Establishing the diagnosis of tuberculous vertebral osteomyelitis

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Abstract

Purpose The aim of this article has been to analyze the clinical and radiological data suggesting tuberculous vertebral osteomyelitis (TVO), and then discuss the steps to be followed to achieve an aetiological diagnosis.

Methods A thorough literature search was carried out to identify the best clinical and microbiological evidence for a fast and efficient diagnosis of TVO.

Results The clinical and radiological diagnosis of spinal tuberculosis suffers from serious limitations, with a high percentage of cases requiring vertebral biopsy to reach a definitive diagnosis. The increasing incidence of multi-drug-resistant tuberculosis has highlighted the insufficiency of the histopathological diagnosis and the need for microbiological diagnosis. Unfortunately, the maximum sensitivity of spinal tuberculosis cultures is 80 %, and traditional methods require 6 to 8 weeks for the isolation, identification and sensitivity study. New culture media and identification methods have improved sensitivity and reduced the time required for the identification. Molecular methods have now been integrated into a single test, with identification of the mycobacterium responsible and its sensitivity to rifampicin. Additionally, multiplex-PCR tests have been developed that allow a rapid differential diagnosis between granulomatous spondylodiscitis.

Conclusions All patients with subacute inflammatory back or neck pain showing suggestive radiological findings

should be studied to rule out TVO. If there is no clear evidence of tuberculosis from another location or indication for surgery, a percutaneous vertebral biopsy should be performed. When TVO is suspected, all spinal or paravertebral tissue samples should be sent simultaneously to pathology and microbiology laboratories for appropriate processing.

Keywords Tuberculosis · Vertebral osteomyelitis · Diagnosis · Molecular methods

Introduction

Despite all the advances in medical diagnostic technology over the last 20 years, vertebral osteomyelitis, in general, and tuberculous vertebral osteomyelitis (TVO), in particular, continue to present a diagnostic challenge for most doctors [1].

Spinal pain is a very common symptom in clinical practice, and physicians will need to face its initial management in many patients. Although vertebral osteomyelitis should be included in the differential diagnosis of any spinal pain, it is much less frequent than other spinal diseases [2]. This, together with the absence of fever in a high percentage of cases, explains why many physicians fail to consider infection as the cause of the pain [3].

Unlike pyogenic vertebral osteomyelitis, TVO has a lower clinical expressivity and a more subacute course, leading to a greater diagnostic delay [4, 5].

Previous studies have shown that late diagnosis is the factor that most contributes to a worse prognosis in vertebral osteomyelitis [6, 7]. Moreover, patients with a longer clinical course need surgical treatment more frequently than those with an earlier diagnosis [6, 8]. Surprisingly, the

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incorporation of MRI into clinical practice has not significantly improved the diagnostic delay in TVO [9, 10]. This suggests that physicians often remain unaware of this severe form of extrapulmonary tuberculosis.

Most of the literature on TVO is of historical interest only. Most studies refer to series with just a few cases, studied retrospectively, and with nonhomogeneous criteria. In this article we analyze the clinical and radiological data suggesting that a patient might have TVO, and then discuss the steps to be followed to achieve an aetiological diagnosis.

Keep in mind tuberculous vertebral osteomyelitis

Even though TVO was known in ancient Egypt, described by Hippocrates, and reviewed extensively by Sir Percivall Pott in 1779, it still remains a diagnostic challenge in the twenty-first century. In many countries of Asia, Africa and South America the incidence of tuberculosis is higher than 100–200 cases per 100,000 inhabitants, though in most developed countries the incidence does not exceed 10 cases per 100,000 inhabitants [11].

As with any other infection, early diagnosis of TVO depends on several factors, including clinical suspicion and the availability of resources necessary for its diagnosis. As the index of suspicion depends on the experience of the clinician and the prevalence of the disease, many physicians in low-incidence countries do not consider the diagnosis of TVO in a patient with spinal pain. Several recent studies have reported that in developed countries most cases of TVO occur in immigrants [9, 12]. Therefore, in these countries, the possibility of TVO should be considered in an immigrant patient with clinical or radiological data suggestive of vertebral osteomyelitis.

TVO can occur in the context of disseminated tuberculosis, or result from endogenous reactivation of a latent vertebral focus. In the largest series, TVO appeared simultaneously with other locations of extrapulmonary tuberculosis in 10–38 % of cases [5, 12–14].

As with pulmonary tuberculosis, the incidence of extrapulmonary tuberculosis is higher in immunosuppressed patients. This is well documented in both transplant patients and in those infected with HIV. In all these patients, a high percentage have disseminated tuberculosis with lymph node involvement [15, 16]. However, the incidence of spinal tuberculosis in immunosuppressed patients is not well known. The information in the literature is limited to the description of isolated cases [17–19]. It is possible that in the context of disseminated tuberculosis in immunosuppressed patients, many cases of TVO are not identified. In our experience, 19 % of patients with TVO were co-infected with HIV or had other types of immunosuppression [10]. Thus, in any immunosuppressed patient with back pain we should consider the possibility of

TVO, regardless of whether the data are suggestive of disseminated tuberculosis.

