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Q FEVER CHRONIC OSTEOMYELITIS IN TWO CHILDREN

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Abstract: We report 2 cases of chronic Q fever osteomyelitis in 10- and 5-year-old girls who presented with distal right femoral and left parasternal granulomatous osteomyelitis, respectively. Both were treated with ciprofloxacin and rifampin with good response. Q fever osteomyelitis is a challenging diagnosis in children, and the choice of antimicrobial treatment is difficult because of limited available data.

Key Words: chronic Q fever, osteomyelitis, children

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Q fever is a worldwide zoonosis caused by *Coxiella burnetii*, an obligate intracellular Gram-negative bacterium.¹ In Portugal, Q fever has been described for more than 60 years, with mandatory reporting since 1999. This is an endemic disease mainly occurring in the Central and Southern mainland region, with an average incidence of 0.08 cases per 100,000 inhabitants (2004–2008) and involving several *C. burnetii* genotypes.²

Infections are asymptomatic in 60% of the cases or present as an acute self-limiting disease, usually characterized by flu-like symptoms, pneumonia and/or hepatitis.^{1,3} Progression to chronicity occurs in a small number of cases.¹ Chronic Q fever forms include endocarditis, chronic vascular infections and more rarely, osteoarticular infection. In children, chronic Q fever is mostly unrecognized, and the antimicrobial regimen of choice is difficult because of limited information. We report 2 children with Q fever osteomyelitis who were successfully treated with rifampin and ciprofloxacin.

CASE 1

A 6-year-old, previously healthy, Caucasian girl presented in February 2012 with a 3-month history of right knee pain with no relief from analgesics. She reported minor local trauma and denied fever. She was born in Portugal and lived in a rural area of Lisbon with direct contact with farm animals (sheep and cattle). There was no history of consumption of unpasteurized milk. She was afebrile, and her physical examination revealed moderate right knee soft-tissue swelling, with functional impairment. There was no leukocytosis (8100/L) or increased inflammatory markers (C-reactive protein of 0.8 mg/L and erythrocyte sedimentation rate of 10 mm/h). A right distal end femoral lytic lesion was seen in a radiograph. The magnetic resonance imaging showed metaphyseal hyperintensity on short tau inversion recovery sequences, with extension beyond the growth plate into the epiphysis (Fig. 1). Scintigraphy excluded multifocal involvement. Histologic examination revealed noncaseating inflammatory granulomas.

CASE 2

A 5-year-old, previous healthy, Caucasian girl, presented in January 2013 with a 2-week duration of left parasternal pain and swelling. She denied fever, and her physical examination was otherwise normal. She lived in a rural area of Serpa with direct contact with cats, indirect contact with cattle and no history of ingestion of unpasteurized dairy products. The complete blood count and C-reactive protein were normal, but the erythrocyte sedimentation rate was elevated (40 mm/h).

FIGURE 1. Osteolytic lesions on right distal femur and epiphysis (A) and chondrosternal region (B).

TABLE 1. Serological Evaluation by IFA of Anti-*Coxiella burnetii* Phase I and Phase II Antibodies in the 2 Pediatric Cases with Osteomyelitis

		IFA Anti- <i>C. burnetii</i> Phase I/II Titers*							
		Initial	3	6	9	12	18	24	30
Case 1									
IgG		6.400/6.400	3.200/400	3.200/200	1.600/200	800/-	400/-	400/-	200/-
IgM		-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-
IgA		200/-	50/-	50/-	50/-	50/-	50/-	50/-	-/-
Case 2									
IgG		25.600/400	12.800/200	6.400/200	6.400/200	3.200/-	1.600/-	1.600/-	
IgM		-/-	-/-	-/-	-/-	-/-	-/-	-/-	
IgA		200/-	100/-	50/-	50/-	50/-	-/-	-/-	

- represents negative samples, according to IFA cutoff values: IgG < 200; IgM/IgA < 50. Bold values indicate positive IFA titers defined in a clinical compatible context as an evocative of chronic Q fever (phase I IgG ≥ 800).

