

CLINICAL CASE OF THE MONTH

A Young Man with Back and Chest Wall Pain for Three Months

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A 23-year-old man with no significant past medical history presented to the emergency department with complaints of low back pain and bilateral, multifocal rib pain for 3 months. The patient reported several associated symptoms including fatigue, mild headache, intermittent shortness of breath, non-productive cough, decreased appetite, night sweats, and fever. He also noted mild lower extremity weakness concurrent with his back pain but denied any sensory deficits or loss of bowel or bladder function. A chest X-ray revealed a 3.3 x 2.3 cm expansile bony lesion within the right third rib anteriorly; findings were otherwise unremarkable (Figure 1). The patient was referred for further evaluation and management.

The patient denied visual changes, gait abnormalities, hemoptysis, recent weight loss, nausea, vomiting, hematochezia, melena, diarrhea, constipation, hematuria, dysuria, testicular pain, lymph node enlargement, or rash. He also denied any history of trauma to the back or ribs. He had no recent sick contacts. He reported negative human immunodeficiency virus (HIV) and purified protein derivative (PPD) skin testing within the past 2 years.

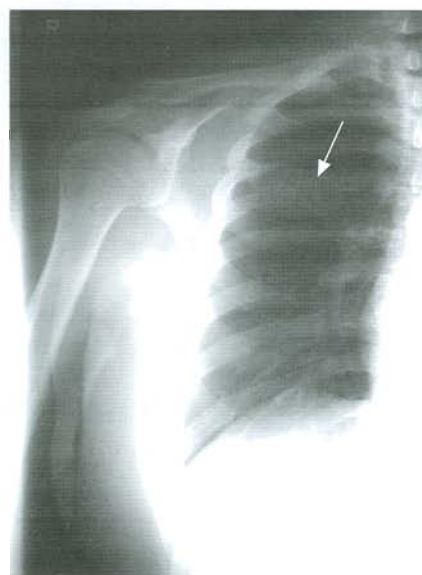


Figure 1. Tuberculous Osteomyelitis: Admit chest X-ray shows expansile osteolytic lesion of the right 3rd rib anteriorly (arrow).

TARGET AUDIENCE

The Clinical Case of the Month is intended for family physicians, general internists, medicine subspecialists, general practitioners, obstetricians-gynecologists, emergency medicine physicians, pediatricians, dermatologists, radiologists, and psychiatrists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be able to better identify and understand the pathophysiology, microbiology, clinical presentation, diagnosis, and treatment of tuberculous bone infection.

CME INFORMATION

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

DISCLOSURE

Dr. Schiro has nothing to disclose.
Mr. Travis has nothing to disclose.
Dr. Kruspe has nothing to disclose.
Dr. Nelson has nothing to disclose.
Dr. Beech has nothing to disclose.
Dr. Imsais has nothing to disclose.
Dr. Lopez discloses that he is a member of the *Journal of the LSMS* Board of Trustees and the *Journal* Editorial Board.

ORIGINAL RELEASE DATE
10/1/2005

EXPIRATION DATE
10/31/2006

Estimated time to complete this activity is 1 hour.

The patient denied any significant past medical history or past surgical history. His family history was significant for diabetes, hypertension, and an uncle who died of tuberculosis when the patient was a young child. He denied the use of any medications and had no known allergies. The patient reported consuming one to two beers on weekends and smoking approximately one cigar each month, but had discontinued the use of both approximately 2 months before presentation. He denied any illicit drug use. He was engaged and lived with his fiancée and his grandmother in New Orleans. Within the past 2 years he had traveled to the northern United States and had spent a short time living in a homeless shelter. He was unemployed at the time of presentation but reported that he had worked previously as a security guard. He denied any history of incarceration.

