made a good functional recovery, with no evidence of recurrence or multifocal lesions during 12 months of follow-up. Results of serological analysis 14 months after presentation revealed an unchanged anti–phase I IgG titer of 1:10,240. At the time of writing, the anti–phase I IgA titer had also remained elevated (>1:640).

**Methods**

The diagnosis of chronic Q fever rested on consistent results of serological analysis for all 3 patients and, for 2 of the 3 patients, was supported by detection of *C. burnetii* DNA by means of PCR. The serological techniques included in-house CFT (Serion Immunodiagnostica) using phase I and II antigens to Q fever antibodies. Samples from each patient were analyzed with a complement control and a tissue control together with positive control serum specimens. Results were only accepted when titers for control specimens decreased to within ±1 titer of the expected titer. Serum specimens were serially diluted commencing at a dilution of 1:8. Isotype testing of antibodies (IgG, IgA, and IgM) to both phase I and II antigens was performed using IFA with fluorescein-labeled antibody to detect specific antibodies. Slides fixed with phase I and II antigens were prepared in-house or were purchased from the Infectious Diseases Laboratories Institute of Medical and Veterinary Studies (Adelaide, Australia) [4]. IgG antibodies were serially diluted, commencing at a titer of 1:40 and continuing until a titer of 1:40,960 was achieved for both antigens. A rheumatoid factor absorbent was used to remove IgG before the determination of IgA and IgM titers. Serial dilution of IgA and IgM antibodies commenced at 1:20 and continued until a titer of 1:640 was achieved, with the end point dilution still showing a positive reaction for >50% of the *C. burnetii* isolates that were present in the well.

PCR analysis was performed at Queensland Health Scientific Laboratories for patients 2 and 3 and by the Q Fever Research Group at the University of Adelaide for patient 1. For patient 3, *C. burnetii* DNA was detected by both a nested and TaqMan PCR directed against the *com-1* gene encoding a 27-kDa outer membrane protein [5], and the result was confirmed by sequencing the DNA product. Multiple samples obtained from patient 1 tested positive by means of TaqMan PCR amplification of the insertion sequence region [6]. No immunohistochemical methods were available to detect the presence of *C. burnetii* in involved tissue.

**DISCUSSION**

To our knowledge, there are only 14 published reports of Q fever osteomyelitis (including the above 3 cases) [3, 7, 8, 9, 10, 11] (table 1), 6 of which describe children. The majority of children experienced symptoms for a lengthy period (e.g., 5 years for patient 1) before diagnosis. The 3 children we de-

