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Bones and Joints Tuberculosis

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Tuberculosis appears to be increasing throughout the world after years of continuous decline, despite the introduction of effective chemotherapy. This resurgence is related to the increasing number of patients immunocompromised by chemotherapeutic agents used to treat other diseases or AIDS; the appearance of multiple drug-resistant strains of tuberculosis, and aging population. Several species of mycobacteria other than *Mycobacterium tuberculosis* or *M. bovis* are known to cause infections of bones and joints. The predisposing factors are malnutrition, environmental conditions and poor living standards. Musculoskeletal tuberculosis arises from haematogenous seeding of the bacilli soon after the initial pulmonary infection. The clinical symptoms are insidious onset, pain, swelling of the joint and limited range of movements. Investigations for suspected cases include: Mantoux test, radiological imaging, fine needle aspiration biopsy, surgical biopsy, bacteriological examination, histopathological examination, and polymerase chain reaction (PCR) of a suitable specimen. The mainstay of treatment is multidrug antitubercular chemotherapy. Surgical intervention is indicated in patients with abscess formation, intractable pain, neurological deficit, spine instability, kyphosis, and unsatisfactory response to chemotherapy. The main reason for poor outcome is delayed diagnosis.

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Tuberculosis (TB) is still the second most frequent infectious disease after malaria on a worldwide basis and remains a major cause of skeletal infection in many parts of the world[1,2]. Each year, 3.8 million new cases of tuberculosis are reported globally, the vast majority in the developing countries[3]. The tubercle bacillus infects one-third of the world's population. It is the most common single agent causing death in young adults and causes two million deaths each year around the world[4]. In developed countries the incidence of TB, which had been declining over the past decades, has shown an alarming resurgence, due to several factors, which include arrival of immigrants from area where TB is endemic, the rise in the number of people who have immunodeficiency, outbreaks of TB in facilities, the advent of multidrug-resistant (MDR) TB, an aging population, and an increase in the number of health care workers who are exposed to the disease[1,2,5]. Some developing countries in Africa and Asia and some new states of the former Soviet Union have experienced dramatic increases in the number of pulmonary tuberculosis cases[6]. Therefore, an increase in the incidence and prevalence of joint and bone tuberculosis can also be suspected. Tuberculosis of bones and joints accounts for approximately 10% to 15% of all extrapulmonary forms of tuberculosis[7].

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The predisposing factors are malnutrition mainly of protein, environmental conditions and living standards such as poor sanitation and over crowded housing, repeated pregnancies and lactation in women, diabetes mellitus, and acquired immunodeficiency syndrome[8]. Women, blacks, and HIV-positive tuberculosis patients were reported to be more likely to develop extrapulmonary TB[9].

METHOD

A systematic literature search was conducted using the EBSCO and MEDLINE databases for articles published through 2006. The following phrases were used for searching the articles: bone and joint tuberculosis, bone tuberculosis, joint tuberculosis. Manual search for related references was performed too. Some websites specializing in issues related to bone and joint tuberculosis were also searched.

Bacteriology

Several species of mycobacteria other than *Mycobacterium tuberculosis* or *M. bovis* are known to cause infections of bones or joints[8,10]. These are atypical mycobacteria which have been reported in lesions of the synovial sheath. The following factors are considered in the transmission of atypical mycobacteria: trauma, local steroid injection, surgical trauma, diabetes mellitus, immunosuppressive drugs in organ transplantation, and acquired immunodeficiency syndrome[8].

The colony counts in joint tuberculosis are 1000 times lower than in pulmonary disease[11]. *M. tuberculosis* does not grow on ordinary culture medium. It has a slow growth rate, therefore, several weeks may be required for colonies to be identified.

