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Short Communication

Delayed Diagnosis of Tuberculous Arthritis

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SUMMARY: Monoarticular tuberculosis (TB) affecting the knee is rare in all forms of TB (0.1 - 0.3%). We present the case of a patient with tuberculous arthritis in whom the diagnosis was belated due to a lack of familiarity with the disease; here, we emphasize the difficulties associated with the diagnosing joint TB. A 20-year-old man was referred to our department due to swelling of the right knee and the presence of persistent, mild pain for 4 years. The lack of systemic evidence of this disease, the indolent course of disease, and the presence of non-specific symptoms renders early recognition of this disease difficult. Furthermore, in cases in which a diagnosis cannot be reached simply by culturing the synovial fluid, synovial biopsy cultures should be considered in the diagnostic process, due to the high rate of positivity of such cultures. The diagnosis and treatment of articular TB are both urgent matters; surgical debridement and strict adherence to antituberculous chemotherapy tend to yield a satisfactory functional outcome.

Extrapulmonary tuberculosis (EPTB) is observed in approximately 20% of all tuberculosis (TB) cases; moreover, an increased incidence has been observed in recent years (1). The incidence of osteoarticular TB constitutes approximately 10% of cases with EPTB, and the number of such cases continues to rise (1-3). Eventually, the incidence of osteoarticular TB is expected to account for 1 - 3% of all forms of TB (4). Five different osteoarticular TB clinical syndromes are commonly recognized: Pott's disease; peripheral arthritis; osteomyelitis and dactylitis; tenosynovitis and bursitis; and Poncet's disease (2,3). Peripheral arthritis is responsible for 30% of osteoarticular TB cases, and 90% of patients with this type of TB present with mild, slowly progressive, chronic monoarthritis (2,3,5). The weight-bearing joints are usually affected, whereby involvement of the knee and hip account for approximately 50% of the cases of peripheral arthritis (3). It should be noted that monoarticular TB affecting the knee is rare in all forms of TB (0.1 - 0.3%).

We present the case of a patient with tuberculous arthritis in whom the diagnosis was belated due to a lack of familiarity with the disease; here, we emphasize the difficulty of diagnosing joint TB. A 20-year-old man was referred to our department due to swelling of the right knee and the presence of persistent, mild pain for 4 years. Following a diagnosis of chronic, non-specific synovitis, the patient had been intermittently treated for the most recent 2 years with non-steroid anti-inflammatory drugs, which provided only minimal benefits. There was no history of antecedent injury to his knee. The patient denied having fevers, anorexia, weight loss, and night sweats.

On physical examination, a tender swelling with mild effusion was noticed on the right knee. The patient was unable to fully extend the knee, and flexion was also somewhat limited. The rest of the systemic examination of this patient was unremarkable. Laboratory examination revealed a hemoglobin value of 14.6 g/dl, and a total leukocyte count of 5,400/mm^3. The ESR (Westergren) was 27 mm/h and the C-reactive protein was 42 mg/L. All other laboratory results, i.e., routine biochemistry and autoantibody screening assays, were within the normal range and negative, respectively.

The patient underwent thorough investigation and received a diagnosis of chronic monoarthritis. A plain radiograph of the right knee revealed a narrowing of the joint space with several erosive lesions at the site of the epicondyles of the femur. Magnetic resonance imaging (MRI) was performed in the axial, sagittal and coronal planes using spin echo T1-weighted (TR 440, TE 12), gradient-echo T2-weighted (TR 640, TE 18, flip angle 30°), and fat-saturated turbo spin echo T2-weighted (TR 4000, TE 96) sequences. The T1-weighted sequence was repeated after intravenous (i.v.) administration of a paramagnetic contrast medium with and without fat saturation. The bone marrow of the proximal tibial epiphysis revealed hyperintensity on T2-weighted scans with contrast enhancement following i.v. contrast injection; these findings were suggestive of osteomyelitis. Destruction of the femur and tibia articular surfaces was present. Thickening and contrast enhancement of the articular synovium with joint effusion were suggestive of articular synovitis. Between the head of the fibula and the lateral gastrocnemius muscle, abscess cavities were observed, as characterized by low T1- and high T2-signal intensities showing ring-shaped contrast enhancement. Several lymphadenopathies were also present in the popliteal fossa (Fig. 1).

Synovial fluid analysis was then performed, and the following results were obtained: the white cell count was 26,000 cells/mm^3, and a 65% of lymphocyte ratio was observed. Gram staining revealed no bacteria, and no crystals were seen on microscopic examination of the synovial fluid. In addition, the following tests all gave negative results: synovial fluid smear for acid-fast bacilli (AFB), and cultures for mycobacteria and pyogenic bacteria.