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**Figure 3.** Sagittal, T1-weighted, postgadolinium MRI showing diffuse abnormal contrast enhancement within calcaneus, with a 15-mm focal abscess collection at the inferoposterior margin (correlating with radiograph findings), as well as abnormal contrast enhancement along the subcutaneous track to the skin surface.
Table 1. Summary of cases of osteomyelitis attributed to *Coxiella burnetii*.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in years/sex</th>
<th>Risk factor (location)</th>
<th>Health status</th>
<th>Sites involved</th>
<th>Serological test results at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4/M</td>
<td>Visited dairy farm (Queensland, Australia)</td>
<td>Healthy</td>
<td>CRMO over 5 years: right foot, chest wall, T10 vertebrae, left foot, and right heel</td>
<td>Phase I CFT, 1:256; anti–phase I IgG titer &gt;1:2560; anti–phase I IgA &lt;1:10</td>
</tr>
<tr>
<td>2</td>
<td>7/M</td>
<td>Visited cattle property (New South Wales, Australia)</td>
<td>Healthy</td>
<td>CRMO over 13 months: left tibia and right radius</td>
<td>Phase I CFT, 1:128; anti–phase I IgG titer, 1:10,240; anti–phase I IgA titer, &gt;1:640</td>
</tr>
<tr>
<td>3</td>
<td>3/M</td>
<td>Visited horse and cattle property (Queensland, Australia)</td>
<td>Healthy</td>
<td>Unifocal single episode: left radius</td>
<td>Phase I CFT, &gt;1:128; anti–phase I IgG titer, 1:1024; anti–phase I IgA titer, &gt;1:640</td>
</tr>
<tr>
<td>4</td>
<td>7/M</td>
<td>Spent time on farm with goats (France)</td>
<td>Healthy</td>
<td>CRMO over 8 months: L3 spondylitis and right hip</td>
<td>Anti–phase I IgG titer, 1:1600; anti–phase I IgA titer, 1:100 (measured during the second episode)</td>
</tr>
<tr>
<td>5</td>
<td>9/M</td>
<td>Cat contact at home (France)</td>
<td>Healthy</td>
<td>Unifocal single episode: talus</td>
<td>Anti–phase IgG titer, 1:5120</td>
</tr>
<tr>
<td>6</td>
<td>2/F</td>
<td>Farm holiday playing with goats (France)</td>
<td>Healthy</td>
<td>CRMO over 3 years: left fibula, radius, and humerus and right carpus</td>
<td>Anti–phase I IgG titer, 1:3200; anti–phase I IgA titer, 1:200</td>
</tr>
<tr>
<td>7</td>
<td>51/M</td>
<td>Killed a baby goat (France)</td>
<td>Diabetic</td>
<td>Unifocal single episode: right hip</td>
<td>Anti–phase I IgG titer, 1:800; anti–phase I IgA titer, 1:25</td>
</tr>
<tr>
<td>8</td>
<td>59/NA</td>
<td>NA</td>
<td>NA</td>
<td>Unifocal single episodes: sacroiliitis</td>
<td>Anti–phase I IgG titer, 1:800</td>
</tr>
<tr>
<td>9</td>
<td>61/F</td>
<td>NA</td>
<td>NA</td>
<td>Lumbar spondylitis</td>
<td>Anti–phase I IgG titer, 1:800</td>
</tr>
<tr>
<td>10</td>
<td>65/NA</td>
<td>NA</td>
<td>NA</td>
<td>Distal femoral abscess</td>
<td>Anti–phase I IgG titer, 1:800</td>
</tr>
<tr>
<td>11</td>
<td>39/M</td>
<td>Dairy farmer (Scotland)</td>
<td>NA</td>
<td>Unifocal single episode: L5 lumbar spondylitis</td>
<td>Phase I CFT, 1:128; phase II CFT, 1:512</td>
</tr>
<tr>
<td>12</td>
<td>76/F</td>
<td>Wife of a farmer (Scotland)</td>
<td>NA</td>
<td>Unifocal single episode: T12/L1 vertebral spondylitis with psoas abscess</td>
<td>Phase I CFT, 1:512; phase II CFT, 1:1024</td>
</tr>
<tr>
<td>13</td>
<td>23/M</td>
<td>Dairy farmer (Scotland)</td>
<td>Fascia lata homograft repair for treatment of congenital aortic stenosis</td>
<td>Periosteal new bone formation in lower tibiae and fibulae plus other embolic stigmata of endocarditis</td>
<td>Phase I CFT, not tested; phase II CFT, 1:2048</td>
</tr>
<tr>
<td>14</td>
<td>61/M</td>
<td>Agricultural laboratory officer (Scotland)</td>
<td>Diacron abdominal aortic graft for treatment of an aneurysm</td>
<td>Multiple areas of osteomyelitis thought most likely to be embolic</td>
<td>Phase I CFT, 1:256; phase II CFT, 1:256</td>
</tr>
</tbody>
</table>

**NOTE.** CFT, complement fixation titer; Chl, chloramphenicol; Clm, clarithromycin; Cm, clindamycin; Cpfx, ciprofloxacin; CROM, chronic recurrent osteomyelitis; Dox, doxycycline; Eth, ethambutol; Hycq, hydroxychloroquine; INH, isoniazid; Lm, lincomycin; NA, not available; Oxa, oxacillin; Rif, rifampicin; Tet, tetracycline; TMP-SMZ, trimethoprim-sulfamethoxazole.

