Reminder of important clinical lesson

Extrapulmonary tuberculosis: importance of differential diagnosis

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Summary

Patients with tuberculosis (TB) typically present with pulmonary TB, but extrapulmonary TB is also an important clinical problem. In particular, osteoarticular TB has a great morbidity and its diagnosis gold-standard includes culture and histopathology of the infected area. The present case study describes a 53-year-old female Portuguese farmer who had initial clinical and imaging features suggestive of tuberculous osteomyelitis. However, she denied any TB contacts and the tuberculin skin-test and interferon- release assay result were negative. *Brucella melitensis* was isolated from a tissue biopsy cultural examination, and treatment for brucellosis was started, yielding a favourable outcome. In similar circumstances, a precise diagnosis, that considers the epidemiological context, is crucially important for adequate treatment and reduction of morbidity.

BACKGROUND

In recent years, a significant worldwide increase in the prevalence of tuberculosis (TB) and of extrapulmonary manifestations of TB have been noted.^{1 2} This increase is attributable to a rise in the number of subjects with suppressed immune systems, development of drug-resistant strains of *Mycobacterium tuberculosis* (MT), ageing population demographics and a rise in the number of healthcare workers exposed to TB.³ Osteoarticular TB accounts for 1%–2% of all TB cases in the western world.⁴

The spine is the most common site of TB osseous involvement, accounting for about 50% of cases.⁵ The clinical signs and symptoms are rather non-specific, and frequently include spinal pain, paravertebral muscle spasm, spinal deformities and neurological deficits. The uses of

CT and MRI have significantly improved the sensitivity and specificity of diagnosis. Imaging features that support a diagnosis of osteoarticular TB include multiple levels of spinal involvement, relative sparing of the intervertebral disc, large paravertebral abscesses, subligamentous spread, multicentric involvement and heterogeneous signals with rim enhancement visible on MRI.⁶

Etiological diagnosis of vertebral osteomyelitis is frequently difficult, and 30%–70% of patients are subjected to percutaneous or surgical bone biopsy.⁷ Despite the high rate (>50%) of false-negative bacteriological and histological results, Colmenero *et al.* reported that bone biopsy was necessary for diagnosis of osteoarticular TB in almost 75% of patients.⁷ In fact, diagnosis of osteoarticular TB is often based on epidemiological data, clinical features, physical

Figure 1 Lumbar MRI at presentation. An axial T2-weighted image (A), a T1-weighted image (B), and a postcontrast T1-weighted image (C) show granulation tissue distributed circumferentially around the vertebral body (B and C: arrows), enhancement of the perivertebral space (C: arrows) with bilateral paravertebral abscesses (A: arrows), and low-level epidural invasion (C: arrowhead).

Figure 2 Lumbar MRI at presentation. A sagittal T2-weighted image (A), a postcontrast T1 STIR-weighted image (B), and a postcontrast coronal T1-weighted image (C) indicate hyperintensity of the anterior portion of the vertebral bodies (A: arrow) without collapse of such bodies, with postgadolinium enhancement (B and C: arrows), including the paravertebral space (C: arrow) and relative preservation of the L3-L4 intervertebral disk.

findings and laboratory results, but the gold-standard for diagnosis includes culture of the pathogen and analysis of the histopathology of the infected bone.

CASE PRESENTATION

A previously healthy, 53-year-old female farmer from Portugal who experienced increasing lumbar back pain for 6 months presented to our department. A lumbar MRI indicated abnormalities along the L3-L4 vertebral bodies, relative preservation of the intervertebral disk and adjacent paravertebral masses with cystic formations (figures 1 and 2). These features are suggestive of a granulomatous aetiology such as TB, and the patient was thus referred to our outpatient clinic. The patient reported no previous TB contacts and no respiratory or constitutional complaints. A physical examination indicated lumbar paravertebral tenderness but no neurological deficit.

INVESTIGATIONS

Chest radiography was normal and tuberculin skin-test (TST) and the result of interferon- γ release assay (IGRA) (Quantiferon-TB Gold in-tube) were negative. Because no definite diagnosis had been made, a percutaneous spinal biopsy was conducted. Its microbiological analysis confirmed the presence of brucellar spondylodiscitis caused by *Brucella melitensis*. The mycobacterial culture was negative, excluding a TB diagnosis. In agreement with the culture result, Wright's reaction indicated an elevated serum antibody titre ($\geq 1:1600$).