A conventional radiograph of the thorax showed infiltrative lesions at the apex of the left lung. A spiral computed tomography (CT) scan of the thorax was consistent with the conventional radiograph, both of which revealed infiltrative apical lesions of both of the lungs; these results could be

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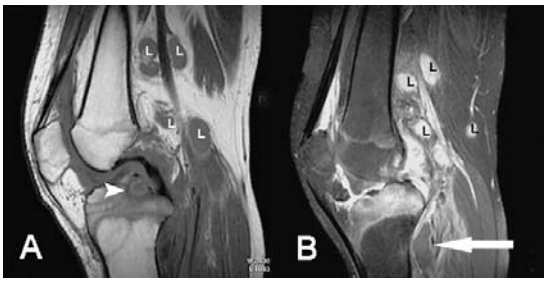

Fig. 1. Sagittal non-contrast T1-weighted MRI images of the right knee before (A) and after (B) the administration of i.v. contrast medium; the images demonstrate marrow edema at the tibial plateau with contrast enhancement (B). Cartilage and bone erosion (arrowhead in A), joint effusion and synovial enhancement (in B), and multiple contrast-enhanced lymphadenopathies (L in A and B) are indicated. Fluid accumulation with a ring-shaped enhancement pattern on the post-contrast scan was consistent with the presence of an abscess (arrow in B).

interpreted as demonstrative of old tuberculous lesions. The immune status of the patient was normal. The test for purified protein derivatives (PPD) was reactive, with an 18-mm induration at 72 h.

Open synovectomy with the removal of surgical debris was performed; pathologic review of the tissue samples showed granulomatous synovitis. A negative result was obtained by histochemical Ziehl Neelsen (ZN) staining, and aerobic and anaerobic bacteria cultures were also found to be negative. Various specimens including aspirates of the sputum, urine, and transbronchial biopsy tissues were examined with ZN staining for the presence of mycobacteria; all of these tests produced negative results. Due to the presence of the apical lung lesions that were concomitant with the granulomatous lesions found in the synovial biopsy specimens, a decision was made to start anti-TB treatment while waiting for the culture results. Both conventional (Löwenstein Jensen medium, Salubris Inc., Istanbul, Turkey) and radiometric (BACTEC 460TB culture system, Becton Dickinson Diagnostic Instruments, Sparks, Md., USA) culture examinations of the synovial biopsy specimens revealed the growth of the *Mycobacterium tuberculosis* complex (MTC). Differentiation of the MTC and non-tuberculous mycobacteria was achieved by selective inhibition of the MTC in the presence of 5 μl/mL of p-nitro-α-acetyl-amino-β-hydroxypropiophenone (NAP) according to the BACTEC manual (6). The joint fluid and sputum samples were also tested via radiometric and conventional cultures; however, no mycobacteria were detected in these samples. All of these samples were tested by polymerase chain reaction (PCR) assay for MTC. A standard protocol for the extraction of MTC-DNA was used (7). The clinical samples were digested in a buffer (200 μg/mL proteinase K in 50 mmol/L Tris-HCl pH 8.5) for 6 h at 55°C and were then boiled for 10 min. Phenol-chloroform extraction was performed, and the ethanol-precipitated DNA was resuspended in TE buffer (10 mmol/L Tris-HCl, 1 mmol/L EDTA, pH 7.4) and used for amplification. The primer sets used to amplify the 123-bp IS*6110* gene fragment consisted of TBC1 (5′-CCT GCG AGC GTA GGC GTC GG-3′) and TBC2 (5′-CTC GTC CAG CGC CGC TTC GG-3′). The amplification reactions were performed by using *Taq* polymerase and reagents according to the manufacturer's instructions (Bioron GmbH, Biotechnica Co., Ludwigshafen, Germany). Five microliters of DNA were added to the mixture, which was subjected to 40 cycles of amplification (95°C, 30 sec; 68°C, 30 sec; 72°C, 30 sec) followed by a 5-min extension at 72°C (Thermocycler; MJ Research, Watertown, Mass., USA). Fifteen microliters of the amplification products were analyzed by electrophoresis carried out in ethidium bromide-stained 2% agarose gel, and the results were visualized by ultraviolet light. However, the results of the MTC-PCR tests were negative.

The anti-TB drug susceptibility testing of MTC isolates to four first-line anti-TB drugs (isoniazid [INH], rifampicin [RMP], ethambutol [EMB], streptomycin) was evaluated using a BACTEC 460TB radiometric system (6). The isolates were found to be susceptible to these four first-line anti-TB drugs. Chemotherapy for TB monoarthritis was initiated orally with the following four drugs, INH (300 mg/day), RMP (600 mg/day), EMB (1.5 g/day), and pyrazinamide (PZA) (2 g/day) during the first 2 months, followed by INH and RMP for 4 months. The treatment duration was set at 6 months due to the removal of therapeutic debris, which had been performed during the synovial biopsy. High-dose pyridoxine was administered to the patient due to possible INH-related neuropathy. Treatment resulted in complete resolution of the signs and symptoms of disease.

