Enferm Infecc Microbiol Clin. 2012;30(7):424–428

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Scientific letters

Multidrug-resistant tuberculous spondylitis

Espondilitis por tuberculosis multirresistente

To the Editor,

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampin, is an important public health problem.[1] The skeletal system can be involved in 1–3% of all tuberculosis cases[2]; however, there are very few reported cases of skeletal MDR-TB. In addition to the challenges encountered when treating pulmonary MDR-TB, osteoarticular MDR-TB poses additional difficulties, due to the lack of evidence to guide treatment, the unknown efficacy of second-line antituberculous drugs in the bone, and the paucity of reports on this condition. We present a patient with MDR-TB spondylitis with successful response to treatment.

A 32-year-old woman arrived in the emergency department with a neck injury. One year before admission, she started having posterior cervical pain and paresthesias in both hands. On admission, the radiography of the cervical spine showed destruction and collapse of C_7 vertebral body (Fig. 1), and a magnetic resonance showed collapse of C_7 and oedema of C_6, C_7, T_1, and T_2 vertebral bodies. She underwent surgical repair with implantation of C_7 vertebral prosthesis for stabilisation. The bone biopsy of C_7 showed chronic osteomyelitis and granulomata with central necrosis. The acid-fast stain was negative. The culture yielded Mycobacterium *tuberculosis*, resistant to isoniazid, rifampicin and pyrazinamide, and sensitive to ethambutol, streptomycin, amikacin, levofloxacin, ethionamide, cycloserine and para-amino salicylic acid.

She was transferred to our tuberculosis unit. On admission, the physical examination was normal, the HIV serology was negative, and the chest X-ray was normal.

She started directly observed treatment with ethambutol 1400 mg/day, ethionamide 750 mg/day, cycloserine 750 mg/day, levofloxacin 500 mg/day and intramuscular amikacin 1 g every 48 h. All drugs were administered for 18 months except amikacin, which was administered for 3 months. There were no adverse effects except polyarthralgias (which improved after substituting moxifloxacin for levofloxacin in the third month). After 18 months of therapy, she had no symptoms and a CT scan showed complete resolution of the vertebral lesions. She declined to continue treatment and she did not return for follow-up. However, we contacted her by telephone 28 months after the end of treatment and she told us she had no symptoms of relapse.

Spondylitis due to MDR-TB is very infrequent: we have only found 6 case reports and two small series[3,4] in the literature, with very little information on drug treatment. The optimal treatment for osteoarticular MDR-TB is unknown. The treatment of non-resistant spinal TB is mainly medical, and surgery is reserved for managing complications or failure of antimicrobial therapy.[2,5,6] However, the role of medical and surgical therapy in skeletal MDR-TB is not well established, nor is it known what drug combinations would be best to treat this condition. Guidelines for the treatment of MDR-TB have been published,[1,7,8] but they give no specific recommendations for osteoarticular MDR-TB.

At the time our patient was treated, we followed the 2008 WHO guidelines,[1] which recommended the use of at least four anti-tuberculosis drugs with either certain, or almost certain, effectiveness, given as directly observed therapy for a minimum of 18 months after culture conversion. We used a first-line oral agent (ethambutol), an injectable agent, a fluroquinolone, and two oral bacteriostatic second-line agents (cycloserine and ethionamide), as recommended in the WHO guidelines. Although we did not use it, linezolid is probably worth considering, as it has been extensively used to treat osteoarticular infections and it has good activity against MDR-TB.[9,10] In our case, it was not possible to assess culture conversion, and it might have been reasonable to extend the treatment time; however, we decided to stop the treatment after

