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REVIEW ARTICLE

Microbiological diagnosis of spinal tuberculosis

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Abstract
Purpose The purpose of this study was to review the clinical features and diagnosis of spinal tuberculosis cases reported in the literature.
Methods A medical literature search in the Medline Pubmed database was undertaken to review tuberculosis spinal infection and extra-pulmonary tuberculosis diagnosis improvement. We introduced the following search items and boolean operators: "spinal infection", "spinal tuberculosis infection", "microbiological diagnosis of spinal tuberculosis" and "spinal tuberculosis PCR." Single cases or series without microbiological diagnosis were rejected. Manuscript language was restricted to Spanish, French, and English versions.
Results and conclusions Spinal tuberculosis is more common in developing countries and is probably underdiagnosed. Delayed diagnosis is characteristic; it worsens the prognosis and increases morbidity. The microbiological diagnosis is crucial for several reasons. Despite surgical treatment, medical treatment with anti-tuberculous drugs is always necessary. A total of 20–40% of the spinal tuberculosis patients show another locus of infection. Pulmonary location can become a public health problem. Previously treated patients for other tuberculosis locations, incomplete treatments, or poor adherence can change the *M. tuberculosis* sensitivity pattern. Drug resistance test becomes a major need in the microbiology laboratory. PCR diagnostic techniques advance the diagnosis and increase the sensitivity and specificity rate.

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Introduction

The principal infection causing death in the world is tuberculosis (TB). It is estimated two billion people are infected with TB, who can develop TB disease [1]. The risk of developing the disease depends on the patient (host characteristics) and the geographical precedence because of the different incidence of TB in each country. In a study made in the United Kingdom, the risk in the white population increases with age from 0.8 to 10.9/100,000, whereas, the risk in people from the Indian subcontinent increases with age from 28.7 to 405.7/100,000; thus, they realised that anyone of any ethnic group has an increased risk of 10–20 times, but this reduces after five years in the United Kingdom [2].

Extrapulmonary tuberculosis affects 15–20% of patients with TB. The most common are pleural and lymphatic disease. Skeletal TB occurs in 10% of extrapulmonary manifestations, of which spinal TB accounts for approximately 50%. This gives an incidence of between one and two percent for osteoarticular TB and half to one percent for spinal TB [1, 3]. Most postoperative infections following spine surgery are caused by bacterial organisms. *Staphylococcus aureus* is known to be the most common single pathogen, and the earlier postoperative infection is related to methicillin-resistant *Staphylococcus aureus* (MRSA) or Gram-negative bacteria. However, there are few reports of postoperative infection with *Mycobacterium tuberculosis* [4]. Spinal infection is a relatively rare condition and accounts for 2–16.7% of all cases of osteomyelitis [5].

Spinal TB accounts for one to three percent of all TB infections [6]. Spinal tuberculosis is the most common and the most serious form of tuberculosis lesions in the skeleton.

A total of 101 countries reported notifications of new cases of extrapulmonary TB (these countries accounted for 50% of total notifications of extrapulmonary TB). There were 195,002 male cases and 180,310 female cases, giving a male:female ratio of 1:1. Among new extrapulmonary patients, this is much lower than the ratio for smear-positive TB patients. Understanding the reasons for this difference and the logistical implications requires further investigation and research. The resurgence of TB can be expected to be associated with a concomitant increase in the incidence of extra-pulmonary TB, including Pott's disease. The incidence of patients with spinal infection has been reported to have increased [7]. This is probably a result of an aging population, easy access to better diagnostic methods including magnetic resonance imaging (MRI) and an increase in the prevalence of immunocompromised hosts [8]. Most recent studies highlight their appearance in elderly patients (mean age of 50–60 years) with a clear predominance of males [9]. Studies in Spain have shown a similar incidence (0.7–2.4 cases per 100,000 inhabitants) with a tendency towards the disappearance of spondylodiscitis caused by *Brucella* and stabilisation of pyogenic and tubercular spondylodiscitis [10].

Neurological deficit due to spinal infection can pose a wide range of problems for the patient and the surgeon. Most spinal infections in developed regions are the result of pyogenic organisms, whereas non-pyogenic organisms are responsible for most spinal infections in areas of the developing world, and in the immunocompromised population of developed nations. *Mycobacterium tuberculosis* is the most common organism among these areas. Accurate diagnosis is essential in order to effectively eradicate the infecting organisms. Subsequent management of the diagnosed infection remains controversial with the National Tuberculosis Control Programmes [11].

