Original Article

Diagnosis of tuberculous vertebral osteomyelitis (TVO) in a developed country and literature review

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Study design: Review of medical and radiological records and literature to study the diagnosis of tuberculous vertebral osteomyelitis (TVO) and the differential diagnosis between TVO and pyogenic vertebral osteomyelitis (PVO).

Objective: To identify the correct criteria for the diagnosis.

Setting: National Spinal Injuries Centre, UK.

Methods: (1) Medical and radiological records of 10 patients diagnosed as vertebral osteomyelitis and treated elsewhere but later admitted to the NSIC were reviewed retrospectively. (2) Medical literature on vertebral osteomyelitis were reviewed.

Results: (1) *Case review:* Before the study, four of the 10 patients TVO had been diagnosed based on positive bacteriology. Of the other six, the diagnosis of PVO had been made in one based on positive blood culture of staphylococcus while in another without any positive result of bacteriology. The diagnosis had been uncertain in four because of negative results of both bacteriology and histology on both tuberculous and pyogenic infection. The author made the diagnosis of TVO in all 10 cases based on clinical manifestations and plain radiographs. Highly raised ESR with moderate rise of or normal WBC in eight cases supported TVO. Computer tomography and magnetic resonance imaging did not contribute to the differential diagnosis. Laminectomy in five patients led to some clinical improvement. The five patients without surgery deteriorated. Two of them died. (2) *Literature review:* A total of 188 articles were reviewed. The crucial role of plain radiographs in the diagnosis of TVO and the high incidence of false-negative of tuberculosis in both bacteriological and histological tests were neglected in most articles. Polymerase chain reaction (PCR) was more reliable in diagnosing tuberculosis.

Conclusion: Clinical manifestations, discrepancy between ESR and WBC, plain radiographs and PCR are keys to a correct diagnosis of TVO.

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Keywords: differential diagnosis; clinical manifestations; ESR and WBC; plain radiography; bacteriology; histology

Introduction

Tuberculous vertebral osteomyelitis (TVO) is rare in the developed world. As a result, lack of experience has caused difficulty in its diagnosis, particularly in cases with atypical manifestations.^{1–13} It is noteworthy to draw attention to the correct methods and criteria of diagnosing TVO when tuberculosis is on the increase in this part of the world and remains high in the developing world.^{14–31} Since the main difficulty lies in determining the aetiology even when the diagnosis of vertebral osteomyelitis is established, this article will focus on differential diagnosis between TVO and pyogenic

vertebral osteomyelitis (PVO), which is essential for deciding effective treatment.

Materials and methods

The study consists of two parts: case review and literature review.

Case review

Medical records, films of imaging examination of 10 consecutive patients of vertebral osteomyelitis were reviewed retrospectively. They had been treated elsewhere but later admitted to the NSIC, SMH, Aylesbury, UK in the period of 1986–1995. As the centre is

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specialised in the management of spinal cord lesions, all patients were paraplegic or tetraplegic.

Prior to this study, the diagnosis had been TVO in four patients, PVO in two and inconclusive in four. The diagnosis was re-examined and all 10 patients were diagnosed as TVO in this study. Patients from other countries with an established diagnosis of TVO were excluded.

Six patients were male and four female. Their age ranged from 19 to 69 years with a mean of 54 years.

The level of single vertebral lesion was cervical in three and thoracic in six. One patient had two lesions: T9 and L3 vertebrae. The level of neurological impairment was cervical in four, thoracic in five and lumbar in one. In one patient, myelomeningitis caused tetraplegia at cervical level while the level of vertebral lesion was T11.

Specimens for bacteriological and histological examinations were collected through computer tomography (CT)-guided needle biopsy in five, open biopsy in four and both methods in one. Only pus or granulation tissue were obtained. Culture for pyogenic bacteria was done in all 10 patients. Smear for acid-fast staining or (and) culture for mycobacteria was done in six patients.