Vital signs at presentation included a temperature of 100.4° F, pulse of 88 beats per minute, blood pressure of 119/60 mmHg, respiratory rate of 20 breaths per minute, and an oxygen saturation of 98% on room air. The patient was in no apparent distress. He was alert, oriented, and cooperative with the interview. He had anicteric sclera, and examination of the head, eyes, ears, nose, and throat was unremarkable. A 2 to 3 cm right supraclavicular lymph node was noted. The node was minimally tender to palpation, soft, and fixed. No additional lymphadenopathy was appreciated. Tenderness over the left lower ribs and subtle bilateral gynecomastia were also noted. The patient's cardiac examination revealed no abnormalities, and his lungs were clear to auscultation bilaterally. The abdomen was soft, nontender, and nondistended; normoactive bowel sounds were appreciated. No hepatosplenomegaly and no palpable abdominal masses were noted. Rectal examination demonstrated a normal sphincter tone with a normal-sized prostate without nodularity, and stool examination was heme-negative. No scrotal masses were appreciated on genital examination. Skin, extremity, and neurological assessments revealed no abnormalities.

Serum chemistries at presentation demonstrated a sodium of 136 mmol/L (normal range, 135-146 mmol/L), potassium of 4.3 mmol/L (normal range, 3.6-5.2 mmol/L), chloride of 101 mmol/L (normal range, 96-107 mmol/L), bicarbonate of 25 mmol/L (normal range, 24-32 mmol/L), blood urea nitrogen of 8 mg/dL (normal range, 7-25 mg/dL), creatinine of 1.0 mg/dL (normal range, 0.8-1.5 mg/dL), glucose of 89 mg/dL (normal range, 65-99 mg/dL), calcium of 9.5 mg/dL (normal range, 8.4-10.3 mg/dL), magnesium of 2.3 mg/dL (normal range, 1.5-2.6 mg/dL), and phosphorus of 4.1 mg/dL (normal range, 2.5-4.7 mg/dL). Liver panel revealed a total protein of 7.7 gm/dL (normal range, 6.0-8.0 gm/dL), albumin of 3.4 gm/dL (normal range, 3.4-5.0 gm/dL), total bilirubin of 0.3 mg/dL (normal range, <1.3 mg/dL), AST of 21 U/L (normal range, <45 U/L), alkaline phosphatase of 51 U/L (normal range, 20-120 U/L), and ALT of 17 U/L (normal range, <46 U/L). The patient's

complete blood count revealed a white blood count of $8.6 \times 10^3 / \mu\text{L}$ (normal range, $4.5\text{-}11.0 \times 10^3 / \mu\text{L}$), a hemoglobin of 12.1 gm/dL (normal range, 13.5-17.5 gm/dL), a hematocrit of 37.5 % (normal range, 40-51%), a platelet count of $531 \times 10^3 / \mu\text{L}$ (normal range, $130\text{-}400 \times 10^3 / \mu\text{L}$), a mean corpuscular volume of 80 FL (normal range, 80-100 FL), and a red cell distribution width of 13.1% (normal range, 11.5-14.5%). His coagulation parameters revealed a prothrombin time of 13.4 sec (normal range, 10.0-13.0 sec), a partial thromboplastin time of 32.7 sec (normal range, 24.0-35.0 sec) and an INR of 1.2. Urinalysis was remarkable for a small amount of blood with 0-2 RBCs/hpf and a few bacteria with 0-2 WBCs/hpf. Thyroid stimulating hormone (TSH) was 2.40 uIU/mL (normal range 0.5-5.0 uIU/mL), and a prostate specific antigen (PSA) was 0.7 ng/mL (normal range <2.6 ng/mL). β -human chorionic gonadotropin (β -HCG) demonstrated a level of <5 mIU/mL (normal range <5 mIU/mL), and an alpha fetoprotein (AFP) level was 1.70 ng/mL (normal range <15 ng/mL).