Tuberculosis has a propensity to spread along soft tissue planes, particularly anteriorly under the anterior longitudinal ligament, involving multiple vertebrae, in time giving the so-called "aneurysmal syndrome" (scalloping of the anterior vertebral margins) [12]. Tuberculosis demonstrates a variety of clinical and radiological findings and shows a known propensity for dissemination from its primary site; therefore, it can mimic a number of disorders. Tubercular spinal epidural abscess is usually secondary to tubercular spondylitis, but may rarely develop by haematogenous spread from any primary focus [13].

The symptoms of tuberculous bone and joint infections are nonspecific, and the clinical course is often indolent, usually leading to significant delays in diagnosis and resultant bone or joint destruction. About 50% of the patients with bone and joint tuberculosis have chest radiographs suggestive of tuberculous infection, further obscuring the diagnosis [14]. Differentiation between pyogenic spondylodiscitis (PS) and tuberculous spondylodiscitis (TS) is essential to decide on the appropriate therapeutic regimen. The aim of this study was to compare the characteristics of the two forms of spondylodiscitis. TS was frequently associated with active tuberculosis of other organs (0% in PS vs. 31.9% in TS), and longer diagnostic delay (47.6 days in PS vs. 106.3 days in TS) [15].

The clinical non-specificity of mycotic aneurysm or infective spondylitis makes diagnosis in the affected patients challenging. Although neurological deficit was statistically significant in patients with spontaneous infective spondylitis with mycotic aneurysm, this unique clinical characteristic was always noted in late stages of infective spondylitis [16].

If the patients are diagnosed early, they can be treated medically. This situation is a major problem in bone and joint TB, due to the delay in the diagnosis; therefore many patients need surgical treatment [17]. Nevertheless, spinal tuberculosis progresses slowly and insidiously, and early diagnosis before abscess formation and disc affectation is difficult. For this reason, a detailed patient history is very important in these cases. In the early stages, single-level disc degeneration can be detected by MRI. Despite this, disc degeneration may be suspected, and the probability of diagnosing the condition as an infection is very low. In either case, painful symptoms of patients can be relieved with medical treatment. If there is a tuberculosis history (in the patient or a family member), night sweats and weight loss, detailed MRI investigations focusing on the lesion are necessary for an early diagnosis and allow medical therapy. The diagnosis of spinal tuberculosis (ST) is difficult and it commonly presents at an advanced stage. The management and follow-up is complicated by a lack of guidance on the appropriate use and interpretation of spinal magnetic resonance studies (MR) [5].

The microbiological diagnosis is a problem in some parts of the world. For example, in the busiest clinics in Cape Town, up to 46% of pulmonary TB cases are not confirmed bacteriologically, and South Africa has one of the highest rate of tuberculosis infection [1]. Positive cultures were reported in only 27 (62%) of 47 patients with tuberculous spondylitis [18]. Nevertheless, many spinal tuberculosis cases are diagnosed after the progressive degenerative process. These cases must be treated surgically [19]. Pott's disease, an extrapulmonary form of TB, is marked by the weakening and resorption of spinal vertebrae. This role could be related to the physical depletion of calcium in bones and/or the disruption of calcium signalling in host cells during long-term TB infection [20, 21]. The diagnosis of extra-pulmonary tuberculosis (EPTB) remains an important clinical problem, primarily because of the inadequate sensitivity of conventional bacteriological methods for detecting *Mycobacterium tuberculosis* in extrapulmonary specimens. The recent demonstration that nucleic acid amplification techniques are rapid and sensitive has

modified strategies for the detection of *Mycobacterium tuberculosis*. Since the application of the polymerase chain reaction (PCR) in the diagnosis of TB, diagnostic protocols using varying methods of DNA purification and different *M. tuberculosis* target sequences have been evaluated [23, 24]. Early diagnosis followed by proper medication is essential to prevent both morbidity and mortality. PCR is a good option for the rapid diagnosis of tuberculosis [22]. Although the conventional technique of direct smear examination is cheap and easy to perform, its low sensitivity is a major drawback. On the other hand, the molecular-based diagnosis by PCR technique is faster and more sensitive [25]. Serological tests are frequently used in developing countries, but a lot of work is yet to be done to consider them optimal [26].

All patients with tuberculosis should be referred to a chest physician trained in managing tuberculosis, but patients often return to their general practitioner with questions about their drugs. Antituberculous drugs interacting with other drugs is also a major concern. Sometimes, side effects of treatment may present, such as rashes caused by isoniazid [27]. The detection of smear-negative and extrapulmonary cases also lags behind the Global Plan, and by a larger amount (51% estimated for 2007 compared with the Global Plan Milestone of 69%) [23].