Literature review

Medical publications on TVO and PVO from 1961 to 2000 were searched through the Medline. The search included publications on PVO in order to examine if any TVO could have been misdiagnosed as PVO as our case review has shown. Articles on PVO of direct spread and penetrating wound were excluded. Totally, 188 were found. Those that were relevant to the aetiological diagnosis were thoroughly reviewed while the rest are also listed for further reading.

Results

Case review

In all 10 patients, the initial symptom was localised or radiating pain. All progressed to paraplegia or tetraplegia. Only then the diagnosis of vertebral osteomyelitis was considered. No details about general manifestations of tuberculosis could be found in the records. One patient had classical quadrad of tuberculosis, namely: pleuritis, endocarditis, ascitis and myelomeningitis. However, these typical combined manifestations of disseminated tuberculosis were considered as separate lesions. His myelomeningitis at cervical level on magnetic resonance images (Figure 1) was initially overlooked. Most physicians and surgeons described the case as an enormous diagnostic difficulty.

Eight patients had their WBC and ESR tested on the same day during their stay at the NSIC. In six of them, WBC was normal while ESR was 2–16 times the upper normal limit. Two of them were bacteriologically confirmed tuberculosis. Of the remaining two of the eight, one had both WBC and ESR raised. His WBC was less than twice the upper limit of normal, while ESR

Figure 1 The vertebral lesion and the myelomeningitis are clearly illustrated on MRI

Table 1 Methods of imaging diagnosis used

Method	Number of patients
Plain radiography	10
Computer tomography	3
Magnetic resonance imaging	5
Myelography	1

was 12 times the upper limit of normal. In another patient whose WBC and ESR were normal, the tests were performed after he had improved after long bedrest and a regimen of antituberculous drugs. Three patients had C-reactive protein tested. It was elevated from 50% to 16 times the upper normal limit while the WBC was always normal. One hospital gave the results of WBC and another ESR. None of the referral hospitals gave both results.

Table 1 presents the methods of imaging diagnosis used. Plain radiographs of all 10 patients demonstrated combination of low and high density of the affected vertebrae characteristic of TVO (Figure 2). In one patient the lesion was stabilised after a long course of treatment, high density prevailed and the affected vertebrae were solidly fused (Figure 3). Paravertebral shadow was seen in two patients (Figure 4). In one patient with cervical lesion a typical aneurysmal syndrome (Figure 5) was demonstrated. In none of the patients, CT, magnetic resonance imaging (MRI) and myelography alone help differentiate between TVO and PVO, although they gave a better understanding of the extent of the lesion and anatomical relation with neighbouring structures.

In six patients, repeated flexion–extension radiographs were taken to examine the mobility of the spine when the lesion was still active (Figure 2).

Before this study, the diagnosis of TVO was made in four cases based either on positive acid-fast bacilli or culture of microbacteria. In all other six cases where such results were not positive, TVO was not considered

Figure 2 Combination of low and high density is clearly illustrated

Figure 3 High density prevails when the lesion is stable or cured

and PVO remained the main suspect. In one case, PVO was diagnosed even though the result of bacteriological test of pyogenic bacteria was negative. The diagnosis of PVO in this case was simply based on the assumption that tuberculosis was rare in a developed country. In one patient with pressure sore, *Staphylococcus aureus* was positive in blood culture. The previous diagnosis of TVO based on caseous material seen at exploration of the spine was turned down and PVO was thought to be established. The author diagnosed TVO in all 10 cases

Figure 4 Large paravertebral shadow is common in TVO

Figure 5 A rare feature of aneurysmal syndrome

Table 2 Summary of findings according to aetiological diagnosis before this study