Pathophysiology

Musculoskeletal tuberculosis arises from haematogenous seeding of the bacilli soon after the initial pulmonary infection. Osteoarticular tuberculosis usually starts as osteomyelitis in the growth plates of bones, where the blood supply is best, and then spreads locally into the joint spaces[12]. Less commonly, it can occur by spreading through the lymphatic system[13]. Joints can become infected by activation of dormant lymphatic or blood stream areas of morbidity[14]. In the long bones TB originates in the epiphysis and causes tubercle formation in the marrow, with secondary infection of the trabeculae[13]. The joint synovium responds to the mycobacteria by developing an inflammatory reaction, followed by formation of granulation tissue. The pannus of granulation tissue formed then begins to erode and destroy cartilage and eventually bone, leading to demineralization[15]. Because TB is not a pyogenic infection, proteolytic enzymes, which destroy peripheral cartilage, are not produced. The joint space, therefore, is preserved for a considerable time. If allowed to progress without treatment, however, abscesses may develop in the surrounding tissue[15]. Since space-occupying exudates with extensive disruption of vascular supply do not occur, sequestration of bone is rare. Therefore, bone destruction without sequestra and with minimal new bone formation characterizes the active phase of tuberculous osteomyelitis[16].

Spinal TB is the most common form of skeletal system TB, comprising 50% of all cases[17]. Wherever the primary site of TB infection is, it travels by subligamentous spread in the

spine, as well as into paravertebral spaces and adjacent soft tissues[18]. It causes osteonecrosis characterized by loss of the exracellular matrix of vertebral bone and collapse of the vertebrae[19]. The bone is devitalized by an exotoxin produced by the acid-fast bacilli[20]. The anterior portions of two or more contiguous vertebrae are involved owing to haematogenous spread through one arteria intervertebralis feeding two adjacent vertebrae[21]. The spinal cord may become involved either by compression by bony elements and/or expanding abscess; or direct involvement of cord and leptomeninges by granulation tissue[22]. Neurological deficits are usually more symmetrical and more gradual in onset than those resulting from other pathologies[23]. The spinal TB can involve vertebral bodies at two or three different sites and these are referred to as "skipped lesions" [24,25].

Clinical features

Bone and joint tuberculosis is encountered in any age group[2,5]. No bone is immune from involvement by TB, and the arthritis is monoarticular in 90% of cases. The most common location in childhood is spine, accounting for 60% to 70% of cases. The most frequently involved joints are the weight-bearing joints such as hip, knee, shoulders, or elbow[2].

The clinical symptoms are insidious onset, pain, swelling of the joint and limited range of movement[26]. Other symptoms include fever, night sweats, or weight loss[13]. In some cases, sinuses are the sole presentation, which could be misdiagnosed as pyogenic infection or diabetic foot[27]. Joint deformity may develop and granulomatous process eventually causes a boggy or doughy feeling to the joint and periarticular structures[14]. Localized pain may precede other symptoms of inflammation or radiographic changes by weeks or even months[14]. When diagnosis is late, joint contractures and limited functional improvement after treatment are more likely to occur, especially if bone and articular cartilage are destroyed[28].

In most cases of spine TB, the lesion is insidious in onset and only rarely there is an acute manifestation. Locally, there is stiffness, painful restricted joint movements in all directions and severe spasm of the surrounding muscles. If the lesion has been present for a sufficiently long time, a cold abscess occurs in the soft tissues, penetrating through the inter-muscular planes. A deformity, in the spine can be present as kyphosis along with local tenderness[8]. TB spine may cause psoas abscess that presents as huge swelling in the upper part of the thigh. Delayed diagnosis of spine TB in the younger age group, especially in the poor communities, leads to severe deformity of the spine with angular kyphosis.

Diagnosis

Diagnosis is by a high index of clinical suspicion, positive Mantoux test, radiological features, fine needle aspiration biopsy, aspiration of purulent material or synovial fluid for bacteriological examination, and biopsy for histopathological examination. Newer method of diagnosis, including the use of polymerase chain reaction (PCR) on obtained joint tissue biopsies, appears promising in the early diagnosis of tuberculous arthritis[29]. Nevertheless, the gold standard for the diagnosis of osseous tuberculosis is culture of mycobacteria from bone tissue or synovial fluid.