Despite progress in imaging techniques, the diagnostic delay in TVO is still very long. In most studies, the time to diagnosis ranged between 4 and 6 months, with no difference between developed and developing countries [10, 12, 20, 21].

In developing countries, TVO mainly affects young people [22]. By contrast, in developed countries, the age of the patient with spinal tuberculosis has a bimodal distribution with two peaks, one between 20 and 40 years of age and another between 60 and 80 years [10]. The first peak usually concerns immigrants or patients with HIV infection, and the second, immunosuppressed patients or patients with debilitating diseases.

As with vertebral osteomyelitis of any aetiology, the main symptom of TVO is back or neck pain. Fever, sweating, constitutional symptoms, neurological deficits and symptoms suggestive of the involvement of other organs occur in less than 50 % of cases.

Although the pain may occasionally begin more or less suddenly, in most cases, it is of insidious onset, but almost always progressive and with inflammatory characteristics (unrelieved by rest). Accordingly, in any patient with inflammatory spinal pain, we should consider the possibility of vertebral osteomyelitis and act accordingly.

Most physicians tend to associate fever with infection. Thus, the absence of fever would normally go against the infectious nature of the symptoms. However, this is generally not the case in vertebral osteomyelitis and even less, so in TVO. In our experience, only one-third of patients with TVO have fever over the course of their disease [10]. Similar results have been reported by other authors [4, 5, 9, 12, 21, 22]. The absence of fever in a high percentage of patients and the subacute course of vertebral tuberculosis are the main determinants of the high diagnostic delay that occurs in this type of infection.

TVO most often affects the thoracic segment and the thoraco–lumbar hinge, followed by the lumbar segment, and to a much lesser extent, the cervical segment. Multiple spinal segments are affected in 3–10 % of cases [5, 10, 12].

The granulomatous inflammation caused by *M. tuberculosis* results in a marked osteolytic effect on vertebral tissue. Although the mechanisms by which *M. tuberculosis* induce bone resorption remain unknown, chaperonin 10, a protein of *M. tuberculosis* could be responsible for the massive bone resorption that occurs in TVO [23]. On the other hand, experimental work has shown that infection of osteoblasts by *M. tuberculosis* and *S. aureus* results in differential up-regulation of chemokine secretion, indicating a pathogen-specific response, and the magnitude of chemokine secretion after stimulation by *M. tuberculosis* is much greater than after stimulation by *S. aureus* [24]. In

tuberculous osteomyelitis, foci of caseous necrosis tend to coalesce to form abscesses that spread via the subligamentous path. Contrary to what happens in other granulomatous or pyogenic infections, in TVO bone, regeneration is very low, resulting in a large destructive effect that leads to vertebral collapse. This, coupled with the fact that most cases of TVO affect the thoracic segment or thoracolumbar hinge, explains the progressive kyphosis that is a common clinical finding in TVO [25].

Among the different aetiologies of vertebral osteomyelitis, TVO is that which more often causes neurological symptoms [4, 5, 8, 26]. This is not surprising if we consider that in TVO, diagnostic delay, vertebral collapse and abscess formation are all more frequent than in other causes of vertebral osteomyelitis. In our experience, 45 % of patients with TVO have one or more neurological deficits at the time of diagnosis [10]. This figure is right in the middle of the incidence (20–69 %) reported in the largest series in the literature [4, 5, 12, 14, 20, 21].

In conclusion, the presence of inflammatory back or neck pain, with a neurological deficit on physical examination, even in the absence of fever, should suggest the existence of TVO and action be taken accordingly. The pretest likelihood is even greater if there is kyphosis, or data are suggestive of pulmonary tuberculosis or other extrapulmonary location.

From syndromic to aetiological diagnosis

The paradigm for efficient treatment of infectious diseases is to reach an aetiological diagnosis and, if possible, isolate the causative agent. In the case of tuberculosis, this is now especially important because of the increased incidence of multidrug-resistant tuberculosis in many countries [27–29].

In most instances, diagnosis of vertebral osteomyelitis is based on clinical and radiological criteria. Although certain clinical data may suggest TVO, unfortunately none of them is specific enough to establish the diagnosis [8, 30]. In addition, the radiological findings of spinal tuberculosis are often atypical, and descriptions exist of osteolysis of just one vertebral body with no disc involvement, involvement limited to the posterior elements, and multifocal extensive spinal tuberculosis [31–34].