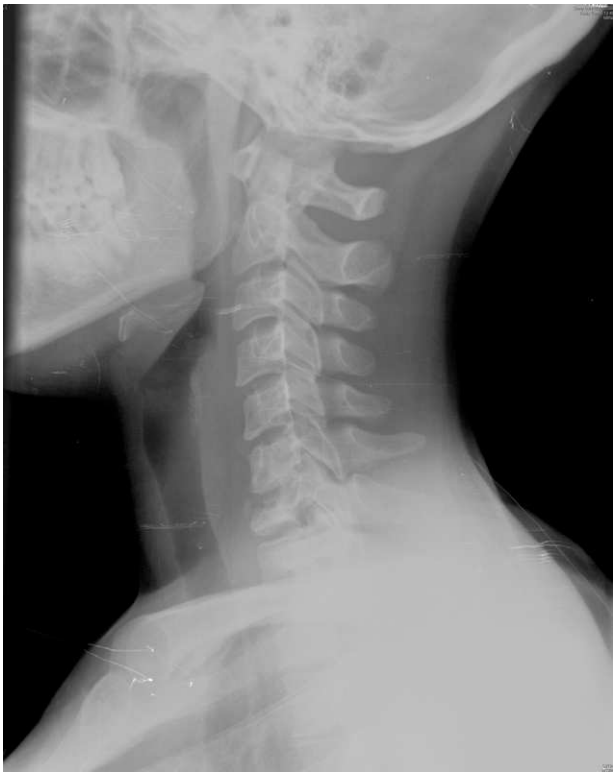

Fig. 1. Radiography of the cervical spine showing destruction and collapse of C_7 vertebral body.

18 months since the patient did not wish to continue, she was asymptomatic, and there was radiologic evidence of complete recovery of the bone lesions. The 2011 update to the WHO guidelines has recently increased the recommended treatment time to a minimum of 20 months.[7]

References

1. WHO. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. Geneva: World Health Organization; 2008.
2. Tuli SM. General principles of osteoarticular tuberculosis. Clin Orthop Relat Res. 2002;398:11–9.
3. Pawar UM, Kundnani V, Agashe V, Nene A. Multidrug-resistant tuberculosis of the spine—is it the beginning of the end? A study of twenty-five culture proven multidrug-resistant tuberculosis spine patients. Spine (Phila Pa 1976). 2009;34:E806–10.
4. Buyukbebeci O, Karakurum G, Daglar B, Maralcan G, Guner S, Gulec A. Tuberculous spondylitis: abscess drainage after failure of anti-tuberculous therapy. Acta Orthop Belg. 2006;72:337–41.
5. Jutte PC, Van Loenhout-Rooyackers JH. Routine surgery in addition to chemotherapy for treating spinal tuberculosis. Cochrane Database Syst Rev. 2006:CD004532.
6. van Loenhout-Rooyackers JH, Verbeek AL, Jutte PC. Chemotherapeutic treatment for spinal tuberculosis. Int J Tuberc Lung Dis. 2002;6:259–65.
7. WHO. Guidelines for the programmatic management of drug-resistant tuberculosis. 2011 update. Geneva: World Health Organization; 2011.
8. Caminero JA, Sotgiu G, Zumla A, Migliori GB. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Dis. 2010;10:621–9.
9. Yew WW, Chau CH, Wen KH. Linezolid in the treatment of 'difficult' multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2008;12:345–6.
10. Koh WJ, Kwon OJ, Gwak H, Chung JW, Cho SN, Kim WS, et al. Daily 300 mg dose of linezolid for the treatment of intractable multidrug-resistant and extensively drug-resistant tuberculosis. J Antimicrob Chemother. 2009;64:388–91.

Inés Suárez-García[a,*], José Ramón Paño-Pardo[b], Arturo Noguerado[c]

[a] *Infectious Diseases Unit, Department of Internal Medicine, Hospital Infanta Sofía, San Sebastián de los Reyes, Spain*
[b] *Infectious Diseases Unit, Department of Internal Medicine, Hospital Universitario La Paz, Madrid, Spain*
[c] *Tuberculosis Unit, Department of Internal Medicine, Hospital Cantoblanco-La Paz, Madrid, Spain*

* Corresponding author.
E-mail address: inessuarez@hotmail.com (I. Suárez-García).

doi:10.1016/j.eimc.2012.02.018

Fever of intermediate duration in an 8-year-old boy: Is this a condition worth investigating in childhood?