Methods

A medical literature search in PubMed Medline database was undertaken to review spinal tuberculosis infection and extra-pulmonary tuberculosis diagnosis improvement. On one hand, we selected studies to review the length of symptoms before diagnosis, concomitant pulmonary TB, success of treatment, microbiological diagnosis, as Ziehl-Neelsen staining results and resistant strains.

On the other hand, we chose studies about the sensitivity of molecular biology techniques for the diagnosis of spinal TB. We introduce the following search and boolean operators items: "spinal tuberculosis infection", "microbiological diagnosis of spinal tuberculosis" and "spinal tuberculosis PCR". No publication date restriction was applied. Manuscript language restriction was to English, French, and Spanish versions.

Inclusion criteria of studies:

- Data from case series studies or meta-analysis that provided spinal TB cases diagnosed by microbiological tests.
- Studies that provided data on the microbiological diagnosis of spinal tuberculosis.

Exclusion criteria:

- Studies performed only in the paediatric population.
- Items with unique cases or case reports.

Table 1 Tuberculosis (TB) clinical and microbiological features

Study	Period	Country	Patient number	Symptoms length (days)	Concomitant pulmonary TB	Success	Microbiological diagnosis	Positive smear	Sensitive strains
Weng et al. [18]	1998–2007	Taiwan	38	60 (3–720)	12/38 (32%)	35/38 (92%)	24/38 (63%)	22/38 (58%)	18/38 (75%)
Nagashiman et al. [17]	1956–2005	Japón	31	–	–	–	31/121 (25.6%)	–	–
Cormican et al. [2]	1999–2004	UK	23	330 (45–1080)	3/23 (14%)	13/23 (56.3%)	16/23 (76%)	15 (75%)	69%
AlOthman et al. [13]	1985–1998	Arabia Saudí	69	–	–	63 (91%)	57/69 (87.7%)	20/57 (35%)	
Polley et al. [1]	2001–2006	Cape Town	16	–	–	11 (68.75%)	8 (15)	4/14 (28.6%)	6/8 (75%)
Pertuiset et al. [28]	1980–1994	Paris	103	–	–	–	85/103 (83%)		103 (100%)

A dash (-) indicates no available data

Results

Clinical and microbiological characteristics of spinal tuberculosis patients

A total of six articles from 90 analysed were chosen. The studies did not follow the same methodology but the data we have selected are comparable. They define cases of spinal tuberculosis and describe clinical features, evolution and isolations (Table 1).

Out of 270 patients, the average time to diagnosis was between 20 and 61 days (range 3–1,080 days), indicating that there are long periods with symptoms of the disease. Twenty of 70 patients (28.6%) had pulmonary tuberculosis at the same time.

The microbiological diagnosis by culture was achieved in 213/359 patients (59.3%) and 45.2% Ziehl-Neelsen positive microscopy.

The number of drug-resistant strains isolated is significant (40/69) (58%). This relates to the geographical locations of the study, which varies by country.

In Taiwan, Weng et al. [18] retrospectively studied 38 patients with positive TB cultures. The average duration of symptoms was 60 days until the diagnosis. Twelve out of 38 patients had concomitant pulmonary TB (32%), while 13% (three patients) were infected with resistant strains.

In Japan, Nagashimanet et al. [17] retrospectively studied 31 patients with spinal TB Infection. Over a period of 49 years microbiological diagnosis was provided exclusively in 25.6% of cases.

In Saudi Arabia, AlOthman et al. [13] studied 69 patients with spinal TB infection for 14 years. The culture was positive of 87.7% (57/69). PCR was not performed.

Polley et al. [1] retrospectively analysed 16 spinal TB patients for five years in Cape Town. The microbiological culture was positive in eight cases (53.3%), six of which were sensitive strains.

Pertuiset et al. [28] studied 103 cases of spinal TB for 14 years. Cultures were positive in 83% of patients, without any resistant strains.

Spinal tuberculosis microbiological diagnosis methods

We chose four articles to compare the microbiological diagnosis of tuberculosis infection relating samples. The methodology and the cases or samples included are different in each study. Given the importance of the diagnosis of *M. tuberculosis,* we analysed the outcomes of conventional diagnostic methods and new techniques such as PCR [29]. Table 2 shows four studies that compare and analyse the sensitivity of the PCR.

In Pakistan, Amin et al. [30] analysed 766 samples with suspected TB and found a total of 356 (46.5%) positive by the PCR method. They noted that the efficiency of the PCR depends on the sample, with values of 70% in respiratory samples such as bronco alveolar lavage and 4.8% in serum.