*Expressed by the equivalent of the last dilution that gave positive results on indirect IFA, after testing the serum in sequential serial dilutions.

Magnetic resonance imaging revealed a 4-cm chondro-sternal heterogeneous, hemorrhagic and partially necrotic mass on T2, with no other lesions shown on bone scintigraphy (see Fig., Supplemental Digital Content 1, <http://links.lww.com/INF/C207>). The histopathology showed a chronic necrotizing granulomatous inflammatory process.

In both cases, the findings of culture tests for bacteria and fungi, including mycobacteria, were negative. The findings of Mantoux and serological tests for *Borrelia burgdorferi*, *Bartonella spp.* and *Francisella tularensis* were also negative. Elevated immunofluorescence assay (IFA) antibody titers against *C. burnetii* phase I were present in both patients, suggesting potential chronic infections (laboratory criteria: phase I: IgG ≥ 800; Case 1: phase I: IgG = 6400, IgM < 50, IgA = 200 and phase II: IgG = 6400, IgM < 50, IgA < 50; case 2: phase I: IgG = 25,600, IgM < 50, IgA = 200 and phase II: IgG = 400, IgM < 50, IgA < 50). Diagnosis was confirmed by *C. burnetii* DNA amplification on existing paraffin-embedded biopsies performed during case investigation. For molecular testing, a TaqMan real time-polymerase chain reaction (PCR) protocol, targeting the *C. burnetii* repetitive element *IS1111*, was used.⁵ Agent identity was confirmed by sequence determination and homology searches on GenBank database. Because of the lack of fresh biopsies, blood samples were additionally used for agent isolation attempts with negative results (also confirmed by PCR).

Echocardiogram ruled out endocarditis. Further immunologic investigations including normal oxidative burst assessed by di-hydro-rhodamine, IL-12-INFγ pathway and lymphocyte count were normal for age. Antimicrobial therapy with rifampin (20 mg/

kg/bid) and ciprofloxacin (20 mg/kg/bid) was started and maintained for 18 months. A gradual clinical and serological improvement was registered for case 1, and 6 months after the suspension of therapy, there was no recurrence of the disease, and antibody titers remained low (Table 1). In case 2, antibody titers decreased slowly, with a 4-fold reduction at 12 months. At 18-month follow-up, despite the elevated phase I IgG titer of 1600 (8-fold decrease), there was no clinical evidence of disease, and treatment was discontinued. Three months later, no further recurrence of the disease was noted although the titers remained unchanged (Table 1).

DISCUSSION

Q fever osteomyelitis is a rare diagnosis, and to our knowledge only 21 cases, 8 in children between 2 and 9 years old, have been reported.^{6,7}

Because of its nonspecific clinical presentation, chronic Q fever is probably underestimated, and the majority of patients experience symptoms for a lengthy period before diagnosis.³ The range of osseous involvement is broad, from long to short bones. Single or multifocal involvement, with or without focal abscess collection, and sometimes multiple subcutaneous abscesses and fistulas have been described.^{7,8} Indeed in our patients the mild inflammatory markers and the unspecific clinical complaints, added to the low suspicion rate, deferred diagnosis. Also, in case 1 there was involvement of metaphysis and epiphysis, with growth plate commitment, and in case 2, there was a huge

sternal infection, which was both very unusual and not previously described.

Chronic Q fever diagnosis usually relies on specific laboratory testing with antibody detection using the standard indirect IFA. Yet, the optimal IFA cutoff value for phase I IgG is a matter of debate.⁴ Levels within the range of 800–1024 have been mostly accepted.^{4,9} However, Frankel et al¹⁰ have demonstrated that the positive predictive value of phase I IgG = 800 for proven chronic infection was only 37%. In children, the immune response after acute infection is very high, and titers up to 3200 have been demonstrated without chronic infection.⁴ Given these data, Raoult et al⁴ have proposed that for bone and joint Q fever infection a positive serological result should be confirmed by PCR or culture of the lesion.

