REFERENCE LIST


CHAPTER 3
MISDIAGNOSIS AND MISTREATMENT OF SPINAL TUBERCULOSIS

Causes of misdiagnosis and mistreatment of spinal tuberculosis with radiotherapy in non-endemic areas - a pitfall in diagnosis and treatment: hazards of radiotherapy on the tuberculous lesion

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ABSTRACT

This is a report of a previously undescribed misdiagnosis and subsequent mistreatment with radiation for tuberculosis of the spine. Two patients received radiotherapy on spinal lesions of suspected malignant origin. In both patients the lesions were of tuberculous origin and the lesions increased during radiotherapy. In case 2 the paraplegia did not heal.

It is not seldom that radiation therapy is provided for suspected malignant spinal lesions without histological confirmation. Literature is not available on harmful effects of radiation therapy for tuberculosis of the spine. Radiotherapy locally aggravates tuberculous spinal lesions. In case of a spinal lesion of unknown origin, tuberculosis should always be considered. Adequate biopsy for cultures and histology is mandatory. Open surgical biopsy can provide sufficient material and instant decompression.

INTRODUCTION

Radiation therapy holds a fundamental role in oncological emergencies. In responding patients, it is associated with an improved quality of life and a longer survival time. It is not seldom that radiation therapy is provided for suspected malignant spinal lesions without histological confirmation. In our institution this happens approximately 5 times annually. No data on this were found in the literature.

The distinction in imaging studies between tuberculosis (TB) and malignancies of the spine can be difficult. Throughout the years, several reports have addressed this topic. Data on the frequency of this diagnostic dilemma could not be found. Until three decades ago, reports on non-endemic tuberculous areas addressed the importance of tumours in differential diagnostics of spinal tuberculosis. This was gradually reversed to stressing the importance of TB in differential diagnostics of tumour metastasis as the incidence and importance of TB in many countries diminished.
In non-endemic areas for TB, spinal tuberculosis or Pott’s disease is a forgotten diagnosis. We report 2 cases with a previously undescribed misdiagnosis and subsequent mistreatment with radiotherapy for tuberculosis of the spine. In doing so, we hope to promote awareness for tuberculosis in non-endemic areas.

ILLUSTRATIVE CASES

**Case 1**
A 26-year-old man, a refugee living in the Netherlands for 3 years, came to our institution with a 3-month history of backache. He was HIV-negative and had been medically treated for 2 years for chronic myeloid leukaemia (CML). Normal radiographs revealed no abnormalities in the painful thoracic area; 2 fused vertebrae were seen in the lumbar spine: L1-2. Chest X-ray was normal. Laboratory work-up showed elevated leucocytes 12.6 $10^9$/L (4.0-10.0) and low haemoglobin 7.3 mmol/L (8.7-11.2), C-reactive protein (CRP) was only slightly elevated at 21 (0-10), and raised erythrocyte sedimentation rate (ESR) was 80 mm (<10). Mantoux test was not performed.

Magnetic Resonance Imaging (MRI) without contrast enhancement showed a paravertebral mass left of Th8 (Figure 1a). Radiological differential diagnosis included chloroma, metastasis, and abscess of bacterial or tuberculous origin. A Computer Tomography (CT) guided fine-needle aspiration was performed since the lesion had a close relationship with the pleura and the intervertebral foramen. The risk of creating a pneumothorax with a trochar biopsy was considered too high. Only cytologic examination could be performed and no histology. The specimen of 20 ml. was poor in cells, and showed only erythrocytes and some atypical myeloid cells with enlarged polymorphic nuclei, some lymphoid cells, fibroblasts and muscle cells. Tuberculosis was considered but could not be confirmed by Polymerase Chain Reaction (PCR) and acid-fast bacilli stain, as both were negative. Cultures for TB were not performed.

Diagnosis chloroma was suspected, based on the known association with CML, and radiation therapy started. A total dose of 16 Gray was given. A second MRI, two months after the first, showed an increase of the paravertebral mass from Th8 to Th10 and a new partial destruction of the arches of Th8 and Th9 (Figure 1b).

