

Can it be TB?

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Key words: tuberculosis, Pott's diseases, pregnancy, immigrants

IMAJ 2004;6:427-429

Many people erroneously think that tuberculosis is a disease of the past – an illness that no longer constitutes a public health threat. In fact, tuberculosis remains a major cause of morbidity and mortality, mostly, but not only, in developing countries. Tuberculosis has accompanied humankind since the beginning of history. The earliest evidence of tuberculosis in man is provided by bone finds showing the gibbus typical of tuberculous Pott's disease. The oldest examples of spinal tuberculosis, in the form of fossil bones, date back to about 8000 BC. Findings in Egyptian mummies clearly indicate that spinal caries existed around 2400 BC. The depictions of a gibbus in statuettes of ancient Egyptian and pre-Columbian origin represent clear evidence of spinal tuberculosis. Acid-fast bacilli were demonstrated in smears taken from a psoas abscess in the well-preserved mummy of an Inca child from around 700 BC, clearly documenting a case of tuberculosis of the lumbar spine. DNA analysis revealed *Mycobacterium tuberculosis* in a vertebral lesion of a 12 year old girl who lived around 1000 AD. Percival Pott presented the classic description of spinal tuberculosis in 1779 [1]. The improving socioeconomic conditions in industrialized countries and the advent of antibiotics in the twentieth century both contributed to a remarkable reduction in the prevalence of the disease. Since the 1980s, however, the incidence of tuberculosis is increasing again in the developed world. This resurgence has been caused mostly by cases diagnosed in foreign-born individuals who emigrated from endemic countries, although the AIDS epidemic has also been playing a significant role in the recent spread of the disease [2-5]. In Israel, an increase in the incidence of active tuberculosis was observed in the 1990s, coinciding with the waves of immigration from the former Soviet Union and Ethiopia. Among recent immigrants the prevalence of the disease is approximately fivefold higher than in the rest of the population. A sharp increase in the prevalence of extrapulmonary tuberculosis has been registered since 1997 (Source: Department of Tuberculosis & AIDS, Ministry of Health, Jerusalem).

Because of its diverse clinical presentations, extrapulmonary tuberculosis has always been a diagnostic challenge to the clinician. More recently, the rarity of some of these forms of tuberculosis in developed countries has rendered them unfamiliar to many physicians, thus lowering the index of suspicion and delaying the diagnosis. Two such cases of spinal tuberculosis in which the diagnosis was not considered initially are reported in this issue of *IMAJ* [6,7]. Skeletal infection may account for up to 35% of cases of extrapulmonary tuberculosis and, overall, for 3-5% of all cases of tuberculosis [5,8]. Skeletal tuberculosis involves the spine

in approximately one-half of patients [5,9]. According to European data, up to 70% of patients with spinal tuberculosis (Pott's disease) are immigrants from developing countries, mostly from Africa [5]. One of the patients described in this issue of *IMAJ* was a foreign worker from Thailand [6], while the other had emigrated from Yemen many years ago [7]. Bone may be infected on the occasion of hematogenous seeding of organisms throughout the body that occurs during the primary tuberculous infection. Vertebrae are especially affected by this seeding since the local blood flow remains high even in adulthood. Small foci of disseminated infection are confined by local immune processes and the extrapulmonary infection remains clinically unapparent [10]. When the immune defense is weakened by conditions such as poor nutrition, advancing age, corticosteroid therapy, human immunodeficiency virus infection or renal failure, reactivation with progression to clinically apparent disease may occur [10]. More recently, a high rate of tuberculosis was documented among patients treated with infliximab, a humanized antibody against tumor necrosis factor-alpha [11]. In highly endemic areas, skeletal tuberculosis usually manifests within about one year after primary lung infection and mainly occurs in young subjects. In industrialized countries, tuberculosis of the bone is more commonly associated with late reactivation of infection and is observed mainly in adults. Spinal tuberculosis most often affects the lumbar and lower thoracic region; upper thoracic and cervical disease is less common but potentially more disabling [12]. Infection usually starts in the antero-inferior aspect of the vertebral body with inflammatory bone destruction and caseating necrosis. Active infection may spread down behind the anterior ligament to involve the adjacent vertebral body. Local destruction often produces collapse of bony structures and herniation of the disk into the vertebral bodies. Vertebral collapse can lead to spinal instability with gibbous deformity (or "step" kyphosis), and possibly to spinal cord compression. Paraspinal cold abscesses develop in at least 50% of patients. Abscess formation can occur in the form of an epidural abscess that can produce pressure on the cord, or a psoas abscess that can spread down to the groin.