Diagnosis	TVO	PVO	Uncertain
Total of patients	4	2	4
General clinical manifestations of TB	No description	No description	One typical quadrad recorded but not recognised as tuberculosis until this study. No description of the other three
Chest radiograph	No TB in all	No TB in all	Pleuritis as part of multiple serositis but was not recognised as tuberculosis in one patient. No TB in the other three
Elevation of ESR > elevation of WBC tested on the same day	Tested in all. Three affirmative, one negative	Tested in all, both affirmative	Tested in two on the same day, both affirmative. The other two were tested but not on the same day
Plain radiograph of the spine	Combination of high and low density in all	Combination of high and low density in all	Combination of high and low density in all
Histology of material from needle biopsy or (and) open biopsy	All had this procedure but no tuberculosis was found	All had this procedure. No tuberculosis was found although in one case caseous material was seen during exploration of the affected spine	All had this procedure but no tuberculosis was found
AFB or microbacteria of material from biopsy	All four positive	Not done	The tests were performed in all cases but the results were negative
Staphylococcus of blood culture, pressure sore or biospsy material	One positive, three negative	One positive and one negative	All negative

Table 3 Method of treatment

Intervention	Anti TB drug	Total
Laminectomy	Yes	1
Laminectomy	No	1
Laminectomy + internal fixation	Yes	1
Laminectomy + anterior debridement + bone grafting	Yes	1
Laminectomy + internal fixation	No	1
Skull traction	Yes	1
No surgery, no skull traction	Yes	4

based on clinical manifestations, discrepancy in elevation between WBC and ESR and plain radiographs even if the bacteriological tests on AFB or (and) microbacteria were negative or *S. aureus* was positive in culture of blood or (and) other specimens. The findings of the methods used for diagnosis before the study are summarised in Table 2. It can be seen that the diagnosis of TVO was made on positive acid-fast bacteria or culture of microbacteria (letters in bold) alone despite all patients presented with combination of high and low density on plain radiographs (letters in bold) and most patients showed discrepancy in elevation between WBC and ESR (letters in bold).

Table 3 summarises the method and outcome of treatment. The length of follow-up from onset of paralysis to date last seen was 6–128 months with a mean of 25 months. All five patients who had surgery improved both neurologically and systematically. All five patients who did not have surgery deteriorated

despite the use of antituberculous drugs. Although four of them had remissions, two died later. The clinical cause of death was aggravation of tuberculosis in one patient while liver failure as a result of combination of both antituberculous drugs and alcohol in the other. In the latter case, TVO was confirmed macroscopically (caseous material) at post mortem while in the former it was not done.

The first case of the two deaths merits further description. A female of 58 years of age complained of back pain and weakness in her legs. Radiographs of the spine demonstrated collapse of T10 vertebra. The empirical diagnosis of tuberculosis of the spine was made and antituberculous drugs were commenced. Surgery was advised but refused by the patient. The patient became completely paralysed and pressure sores developed. The blood culture revealed *S. aureus* while open biopsy of the bone lesion was negative. Based on these results, the original diagnosis of TVO was turned down and antituberculous drugs were discontinued while antibiotics against pyogenic infection started. The condition deteriorated and the patient died 10 years after the onset of paraplegia.

Literature review

Publications of the Hong Kong team headed by Dr Hodgson and those of the Medical Research Council Working Party on Tuberculosis of the Spine were recognised worldwide as the authoritative view about the diagnosis and treatment of tuberculosis of the spine.^{32–56} XZ Fang had long worked as a member of the Hong Kong team before returning to mainland

China. He introduced its principles and anterior surgery to the mainland. His work could be seen as part of the Hong Kong Team because he shared its view in all respects.⁵⁷

Other papers published in the last 20 years on TVO and PVO indicate the following:

1. The worldwide increase of vertebral osteomyelitis and awareness of the condition was reflected in the dramatic increase of number of publications on the subject in the last two decades of last century (Table 4). From the less developed world, the majority of publications were on TVO while from the developed world the numbers of publications on both subjects were almost equal (Table 5).
2. The chief initial complaint was pain in almost all cases of all reports.
3. The simple description of general manifestations and clinical course or lack of it did not allow confident distinction between TVO and PVO. However, almost all reports recorded an insidious course whether the patient was diagnosed as TVO or PVO. The more time went on of the last century, the more the diagnosis was based on technologies. Few articles attached importance of clinical features to correctly diagnosing TVO except publications on general medicine. The Oxford Textbook of Medicine has made clear that clinical circumstances are decisive.²⁴ Negative laboratory tests of *Microbacteria tuberculosis* should not rule out clinically suspected tuberculosis because microbacteria can be easily overgrown by other fast growing bacteria.^{24,58}
4. In many articles both records of ESR (or CRP) and blood WBC before treatment could be found. It was not clear if they were done on the same day. The ESR