The backache had worsened. After the second MRI a surgical biopsy was performed of the paravertebral mass. Histologic examination showed caseous granulomatous necrotic tissue, suspect for tuberculosis. Tuberculosis therapy was started according to protocol: 2 months of pyrazinamid and ethambutol and 6 months of isoniazid and rifampin. The PCR and acid-fast bacilli stain of the specimen again were negative, but the culture became positive after four weeks with a fully sensitive *Mycobacterium tuberculosis*. Treatment result regarding tuberculosis was good, the painful lesion subsided and there was no relapse.

**Case 2**
A 55-year-old man came to another hospital with signs of paraplegia. He had loss of motor function of the legs, and loss of sphincter control of bladder and rectum. He had been well up until 1 month earlier, when he started suffering from low backache and mild paresthesia of both legs. On admission he had an incomplete motor and sensory paraplegia (Frankel grade C), at level Th11. Routine biochemical and haematological investigations were normal, CRP was 14, and ESR was mildly elevated at 40 mm. His chest X-ray showed calcified hilar lymph nodes. Previous radiographs revealed a fusion of C4-5 of the cervical spine and there were signs of post-infectious
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calcified arthritis in both hips, the left knee joint and both ankles. Overview of the abdomen showed multiple mesenteric calcifications. Radiographs of the thoracic spine at first presentation showed (in retrospect) a paravertebral mass at the lower thoracic vertebrae (Figure 2). MRI revealed a destructive lesion with abscess formation and spinal cord compression at Th11-Th12 with disc destruction (Figures 3a and 3b). CT-guided trochar biopsy of the lesion did not reveal a diagnosis due to an insufficient amount of mainly necrotic tissue. There were no further attempts to obtain material from the lesion. The primary care physician made a diagnosis of metastasis. Tuberculosis was never considered in differential diagnostics. The neurological deficit had already been present for some weeks. The treating physicians did not expect an improvement of neurological function by surgical means, and the aim of treatment was to prevent further deterioration with radiotherapy. During the course of radiation, because of clinical worsening and progression of the paresis, corticosteroids in high doses were added. Laboratory parameters had also worsened: ESR was raised to 120 mm, Hb had decreased to 5.7, and he had developed leucopenia at 1.5.

Six weeks later he was critically ill; a sputum sample revealed acid-fast bacilli. The next day, with the diagnosis of disseminated tuberculosis, he was transferred to our tuberculosis unit. Tuberculosis treatment was started: 2 months of pyrazinamid and ethambutol and 6 months of isoniazid and rifampin. MRI scan at that time revealed progression of the lesion and abscess formation on both sides of the spine (figure 3c). The tuberculosis was cured, but regrettably there was no reversal of the neurological deficit.

**DISCUSSION**

Two patients are reported with a previously undescribed misdiagnosis and subsequent mistreatment with radiotherapy for tuberculosis of the spine. During radiotherapy both lesions increased, in case 2 the paraplegia did not heal. One of the reasons for misdiagnosis was probably the low incidence of tuberculosis in the Netherlands, as it is one of the countries approaching the elimination phase of tuberculosis, and so spinal tuberculosis is a forgotten diagnosis. At present, approximately 40
calcified arthritis in both hips, the left knee joint and both ankles. Overview of the abdomen showed multiple mesenteric calcifications. Radiographs of the thoracic spine at first presentation showed (in retrospection) a paravertebral mass at the lower thoracic vertebrae (Figure 2). MRI revealed a destructive lesion with abscess formation and spinal cord compression at Th11-Th12 with disc destruction (Figures 3a and 3b). CT-guided trochar biopsy of the lesion did not reveal a diagnosis due to an insufficient amount of mainly necrotic tissue. There were no further attempts to obtain material from the lesion. The primary care physician made a diagnosis of metastasis. Tuberculosis was never considered in differential diagnostics. The neurological deficit had already been present for some weeks. The treating physicians did not expect an improvement of neurological function by surgical means, and the aim of treatment was to prevent further deterioration with radiotherapy. During the course of radiation, because of clinical worsening and progression of the paresis, corticosteroids in high doses were added. Laboratory parameters had also worsened: ESR was raised to 120 mm, Hb had decreased to 5.7, and he had developed leucopenia at 1.5.

