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Case reports and series

Q fever vertebral osteomyelitis in the absence of cardiovascular involvement: Two cases and a literature review

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ABSTRACT

Chronic Q fever, most commonly manifesting as infective endocarditis or endovascular infection, complicates 1–5% of *Coxiella burnetii* infections. Vertebral osteomyelitis has been described, occurring mostly in the setting of adjacent vascular involvement. We describe two cases of isolated vertebral osteomyelitis, adding further insight into this rarely reported clinical entity.

Case 1

A 55-year-old man presented to hospital for investigation of multiple thoracic vertebral body lesions, considered likely to represent secondary malignancy. His past medical history included chronic hepatitis C with Child Pugh B liver cirrhosis, and anterior C3/4 and C6/7 discectomy and fusion 10 years previously for cervical myelopathy. His regular medications included spironolactone, furosemide, thiamine, and transdermal buprenorphine. He reported worsening generalised thoracic back pain and associated 6-kg weight loss over a 6-month period. He remained systemically well with no fevers or night sweats, and had no risk factors for *Mycobacterium tuberculosis* infection. A CT scan 3 months previously had demonstrated paravertebral soft tissue swelling and a specimen from fine needle biopsy demonstrated fibrofatty tissue on histology. A PET scan demonstrated increased uptake throughout T7-T11, suspicious for metastatic disease, with CT of the abdomen failing to identify a possible underlying primary malignancy.

His occupational exposure history was significant for both meat packing and abattoir work. Until 15 years ago, he worked on a cattle farm, and had spent the last 12 months living in a converted dairy farm shed. He enjoyed hunting, predominantly foxes, kangaroos and rabbits.

Physical examination was consistent with compensated chronic liver disease. He was afebrile with generalised thoracic tenderness to palpation. Cardiovascular examination was unremarkable. Neurological examination demonstrated myelopathic features with brisk reflexes globally in the upper and lower limbs. Power and sensory examinations were normal. Inflammatory markers were mildly elevated with a C-reactive protein (CRP) of 16 mg/L (<5). A normochromic normocytic anaemia with haemoglobin of 107 g/L (130–180) and liver enzyme derangement in keeping with his known history of cirrhosis were noted. Myeloma screen was unremarkable. A differential diagnosis of vertebral osteomyelitis was considered, however, two sets of blood cultures failed to yield a causative organism.

Brucella and Q fever serology were requested with Q fever serology strongly suggestive of chronic Q fever. Quite unusually, however, in each of 10 sera collected over a 3-year period, the phase 2 IgG antibody titre was always higher than the phase 1 IgG antibody titre, usually by 3-doubling dilutions, e.g. 1:6400 v 1:800. Whole spine MRI demonstrated T8-T11 discitis and osteomyelitis with two collections located at levels T8/9 and T10/11 with resulting spinal cord compression. A transoesophageal echocardiogram was not suggestive of infective endocarditis. CT guided vertebral body biopsy demonstrated no evidence of active inflammation or neoplasm. No polymorphs were present and there was no growth on culture.

He was commenced empirically on oral doxycycline 100 mg twice daily and hydroxychloroquine 200 mg three times daily, with Q fever confirmed retrospectively using qPCR testing of the vertebral biopsy

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specimen following removal from the histopathology paraffin block. The positive in-house assay was performed at the Australian Rickettsial Reference Laboratory, Geelong, Victoria, detecting the Com1 gene and the heat shock operon htpAB (primers htpAB_F: 5′-GTGGCTTCGCGTACA TCAGA-3′ and htpAB_R: 5′ CATGGGGTTCATTCCAGC A-3′, and probe htpAB_P: 5′-FAM-AGCCAGTAC GGTCG CTGTTGTGGT-BHQ1-3′), both unique to this bacterium [1].

The treatment course over the subsequent 20 months was complicated by persistent nausea and photosensitivity rash. Serology improved markedly and treatment was ceased. Follow-up serology at 12 months, however, was indicative of relapse and he was recommenced on trimethoprim/sulfamethoxazole 160/800 mg twice daily as an alternative treatment option which is ongoing.

Case 2

A 58-year-old cattle farmer presented for further investigation of L5/S1 vertebral osteomyelitis, diagnosed in the context of increasing lumbosacral pain of 4-months duration. His past medical history was significant for acute Q fever 18 months previously, manifesting as fever and acute hepatitis. Q fever serology performed following resolution of this illness was compatible with recent *C. burnetii* exposure, demonstrating phase 2 IgM and IgG antibody titres >1:3200 and phase 1 IgG antibody titre of 1:400. Unfortunately, he received no antimicrobial therapy at this time, which may have prevented the development of chronic Q fever. Repeat Q fever serology performed 6-months post illness demonstrated persistent elevation of phase 2 IgG (antibody titre 1:102400) while the phase 1 IgG (antibody titre 1:800) was considerably lower. Serology was repeated 12 months later in the context of worsening back pain, with phase 1 IgG now significantly elevated at 1:12800 and phase 2 IgG >102400. Systemic features were absent with no growth on blood cultures. Inflammatory markers were minimally elevated with CRP of 13 mg/mL (<5). Oedema within the vertebral bone marrow at L5/S1 and fluid enhancement within the intervertebral discs were demonstrated on MRI. Endplate destruction and paraspinal enhancement were observed, without epidural abscess.