Tuberculin skin test (TST) and interferon gamma release assay (IGRA tests)

Mycobacterium tuberculosis infection leads to a T-lymphocyte mediated immune response which remains for a long time regardless of whether it progresses toward latent infection or active disease. Since *M. tuberculosis* infection is a prerequisite for active tuberculosis, reliable determination of the infection status could accelerate the

diagnostic assessment by enabling rapid exclusion of tuberculosis. This immune response can be measured by skin reactivity following the intradermal injection of a concentrated filtrate from cultures of *M. tuberculosis*. TST, introduced in 1910 by Mantoux, is one of the oldest diagnostic tests used in clinical medicine.

The usefulness of the TST in the diagnosis of tuberculosis has been questioned due to inter-reader variability, cross-reactivity with non-tuberculous mycobacteria and false positive results in patients vaccinated with BCG. Furthermore, TST also has a low sensitivity in immunosuppressed patients. Recently, IGRAs for tuberculosis have overcome most of these limitations. These immunoassays detect in vitro interferon- γ secreted by peripheral blood mononuclear cells in response to specific antigens of *M. Tuberculosis*. Currently, multiple data show that IGRA tests are equally sensitive but more specific than TST in diagnosing latent tuberculosis infection and active tuberculosis [35, 36]. This seems true both in immunocompetent and immunocompromised patients [36, 37]. Kim et al. [38, 39] studied 179 patients with suspected extrapulmonary tuberculosis and found that the IGRA test was significantly more sensitive than the TST in immunosuppressed patients with extrapulmonary tuberculosis.

In countries with a high prevalence of tuberculosis, the usefulness of TST and IGRA in the diagnosis is very limited, as these tests cannot differentiate between latent infection and active disease. However, their negative predictive value is very high, regardless of the prevalence of tuberculosis. For these reasons, it seems advisable to perform an IGRA test in any patient suspected as having tuberculous vertebral osteomyelitis, because, regardless of the prevalence of tuberculosis, a negative IGRA test makes the diagnosis of spinal tuberculosis very unlikely, and thus requires other causes of vertebral osteomyelitis to be ruled out.

Vertebral biopsy

Spinal tuberculosis often coexists with pulmonary tuberculosis or other forms of extrapulmonary tuberculosis. Pertuiset et al. [12] reported that 18 % of their patients had been previously diagnosed with tuberculosis and 27 % of them had extraskelatal sites of active TB. In our experience, 28.2 % of patients with TVO had clear evidence of previous or current tuberculosis [10]; similar results have been reported by other authors [4, 5, 14, 34]. Only in the case of the coexistence of a clinical and radiological picture typical of vertebral osteomyelitis, with microbiologically documented pulmonary or extrapulmonary tuberculosis, can we assume the same aetiology and limit the diagnostic effort. In all other cases that have no indication for surgery a vertebral biopsy or aspiration of

Table 1 Histopathological and microbiological findings in vertebral biopsy

Author [references]	Number of cases	Pulmonary or extravertebral tuberculosis no. (%)	Vertebral biopsy no. (%)	Histopathology Necrotizing granulomas no. (%)	Microbiological findings	
					Microscopy no. positive/no. samples (%)	Cultures no. positive/ no. samples (%)
Lifeso et al. [34]	107	41 (38.3)	31 (29)	NS	NS	20/31 (64.5)
Buchelt et al. [4]	56	24 (42.8)	32 (57.1)	19 (59.4)	NS	NS
Perrone et al. [5]	31	13 (41.9)	15 (48.4)	NS	NS	NS
Nussbaum et al. [14]	29	15 (51.7)	17 (58.6) ^a	NS	NS	17/25 (68)
Pertuiset et al. [12]	103	49 (47.6)	86 (83.5)	51 (70)	30/93 (32.2)	77/93 (83)
Alothman et al. [17]	69	2 (2.9)	50 (72.4)	35 (70)	15/50 (30)	25/50 (50)
Colmenero et al. [10]	78	22 (28.2)	62 (79.4)	44 (56.4)	NS	35/62 (56.4)
Weng et al. [21]	38	15 (31.91)	38 (100)	32 (84.2)	22/38 (57.9)	24/38 (63.1)
Overall	511	181 (35.4)	331 (64.8)	181 (67.5)	67/181 (37)	198/299 (66.2)

NS not shown

^a Only open biopsy

paraspinal collections should be performed to confirm the diagnosis of tuberculosis.