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new patients are seen nationwide in the Netherlands (population 16,000,000)\textsuperscript{11}. With decreasing incidence, clinical expertise declines too\textsuperscript{11}. This results in a lack of experience in recognising tuberculosis in imaging studies and a low index of suspicion. Average delay in the Netherlands for the year 2000 in diagnosis for spinal TB was 29 weeks\textsuperscript{11}.

The work-up of patients with spinal lesions of unknown origin should include the search for TB. It starts with a thorough history-taking. Anamn
    
    medical history can be very helpful in diagnosing TB. The risk of developing tuberculosis increases manifold if a patient belongs to a risk factor group that includes inmates and staff of correctional facilities, residents and staff of nursing homes, homeless people, health care workers, prostitutes, substance abusers, immigrants from endemic areas, immunocompromised people, and people with a past history of TB\textsuperscript{12}. In the patients presented here, solely from an anamnestic point of view, TB should have been suspected and adequate actions taken. Patient 1 was an immigrant from an endemic area who used immunosuppressive medication. History in case 2 revealed coxitis tuberculosa at the age of 7. This was just before the start of the tuberculostatic era, and he was never treated subsequently with tuberculostatic drugs.

Immunosuppression is a well-known risk factor for TB. In a series of bone marrow transplant recipients, 5.5% developed tuberculosis, mainly via disruption of host reconstitution of immune defenses\textsuperscript{13}. Therefore we agree with Karnak et al. that it seems highly likely that radiation therapy will locally aggravate the destructive tuberculous process by diminishing local immune responses\textsuperscript{14}. In both patients the radiotherapy was finished before the chemotherapy started. The local response to the tuberculosis drugs was good in both cases and did not show diminished healing.

Work-up often comprises a Mantoux test. In neither of the two cases presented here was a Mantoux test performed. It is questionable whether the test would have aided in diagnosis. Since patient 1 was an immigrant from an endemic country, and patient 2 was born in a period when TB was very common, both would probably have had a positive test; this would however not prove active disease. A negative test in case 1 would not have been helpful either, because of the possibility of a false-negative tuberculin reaction in immunosuppressive patients\textsuperscript{15}.

Chest X-ray will only be positive in 15% of people with bone and joint tuberculosis\textsuperscript{16}. Normal radiographs may not be sufficient for diagnosis of spinal TB, especially in non-endemic countries. However, in both patients presented here, radiographs showed fused vertebrae at other levels, most likely to be signs of previous spinal TB. In case 2 radiographs showed a paravertebral mass at the lower thoracic vertebrae, a sign of the infectious nature of the lesion (Figure 3). The characteristic radiological image of an active tuberculobous spondylitis is that of affected vertebral bodies on both sides of a destroyed disc. Vertebral collapse and abscess formation are important radiological clues as well\textsuperscript{17}. CT and MRI can accurately assess formation and extent of abscesses, as well as narrowing of the spinal canal. A septic spondylitis usually gives instant symptoms, while a tuberculous lesion has a much more insidious onset. Because of the relatively slow onset of TB, large abscesses can develop with huge bony destruction before clinical symptoms are prevalent\textsuperscript{18}. MRI scans showed in both cases the typical signs of an abscess, hardly compatible with malignancy. Tumour expansion can give a paravertebral mass like the one shown in Figure 3, but without abscess formation\textsuperscript{19}. In both cases presented here, the infectious nature of the disease should have been identified based on imaging studies. In case 1, based on MRI findings infection was considered, even tuberculosis, however this diagnosis was discarded because of the negative results of the PCR and acid stain.

Preferably material from the lesion should be acquired for PCR, acid stain, cultures and histology. In both cases, cultures for TB should have been performed. The only definite proof for a skeletal lesion is a positive culture of material from the lesion, but even then only 47-81% positive results can be expected\textsuperscript{16-19}. A CT-guided biopsy is a minimally invasive way to provide tissue from a lesion for further analysis. It is essential to harvest sufficient material for histology and cultures. It is mandatory to specifically ask the pathologist to consider tuberculosis. In both cases presented here, diagnosis was not established on biopsy material, probably due to insufficient amounts. Surgical biopsy should have been performed. In case 1 the fine needle aspiration revealed fluid; this should have been suspected as a product of infection in the absence of central massive tumour necrosis. In case 2, the treating physicians were convinced of the metastasis diagnosis, in spite of the previous history of tuberculosis and the abscess formation on MRI (2 clues for the diagnosis of TB). If metastasis had been the correct diagnosis, radiation therapy could have been indicated. Since the paraplegia had already been present for some weeks, the treating physicians did not expect a recovery with either surgery or radiotherapy. Aim of radiation was prevention of further deterioration. Surgery should have been performed. There is of course no certainty as to what the effect on the neurological status would have been. In this patient the local lesion progressed, so there was virtually no chance of neurological recovery; surgery however would have provided instant decompression as well as sufficient biopsy material.

