Case Report

Case report of infective spondylodiscitis due to nalidixic acid-resistant *Salmonella paratyphi* A

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Abstract

Spondylodiscitis due to typhoidal Salmonella presents a therapeutic challenge for clinicians. Factors that complicate treatment include drug-resistant strains, poor antibiotic bone penetration, potential for neurological compromise and lack of established protocols and guidelines. We discuss a 57-year-old man with *Salmonella paratyphi* A spondylodiscitis involving lower thoracic vertebrae and discuss various aspects of management.

Keywords: Salmonella osteomyelitis, *Salmonella paratyphi* A, Salmonella spondylodiscitis

Introduction

Typhoidal Salmonella (*Salmonella enterica* serovars Typhi and Paratyphi A, B, C) are gram-negative bacilli that usually present as undifferentiated febrile illness.[1] Salmonella osteoarticular infections are common in sickle cell anaemia and immunocompromised hosts.[2-4] However, Salmonella osteomyelitis has also been reported in immunocompetent individuals.[5-7] We present an immunocompetent patient with nalidixic acid-resistant *Salmonella paratyphi* A (NARST) spondylodiscitis.

Case History

A 57-year-old banker presented with high-grade fever for 6 weeks and severe backache for 4 weeks. He went on frequent official trips to different cities and had history of consuming foods in restaurants on these trips. He denied history of diarrhoea, joint pain, weight loss, bowel/bladder incontinence, urinary retention and motor weakness. He was a known case of systemic hypertension for 17 years and diabetes mellitus for 1 month and was on regular medicines.

Examination of the spine revealed lower thoracic tenderness and restricted lateral flexion. He had Class I obesity (body mass index 33). Blood investigations showed high erythrocyte sedimentation rate and mildly elevated C-reactive protein levels [Table 1].

In this patient with subacute history of back pain and fever, we considered differential diagnoses of infective spondylodiscitis, epidural and paraspinal abscess. Magnetic resonance imaging showed contrast enhancement in the 11th and 12th thoracic vertebra and intervening disc [Figure 1].

Computed tomography-guided biopsy from thoracic vertebra showed necrotic bone with lymphocyte and neutrophil infiltration. Biopsy specimen and blood culture showed growth of NARST. Widal test was positive for *Salmonella paratyphi* A in 1280 dilutions. Drug susceptibility testing showed sensitivity to chloramphenicol, ceftriaxone, trimethoprim-sulfamethoxazole and azithromycin. Minimum inhibitory concentration (MIC) for ciprofloxacin and azithromycin were 0.5 μg/dL and 8 μg/dL, respectively. We started injection azithromycin 1 g intravenously once daily. However,

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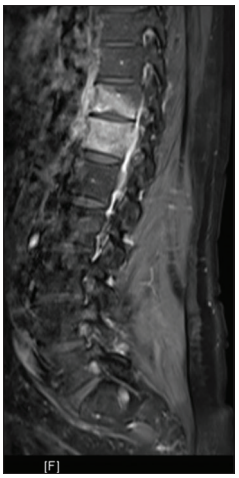

Figure 1: Magnetic resonance imaging of thoracolumbar spine shows contrast enhancement of 11th and 12th thoracic vertebrae and intervening disc. Irregularity of end plates and small pre-vertebral and paravertebral soft tissue swelling are also noted

Table 1: Relevant blood investigations

Laboratory parameter	Patient's value	Laboratory parameter	Patient's value
Haemoglobin	11.2 g/dL	Creatinine	1 mg/dL
Total leucocyte count	5,500 cells/ml	HbA1c	7.1%
Neutrophils	47%	Total protein	7 g/dL
Lymphocytes	37%	Albumin	4.2 g/dL
Eosinophils	5%	Alkaline phosphatase	55 units/L
Monocytes	10%	ESR	59 mm/h
Basophils	1%	CRP	9 mg/L

he continued to have high-grade fever 1 week after initiation of azithromycin. Reasons for persistent fever that we thought of were metastatic and endovascular foci of infection and suboptimal antibiotic delivery due to poor bone penetration. Echocardiogram, ultrasound abdomen and bone scan were normal. In view of clinical failure with azithromycin, we decided to start intravenous ceftriaxone (2 g once daily) and oral trimethoprim-sulfamethoxazole (800/160 mg) twice daily. Defervescence occurred 5 days after initiation of ceftriaxone. He was seen by spine surgeons who advised conservative management. He was managed with intravenous azithromycin and ceftriaxone for 2 weeks followed by oral azithromycin (1 g once daily), ciprofloxacin (750 mg twice daily) and trimethoprim-sulfamethoxazole for 10 weeks. At his 3-month follow-up, back pain had decreased by 90%. Repeat MRI spine showed disease regression.1