Tuberculin skin test may well be negative during the first weeks of disease. If negative early, the tuberculin skin test should be repeated after 6 weeks of arthritis[30]. The possibility

of TB must be considered in any child with monoarticular arthritis who has a positive tuberculin test[30,31]. Mantoux skin test is beneficial in the diagnosis of skeletal disease in childhood, particularly in communities where the incidence of TB is high[30,31]. In one case series, the rate of false-negative results of Mantoux test was 14%[32]. For this reason a positive Mantoux test result can be helpful in confirming a diagnosis of tuberculosis, but a negative result cannot exclude it.

Radiographic changes in the joint are absent or non-specific in the early stages of disease, but soft-tissue swelling with little periosteal reaction, osteopenia, narrowing of the joint space (a late finding) and subchondral erosions of both sides of the joint suggest tuberculosis[33]. MRI has become the preferred imaging technique for spinal tuberculosis because it can differentiate between granulation tissue and abscess, identify soft-tissue masses and assess the degree of bone destruction. However, bone anatomy and abnormalities, including calcifications and sequestra, are better seen on CT scanning[34,35]. Chest radiographs may show evidence of pulmonary disease in 50% of patients with osteoarticular tuberculosis, but active pulmonary disease is present in less than 1 in 5[36].

By fine needle aspiration biopsy, granulamatous reaction, with or without caseation necrosis, was found in 73%. Acid-fast bacilli were found in 64%, and the *M. tuberculosis* cultures were positive in 83% of all cases[37]. Positive Ziehl-Neelsen staining for acid-fast bacilli requires at least 10^4 acid-fast bacilli per milliliter of specimen and does not differentiate between tuberculous and non-tuberculous mycobacteria[38]. The advent of DNA detection by PCR may increase sensitivity of mycobacterial detection and allow for the exclusion of non-tuberculous mycobacteria that also cause soft tissue infections.

Operative specimens, including purulent material or synovial fluid, of patients with osteoarticular tuberculosis revealed positive mycobacteria on direct smear in 27%, and on culture in 63%[27]. Culture of synovial fluid often gives positive results but synovial biopsy may be required to grow the organism. Mycobacteria might be identified from sinus-track culture whereas operative culture, histopathological and clinical examination could fail to confirm the diagnosis of tuberculosis[27]. Thus, sinus-track specimen should not be omitted as concern of contaminants. It is an excellent source for isolation of mycobacteria. Tuberculous bone infection should be suspected if there is no growth of any pyogenic bacteria or if there is growth of *Staphylococcus epidermidis* alone on routine aerobic and anaerobic sinus-track specimen cultures[39]. On a very rare occasion, mycobacteria and pyogenic bacteria were isolated concomitantly from operative specimen of spinal tuberculosis[40]. Therefore, isolation of pyogenic bacteria from operative or sinus specimen does not exclude the possibility of tuberculosis.

Biopsy of the bony lesion, synovium or soft tissue masses may be required to clear up diagnostic confusion[41]. It is the most definitive test for tuberculous arthritis[14]. It is of significant value in cases where the organisms have not been seen on smear or culture, but caseating granulomas will be demonstrated on histological examination. Therefore, histological investigations must be performed in cases in which microbiologic tests give negative results in order to confidently exclude tuberculosis as a cause of chronic arthritis.

Molecular diagnostic techniques like the polymerase chain reaction (PCR) and other form of nucleic amplification tests are being applied nowadays to tissue samples. Although DNA-based PCR can be quite sensitive, it may not distinguish between viable and non-

viable bacilli[42]. In one study, the sensitivity of the PCR test applied to synovial fluid was 57.7%, less than the sensitivity for sputum (81%) or pleural fluid (64.2%) samples[43]. PCR also revealed false-positive results which could perhaps be explained by a subclinical dissemination of *M. tuberculosis* in the absence of clinically overt disease. It is therefore unclear whether the suspicious cases represent false-positive or true-positive results[29,24].