Treatment of chronic Q fever has been much more difficult than that of acute disease.¹ In adults, preferred treatment of endocarditis, the most frequent form of chronic infection, is well established, consisting of doxycycline and hydroxychloroquine for at least 18 months.⁶ Alkalinization of *C. burnetti*-containing vacuoles with chloroquine results in bacterial growth inhibition and improvement of doxycycline bactericidal activity. Indeed, this combination seems to reduce the treatment duration and the relapse rate to less than 5% in adults.¹ In children, treatment of Q fever osteomyelitis is much more debatable, and few data are available.^{4,7}

In children younger than 8 years, the doxycycline plus hydroxychloroquine combination should be used with caution because of the perceived risk of teeth discoloration, photosensitivity and retinal toxicity.⁷ The long-term effectiveness of this regimen for osteomyelitis is also questioned.⁷

Alternatives are trimethoprim-sulfamethoxazole, ciprofloxacin, rifampin and clarithromycin, but their efficacy is not proven. Rifampin and quinolones have been used with success in treatment. Given its high bone penetration and less side effects and based on previous pediatric case reports,^{3,7} ciprofloxacin plus rifampin was preferred by us, which was well tolerated, with only persistent cheilitis as a side effect in case 1.

Duration of antimicrobial treatment and follow-up should be guided by clinical and serological responses and may need to be maintained for long periods.¹ The decrease in antibody titers is often delayed, with some patients maintaining markedly raised values for a long period, as noticed for case 2. After the first year of treatment, a 2-fold phase I IgG decrease is considered a favorable response, and a 4-fold decrease is usually indicative of cure.¹ However, a phase I IgG < 800 is the most common accepted criterion to discontinue therapy, and it was accomplished in case 1. Given the high initial titer in case 2, we opted for a 4-fold decrease to stop treatment.

In conclusion, the treatment with a combination of ciprofloxacin and rifampin may be effective for some cases of chronic Q fever osteomyelitis, but further reports are needed.

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PREDICTORS OF PERTUSSIS POLYMERASE CHAIN REACTION POSITIVE RESULTS IN MINNESOTA, 2005–2009

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Abstract: Predictors of polymerase chain reaction (PCR) positivity for pertussis were assessed using Minnesota active surveillance data. Report of an exposure to pertussis and testing within the optimal time frame of ≤2 weeks were significantly associated with testing PCR positive, emphasizing the importance of asking about epidemiological factors when assessing patients for pertussis, and timely PCR testing.

Key Words: pertussis, disease predictors, polymerase chain reaction predictors, pertussis exposure

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Pertussis incidence rates declined considerably in the US after the introduction of a pertussis vaccine in 1942; however, incidence rates have been increasing since the 1980s.¹ In Minnesota, rates of pertussis in outbreak years have exceeded 20 cases per 100,000 population since 2004, which is nearly double the incidence rate of outbreak years before 2004.² This trend can be attributed, in part, to changes in vaccine formulation,³ evolution of the bacteria,⁴ and improved laboratory testing. Polymerase chain reaction (PCR) is commonly used to test for pertussis.^{5–8} PCR is more sensitive than culture and can detect nonviable bacteria^{5,6}; however, similar to culture, PCR accuracy relies heavily on the timing of specimen collection.^{7,8} Using PCR during the first 2 weeks of symptoms facilitates effective identification of pertussis, which can often be misdiagnosed as other upper respiratory tract infections.^{5,7,8} Although early detection and treatment of pertussis is essential in reducing transmission and protecting high-risk contacts, maximizing the appropriate use of PCR testing must be considered. The aim of this study is to assess the clinical and epidemiologic factors associated with pertussis PCR positivity to inform judicious use of PCR testing.