A computed tomographic (CT) scan of the chest demonstrated multiple lytic osseous lesions within the chest with soft tissue and pleural extension, the largest being a 5.8 x 3.9 cm lesion involving the anterolateral portion of the left ninth rib. Other findings included diffuse lymphadenopathy and additional lytic bony lesions within the ninth thoracic vertebra (T9) and the first and second lumbar (L1 and L2) vertebrae with local destruction of the posterior bony elements and invasion into the soft tissues. Magnetic resonance imaging (MRI) of the lumbar and thoracic spines demonstrated a right paravertebral mass measuring 4 x 3 cm at the level of L2 producing a destructive lesion involving the pedicles and transverse process with resulting spinal canal stenosis (Figures 2 and 3). Reactive inflammatory changes were noted in the psoas muscle. Areas of abnormal enhancement were also seen in the L4 and L5 vertebral bodies and a lesion in the left iliac crest measured 2.3 x 1.8 cm. A bone scan revealed multiple areas of abnormal radiotracer uptake in the sternum, L1, L2, L4, and L5 vertebral bodies, T3 and T9 vertebral bodies and posterior elements, right third and eighth ribs anteriorly, left ninth rib anterolaterally, and right pubic ramus superiorly.

Routine blood cultures, fungal blood cultures, and acid-fast bacilli (AFB) blood cultures were collected and were negative during the patient's hospitalization. Rapid plasma reagin (RPR) and HIV tests were non-reactive, and a serum protein electrophoresis was unremarkable. A CT scan of the abdomen and pelvis with intravenous contrast demonstrated the previously seen lytic osseous lesions within the chest and spine; abdominal and pelvic viscera were noted to be normal in appearance. Head CT with contrast, mammogram, and testicular ultrasound were unremarkable.

A fine needle aspirate (FNA) of the patient's enlarged right supraclavicular lymph node was performed. Results obtained at the time of the procedure revealed lymphad-

enitis with abundant neutrophils. Gram stain was negative for organisms, and fungal and AFB smears were not performed because the amount of specimen was insufficient for further evaluation. Based on the finding of cervical lymphadenitis, a PPD was placed; the patient was moved to respiratory isolation, and successive sputum specimens were obtained for AFB smear and culture. AFB smears performed on the patient's sputum specimens were uniformly negative, but his PPD skin test was reported as positive (>15mm induration) within 72 hours.

A CT-guided biopsy of the soft tissue mass surrounding the lumbar bone lesion was obtained, and a FNA was taken of the L2 vertebra itself. Granulomatous inflammation was noted in both specimens, and rare acid-fast bacilli were seen within the soft tissue mass surrounding the L2 vertebra (Figures 4 and 5). A presumptive diagnosis of multifocal skeletal tuberculosis (TB) was made, and the patient was started on anti-tuberculous treatment with rifampin, isoniazid, pyrazinamide, and ethambutol. Approximately one month following discharge, cultures obtained from the patient's sputum, supraclavicular lymph node FNA, and L2 vertebral FNA and soft tissue biopsy revealed the growth of *Mycobacterium tuberculosis*, thus firmly establishing the diagnosis of multi-focal TB.

DISCUSSION

Extrapulmonary tuberculosis is not uncommon in under-developed areas of the world where TB is endemic. Indeed the World Health Organization estimates the incidence of extrapulmonary TB to be as high as 34% in some countries.¹ However, the incidence of skeletal TB is much lower, representing approximately 1-2% of all cases of TB, with most cases reported in children.² Of particular interest in this case is the finding of tuberculous osteomyelitis with rib involvement, which reportedly accounts for only 0.1% of all tuberculous infections.³ Although there has been a continued decline in the incidence of tuberculosis over the past several years, this case demonstrates that unusual presentations of the disease should not be overlooked. The remainder of this discussion will primarily address tuberculous bone infection, i.e., its presentation, diagnosis, and treatment.