Discussion

Gram-negative organisms account for 12% of vertebral osteomyelitis, and *Enterobacter species*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are usually implicated.[8-10] *Salmonella* accounts for 50% of acute osteomyelitis in sickle-cell patients. Bone infarcts, autosplenectomy and hypocomplementemia predispose to infections in sickle cell disease.[2]

1 Informed written consent was taken from the patient for publication of this case report.

Though *Staphylococcus aureus* and *Mycobacterium tuberculosis* are common pathogens causing spondylodiscitis, infections due to Salmonella have also been described.[5,6,11-14] Salmonella vertebral osteomyelitis may have been underdiagnosed, as imaging-guided/open surgical biopsy is required to confirm the diagnosis. In the absence of microbiological diagnosis, many patients may have been treated with empirical therapy directed against Mycobacteria or gram-positive organisms.

Amritanand *et al*. reported 11 patients with typhoidal Salmonella spondylodiscitis treated with 12 weeks of antibiotics. Half[5] required surgery due to pain or osseous instability, and 91% (10/11) had good outcomes after 1 year.[6]

Rohilla *et al*. reported a 17-year-old immunocompetent patient with *Salmonella typhi* spondylodiscitis initially treated with empirical anti-tuberculous therapy. He was eventually managed with cefuroxime and decompressive laminotomy.[5]

In a review of 44 cases of Salmonella vertebral osteomyelitis, common vertebrae involved were lumbar (50%) and thoracic (20%). Diarrhoea and abdominal pain were present in merely 16% and 8%, respectively. Vertebral osteomyelitis led to neurological deficits in 8%. Cervical/Thoracic vertebral involvement, epidural abscess, *S. aureus* osteomyelitis and CRP levels >150 mg/L are associated with motor weakness in vertebral osteomyelitis.[14]

Management of osteomyelitis poses a therapeutic challenge for clinicians. Poor vascularity of necrotic bone leads to reduced antibiotic delivery to infective focus. Our case report shows that antibiotic choice should be based upon drug sensitivity, bone penetration and synergism between antibiotics. Azithromycin is concentrated in macrophages and neutrophils, with low plasma and bone concentration.[15] Azithromycin MIC ≤ 16 μg/mL is considered susceptible for invasive Salmonellosis. However, there is a lack of clinically validated MIC cut-off for azithromycin for Salmonella infections.

Garazinno found that bone penetration of ceftriaxone was adequate in cancellous bone but low in cortical bone.[16] Trimethoprim-sulfamethoxazole is used as monotherapy for Staphylococcal osteoarticular infections. Trimethoprim attains 50% of plasma concentration in bone, whereas concentrations in synovial fluid and plasma are similar.[17] Ciprofloxacin has excellent bone penetration and has been used as monotherapy and combination therapy in pyogenic osteomyelitis.[8,18-20]

Nalidixic acid resistance is greater than 75% and 60% for *S. typhi* and *S. paratyphi*, respectively, in India and is associated with mortality.[1,21] Our decision to start combination therapy was shaped by various factors including drug-resistant pathogen, vertebral involvement and clinical failure with azithromycin.

At primary care level, it is important to identify patients with infectious cause of back pain. Primary care physicians should look for fever, localized spine tenderness and restricted spine motion to identify these patients.[22,23] These patients require urgent spine imaging and specialist referral to prevent complications.[24,25]

Incidence of spondylodiscitis is likely to increase in parallel to the surge in number of organ transplants, intravascular devices and invasive spinal procedures. Typhoidal Salmonella can cause vertebral osteomyelitis in immunocompetent patients. Obtaining a microbiological diagnosis is an essential step in management.[26] Treatment is challenging due to long duration of antimicrobial therapy, drug resistance, variable drug delivery to infected focus and risk of neurological complications.

Key Messages

Salmonella spondylodiscitis in immunocompetent hosts is an underdiagnosed entity. Imaging-guided biopsy/open surgical biopsy and culture are required to establish a diagnosis and obtain antibiotic susceptibility profile. Infective spondylodiscitis due to Salmonella poses a therapeutic challenge due to poor antibiotic bone penetration, resistant pathogens and risk of neurological complications.

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Conflicts of interest

There are no conflicts of interest.