(or CRP) was raised much more frequently and in a much larger scale than WBC.^{1,59-92} These patients were diagnosed PVO. Only one of the authors mentioned that such discrepancy was characteristic of TVO instead of PVO.⁸⁹ Carragee *et al*⁹³ used ESR as a measurement of recovery of PVO without giving details about WBC for comparison and plain radiographs to determine if the diagnosis was correct in the first place.

5. Dr Hodgson's described the X-ray appearances of TVO in general terms as combination of and balance between low and high density of the affected bones.⁴¹ After that, no articles reiterated the importance of this history-making general description. All authors preferred specific description such as erosion, destruction, sclerosis, narrowing of disc space, etc. Very few articles described the role of plain radiographs as basic or crucial in the diagnosis of TVO.^{8,94-96} Some of the published radiographs presented with a combination of low- and high-density characteristic of TVO but they were diagnosed as PVO.^{32,66,69,71-72,81,97,98} There was a tendency to go to CT, MRI straight away without presenting and discussing the plain radiographs in the first place.⁹⁹⁻¹⁰⁷
6. In the 1960s and 1970s, bone scanning was used in addition to radiography to diagnose vertebral osteomyelitis,^{66,72,104,108,109} while some authors went directly to biopsy without scanning.¹¹⁰⁻¹¹³ In the 1980s it was, to a large extent, replaced by CT, which is nowadays used frequently to guide needle biopsy.¹¹⁵⁻¹²⁴ However, bone scanning remained in use throughout 1980s and 1990s.^{9,62,64,67,69,114} Kattapuram used X-ray attenuation to study the appearance of PVO but such method was not extended to the differential diagnosis between TVO and PVO.¹²⁴ Since the late 1980s, there has been an explosion of using MRI.^{5,7,9-14,18,19,21-23,25-29,125-185} Only two papers gave description of MRI features that could differentiate TVO and PVO.^{150,151} One described them as hypointensive signal or combination of hypo- and hyperintensive signals on T1W images in TVO while only hypotensive signals in T2W images. In T2W images, both TVO and PVO show hypertensive signals.¹⁵⁰ Another report considered heterogenous intensity and rim enhancement as signs favouring TVO.¹⁵¹
7. Almost in all articles written by surgeons and radiologists, the diagnosis of TVO was based on positive results of smear for acid-fast bacteria or culture for *M. tuberculosis*. If the results were negative, TVO was ruled out and PVO was diagnosed regardless of whether there were positive results of culture of pyogenic bacteria or not. On the other hand, physicians, bacteriologists and pathologists realised that bacteriology and histology could fail to disclose the diagnosis.^{3,24,58}
8. Polymerase chain reaction (PCR) came into use to establish the diagnosis of tuberculosis in the late 1980s.^{24,25,29,140,186-188} In two reported cases the

Table 4 Number of publications on TVO and PVO since 1980

Year	Number
1980-1989	28
1990-1999	106
2000	21
Total	155

Table 5 Number of papers according to subject since 1980

Subject	Number of publications		
	Developed world	Less developed world	Total
TVO	51	45	96
PVO	59	6	61
Both	25	2	27
Total	135	53	188

initial clinical diagnosis was PVO because nontuberculous pathogen was positive in culture of urine in one and of blood in the other.^{25,140} The diagnosis was later reversed because tuberculous vertebral osteomyelitis was confirmed by PCR of tissues collected from surgery and autopsy, respectively.

9. Francis *et al*¹²³ gave details regarding which part of the lesion, the necrotic bone (sequestrum), the neighbouring bone, the granulation or the abscess wall was taken for biopsy and histological examination. In most papers, the specimen collected was described in general term as bone or tissue.