Fiebre de duración intermedia en un niño de 8 años: ¿merece la pena estudiar esta entidad en la infancia?

Dear Editor:

An otherwise healthy 8-year-old boy who lived in a rural area in Majorca was admitted due to an 11-day history of fever, abdominal pain, listlessness, anorexia, and 2 kg weight loss. He also had headache and myalgias during the first few days of the illness. There were no enlarged lymph nodes, hepatosplenomegaly, or other positive physical examination findings. The initial laboratory tests showed 10,600 leucocytes/mm^3, with 50% neutrophils, and a C-reactive protein of 15.9 mg/dL. Further laboratory evaluation on admission including serum alanine and aspartate aminotransferase levels, an ultrasound examination of the liver and the spleen, and a chest radiography revealed no abnormalities. On the basis of a working diagnosis of fever of unknown origin (FUO) a hospital diagnostic work-up was carried out over the following 2 weeks. The assessment consisted of the following studies: repeated measurements of full blood count (FBC), peripheral smear, erythrocyte sedimentation rate (ESR), and serum biochemistry, Mantoux skin test, blood and urine cultures, serology for Epstein-Barr virus (EBV), cytomegalovirus (CMV), adenovirus, influenza virus, enteroviruses, herpes simplex viruses, and for *Rickettsia conorii*, bone marrow aspirate to rule out malignancies, visceral leishmaniasis and miliary tuberculosis. The only positive finding was a gradual increase in the ESR value until a peak of 72 mm/h on hospital day 14. In the meantime, he continued to be febrile with spikes up to 39.7 °C late evening or at night, despite his good general condition and an unremarkable physical examination. However, the child's history of exposure to domestic cats found out on day 9 of hospitalization prompted us to order serology for *Bartonella henselae*. Serology for *B. henselae*, performed by indirect immunofluorescence assay, revealed a positive IgM with an IgG titre of 1:1024. The fever abated spontaneously 15 days after admission.

B. henselae infection should be included in the differential diagnosis of children with FUO, especially if there is a history of kitten or cat contact, as atypical cat-scratch disease (CSD) can present, irrespective of the immune status of the host, as FUO associated with hepatosplenomegaly due to hepatosplenic granulomatosis or, even more rarely, without hepatosplenic involvement.[1]

Fever of intermediate duration (FID) is a new syndrome, recently defined by adult infectious diseases specialists in our country as fever of 7–28 days which remains unexplained after the patient's history, physical examination, and basic laboratory and imaging screening. Since treatable infections with a good prognosis are by far the most commonly aetiology, the proposed diagnostic approach to this entity allows clinicians to avoid some expensive and uncomfortable procedures recommended for patients with classic FUO.[2,3] Likewise, although FID has never been studied in children, the aetiology and prognosis of prolonged fever also varies greatly depending on whether the fever lasts for more or less than 4 weeks. For example, overall, infections can account for up to 50% of FUO in children in developed countries.[4] The infections most commonly involved, regardless of local epidemiological particularities, are tuberculosis, EBV and CMV infection, other prolonged viral infections, CSD, osteomyelitis, and urinary tract infections.[4,5] Most of these conditions can currently be diagnosed before fever reaches 4 weeks with the microbiological tests available. However, the likelihood of conditions with a worse prognosis such as connective tissue diseases, malignancies or inflammatory bowel disease dramatically increases when fever persists for more than 4 weeks without a clear origin.[5–8] In times of budget constraints in healthcare, the aetiology of FID is also worth studying in the paediatric population to optimise its management. We believe that a thorough clinical history, a meticulous physical examination, and a limited number of laboratory and imaging tests could be a rational initial approach to well-appearing and immunocompetent children. Additional investigations can be driven by new diagnostic clues discovered by revisiting the history and repeated physical examination.