The indolent nature of skeletal tuberculosis often leads to delayed or missed diagnosis, sometimes with severe consequences for the patient. Both patients with spinal tuberculosis described in this issue of *IMAJ* [6,7] presented with pain but no systemic symptoms. Indeed, when the spine is affected the most common symptom is local pain, which becomes increasingly severe over several weeks to months. Constitutional symptoms, fever and

weight loss are present in less than 50% of cases [5,13,14]. The most threatening complication is paraplegia, which might be due to arachnoiditis and vasculitis or, less frequently, to cord compression. In countries where the incidence of tuberculosis is low, the diagnosis of spinal tuberculosis is often greatly delayed because of a low index of suspicion [13]. The median time from symptom onset to diagnosis in the series by Pertuiset et al. [5] was 4 months (range 1 week to 3 years). In the case reported by Attia et al. [7], the patient suffered from neck pain for 2 months before the diagnosis. In highly endemic areas diagnosis is often delayed because of poor access to medical care and/or poverty; 40–70% of patients from highly endemic regions have symptoms and signs of cord compression at the time of diagnosis [13].

The most common cause of delay in the diagnosis of skeletal tuberculosis is failure to consider the diagnosis, especially in patients who have normal chest radiographs. Clues to the diagnosis of extrapulmonary tuberculosis usually come from the history, which should include questions on the country of birth, a family history of tuberculosis, and a history of prior known or possible tuberculosis contact. Patients with altered cellular immunity are at particular risk of reactivation of tuberculosis [11]; the incidence of tuberculosis is 1,000-fold higher in HIV-seropositive individuals than in the seronegative population [15]. Chest radiography is often not useful in the diagnosis of skeletal tuberculosis since more than half of such patients do not have evidence of active pulmonary disease [9,13]. On the other hand, the diagnosis of skeletal tuberculosis should be considered in patients with focal bony abnormalities and signs of old or active tuberculosis on chest X-ray [16]. There are no skeletal radiographic characteristics pathognomonic of tuberculosis. The early changes are usually seen in the anterior aspect of a vertebral body, with demineralization of the end-plate and loss of definition of the bony margin. Shortly thereafter the adjacent vertebra becomes involved and a paravertebral abscess may be detected on plain films. As infection progresses, the disk space becomes obliterated with anterior wedging and angulation. Reactive sclerotic changes remain localized and the remaining vertebral structures are often spared [17]. In some patients spinal tuberculosis may present with pure osteolytic lesions without disk space involvement. These lesions occur more often at multiple spinal sites, are more likely to be associated with extraspinal skeletal tuberculosis, and are more commonly seen in immigrants from endemic areas [5]. Other radiographic modalities, such as computerized tomography, myelography and magnetic resonance imaging, are occasionally useful in the diagnosis of skeletal tuberculosis; bone lesions can be demonstrated earlier by CT and MRI than by plain radiographs [5]. Whenever possible, the diagnosis of tuberculosis should be confirmed by microscopy and culture of infected material obtained by needle aspiration or biopsy. Pertuiset and collaborators obtained positive cultures in 83.5% of their cases [5]. Moreover, in view of the increasing problem of multidrug resistance [18], information on the antimicrobial susceptibility of the pathogen is extremely important to assure successful treatment. This can be achieved only if an

attempt is made to isolate the mycobacterial pathogen. If a lesion is biopsied in a patient with risk factors for tuberculosis, it might be a rewarding practice to store in -20°C some of the biopsy material for ulterior culture if histology is suggestive of tuberculosis or another infection for which special culture methods are indicated. The mainstay of treatment of skeletal tuberculosis consists of antituberculous chemotherapy using regimens that are adequate for pulmonary tuberculosis. Surgery is a useful adjunct to medical therapy for selected patients who require drainage of an abscess, debridement of infected material, stabilization to prevent or correct kyphotic deformity, and decompression of a suffering spinal cord.

The clinical management in the case reported by Lowenstein et al. [6] was complicated by the fact that the patient was pregnant. There is no clear increase in the risk of tuberculosis associated with pregnancy, and pregnancy has no effect on the response to the tuberculin skin test. The diagnosis of tuberculosis may be delayed during pregnancy, however, due to gestation-associated malaise and fatigue, or because there is reluctance to perform imaging studies [19]. The benefits of treating active tuberculosis in pregnancy dramatically outweigh any potential drug toxicity [20]. Pregnancy does not significantly alter the response to antituberculous medications, and tuberculosis is not a medical indication for abortion. However, streptomycin should not be used because of possible ototoxicity in the fetus, while pyrazinamide is not recommended because of lack of data on the risk for teratogenicity. Congenital transplacental transmission of tuberculosis is rare and occurs almost exclusively when the placenta is actively infected, although placental involvement does not necessarily lead to congenital tuberculosis [19]. Adverse fetal outcomes are more frequent with extrapulmonary disease than with lung infection. One study that compared pregnancy outcomes in 21 pregnant women with extrapulmonary tuberculosis (excluding lymphadenitis) versus 132 healthy controls found significantly higher frequencies of low birth weight infants (33% versus 11%) and infants with Apgar scores <7 (19% versus 3%) among mothers with extrapulmonary tuberculosis [21].

Pott's disease has been coined the great mimicker or the great masquerader. In the presence of a patient with indolent clinical manifestations, especially in the immunosuppressed, the immigrant or the elderly, the clinician should always ask the question: "can it be TB?"

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HIV = human immunodeficiency virus

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