The speed and ease of handling mean that paravertebral tissue or abscess samples are preferable for the aetiological diagnosis of TVO. As TVO has a great tendency to produce paravertebral and epidural masses and psoas abscess [40] there should be no great difficulty in obtaining an adequate sample for pathological and microbiological diagnosis. Fine-needle aspiration or biopsy guided by fluoroscopy or CT have proven to be useful tools for the aetiological diagnosis of spinal tuberculosis. In the largest series, the diagnostic yield of aspiration and/or vertebral biopsy was higher than 62 % [4, 9, 10, 12, 34]. Considering that the maximum diagnostic yield is obtained when the sample is processed microbiologically and pathologically [10, 12, 34, 40], it is advisable whenever possible to obtain two samples, one for microbiological study and the second to send to the pathology laboratory. Since the presence of granulomas is not pathognomonic of tuberculosis [41], when it is only possible to take one sample and this cannot be divided or the sample is from an abscess, priority should always be given to the microbiological study. In the case of paravertebral or psoas abscess, CT-guided aspiration not only helps in the diagnosis but also avoids surgical drainage in a high percentage of cases [42].

When lesions are limited to the vertebral bodies a vertebral biopsy is recommended. Percutaneous core needle biopsy is considered a safe, accurate, and relatively inexpensive technique for the diagnosis of vertebral osteomyelitis [43–46]. Percutaneous biopsy has advantages over open biopsy, in that, it is less painful, less invasive, results in fewer complications and usually does not require general anaesthesia or hospitalization, all of which can reduce expenses.

Vertebral biopsy is usually performed by the transpedicular or posterolateral approach. When the lesion is confined to a particular area, the needle should be specifically directed to that area, and if the vertebra is diffusely affected, the subchondral area is preferred [47, 48].

When microbiological and histological results are considered together, the diagnostic yield of percutaneous biopsy in TVO ranges between 42 and 76 % [4, 5, 12, 14]. In our experience with 78 patients with TVO, 25 (40.3 %) required a percutaneous vertebral biopsy. Culture was positive in 48 % of cases. Pathological study showed the presence of caseating granulomas in five patients whose cultures were negative. The diagnostic yield for the percutaneous biopsies was, therefore, 68 % [10]. The yield of diagnostic tests reported by different authors is shown in Table 1.

Detection of M. tuberculosis from vertebral samples

Although the initial suspicion of TVO is often based on clinical and radiological data, definitive diagnosis usually involves the isolation and identification of the infecting organism in the laboratory. The usual laboratory procedure for clinical specimens involves microscopic examination for the presence of acid-fast bacilli (AFB), isolation of the organism by culture, and identification and drug susceptibility testing of the recovered organism.

All samples with the suspicion of TVO sent to a microbiology laboratory should be processed for direct microscopic examination and culture. Microscopy for mycobacteria has traditionally been performed by an acid-fast staining (e.g., Ziehl–Neelsen or Kinyoun staining). Ziehl–Neelsen staining is time-consuming and positivity requires the presence of at least 5×10^3 AFB/ml [49]. Both

the sensitivity and speed of the microscopic study can be improved with the introduction of fluorescent microscopy and staining with auramine phenol [50]. Whatever the case, due to a lower specificity, any sample with a positive auramine stain should be confirmed by Ziehl–Neelsen staining.

Unfortunately, in contrast to the situation in pulmonary tuberculosis, the bacilli population in extrapulmonary samples is much lower, which explains the low diagnostic yield of microscopy in spinal tuberculosis. In none of the studies published to date did the microscopic examination positivity of the vertebral or paravertebral samples exceed 36 % [12, 51].

Traditionally, solid media such as Lowenstein–Jensen have been used for the isolation of mycobacteria. As *M. tuberculosis* complex are slow-growing micro-organisms, the rescue time may be prolonged up to 3 to 8 weeks with this technique. Currently, liquid media such as Middlebrook can reduce the time required for isolation to 2 or 3 weeks. New systems that rely on non-radiometric detection of growth have been developed, such as the MB/BacT, MGIT and BACTEC 9000. Several studies have compared the performance of the different culture systems available. The BACTEC 460 system remains the fastest and most sensitive, followed by the MGIT culture systems, with the solid media systems being the slowest [49].

In the study carried out by Pertuiset et al. [12] between 1980 and 1994, the median time to culture growth was 4 weeks (range 2–12 weeks). By contrast, in a recent study from our group that included 11 patients with TVO, the rescue time of *M. tuberculosis* using Middlebrook medium (BACTEC MGIT 960) was 9.5 ± 4.4 days [52].

The final aim of any diagnostic process is to obtain the information necessary to ensure the success of treatment. Therefore, after the isolation of *M. tuberculosis*, accurate drug-susceptibility testing is an intrinsic part of the diagnostic process. The current recommendation is to study the sensitivity of any isolate of *M. tuberculosis*. This is especially important in areas where the rate of resistance to first-line anti-tuberculosis drugs is high or in patients who have previously been treated [53].