PATHOPHYSIOLOGY

Mycobacteria are believed to spread to the vertebrae through hematogenous or lymphatic dissemination. The most common sites of infection are the thoracic and lum-

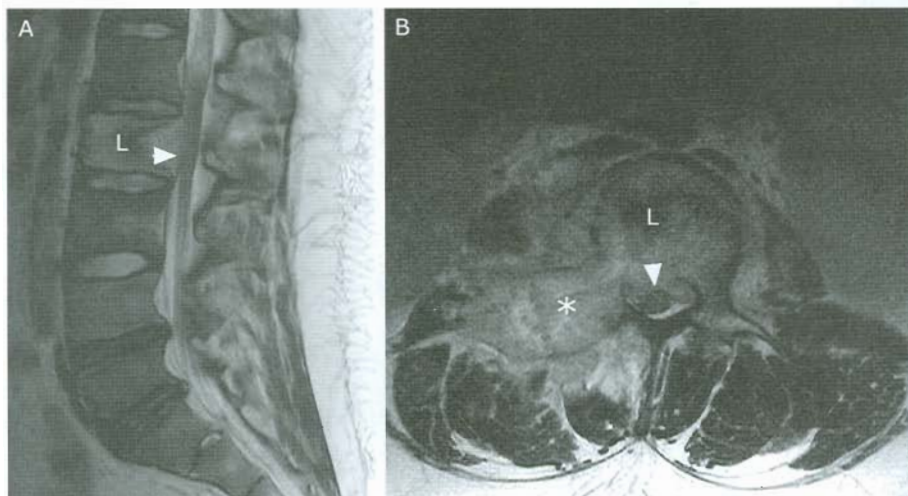


Figure 2. Tuberculous Spondylitis (Pott's Disease): T2-weighted sagittal (A) and axial (B) magnetic resonance (MR) images reveal abnormal signal of the lumbar vertebral body (L). Paravertebral abscess formation results in destruction of the right pedicle (*) and effacement of the anterior spinal cord (arrowhead).

bar spine—often referred to as Pott's Disease—with multifocal involvement occurring in only 6%.⁴ Involvement of the laminae, spinous processes, and transverse processes (posterior elements) is uncommon, occurring in 0.2% of patients in one series.⁵ Generally few bacteria are found within the bony tissue when compared to the numbers found in sputum. Subsequently, the infectious process itself does not lead to robust inflammation, but rather a slow process of bone resorption and bone formation. It is not uncommon for fusion of the vertebrae to occur with formation of paravertebral and extradural abscesses. These abscesses may lead to compression and local invasion of the dura, spinal cord, and nerve roots with resulting neurological deficits.^{6,7}

CLINICAL PRESENTATION

As with pulmonary TB, constitutional symptoms of fever, night-sweats, and weight loss are often the presenting complaints of patients with skeletal TB. Symptoms of vague back or chest wall pain are also commonly reported. In more advanced stages, point tenderness over the spinous processes can develop. With extensive destruction of the vertebral bodies, scoliotic deformities occur and symptoms of spinal cord or nerve root compression may ensue. Concurrent complaints of cough, hemoptysis, or other pulmonary symptoms often are not present as active pulmonary TB occurs in less than 50% of skeletal TB cases.² Purified protein derivative (PPD) skin testing is usually positive, but can be negative in the immunosuppressed, elderly, or those with overwhelming disseminated disease. Blood chemistries and complete blood cell counts are generally not helpful. Elevations in erythrocyte sedimentation rate and serum alkaline phosphatase (associated with bony destruction) may be noted but are non-specific.