Laboratory parameters in general are not very helpful in tuberculosis. ESR can be elevated and so can CRP. In both cases ESR values were elevated, compatible with both malignancy and infection. CRP values were hardly elevated in both patients, making the possibility of an infectious cause for the lesions less likely. A high CRP would certainly have raised the suspicion of an infection. Tuberculous infection may very well be accompanied by a low CRP.

In neither case presented here was there an histological confirmation of the diagnosis. In our institute, about 5 patients receive radiotherapy without histologic
new patients are seen nationwide in the Netherlands (population 16,000,000)\textsuperscript{11}. With decreasing incidence, clinical expertise declines too\textsuperscript{11}. This results in a lack of experience in recognising tuberculosis in imaging studies and a low index of suspicion. Average delay in the Netherlands for the year 2000 in diagnosis for spinal TB was 29 weeks\textsuperscript{11}. The work-up of patients with spinal lesions of unknown origin should include the search for TB. It starts with a thorough history-taking. Anamnesis and past medical history can be very helpful in diagnosing TB. The risk of developing tuberculosis increases manifold if a patient belongs to a risk factor group that includes inmates and staff of correctional facilities, residents and staff of nursing homes, homeless people, health care workers, prostitutes, substance abusers, immigrants from endemic areas, immunocompromised people, and people with a past history of TB\textsuperscript{12}. In the patients presented here, solely from an anamnestic point of view, TB should have been suspected and adequate actions taken. Patient 1 was an immigrant from an endemic area who used immunosuppressive medication. History in case 2 revealed coxitis tuberculosa at the age of 7. This was just before the start of the tuberculostatic era, and he was never treated subsequently with tuberculostatic drugs.

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In neither case presented here was there an histological confirmation of the diagnosis. In our institute, about 5 patients receive radiotherapy without histologic
spinal tuberculosis was recently reported. People should raise the suspicion of tuberculosis reactivation, especially in endemic areas of tuberculosis. Pulmonary infections encountered in carcinoma patients or aged individuals may play a role in the reactivation process. In difficult cases, a double diagnosis should be considered too. TB has been reported to complicate malignancy. In patients following spinal radiation treatment, spondylodiscitis is not a very uncommon diagnosis, and such therapy can be locally destructive for this condition. This also applies to tuberculous spondylitis. In case 2, no neurological recovery was substantiated, while in most cases active tuberculosis with paraplegia can be treated successfully by conservative or surgical means.

Furthermore, if the suspicion of tuberculosis is high or the patient is seriously ill with a disorder that is thought to possibly be tuberculosis, tuberculostatic therapy should be initiated promptly—often even before smear results are known and usually before mycobacterial culture results have been obtained. If the diagnosis is confirmed by isolation of M. tuberculosis or a positive PCR test, treatment can be continued. When the initial acid-fast bacilli smears and cultures are negative, a diagnosis other than tuberculosis should be considered and appropriate evaluations undertaken. If there is a clinical or radiographic response within 2 months of initiation of therapy, like surgery. It is not good practice to start a potentially harmful treatment in case of failed biopsy. Especially for patients without neurological deficit, secondary trochar biopsy, or even open biopsy, is indicated. In patients following spinal radiation treatment, spondylodiscitis is not a very uncommon diagnosis, and such therapy can be locally destructive for this condition. This also applies to tuberculous spondylitis. In case 2, no neurological recovery was substantiated, while in most cases active tuberculosis with paraplegia can be treated successfully by conservative or surgical means.