Conventional methods to study the sensitivity can take 2 or 3 weeks to perform when the starting material is a strain of *M. tuberculosis* previously isolated in culture. Therefore, the isolation, identification and sensitivity study from a sample of vertebral or paravertebral tissue can take between 6 and 8 weeks. Reducing this time means ensuring the right treatment, thereby decreasing morbidity and avoiding unnecessary toxicities.

In line with the recommendations of the Centers for Disease Control (CDC) to reduce the time to identification of *M. tuberculosis* cultures and the determination of first-line drug susceptibilities to less than 30 days, many laboratories started exploring the possibilities of molecular

biology for the diagnosis of tuberculosis [54]. During the past two decades, several molecular methods have been developed for the direct detection, identification and susceptibility testing of mycobacteria. These methods can potentially reduce the diagnostic time from weeks to days.

Several commercial systems are currently available for the rapid identification of mycobacterial species from culture isolates. These tests are based on species-specific DNA probes that hybridize with rRNA released from bacteria. For positive culture specimens performance time does not exceed 2 h. These methods are very easy to perform, and no special instrumentation is needed. AccuProbe *M. tuberculosis* complex Culture Identification Test (Gen-Probe) has been evaluated extensively in clinical practice and proven to be rapid, sensitive and specific [55–57].

Polymerase chain reaction (PCR) allows the direct amplification of a defined DNA sequence in an exponential fashion over a short span of several hours. This powerful technology has touched every aspect of medical science and practice, and it has been applied for the diagnosis of infectious, neoplastic and hereditary diseases. The rapid diagnosis of infectious diseases, especially those like tuberculosis that represent a public health concern and whose microbiological diagnosis is difficult or time consuming, has been one of the most important application fields of PCR-based methods.

Although the US Food and Drug Administration recommended that PCR should only be performed for rapid diagnosis in respiratory specimens of either AFB smear positive or negative samples, PCR-based methods have been studied extensively in patients with extrapulmonary tuberculosis [58–60].

Shad et al. assessed the usefulness of the AMPLICOR Mycobacterium tuberculosis (MTB) PCR test (Roche Diagnostic Systems) in 1,090 non-respiratory samples from patients with suspected extrapulmonary tuberculosis. When PCR test results were compared with the confirmed clinical diagnosis of TB, the sensitivity, specificity, positive predictive value and negative predictive value for the PCR were 76.4, 99.8, 92.8, and 99.2 %, respectively. PCR results were available within 6.5 h, compared with an average of 3 weeks for culture of *M. tuberculosis* [58]. More recently, Cheng et al. studied by PCR 690 clinical samples sent for culture, of which 279 were positive for *M. tuberculosis*. The diagnostic sensitivity of TB PCR was 75.9 % (85 of 112) and 81.3 % (117 of 144) in patients with culture-confirmed and clinically diagnosed tuberculosis, respectively. Using culture as the gold standard, the overall sensitivity of TB PCR was 78.3 %, and for pulmonary and extrapulmonary specimens it was 82.3 and 72.0 %, respectively [61]. Unfortunately, in these two studies, as in all others published, the number of patients with osteoarticular tuberculosis and the number of vertebral or

paravertebral tissue samples and psoas abscesses were not specified [62, 63].

In our experience, PCR-based methods can be applied successfully for the rapid diagnosis of TVO. Multiplex-PCR technology even allows the rapid differential diagnosis between tuberculous and brucellar vertebral osteomyelitis. Tuberculosis and brucellosis are granulomatous diseases caused by slow-growth microorganisms. Both have a strong tropism for the osteoarticular apparatus and they are very difficult to differentiate based on clinical, radiological and even histopathological data [52].

Until recently, molecular methods for the diagnosis of infectious diseases in general, and tuberculosis in particular, had the disadvantage of not avoiding the need for the opportune cultures, a “*sine qua non*” condition to study antimicrobial susceptibility. Currently, the possibility exists of integrating in a single test the identification and sensitivity study of some micro-organisms. Xpert MTB/RIF (GeneXpert, Cepheid) is an automated molecular test for *M. tuberculosis* identification and rifampin resistance study. This probe automates DNA extraction, amplification and detection inside a test cartridge that is never reopened, with little chance of amplicon contamination, making it accessible to any clinical laboratory [64].

Vadwai et al. evaluated Xpert MTB/RIF to test its usefulness in 547 patients with suspected extrapulmonary tuberculosis. The overall sensitivity of the Xpert assay was 81, 64 % for smear-negative cases and 96 % for smear-positive cases, with a specificity of 99.6 %. The sensitivity was found to be high (63–100 %) for the majority of specimen types except for cerebrospinal fluid (29 %). The Xpert test correctly identified 98 % of rifampin-resistant cases and 94 % of rifampin-susceptible cases [65]. These results are particularly relevant when we consider the significant reduction in the overall time to obtain results afforded by this technology. In another study by the same group, the median time to detection of tuberculosis for the Xpert test was less than 24 h, compared with 1 day for microscopy, 30 days for solid culture, and 16 days for liquid culture. The median time to detection of resistance was 20 days for the line-probe assay and 106 days (30–124) for conventional drug-susceptibility testing. Use of the MTB/RIF test reduced the median time to treatment for smear-negative tuberculosis from 56 days (39–81) to 5 days (2–8) [66].