Physical examination was unremarkable with no focal tenderness on palpation of the vertebral spine or fever. A CT guided bone biopsy was performed, with S1 vertebral tissue demonstrating profuse polymorphs but no growth. Histology demonstrated fragmented bone and marrow with trilinear haematopoiesis. Q fever DNA was detected with qPCR on fluid aspirated from the L5/S1 intervertebral disc, again performed at the Australian Rickettsial Reference Laboratory. The patient was commenced on doxycycline 100 mg twice daily in combination with hydroxychloroquine 200 mg three times daily for treatment of Q fever vertebral osteomyelitis. A subsequent transthoracic echocardiogram did not reveal any valvulopathy or evidence of infective endocarditis. After 12 months of treatment, Phase 1 IgG had reduced to 1:3200 and CRP normalised at 0.4 mg/L (<5). His back pain improved substantially with treatment, which at this stage is planned for 18 months as a minimum duration.

Discussion

Q fever is a zoonosis caused by the intracellular coccobacillus *C. burnetii*. It is found globally, with the exception of New Zealand, with reservoirs including cattle, sheep and goats [2]. Transmission occurs via aerosolization and subsequent inhalation of bacteria, which are found in high concentrations in the birth products of infected animals [2].

The clinical manifestations of acute Q fever are diverse, with an estimated 50–60% of patients remaining asymptomatic [3]. In a small Australian outbreak associated with an infected milking goat farm, 6 of 24 (25%) infected persons were asymptomatic, but seroconverted. A self-limiting flu-like illness, pneumonia and hepatitis are most commonly reported, with onset of symptoms occurring after a 2–3-week incubation period [2]. Acute cardiac involvement manifesting as pericarditis, myocarditis and infective endocarditis is more rarely reported [2].

Chronic Q fever, or persistent localised infection, complicates 1–5% of acute Q fever cases [3,4], most commonly manifesting as infective endocarditis (60–70%) [5] or infection of endovascular prostheses and aneurysms. Left untreated, mortality is as high as 60% [4]. Important risk factors include male sex, age > 40, valvular heart disease and valve prostheses, vascular grafts and pre-existing vascular aneurysms [2,3]. An immunocompromised state may too be associated with an ncreased risk of developing persistent localised infection [2,3]. Less common manifestations of persisting localised infection include pericarditis, hepatitis and osteoarticular infection encompassing isolated tenosynovitis, long bone osteomyelitis and prosthetic joint infections [4].

Q fever vertebral osteomyelitis is well described, but occurs almost exclusively in the setting of vascular involvement with contiguous spread to adjacent anatomical structures, rather than in isolation [2,6]. In children, it has been described as occurring both in isolation [7], and in the context of chronic recurrent multifocal osteomyelitis (CRMO) [8]. To date, there have been only 10 previously reported cases of isolated *C. burnetii* vertebral osteomyelitis in adults (Table 1) [5,6,9–12], with only scant detail reported with regard to clinical presentation, treatment duration and patient outcome.

Optimal treatment for this rare condition is not known, with recommendations for combination of doxycycline and hydroxychloroquine (minimum 18 month course) having been extrapolated from experience in the setting of infective endocarditis and endovascular infection [12,13]. Treatment duration should be extended in cases where unfavourable clinical or serological outcomes are encountered [12]. As demonstrated in case 1, disease relapse despite prolonged combination therapy can occur, and emphasises the necessity of ongoing clinical and serological monitoring following treatment cessation. Based on expert opinion, the addition of rifampicin for its property of bone penetration has also been suggested [12].

In this case series, combination therapy with doxycycline (dose range 200–300 mg/day) and hydroxychloroquine (dose range 400–600 mg/day) was favoured, with the addition of ciprofloxacin or rifampicin in selected cases. Due to clinical and histopathological similarities, 3 of the 10 previously reported cases were misdiagnosed as tuberculosis, suggesting that focal *C. burnetii* infection is an important differential diagnosis in the setting of osteoarticular infection with findings of granulomatous inflammatory changes and negative Mycobacterial tuberculosis culture and PCR testing.

The unexpected serological ratios detected in these two cases, where the phase 2 IgG antibody titre was higher than the phase 1 IgG antibody titre, is most unusual in chronic Q fever. Whether this was due to the two cases being entirely bone infection, rather than vascular, is not known. Where serological information is provided, a similar trend is also noted in cases 3, 4, 7 and 8 (see Table 1). Further analysis of this laboratory phenomenon will have to await the appearance of further cases of Q fever osteomyelitis.

Ultimately, limited patient numbers and reported long-term outcomes mean that few conclusions are able to be drawn from existing case reports. Further studies are required in order to determine the optimal choice of antimicrobial agents, treatment duration and serological monitoring post treatment cessation, in order to maximise curative outcomes in this difficult to treat disease.