In difficult cases, a double diagnosis should be considered too. TB has been reported to complicate malignancy. Deterioration of immunity due to the tumour itself, chemotherapeutics or radiotherapy may play a role in the reactivation of tuberculosis. Pulmonary infections encountered in carcinoma patients or aged people should raise the suspicion of tuberculosis reactivation, especially in endemic countries. A patient with spinal cord compression due to multiple myeloma and spinal tuberculosis was recently reported.

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proof of metastasis each year. These are patients with an acute onset of neurological symptoms. In our hospital we try to start therapy within 24 hours of onset of symptoms. This can be either radiotherapy or surgical decompression followed by radiotherapy. Recent evidence suggests that surgical decompression, stabilisation and subsequent radiation therapy is superior to radiation therapy alone: patients treated with additional surgery retained the ability to walk longer and regained the ability to walk more often than patients without surgical decompression. In all patients with suspected metastasis of unknown origin, screening is done for the most obvious primary lesions: prostate specific antigen, radiographs of breast and chest. If this reveals a primary lesion, radiation therapy is started. If not, histology is mandatory. Radiation therapy should only be applied in the presence of a clear histologic diagnosis, ruling out tuberculosis. Radiation is an aggressive and potentially harmful therapy, like surgery. It is not good practice to start a potentially harmful treatment in case of failed biopsy. Especially for patients without neurological deficit, secondary trochar biopsy, or even open biopsy, is indicated. In patients following spinal radiation treatment, spondylodiscitis is not a very uncommon diagnosis, and such therapy can be locally destructive for this condition. This also applies to tuberculous spondylitis. In case 2, no neurological recovery was substantiated, while in most cases active tuberculosis with paraplegia can be treated successfully by conservative or surgical means.

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In difficult cases, a double diagnosis should be considered too. TB has been reported to complicate malignancy. Deterioration of immunity due to the tumour itself, chemotherapeutics or radiotherapy may play a role in the reactivation of tuberculosis. Pulmonary infections encountered in carcinoma patients or aged people should raise the suspicion of tuberculosis reactivation, especially in endemic countries. A patient with spinal cord compression due to multiple myeloma and spinal tuberculosis was recently reported.

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CHAPTER 4
CHEMOTHERAPEUTIC TREATMENT FOR SPINAL TUBERCULOSIS

Chemotherapeutic treatment for spinal tuberculosis
Van Loenhout-Rooyackers JH, Verbeek ALM, Jutte PC
Int J Tuberc Lung Dis 2002;6(3):259-65

ABSTRACT

This literature review was done to evaluate whether 6 months of chemotherapy for patients with spinal tuberculosis prevents relapse as effectively as more than 6 months of chemotherapy.

Medline search was performed including references, from January 1978 to November 2000. Inclusion criteria for publications: diagnosis of spinal tuberculosis confirmed bacteriologically and/or histologically, or probable on the basis of clinical and radiological parameters; treatment regimen (whether or not in combination with surgery) included isoniazid (ISO), rifampicin (RIF) and pyrazinamide (PYR); follow-up period after completion of treatment of 12 months or more. Exclusion criteria: patients with relapse who had previously been treated adequately for tuberculosis. Outcome parameters: Relapse rate.

Four publications were found with ISO/RIF/PYR regimens of 6 months duration and 10 publications with ISO/RIF/PYR regimens of >6 months duration. A number of patients had received ISO/RIF and ethambutol (ETH) for >9 months. In the results, no distinction was made between treatment groups. ISO/RIF/PYR for 6 months led to a relapse rate of 0% (0/56) (95%CI 0.0-6.4); follow-up after surgical intervention ranged from 6 to 108 months. ISO/RIF/ETH for ≥9 months (≥119 patients) or ISO/RIF/ETH for ≥9 months (≤71 patients) led to a relapse rate of 2% (4/218) (95% CI 0.6-5.0); follow-up after surgical intervention was 6-168 months.

It was concluded that despite the small number of studies 6 months of therapy is probably sufficient for patients with spinal tuberculosis.

INTRODUCTION

In the literature, there is no uniformity in the duration of chemotherapeutic treatment for spinal tuberculosis. The American Thoracic Society (ATS) recommends 6 months treatment for spinal tuberculosis and osteoarticular tuberculosis in adults, but 12 months in children, because reliable data on shorter treatment durations are lacking. The British Thoracic Society (BTS) recommends 6 months treatment,