Discussion

The case review and literature review show that diagnosis of PVO was mainly based on negative tests on *M. tuberculosis* without considering the extremely high false-negative results.²⁴ By doing so, there could be a high risk of misdiagnosing TVO as PVO. With tuberculosis on the increase in recent years in the developed world, time has arrived to re-examine this attitude.

The difficulty in diagnosis in this series was caused by the following factors:

Clinical manifestations

Familiarity with clinical manifestations of tuberculosis is essential in suspecting and diagnosing TVO. Unfamiliarity was reflected in lack of such details in the medical records. That the textbook disseminated quadrad of tuberculosis in this series was initially overlooked could not be a better example. This is, to a large extent, due to reduced training on the topic. As a result, possible presentations of tuberculosis have been forgotten. This has led to delays in or complete failure of diagnosis, particularly disseminated (miliary) tuberculosis.³

The chief complaint of almost all patients was localised pain in the back or neck, or radiating pain. Careful observation and collection of medical history could have brought to attention to different pattern of pain between PVO and TVO. The progress of pain in tuberculosis is insidious and become severe in later stages. In PVO the pain is usually severe in the early stage of the disease due to rapid rise of pressure within the disc space.

Laboratory tests

ESR is a parameter much more sensitive for tuberculosis than pyogenic infection. In pyogenic infection, leucocytosis is in parallel with raised ESR while in tuberculosis the highly raised ESR is in contrast with a normal or mild to moderate leucocytosis unless there is a secondary infection. ESR became normal or near normal when the lesion is stabilised but not necessarily cured. This was clearly demonstrated in the case review. The discrepancy between WBC and ESR highly suggests tuberculosis while makes pyogenic infection unlikely.

The fact that cases with such discrepancy reported in the literature were diagnosed as PVO raises the serious question if the diagnosis was correct. It is of particular concern that the diagnosis was incorrectly made on negative bacteriological results of *M. tuberculosis* without resorting to Hodgson's classical description of X-ray appearances at all. The relation between WBC and ESR, preferably done on the same day, is a *must* in the differential diagnosis between tuberculosis and pyogenic infection and referring hospitals *must* give results of both tests so that the admitting hospital can judge the correctness of diagnosis and monitor the progress of the lesion.

Radiographic appearances

The criteria for diagnosing TVO with plain radiographs were well established by Dr Hodgson.⁷⁴ They can be summarised as combination of low density and high density of the affected vertebra or vertebrae. Low density indicates destruction while high repair. A solid bone block usually means cure.

It seems difficult to understand why such a general description has more specific value in differential diagnosis between TVO and PVO than specific descriptions such as erosion, destruction, sclerosis, narrowing of disc space, etc. It is necessary to be familiar with the behaviour of *M. tuberculosis* in order to understand this extremely important point.

Mycobacteria are slow-growing. They multiply only in specially designed media for at least 4 weeks in laboratory conditions or when the human body is weakened for a considerable length of time. The slow growth allows the human body sufficient time to build up its immune system to combat the bacteria. However, the bacteria are very resilient and difficult to eliminate. Once the immune system becomes weak again, the bacteria hit back. These two characteristics form a cycle of slowly and constantly interchangeable destruction and repair. This determines the combination of low and high density on plain radiographs that pyogenic vertebral osteomyelites fail to demonstrate. Such combination must be interpreted in dynamics of clinical course of the disease. In early active cases the destructive (lytic) changes prevail. It differs from pictures of PVO in which sclerotic changes are prominent from its early stage and throughout. This is particularly true when the pathogen is coagulase-positive staphylococcus, the pathogen behind most haematogenic PVOs. In TVO sclerotic changes prevail only in the stage of stabilisation leading to cure (Figure 3). Similar features in long bone osteomyelitis are familiar to radiologists and orthopaedic surgeons. The same knowledge does not seem to have been fully transferred to the aetiological diagnosis of vertebral osteomyelitis. Such combination was seen in almost 100% of patients of TVO. This makes it the most reliable criterion of diagnosing TVO of all methods, while imaging high technologies, bacteriology and histology are either unable to differentiate anything or have false-negative results as high as 78%.²⁴

The fact that paravertebral shadows (antevertebral in cervical lesions) are much larger in TVO than PVO is well recognised. It is because the staphylococcal infection tends to localise with a thick wall containing the abscess while the tuberculous cold abscess tends to spread out.