In Bangladesh, Rune et al. [10] studied 135 sputum samples from patients with clinical suspicion of TB. They found that PRC was positive in 93 samples (68.9%); 20 of them (21.5%) had a negative culture, concluding PCR improves the diagnosis in a fast and effective way.

In Hong Kong, Cheng et al. [22] studied 144 patients with suspected TB. A total of 112 had a positive culture. They found that PCR sensitivity is 82.3% for respiratory specimens and 72% for extrapulmonary specimens.

Portillo-Gomez et al. [24] studied 294 samples from 286 patients with clinical suspicion of extrapulmonary TB. They found that PCR sensitivity for extrapulmonary samples was higher than that obtained with culture, depending on the type of sample.

Discussion

Spinal tuberculosis is not a very common entity. It causes significant morbidity and important consequences and sequelae. In our review, we observed that the time until the diagnosis is achieved remains very long, which indicates that the diagnostic techniques should be improved. It should also become part of regular differential diagnosis by physicians, especially in patients and areas where the prevalence of tuberculosis is high.

Table 2 PCR sensibility

Study	Period	Geographical area	Specimens number	TB PCR +	Pulmonary PCR	Extrapulmonary PCR
Amin et al. [30]	2004	Pakistan	766	297.21 (38.8%)	7/10 (70%)(BAL)	17/44 (38.6%)(pus)
Portillo et al. [24]	1995–1997	Mexico	65	61	17/16 (94%)(pleural)	15/14(93%) (ascitic)
Cheng et al. [22]	2002–2004	Hong Kong	224	148 (66.07%)	79/65 (82.3%)	16/13 (81.2%)(tissue)
Runa et al. [10]	2004	Bangladesh	135	93/135 (68.9%)	135	0

It is relevant that 20–40% of patients have active tuberculosis at other sites, so the diagnosis can be performed on clinical specimens as sputum, urine, or lymph node aspirate [9] and we also believe that it is important to check that no other microorganisms are implicated [16].

The TB diagnosis, and specifically spinal TB, should be based on clinical and serological testing (Mantoux test, I, IFN-γ, which are more specific for *M. tuberculosis* than PPD, because they appear in *M. tuberculosis* genes, but are not present in BCG strains provided for vaccination) [2].

One of the main challenges in the microbiological diagnosis of TB has always been the time for culture of *M. tuberculosis.* Microbiological diagnosis is important as it provides aetiology and the foundation for adequate antibiotic treatment. New techniques provide pulmonary and extra pulmonary tuberculosis diagnosis. Aetiology and early diagnosis must be ensured to commence prompt and specific treatment.

PCR is very successful for the rapid diagnosis of several infectious diseases. Achieving this test for TB diagnosis is a major target. This will allow an early diagnosis, earlier targeted treatment and prevention of the spread of the disease, and in the case of TB, a public health problem. Even today these tests are not routinely used for TB management, yet many tests of this type are performed in many parts of the world, as in India, with more than 1.5 million tests [26].

Imaging tests such as CT and MRI are very useful in spinal TB diagnosis. Described by Polley et al. [1], may also help to determine different locations in the spine, as in many patients there is no single locus but several. It is also important to monitor disease progression and treatment [8].

Providing orthopaedic physicians the microbiological diagnosis remains a challenge. The delay in the microbiological results in this disease delays the diagnosis and, therefore, the treatment. Even today, most laboratories do not have PCR techniques to facilitate the diagnosis, as seen in the studies analysed [31, 32].

Nowadays, TB treatment based on PCR techniques is increasingly common, even when cultures or staining results are negative (culture is still considered the gold standard test).

PCR sensitivity sometimes improves culture and staining; therefore, we consider PCR as a very useful tool. However, the FDA only recommends respiratory specimens for TB PCR. As we found in the studies reviewed, there are sufficient criteria to use them in spinal TB [33]. In pulmonary and extra pulmonary TB, PCR is a highly sensitive and specific tool, available for the diagnosis of *M. tuberculosis* in all types of specimens from patients with a clinical suspicion of tuberculosis. When low numbers of bacilli are present, PCR assay has more sensitivity than conventional methods [24]. PCR can become a reliable technique for rapid identification of TB [30].

The antibiogram is crucial for the treatment of spinal TB. Many of these cases occur in countries where the prevalence of resistant strains of TB is high.

Regarding classical treatment, 12–18-month therapies have been recommended, but shorter treatments have their proponents, including six to nine months of isoniazid and rifampicin, with the addition of pyrazinamide for the first two months [34].

Larger studies are needed to demonstrate the utility of PCR in spinal TB, including cost-effectiveness data if we also take into account lost days of life (DAILY) per patient.

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