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Sarah Browning: Conceptualization, Methodology, Writing - original draft.**Katy Lai:**Conceptualization, Methodology, Writing - review &

Table 1
Cases of isolated Q fever vertebral osteomyelitis.

Case no. (ref.)	Patient demographics	Anatomical site	Relevant diagnostic tests[a]	Antimicrobial type and duration	Treatment outcome
1 (this report)	55/M; cattle & abattoir exposure. Liver cirrhosis	T8–T11 vertebral osteomyelitis, T8/9, T10/11 epidural abscess	Ph1 1:800, Ph2 > 1:3200 Vertebral body PCR	DOX 200 mg/d + HCQ 600 mg/d (20 months) TMP-SMX 320/1600/d	Photosensitivity rash & nausea. Serological relapse 12-months post treatment cessation with recommencement of Rx (ongoing)
2 (this report)	55/M; cattle farmer. Acute Q fever 18 months prior	L5/1 vertebral osteomyelitis	Ph1 > 1:25600, Ph2 > 102400 L5/S1 intervertebral disc tissue PCR Ph1 1:1600 at 12-months Rx	DOX 200 mg/d + HCQ 600 mg/d (18 months minimum - ongoing)	Serological & symptomatic improvement
3 [9]	39/M; dairy farmer. Low back pain & pyrexial illness	L5 osteitis	Ph1 1:128, Ph2 1:512; at 1 month. Ph1 1:156, ph2 1:256 at 12 months	TET 500-mg qid (7 weeks; repeated for 4 weeks)	Full return to work at 5-months post Dx
4 [9]	76/F; dairy farmer's wife. Abdominal aneurysm. Back pain	T12/L1 vertebral osteomyelitis Psoas abscess 20 cm	Ph1 1:512, Ph2 1:1024 Histology: caseous material, AFB & culture negative.	Anti-TB Rx 2 years	Sinus failed to definitively heal with anti-TB Rx. No further Rx or follow-up described.
5 [11]	61/F; uterine cancer & pelvic radiotherapy	L3 spondylodiscitis	Seroconversion described	N/A	N/A
6 [10]	67/M. Pyrexial illness	Vertebral osteomyelitis, site not specified	Ph1 1:1024, Ph2 1:1024 Seroconversion described	DOX, HCQ + CIP	Recovered. Details not specified
7 [5]	64/M; rheumatoid arthritis (anti-TNF + MTX), chronic hepatitis C. Pyrexial illness & lumbar back pain	L2/3 spondylodiscitis Paravertebral abscess & psoas infiltration Subsequent L4/5 & epidural involvement	Ph1 1:400, Ph2 800. PCR & culture Repeat PCR & culture negative	DOX 200 mg/d + RIF 600 mg/d 15 days Anti-TB drug added + HCQ 600 mg/d added Duration not specified	Clinical progress with 15d combination DOX + HCQ. Anti-TB Rx ceased. Symptomatic improvement at 2 months
8 [5]	47/M. 2 months right S1 sciatic pain. Afebrile. Acute Q-fever 1 year prior	L5/S1 spondylodiscitis & epidural abscess on MRI	Ph1 1:1600, Ph2 1:3200 Fistula fluid & serum PCR Ph1 1:800, Ph2 1:600 at 12 months	Anti-TB Rx. DOX 200 mg/d + HCQ 600 mg/d + Duration not specified RIF 2.4 g/d fistula instillations(1 month)	Lumbar fistula despite 10d anti-TB Rx Fistula healed 1 month following targeted *C. burnetii* Rx. Reduced abscess size & ongoing inflammatory changes at L2-S1 on MRI at 1 year
9 [6]	80/M	Isolated Spondylodiscitis on ^{18}F-FDG PET/CT	Ph1 1:800	N/A	N/A
10 [12]	64/M. Weakness; back pain	L2/3 vertebral osteomyelitis & psoas abscess	PCR & culture of pus	DOX 200 mg/d + HCQ 600 mg/d for at least 18 months	N/A
11 [13]	66/M. Back & unilateral leg pain	L4/5, L5/S1 vertebral osteomyelitis & paravertebral abscess	Serology Vertebral bone PCR	DOX 300 mg/d + HCQ 400 mg/d for at least 18 months	N/A
12 [13]	59/M. Back pain	L5-S1 vertebral osteomyelitis	Serology Vertebral bone PCR	DOX 200 mg/d + HCQ 600 mg/d for at least 18 months	N/A

M, male; F, female; Rx, therapy; DOX, doxycycline; HCQ, hydroxychloroquine; RIF, rifampicin; CIP, ciprofloxacin; TET, tetracycline; TMP-SMX, trimethoprim/sulfamethoxazole; TNF, tumor necrosis factor; MTX, methotrexate; d, day; ^{18}F-FDG PET/CT, 18F-fluorodeoxyglucose positron emission tomography/computed tomography; Ph1, Phase 1 antibodies; Ph2, Phase 2 antibodies; Dx, diagnosis.
[a] Phase 1 and phase 2 Q fever serology reported as IgG.

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Declaration of competing interest

None.

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