There is no such thing as stable spine in TVO without consolidation. When there is consolidation the stability is eminent and there is no need for flexion–extension radiographs. Therefore, the practice of checking mobility and stability of the affected vertebrae in spinal injury by flexion–extension radiographs is not advisable for TVO because it could further destabilise the lesion when it is still active.

The role of MRI in early diagnosis of a vertebral or disc lesion and assessing the extent of the lesion and its relation with neighbouring structures is indisputable. However, only one gave some clues how to differentiate TVO from PVO. No further report of similar nature was found in our electronic literature search. These findings need further investigation to justify its use as a reliable criterion for differential diagnosis between TVO and PVO.

Both CT and bone scan also failed to offer any information on differentiating TVO and PVO.

Bacteriology

The myth that a condition caused by microorganisms must have bacteriological confirmation seems, only seems, to be reasonable. However, tuberculosis physicians and bacteriologists are not convinced. They know limitations of their sciences better than orthopaedic and spine surgeons and neurosurgeons. Relying on tests of more than 50% negative results is definitely unreliable. Therefore, diagnosis of TVO must be made on ground of clinical manifestations and plain radiographs when bacteriology proves negative.

Histology

CT-guided needle biopsy was commonly used to achieve a definitive diagnosis. Unfortunately, this is not always achievable. The positive results of tuberculosis of needle biopsy and open biopsy varied with technique and experience. This is still less reliable than plain radiographs using Hodgson's criteria. In this literature review, the best results (82%) were achieved by Francis *et al.*¹²³ The discrepancy in success rate is probably due to the accessibility of the lesion, the operator's technique and experience and the number of microbacteria and Langham giant cells in the specimen. Same as bacteriology, relying on tests with an average of more than 50% negative results is definitely unreliable. The cases reported by Pszolla *et al* and Dusmet *et al* clearly demonstrate the danger of misdiagnosis by relying on negative results of bacteriology and histology.^{25,139} Therefore, diagnosis of TVO has to be made on ground of clinical manifestations and plain radiographs when histology proves negative.²⁴

In the author's own practice, specimens were consistently collected from three sites during anterior radical surgery on TVO, namely: (1) the granulated abscess wall, (2) the sequestrum and (3) the seemingly normal bone in the vicinity. Surprisingly, quite often bacteriology and histology was positive only in the seemingly normal bone. Without specimen from site 3 the collection is not complete. The high rate of success of Francis *et al* was probably due to the same practice. The experience is shared by pathologists.¹⁸⁹ Looking for a Langham giant cell characteristic of mycobacterial infection in a chunk of tissue needs experience and patience. Rarity of tuberculosis in the developed world has caused secondary deterioration of detection skills. All these factors combined may have compromised the success rate of histological confirmation of TVO.

Polymerase chain reaction

This is a quick method to diagnose tuberculosis based on DNA technology. However, sometimes the results can also be false negative and culture is still necessary to confirm the diagnosis.²⁴ The high cost of the test has prevented its wide use, particularly in developing countries.

Conclusion

1. Clinical manifestations of tuberculosis, discrepancy between ESR and WBC, combination of low and high density on plain radiographs are keys to a correct diagnosis of TVO. Of these, plain radiograph is the most reliable method because it correlates perfectly with the diagnosis.
2. Bacteriology is unreliable if the results on TVO are negative because of the very high rate of false-negative results.
3. There is no sufficient evidence to support that CT and MRI can differentiate between TVO and PVO although they contribute much to early diagnosis, understanding of extent of the lesion and relation with neighbouring structures.
4. PCR is a quick and more reliable method but it is expensive and also gives false-negative results.

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