* Developed fever 15 days after killing the baby goat.
* Included as part of a review of 1383 patients with Q fever in France.

scribed and 2 of 3 children described elsewhere [8] had lived on cattle or dairy farms or had been exposed to farm animals. One child had had contact with a cat in the home. Most of the adults who were described had had contact with farm animals [11, 12]. History of contact with farm animals for a patient with chronic or relapsing osteomyelitis, particularly if associated with granulomatous bone lesions, should prompt investigation for Q fever. The indirect IFA is the reference diagnostic method for Q fever. Seroconversion usually occurs 2 weeks after the onset of illness. Chronic Q fever is diagnosed on the basis of an anti–phase I IgG titer >1:800 [3]. Detection of *C. burnetii* in tissue specimens by PCR provides useful additional evidence of infection. Of note, none of the 3 children we described had significant systemic symptoms or had elevated acute-phase reactants.

Patients 1 and 2 in this report and patient 6 in Table 1 had
repeated recurrences of osteomyelitis over a period of 5 years, 18 months, and 4 years, respectively, despite receiving therapy directed against Q fever with apparent good compliance. It is likely that children who develop chronic infection with Q fever have a specific immunological defect resulting in unfavorable host/organism interaction and delayed clearance of infection. This hypothesis requires further clarification. Patients with chronic Q fever require prolonged courses of antimicrobial therapy. Recommended agents include doxycycline, rifampicin, ciprofloxacin, and hydroxychloroquine. Treatment with doxycycline and hydroxychloroquine for up to 36 months is recommended for chronic endocarditis [13] and may be necessary for even longer periods in patients with chronic osteomyelitis. Levels of hydroxychloroquine of 1000 ± 200 μg/L are recommended for chronic Q fever endocarditis [13]. It has also been demonstrated that doxycycline levels are correlated with serologic evolution in cases of chronic Q fever [14]. At the time of writing, optimal levels of doxycycline and hydroxychloroquine have not yet been achieved in patient 1, and the future response of Q fever antibody levels to optimal doxycycline and hydroxychloroquine dosing is unknown.

Decreases in antibody levels despite specific therapy are very
slow and, in some patients, plateau without decreasing. Raoult [15] suspects that anti–phase I IgA and IgG titers of <1:200 are indicative of cure, at least for endocarditis, and that treatment must be maintained until that level is reached. This rarely occurs within 2–3 years after initiation of treatment. Evaluation of therapeutic success in patients with chronic Q fever requires prolonged follow-up because of the possibility of later relapse [15].

At the time of writing, the serological profile for the 3 patients described in this report has remained unchanged (for almost 3 years in the case of patient 1), despite ongoing treatment (for patients 1 and 3). In the absence of ongoing symptoms but with a persistently abnormal serological profile, the optimum length of therapy is unclear.

CRMO is an inflammatory bone disease that occurs during childhood and adolescence [16–19]. Features include a protracted disease course with multifocal bone lesions, evidence of chronic bone inflammation revealed by biopsy, and good response to anti-inflammatory agents without response to antibiotic treatment. Most cases have no defined cause. The proposed etiology includes infection, autoimmune disease, or immune dysfunction. Different infectious agents have been implicated, many of which are thought to be contaminating organisms.

Of 6 children described to date with Q fever osteomyelitis, 4 (patients 1 and 2 in this report and 2 described elsewhere [8, 9]) have had clinical courses consistent with CRMO. Of the 14 reported cases of Q fever osteomyelitis, multifocal bone disease is described in 5 [7, 8, 12].

Of 5 patients with CRMO of unknown etiology described in Australia in 1983 [20], a 7-year-old boy (patient 1) and a 6-year-old boy (patient 5) had a course similar to that of patient 1 in this report and had evidence of granulomatous lesions revealed by histological analysis of bone biopsy specimens. One patient received empirical treatment with tetracycline and rifampicin and had a seemingly benign course over 7 years, despite multiple recurrences. An unsuccessful attempt was made to obtain tissue specimens from these patients.

Q fever osteomyelitis is a rare and likely underreported disease that may be particularly prevalent among children. The diagnosis should be considered in cases of chronic relapsing or multifocal osteomyelitis, particularly if there is a history of exposure to farm animals or if granulomatous lesions are evident on histological analysis of bone specimens. Other potential infectious agents that cause granulomatous bone lesions should also be included. These include *Mycobacteria, Bartonella, Francisella, Brucella*, and *Nocardia* species. Issues involving the pathogenesis and optimal treatment-monitoring parameters of and the most effective therapy for Q fever osteomyelitis need to be clarified.

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**References**