Based on the data presented above, the algorithm shown in Fig. 1 could now be used for the diagnosis of TVO. The availability of protocols and adherence to them for the diagnosis of spinal tuberculosis enables diagnosis without delay, as well as avoiding surgical procedures in many cases and preventing functional sequelae.

In conclusion, all patients with subacute inflammatory back or neck pain showing suggestive radiological findings or high serum levels of C reactive protein should be studied

Fig. 1 Diagnostic algorithm for patients with suspected tuberculous vertebral osteomyelitis. Asterisk indicates all specimens should be examined histopathologically and microbiologically

to rule out TVO. If there is no clear evidence of tuberculosis from another location or indication for surgery, a percutaneous vertebral biopsy should be performed. When TVO is suspected, all spinal or paravertebral tissue samples should be sent simultaneously to pathology and microbiology laboratories for appropriate processing. Any sample from a patient with suspected spinal tuberculosis must be subjected to microscopy and culture. There is now broad consensus that all microbiology laboratories should ensure, either themselves or by sending the samples to a reference laboratory, the identification and basic sensitivity study of any isolated *M. tuberculosis* strain within a maximum of 30 days.

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References

- Jain AK (2010) Tuberculosis of the spine: a fresh look at an old disease. *J Bone Joint Surg Br* 92:905–913
- Ross MP, Fleming JL (1976) Vertebral body osteomyelitis. *Clin Orthop* 118:190–198
- McLain RF, Isada C (2004) Spinal tuberculosis deserves a place on the radar screen. *Clev Clin J Med* 71:537–549
- Buchelt M, Lack W, Kutschera HP et al (1993) Comparison of tuberculous and pyogenic spondylitis: an analysis of 122 cases. *Clin Orthop* 296:192–199
- Perrone C, Saba J, Behlout D et al (1994) Pyogenic and tuberculous vertebral osteomyelitis in 80 adult patients. *Clin Infect Dis* 19:746–750
- McHenry MC, Easley KA, Locker GA (2002) Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. *Clin Infect Dis* 34:1342–1350
- Garcia Solis, del Pozo J, Soto MV, Solera J (2007) Vertebral osteomyelitis: long-term disability assessment and prognostic factors. *J Infect* 54:129–134
- Colmenero JD, Jimenez-Mejias ME, Sanchez-Lora FJ et al (1997) Pyogenic, tuberculous, and brucellar vertebral osteomyelitis: a descriptive and comparative study of 219 cases. *Ann Rheum Dis* 56:709–715
- Kenyon PA, Chapman AL (2009) Tuberculous vertebral osteomyelitis: findings of a 10-year review of experience in a UK centre. *J Infect* 59:372–373
- Colmenero JD, Jiménez-Mejías ME, Reguera JM et al (2004) Tuberculous vertebral osteomyelitis in the new millennium: still a diagnostic and therapeutic challenge. *Eur J Clin Microbiol Infect Dis* 23:477–483
- Anonymus Global Tuberculosis Control VHO Report (2010) World Health Organization 2010 Geneva, Switzerland. <http://www.who.int/tb/data>
- Pertuiset E, Beaudreuil J, Lioté F et al (1999) Spinal tuberculosis in adults: a study of 103 cases in a developed country, 1980–1994. *Medicine (Baltimore)* 78:309–320
- Cotten A, Flipo RM, Drouot MH et al (1996) Spinal tuberculosis: study of clinical and radiological aspects from a series of 82 cases. *J Radiol* 77:419–426
- Nussbaum ES, Gaylan MD, Rockswold L et al (1995) Spinal tuberculosis: a diagnostic and management challenge. *J Neurosurg* 83:243–247
- Aguado JM, Herrero JA, Gavalda J, Spanish Transplantation Infection Study Group (1997) Clinical presentation and outcome of tuberculosis in kidney, liver, and heart transplant recipients in Spain. *GESITRA Transpl* 63:1278–1286
- Barnes PF, Bloch AB, Davidson PT, Snider DE Jr (1991) Tuberculosis in patients with human immunodeficiency virus infection. *N Engl J Med* 324:1644–1650
- Lou XF, Wu RH, Xu SZ, Lin XJ (2010) Spinal tuberculosis in post-liver transplantation patients: case reports. *Transpl Infect Dis* 12:132–137