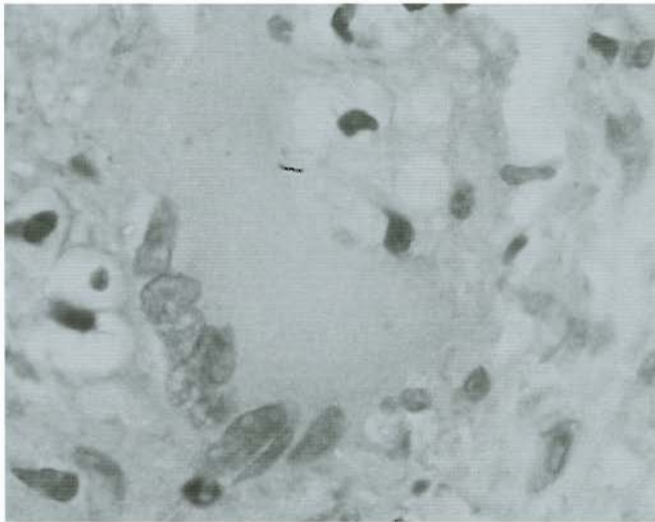


Figure 4. L2 soft tissue mass. Fite stain at 1000X magnification demonstrates a characteristic beaded acid-fast bacillus associated with a Langhans giant cell.

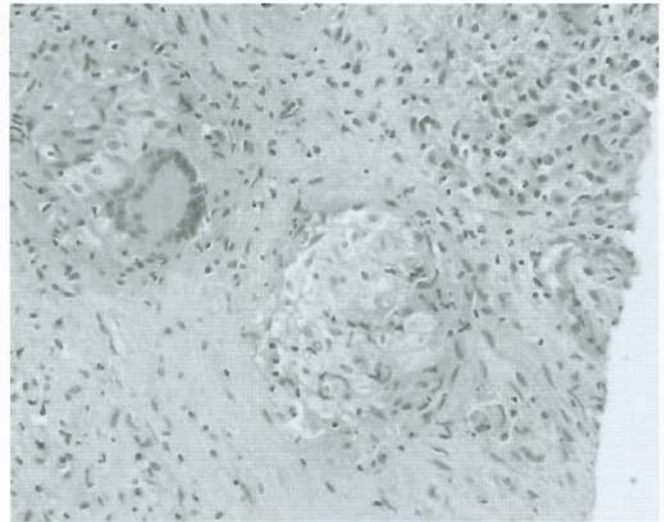


Figure 5. L2 soft tissue mass. Hematoxylin and eosin (H&E) stain at 400X magnification shows noncaseating granulomatous inflammation with nodular aggregate of macrophages (epithelioid cells). A Langhans giant cell with peripherally arranged nuclei is seen to the left of the granuloma.

RADIOLOGY

In the early stages of bone involvement before prominent destruction occurs, plain radiographic films may be normal. As much as 50% loss of bone may be required before radiographic changes are evident. As the disease process progresses, osteopenia and loss of vertebral height may be noted with so-called gibbus deformity, i.e., anterior angulation or collapse of a vertebral body.² With abscess formation, calcium deposits within the abscess may become apparent and are highly specific findings for TB. CT and MRI scans are more sensitive than plain radiographs for the early detection of destructive lesions associated with TB. Involvement of the posterior elements, abscess formation, and extension into the spinal canal are better visualized with these techniques and can help refine further the differential diagnosis.⁷ Radionuclide bone scans can be useful for the detection of other foci of tuberculous spread, but are less sensitive and less specific tests for the initial assessment of TB-associated spondylitis.

DIAGNOSIS

In patients with multiple lytic bone lesions, the diagnosis of tuberculous osteomyelitis is often delayed while other diagnoses are deliberated. The differential diagnosis generally includes metastases from breast or prostate cancer, primary bone tumors such as Ewing's sarcoma and eosinophilic granulomas, other malignancies (e.g., lymphoma), or other causes of osteomyelitis (e.g., fungi, bacteria, or atypical mycobacteria).^{7,8} Differentiation of spinal TB from other diseases is definitively determined