DIFFERENTIAL DIAGNOSIS

Many infectious diseases should be considered in the differential diagnosis of patients with symptoms of osteomyelitis and/or spondylodiscitis, depending on the geographic area and the clinical setting (age, gender, exposure history and immunological state). This case illustrates

the importance of the differential diagnosis of TB and brucellosis. Although TB is more common,² both diseases are present in Portugal (see discussion), and are important public health problems in our Mediterranean country.²⁻⁸ Detailed clinical information, including a history of a lack of contact with a TB patient, complete information on possible occupational exposure (eg, a farmer directly handling raw meat and milk products of possibly infected animals), negative results on initial TB tests (TST and IGRA) and ultimately, culture of a biopsy sample, were essential in our confirmation of aetiology (see discussion).

TREATMENT

After diagnostic confirmation, the patient was referred to the infectious diseases department and treated with doxycycline (200 mg/day) and rifampicin (600 mg/day) for 6 months.

OUTCOME AND FOLLOW-UP

Ultimately, the patient enjoyed favourable clinical, laboratory and radiological outcomes. After completion of antibiotic therapy, she was asymptomatic. Wright's reaction, although still positive, showed a decrease in antibody titre to $\geq 1:800$. Radiologically, a notable reduction in the enhancement of the perivertebral space was evident, the paravertebral abscesses and the epidural invasion disappeared and a decrease in the hyperintensity of the L3 and L4 vertebral bodies was evident (figures 3 and 4).

DISCUSSION

This case is an example of presumptive diagnosis of osteoarticular TB, based on epidemiological, clinical and imaging results, that was incorrect. Portugal has an intermediate incidence of TB (22 cases per 100 000 subjects).² Brucellosis is not eradicated in some areas, but the incidence is only 0.2–2.8 cases per 100 000, depending on the age group.⁸

Figure 3 Lumbar MRI 6 months after initiation of treatment. An axial T2-weighted image (A), a T1-weighted image (B) and a postcontrast T1-weighted image (C) indicate little enhancement of the perivertebral space (C: arrow), no paravertebral abscesses (A: curved arrow in the previous location of an abscess), and no epidural invasion (C). These aspects clearly demonstrate radiological improvement.

Figure 4 Lumbar MRI 6 months after initiation of treatment. A postcontrast sagittal T1-weighted image (A), a postcontrast T2 STIR-weighted image (B), and a postcontrast coronal T1-weighted image (C) indicate slight hyperintensity of the L3 and L4 vertebral bodies (A and B: arrows, C) with postgadolinium enhancement (A: arrow, B, C), without collapse or involvement of the paravertebral space (C: curved arrows in the previous locations), but with a decrease in the height of the intervertebral L3-L4 disk (C: arrowhead).

The 10- to 100-fold higher incidence of TB caused us make an initial presumptive diagnosis of TB rather than brucellosis.

Both TB and brucellosis (the commonest zoonosis in endemic areas) are granulomatous diseases exhibiting great clinical polymorphism. Extrapulmonary forms account for 10%–50% of all cases of TB and are more common in patients co-infected with HIV.² Focal complications are present in 20%–40% of brucellosis patients.⁹ Extrapulmonary TB and focal forms of brucellosis have been described in almost all organs and systems; and osteoarticular, genitourinary, hepatic, or central nervous system involvement is very common in those with either disease.

Osteoarticular brucellosis forms are the most common and spondylodiscitis represents 20%–50% of all cases.¹⁰ Accordingly, in areas with significant incidences of TB and brucellosis, a differential diagnosis is mandatory.

Diagnosis of extrapulmonary TB is often difficult. In the appropriate epidemiological and clinical setting, and

characteristic imaging features, TST and IGRA positive results may support a diagnosis of TB, although active TB may also be present if test results are negative. However, in immunocompetent individuals, the negative predictive value for MT infection is higher than 95% if both TST and IGRA results are negative.^{11–14}

Consequently, in the present case, a diagnosis of TB was unlikely because the patient, although living in a country with an intermediate incidence of TB, had no contact with a TB-infected host, was immunocompetent and yielded negative TST and IGRA results. These combined data, and the fact that identification of the responsible pathogen is crucial for the appropriate management of spondylodiscitis, justified the need for a more invasive diagnostic investigation. Our approach led to a correct diagnosis of brucellosis, a disease that has not yet been eradicated in some areas of Portugal. The differential diagnosis of brucellosis and TB is critical to ensure that appropriate treatment is given and disease morbidity is reduced.

Learning points

- ▶ TB and brucellosis are granulomatous diseases showing great clinical polymorphism.
- ▶ A high level of suspicion and the use of more invasive diagnostic tools are required in some patients with extrapulmonary forms of TB, to confirm the aetiology and to exclude other diseases, such as brucellosis. An incorrect diagnosis could lead to the administration of inappropriate therapy and worsening of the disease.
- ▶ In the present instance, the patient had no history of exposure to TB, was immunocompetent and yielded negative TST and IGRA results; a diagnosis of TB was thus unlikely. This case emphasises the importance of considering all epidemiological, clinical and test data to ensure a correct diagnosis.

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Competing interests None.

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