Treatment

The majority of patients are expected to achieve healing with normal function if osteoarticular TB is diagnosed and treated at an early stage. The cornerstone of treatment is multi-drug anti-tubercular chemotherapy and active or assisted non-weight bearing exercises of the involved joint throughout the period of healing[45]. An initial period of rest is to be followed by supervised gradual mobilization. In spine TB, various types of spinal support in the form of collars, braces and corsets, may need to be used. Adequate nutritional support is also essential, as in all forms of TB. The goals of treatment are to contain and eradicate the infection, relieve pain, and preserve and restore bone and joint function[46]. The main reason for poor outcome is delay in the diagnosis, which is common[47].

Current recommendation of US Center for Disease Control and Prevention for treatment of osseous tuberculosis includes a two-month initial phase of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by 6 to 12 months regimen of isoniazid and rifampicin[48]. The Joint Tuberculosis Committee of the British Thoracic Society recommendation is ambulatory chemotherapy in disease of thoracic and lumbar spine. They recommend six-month regimen comprising rifampicin, isoniazid, pyrazinamide, and ethambutol for the initial two months followed by rifampicin and isoniazid for further four months. They also advice, that surgery plus chemotherapy may be required for the few patients with evidence of spinal cord compression or instability[49]. The Indian practice prefers to continue osteoarticular TB treatment till there is adequate radiological evidence of healing, which can take much longer than 6 months[42].

A study in Saudi Arabia that involved 110 patients who were treated at Riyadh Armed Forces for tuberculous spondylitis; the authors mentioned the advantages of surgical treatment in comparison to non-surgical treatment. These include relief of pain, early ambulation and early recovery from neurological deficit, less angle of kyphosis and short hospital stay. They recommended radical surgery for patients with neurologic deficit, abscess, kyphosis or intractable pain[50]. On the other hand, in Iranian prospective study involving 63 patients with bone and joint tuberculosis; all patients were treated by chemotherapeutic agents whereas no patient needed surgical procedure[51]. Medical Research Councils in Hong-Kong, Korea and India reported that overall outcome was the same for both medical and surgical treatment of spine tuberculosis[52-54].

There are few studies that define the optimal duration of treatment of skeletal tuberculosis, some investigators favor a prolong course of therapy to optimize post-treatment function. Others prefer that the nature of the few number of bacilli in the lesion make 6-month treatment course appropriate. Prolong drug therapy (i.e. in children for a minimum of 12 months) proves effective for eliminating or sterilizing the persistent bacilli, which are small populations of metabolically inactive microorganisms. Treatment should not be delayed waiting for culture results because experience suggests that delay in treatment may result in less than optimal outcome[31]. However, in various studies, the duration of therapy has varied

widely: 6 months in sacral TB, 12-18 months in various spinal sites, 12-18 months in TB of craniovertebral junction,, 14-18 months in sternoclavicular joint involvement, 12-20 months in TB affecting the talus, 12 months in tuberculosis of metacarpals and phalanges[55-60]. Multi-drug-resistant TB should be suspected if osteoarticular disease activity shows no signs of improvement after 4-6 months of uninterrupted therapy. These cases are therapeutically challenging and require second line anti-TB drugs including fluoroquinolones such as ofloxacin and sparfloxacin[42].

Prevention

The only available TB vaccine is BCG (Bacillus Calmette-Guerin), which has some efficacy for most commonly contracted TB in very young children. The effectiveness of the BCG vaccine diminishes over time. A new tuberculosis vaccine trial was announced in USA. The vaccine combines two TB proteins that elicit strong immune responses in humans[61].

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