- Binymin K, Cooper RG (2001) Late reactivation of spinal tuberculosis by low-dose methotrexate therapy in a patient with rheumatoid arthritis. *Rheumatology (Oxford)* 40:341–342
- Weinstein MA, Eismont FJ (2005) Infections of the spine in patients with human immunodeficiency virus. *J Bone Joint Surg Am* 87:604–609
- Alothman A, Memish ZA, Awada A et al (2001) Tuberculous spondylitis: analysis of 69 cases from Saudi Arabia. *Spine* 26:e565–e570
- Weng CY, Chi CY, Shih PJ et al (2010) Spinal tuberculosis in non-HIV-infected patients: 10 year experience of a medical center in central Taiwan. *J Microbiol Immunol Infect* 43:464–469
- Oniankitan O, Bagayogo Y, Fianyo E et al (2009) Spondylodiscitis at a hospital outpatient clinic in Lome, Togo. *Med Trop (Mars)* 69:581–582
- Meghji S, White PA, Nair SP et al (1997) Mycobacterium tuberculosis chaperonin 10 stimulates bone resorption: a potential contributory factor in Pott's disease. *J Exp Med* 186:1241–1246
- Wright KM, Friedland JS (2002) Differential regulation of chemokine secretion in tuberculous and staphylococcal osteomyelitis. *J Bone Miner Res* 17:1680–1690
- Rajasekaran S (2002) The problem of deformity in spinal tuberculosis. *Clin Orthop Relat Res* 398:85–92
- Pintado-García V (2008) Infectious spondylitis. *Enferm Infect Microbiol Clin* 26:510–517
- Signol M, Hosseini MS, Wright A et al (2006) Global incidence of multidrug-resistant tuberculosis. *J Infect Dis* 194:479–485
- Nathanson E, Nunn P, Uplekar M et al (2010) MDR tuberculosis: critical steps for prevention and control. *N Engl J Med* 363:1050–1058
- Lawn SD, Wilkinson R (2006) Extensively drug resistant tuberculosis. *BMJ* 333:559–560
- Kim CJ, Song KH, Jeon JH et al (2010) A comparative study of pyogenic and tuberculous spondylodiscitis. *Spine* 35:E1096–E1100
- Almadi J, Bajaj A, Destian S, Segall HD, Zee CHS (1993) Spinal tuberculosis. Atypical observation at MR imaging. *Radiology* 189:489–493
- Narlawar RS, Shah JR, Pimple MK, Patkar DP, Patankar T, Castillo M (2002) Isolated tuberculosis of posterior elements of spine: magnetic resonance imaging findings in 33 patients. *Spine* 27:275–281
- Turgut M (2001) Multifocal extensive spinal tuberculosis (Pott's disease) involving cervical, thoracic and lumbar vertebrae. *Br J Neurosurg* 15:142–146
- Lifeso RM, Weaver P, Harder EH (1985) Tuberculous spondylitis in adults. *J Bone Joint Surg Am* 67:1405–1413
- Rangaka MX, Wilkinson KA, Glynn JR et al (2011) Predictive value of interferon- γ release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* [Epub ahead of print]
- Dosanjh DP, Hinks TS, Innes JA et al (2008) Improved diagnostic evaluation of suspected tuberculosis. *Ann Intern Med* 148:325–336
- Chapman AL, Munkanta M, Wilkinson KA et al (2002) Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of *Mycobacterium tuberculosis*-specific T cells. *AIDS* 16:2285–2293
- Kim SH, Choi SJ, Kim HB, Kim NJ, Oh MD, Choe KW (2007) Diagnostic usefulness of a T-cell based assay for extrapulmonary tuberculosis. *Arch Intern Med* 167:2255–2259
- Kim SH, Song KH, Choi SJ et al (2009) Diagnostic usefulness of a T-cell-based assay for extrapulmonary tuberculosis in immunocompromised patients. *Am J Med* 122:189–195
- Park DW, Sohn JW, Kim EH et al (2007) Outcome and management of spinal tuberculosis according to the severity of disease: a retrospective study of 137 adult patients at Korean teaching hospitals. *Spine* 32:E130–E135
- Petitjean G, Fluckiger U, Schären S, Laifer G (2004) Vertebral osteomyelitis caused by non-tuberculous mycobacteria. *Clin Microbiol Infect* 10:951–953
- Diñç H, Ahmetoğlu A, Baykal S, Sari A, Sayil O, Gümele HR (2002) Image-guided percutaneous drainage of tuberculous iliopsoas and spondylodiskitic abscesses: midterm results. *Radiology* 225:353–358
- Pierot L, Boulon A (1999) Percutaneous biopsy of the thoracic and lumbar spine: transpedicular approach under fluoroscopic guidance. *AJNR Am J Neuroradiol* 20:23–25