References

1. Bandyopadhyay R, Veeraraghavan B, Yadav B, Jasmine S, Sathyendra S, Rupali P. Effectiveness of treatment regimens for Typhoid fever in the nalidixic acid-resistant S. typhi (NARST) era in South India. Trop Doct 2018;48:182-8.
2. Cannas G, Merazga S, Virot E. Sickle cell disease and infections in high- And low-income countries. Mediterr J Hematol Infect Dis 2019;11:1-9.
3. Berngard SC, Miller M. Salmonella spinal infection: A rare case in a patient with advanced AIDS. J Int Assoc Provid AIDS Care 2013;12:241-4.
4. Chang JW, Tsai HL, Yang LY. Successful treatment of refractory septic arthritis caused by salmonella and *staphylococcus aureus* with preservation of graft function in a long-term renal transplant recipient by total withdrawal of immunosuppressants. Clin Nephrol 2010;73:72-5.
5. Rohilla R, Bhatia M, Gupta P, Singh A, Shankar R. Omar BJ. Salmonella osteomyelitis: A rare extraintestinal manifestation of an endemic pathogen. J Lab Physicians 2019;11:164-70.
6. Amritanand R, Venkatesh K, Sundararaj GD. Salmonella spondylodiscitis in the immunocompetent: Our experience with eleven patients. Spine (Phila Pa 1976) 2010;35:E1317-21.
7. Hashimoto K, Nishimura S, Matsumura D, Ohtani K, Akagi M. Salmonella osteomyelitis of the rib mimicking a mammary tumor: A case report. Tohoku J Exp Med 2020;251:273-7.
8. Graham SM, Fishlock A, Millner P, Sandoe J. The management gram-negative bacterial haematogenous vertebral osteomyelitis: A case series of diagnosis, treatment and therapeutic outcomes. Eur Spine J 2013;22:1845-53.
9. Carvalho VC, Oliveira PR, Dal-Paz K, Paula AP, Félix Cda S, Lima AL. Gram-negative osteomyelitis: Clinical and microbiological profile. Braz J Infect Dis 2012;16:63-7.
10. Fragío GJ, González MR, Salavert LM, Román IJ. Vertebral osteomyelitis: Clinical, microbiological and radiological characteristics of 116 patients. Med Clin 2020. doi: 10.1016/j.medcli. 2019.12.029.
11. Helm C, Huschart E, Kaul R, Bhumbra S, Alexander Blackwood R, Mukundan D. Management of acute osteomyelitis: A ten-year experience. Infect Dis Rep 2016;8:63-7.
12. Feki A, Akrout R, Masmoudi K, Sellami I, Ezzeddine M, Mnejja MA, *et al.* Infectious spondylodiscitis: A twenty-year experience from a single tertiary referral center. Egypt Rheumatol 2019;41:231-5.
13. Effendi FM, Ibrahim MI, Mohd Miswan MF. Salmonella spondylodiscitis of the thoracic vertebrae mimicking spine tuberculosis. BMJ Case Rep 2016;2016:bcr2016215909. doi: 10.1136/bcr-2016-215909.
14. Santos EM, Sapico FL. Vertebral osteomyelitis due to salmonellae: Report of two cases and review. Clin Infect Dis 1998;27:287-95.
15. Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive Salmonella infections. Clin Microbiol Rev 2015;28:901-37.
16. Garazzino S, Aprato A, Baietto L, D'Avolio A, Maiello A, Rosa FG De, *et al.* Ceftriaxone bone penetration in patients with septic non-union of the tibia. Int J Infect Dis 2011;15.
17. Kim BN, Kim ES, Oh MD. Oral antibiotic treatment of staphylococcal bone and joint infections in adults. J Antimicrob Chemother 2014;69:309-22.
18. Leone M. Brain tissue penetration of ciprofloxacin following a single intravenous dose. J Antimicrob Chemother 2002;50:607-9.
19. Thabit AK, Fatani DF, Bamakhrama MS, Barnawi OA, Basudan LO, Alhejaili SF. Antibiotic penetration into bone and joints: An updated review. Int J Infect Dis [Internet] 2019;81:128-36. Available from: doi: 10.1016/j.ijid. 2019.02.005.
20. Park KH, Kim DY, Lee YM, Lee MS, Kang KC, Lee JH, *et al.* Selection of an appropriate empiric antibiotic regimen in hematogenous vertebral osteomyelitis. PLoS One 2019;14:1-12.
21. Veeraraghavan B, Pragasam AK, Bakthavatchalam YD, Ralph R. Typhoid fever: Issues in laboratory detection, treatment options & concerns in management in developing countries. Futur Sci OA 2018;4:FSO312.
22. Casazza BA. Diagnosis and treatment of acute low back pain. Am Fam Physician 2012;85:343-50.
23. Will JS, Bury DC, Miller JA. Mechanical low back pain. Am Fam Physician 2018;98:421-8.
24. Traeger A, Buchbinder R, Harris I, Maher C. Diagnosis and management of low-back pain in primary care. CMAJ

2017;189:E1386-95.

25. Corwell BN, Davis NL. The emergent evaluation and treatment of neck and back pain. Emerg Med Clin North Am 2020;38:167-91.

26. Amsilli M, Epaulard O. How is the microbial diagnosis of bacterial vertebral osteomyelitis performed? An 11-year retrospective study. Eur J Clin Microbiol Infect Dis 2020. doi: 10.1007/s10096-020-03929-1.