An increased incidence of osteoarticular TB has recently been reported. This type of TB is typically the result of a direct hematogenous spread of TB bacilli from a primary focus, i.e., from a pulmonary (30%), genitourinary (20%), or unidentified (50%) site. The more frequent involvement of weight-bearing joints is probably due to the effects of trauma (3). As shown in our patient, chest radiographs may show evidence of pulmonary TB in 50% of cases (8).

Swelling of the involved joint may be observed, and may limit motion. Systemic symptoms of infection are not common. Because of the subtle nature of the symptoms, diagnostic evaluations are often are not undertaken until the disease has progressed (1). The possibility of tuberculous arthritis is often overlooked during clinical examination; therefore, it is necessary to increase clinical awareness to ensure early detection and avoid diagnostic delays (4). Tuberculous arthritis presents with subtle symptoms: joint swelling and pain exacerbated by walking and activity are the most common manifestations. These symptoms are due to synovial proliferation and effusion. Inflammatory signs are mild or absent. Limited range of motion may be present and is caused by pain and synovial hyperplasia. The synovial membrane is the main anatomic structure involved, with marked proliferation and caseating and noncaseating granulomata with multinucleated giant cells (5).

Diagnosis presents clinicians with a number of difficulties, and failure to recognize the disease at an early point in the course of illness occcurs frequently. In fact, tuberculous arthritis is an indolent process, symptoms are mild and non-specific, there is usually no evidence of disease in other organs, and radiographic and laboratory findings are not helpful. Routine biochemical studies do not typically reveal any specific alterations, the synovial fluid is inflammatory, and the ESR is usually elevated. Reliable diagnostic methods include synovial biopsy, which reveals the presence of granulomata in more than 90% of specimens (5).

Radiography enables the visualization of soft tissue swelling and periarticular osteopenia for several months after the appearance of symptoms. Blurring of the subchondral bone, marginal erosions, and joint space narrowing are late findings (5). CT may reveal the extent of bony destruction. MRI may show early soft tissue changes with the presence of joint

effusion (9). MRI imaging has been shown to be superior to either plain radiographs or ultrasound for the diagnosis of joint TB. It may also enable better visualization of soft tissue lesions such as abscesses, which may further enhance the clinical suspicion of an infectious process involving the joint (5).

The PPD test in our patient was positive. However, as frequently observed in Turkey, PPD test results are usually of limited diagnostic value in developing countries due to the high rates of both exposure to mycobacteria and BCG vaccination (7).

The identification of *M. tuberculosis* is essential for the diagnosis of tuberculous arthritis; however, acid-fast stains of the joint fluid are positive in only 20 to 25% of those examined, and *M. tuberculosis* is isolated in approximately 60 to 80% of cases (1,5). On the other hand, the rate of detection rate of *M. tuberculosis* was reported to range between 19 and 94% in another study (4). Biopsies of the synovium have a higher yield and allow histologic examination as well. Evidence of granulomatous inflammation of the joint, even in the absence of mycobacteriologic evidence, is sufficient to justify initiating anti-TB therapy, unless another etiology is found (1). Diagnosis in the case presented here was also established by the isolation of mycobacteria in cultures obtained from synovial biopsy specimens.

If osteoarticular TB were to be diagnosed and treated at an early stage, approximately 90 to 95% of patients would achieve an almost complete cure and retain near-normal function. The mainstay of treatment is multidrug antituberculous chemotherapy (for 9 to 12 months) and active-assisted, non-weight-bearing exercises of the involved joint throughout the period of healing. Operative intervention is required when the patient has not responded after 4 to 5 months of chemotherapy (synovectomy and debridement). Joint replacement may be considered if the disease has remained inactive for 10 years or more. Multidrug resistance should be suspected if the activity of the disease has not subsided after 4 to 6 months of uninterrupted multidrug therapy. Such patients (5 to 10%) present a critical therapeutic challenge. Second-line and potential antitubercular drugs, and possibly also immunomodulation may control such cases (10).

Histopathological examinations, MRI studies, and mycobacterial cultures are very important for the diagnosis of monoarticular TB cases. The lack of systemic evidence of the disease, the indolent course of its progress, and the presence of non-specific symptoms render the early recognition of this disease difficult. Furthermore, in cases in which a diagnosis can not be made based on cultures of synovial fluid alone, synovial biopsy cultures should be considered in the differential diagnosis, due to the relatively high rate of positivity of such cultures. In conclusion, the diagnosis and treatment of articular TB are urgent matters; however, surgical debridement and strict adherence to antituberculous chemotherapy can in many cases yield a satisfactory functional outcome.

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