by obtaining a tissue sample. Demonstration of caseating granulomatous inflammation by histology greatly increases the diagnostic likelihood of tuberculous infection. However, specificity for infection with *M. tuberculosis* does not reach 100% by histology alone; other causes of granulomatous inflammation include sarcoidosis, other mycobacteria, and fungal infections.⁹ Though classic tuberculous granulomas contain central caseation, they may also be noncaseating, as in this case. When clinical suspicion is high and granulomas are present in histologic section, special stains for acid-fast bacilli should be performed, regardless of presence or absence of caseation.¹⁰ The appropriate epidemiologic and clinical setting combined with these histopathologic findings generally provides sufficient information to begin empiric therapy with anti-tuberculous medications. AFB smears are positive in only 20% of percutaneous vertebral biopsies, but sensitivity increases to 59% with needle aspiration of associated paraspinal abscesses.⁴ Culture of *M. tuberculosis* may take up to six weeks for identification of the microorganism, but this increases the diagnostic yield to 76% and 93%, respectively, for percutaneous bone biopsy and abscess aspiration.⁴

TREATMENT

Initial empiric treatment typically consists of four anti-tuberculous drugs: isoniazid (INH) (5 mg/kg, maximum 300 mg), rifampin (10 mg/kg, maximum 600 mg), pyrazinamide (15-30mg/kg, maximum 2000mg), and ethambutol (15-25 mg/kg, maximum 2500 mg). If on testing the organism is sensitive to all of the agents, ethambutol can be discontinued in order to avoid unnecessary ocular toxicity. Pyrazinamide is then discontinued at 2 months,

and INH and rifampin are continued for the remainder of the treatment. Although there is conflicting evidence for duration of treatment, the American Thoracic Society recommends 6-9 months of continuation therapy with INH and rifampin for bony involvement.¹¹ If response to treatment is slow, continuation of the two drug therapy can be sustained until clinical and radiographic improvements are noted. Directly observed therapy is not required for bone-associated TB without pulmonary involvement because it is not directly contagious and thus does not pose a public health risk. Surgical intervention is generally not recommended unless symptoms fail to improve after proper anti-tuberculous therapy or the patient has extensive involvement of contiguous vertebrae.^{7, 11, 12}

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CME QUESTIONS

To earn CME credit, read the preceding CME article and complete the registration, evaluation, and answer form on page 283. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to October 31, 2006. Participants must attain a minimum score of 75% to receive credit.

For each question, choose the one answer that is most correct.

1. All of the following comments are true regarding tuberculous bone infection *except*:
 - a) Concurrent complaints of cough, hemoptysis, or other pulmonary symptoms are commonly not present as active pulmonary TB occurs in less than 50% of skeletal TB cases.
 - b) Purified protein derivative (PPD) skin testing is usually positive, but can be negative in the immunosuppressed, the elderly, or those with overwhelming disseminated disease.
 - c) In the early stages of bone involvement before prominent destruction occurs, plain radiographic films may be normal.
 - d) Elevations in erythrocyte sedimentation rate (ESR) and serum alkaline phosphatase (associated with bony destruction) are very specific for the diagnosis of tuberculous bone infection.
2. True or False? As with pulmonary TB, constitutional symptoms of fever, night-sweats, and weight loss are often the presenting complaints of patients with skeletal TB.
3. True or False? Directly observed therapy (DOT) is not required for bone-associated TB without pulmonary involvement because it is not directly contagious and thus does not pose a public health risk.
4. All of the following statements are false about tuberculous bone infection *except*:
 - a) All bone-associated tuberculous granulomas contain central caseation.
 - b) AFB smears are positive in only 20% of percutaneous vertebral biopsies, but sensitivity increases to 59% with needle aspiration of associated paraspinal abscesses.
 - c) Empiric treatment with anti-tuberculous agents typically consists of two-drug initiation therapy with pyrazinamide (15-30mg/kg, maximum 2000mg) and ethambutol (15-25 mg/kg, maximum 2500 mg).
 - d) Although there is conflicting evidence for duration of treatment, the American Thoracic Society recommends 2 months of 'continuation' therapy with INH and rifampin for bony involvement.
 - e) Surgical intervention is always recommended unless symptoms progress or fail to improve after proper anti-tuberculous therapy or if patients have extensive involvement of contiguous vertebrae.