44. Rieneck K, Hansen SE, Karle A, Gutschik E (1996) Microbiologically verified diagnosis of infectious spondylitis using CT-guided fine needle biopsy. *APMIS* 104:755–762
45. White LM, Schweitzer ME, Deely DM, Gannon F (1995) Study of osteomyelitis: utility of combined histologic and microbiologic evaluation of percutaneous biopsy samples. *Radiology* 197:840–842
46. Yaffe D, Greenberg G, Leitner J, Gipstein R, Shapiro M, Bachar GN (2003) CT-guided percutaneous biopsy of thoracic and lumbar spine: a new coaxial technique. *AJNR* 24:2111–2113
47. Michel SC, Pfirrmann CW, Boos N, Hodler J (2006) CT-guided core biopsy of subchondral bone and intervertebral space in suspected spondylodiskitis. *AJR Am J Roentgenol* 186:977–980
48. Rezanko T, Sucu HK, Akkalp A, Tunakan M, Sari A, Minoglu M, Bolat B (2008) Is it possible to start the treatment based on immediate cytologic evaluation of core needle biopsy of the spinal lesions? *Diagn Cytopathol* 36:478–484
49. Watterson SA, Drobniowski FA (2000) Modern laboratory diagnosis of mycobacterial infections. *J Clin Pathol* 53:727–732
50. Tenover FC, Crawford JT, Huebner RE et al (1993) The resurgence of tuberculosis: is your laboratory ready? *J Clin Microbiol* 31:767–770
51. Colmenero JD, Morata P, Ruiz-Mesa JD et al (2010) Multiplex real-time polymerase chain reaction: a practical approach for rapid diagnosis of tuberculous and brucellar vertebral osteomyelitis. *Spine* 35:E1392–E1396
52. Queipo-Ortuño MI, Colmenero JD, Bermudez P, Bravo MJ, Morata P (2009) Rapid differential diagnosis between extrapulmonary tuberculosis and focal complications of brucellosis using a multiplex real-time PCR assay. *PLoS ONE* 4:e4526
53. Pawar UM, Kundnani V, Agashe V, Nene A, Nene A (2009) 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* 34:E806–E810
54. Catanzaro A, Davidson BL, Fujiwara PI et al (1997) Rapid diagnostic tests for tuberculosis: what is the appropriate use? *Am J Respir Crit Care Med* 155:1804–1814
55. Goto M, Oka S, Okuzumi K, Kimura S, Shimada K (1991) Evaluation of acridinium-ester-labeled DNA probes for identification of *Mycobacterium tuberculosis* and *Mycobacterium avium*-*Mycobacterium intracellulare* complex in culture. *J Clin Microbiol* 29:2473–2476
56. Lebrun L, Espinasse F, Poveda JD, Vincent-Levy-Frebault V (1992) Evaluation of nonradioactive DNA probes for identification of mycobacteria. *J Clin Microbiol* 30:2476–2478
57. Soini H, Musser JM (2001) Molecular diagnosis of mycobacteria. *Clin Chem* 47:809–814
58. Shah S, Miller A, Mastellone A (1998) Rapid Diagnosis of tuberculosis in various biopsy and body fluid specimens by the AMPLICOR *Mycobacterium tuberculosis* polymerase chain reaction test. *Chest* 113:1190–1194
59. Kolk AH, Kox LF, van Leeuwen J, Kuijper S, Jansen HM (1998) Clinical utility of the polymerase chain reaction in the diagnosis of extrapulmonary tuberculosis. *Eur Respir J* 11:1222–1226
60. Chakravorty S, Sen MK, Tyagi JS (2005) Diagnosis of extrapulmonary tuberculosis by smear, culture, and PCR using universal sample processing technology. *J Clin Microbiol* 43:4357–4362
61. Cheng VC, Yam WC, Hung IF et al (2004) Clinical evaluation of the polymerase chain reaction for the rapid diagnosis of tuberculosis. *J Clin Pathol* 57:281–285
62. Kearns AM, Freeman R, Steward M, Magee JG (1998) A rapid polymerase chain reaction technique for detecting *Mycobacterium tuberculosis* in a variety of clinical specimens. *J Clin Pathol* 51:922–924
63. Causse M, Ruiz P, Gutiérrez-Aroca JB, Casal M (2011) Comparison of two molecular methods for rapid diagnosis of extrapulmonary tuberculosis. *J Clin Microbiol* 49:3065–3067
64. Boehme CC, Nabeta P, Hillemann D et al (2010) Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 363:1005–1015
65. Vadwai V, Boehme C, Nabeta P, Shetty A, Alland D, Rodrigues C (2011) Xpert MTB/RIF: a new pillar in diagnosis of extrapulmonary tuberculosis? *J Clin Microbiol* 49:2540–2545
66. Boehme CC, Nicol MP, Nabeta P et al (2011) Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet* 377:1495–1505