A diagnosis of disseminated tuberculosis based on knee arthroscopic guided synovial biopsy in the context of monoarthritis

Fernandes S[1], Vieira-Sousa E[1], Furtado C[2], Costa A[3], Barros R[1], Fonseca JE[1]

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ABSTRACT

Accounting for 2.2-4.7% of all tuberculosis cases in Europe and USA and around 10-15% of extra-pulmonary tuberculosis cases, osteoarticular tuberculosis tends to be chronic, slowly progressive and destructive.

We report the case of an 81-year-old male with 3 weeks of progressively worsening pain, swelling and limited range of motion of the left knee. A knee arthroscopy was performed for synovial biopsy at our department, revealing diffuse synovitis with scarce villi formation. The positive polymerase chain reaction assay for *Mycobacterium tuberculosis* in the synovial tissue allowed the establishment of the diagnosis and synovium histology showed caseating granulomas.

A lengthy delay between first symptoms of osteoarticular tuberculosis and the beginning of treatment has been reported. A high index of suspicion, synovial membrane biopsy and appropriate microbiologic testing are fundamental to avoid a delay in diagnosis.

Keywords: Arthroscopic guided synovial biopsy; Tuberculosis; Osteoarticular tuberculosis

INTRODUCTION

Tuberculosis (TB) remains an important global health problem, causing morbidity and mortality worldwide[1,2]. A total of 2195 new TB cases (rate of 21.1 cases per 100,000 persons) were reported in Portugal in 2013. This represents a 7% reduction from the 2012 incidence rate, which has been diminishing consistently since 2002. Of these incident cases, 70,5% had pulmonary tuberculosis, 10% of which had concomitantly other organ involved, and 29,5% were exclusively extra pulmonary tuberculosis (EPTB)[2]. Accounting for 2.2-4.7% of all TB cases in Europe and United States of America (USA) and around 10-15% of EPTB cases[1], with greater incidence in immunocompromised patients[3], osteoarticular tuberculosis (OAT), tend to be chronic, slowly progressive and destructive[1]. A lengthy delay between first symptoms of OAT and the beginning of treatment has been reported, which results in greater morbidity rather than increased mortality[4].

The herein report describes the case of a patient with knee arthritis as the first manifestation of disseminated tuberculosis.

CASE REPORT

A 81-year-old male with a 2 years history of hairy cells leukemia, medicated with filgrastim, and recently diagnosed and treated for skin squamous cell cancer, was admitted due to 3 weeks of pain, swelling and limited range of motion of the left knee, with progressive worsening of symptoms. He reported high fever (39ºC), starting two months before joint symptoms, with no response to amoxicillin and clavulanic acid, which were prescribed empirically based in a presumed diagnosis of an upper respiratory tract infection. When inquired he referred contact with a pulmonary tuberculosis patient ten years before.

On physical examination, a low body mass index, paleness of the skin and mucosae and a tender swelling with mild effusion of the left knee was noticed, without detectable changes in other organs or systems. Laboratory tests revealed a normochromic normocytic anemia

1. Serviço de Reumatologia e Doenças Ósseas Metabólicas/Hospital de Santa Maria, CHLN, Lisboa, Lisbon Academic Medical Centre;
2. Serviço de Reumatologia/Hospital do Divino Espirito Santo, Açores, Portugal;
3. Serviço de Anatomia Patológica/Hospital de Santa Maria, CHLN, Lisboa, Lisbon Academic Medical Centre

(hemoglobin of 8.8 g/dL), leucopenia of 1510 cells/ /mm^3, lymphocytopenia of 190 cells/mm^3 and 1240/ /mm^3 neutrophils. The erythrocyte sedimentation rate (ESR) was 107mm/1st hour and the C-reactive-protein (PCR) 18.5 mg/dL. Both kidney and liver function were normal. Tuberculin skin test result showed no induration and the interferon gamma release assay was inconclusive. Synovial fluid analysis showed a white cell count of 9533 cells/µL, predominantly neutrophils (75%) and low glucose (35 mg/dl) comparing to serum levels (104mg/dl). Gram staining revealed no bacteria and the synovial fluid smear for acid-fast bacilli was negative. Calcium pyrophosphate crystals were seen on polarized light microscopic examination of the synovial fluid. In addition, cultures for pyogenic bacteria and major infectious serologies (human immunodeficiency virus, B hepatitis, C hepatitis, cytomegalovirus, parvovirus and brucellosis) were negative.

Chest radiography was unremarkable and plain radiographs of both knees showed narrowing of the joint space and the absence of chondrocalcinosis. Ultrasound revealed mild effusion of the left knee and mild proliferation of the synovial membrane.

Given the hypothesis of septic monoarthritis the patient was empirically started on flucloxacillin and ceftriaxone, which was changed four days later to vancomycin and meropenem due to progressive deterioration of the clinical status and increase of inflammatory parameters.

A computed tomography (CT) scan revealed multiple adenopathies along the lumbo-aortic and iliac chains, some of which with central necrosis. No suspicious changes were seen in the lung window.

A knee arthroscopy performed at our department revealed diffuse granular synovitis with scarce villi formation (Figure 1). Synovial membrane exhibited increased vascularization with disorganized vessel pattern and was particularly friable during biopsy (Figure 2). The positive polymerase chain reaction (PCR) assay for *Mycobacterium tuberculosis* (MT) obtained 4 days after synovial biopsy allowed the establishment of the diagnosis and synovium histology further showed caseating granulomas (Figure 3). Anti-TB quadruple therapy (isoniazid 300mg, rifampicin 600 mg, pyrazinamide 1500 mg, ethambutol 1200 mg plus pyridoxine 40mg)) was initiated. Cultures of blood, synovial fluid and synovial biopsy later confirmed the growth of MT. The patient received antituberculosis therapy for 17 days with decrease of the inflammatory parameters. Given his comorbidities and debilitating

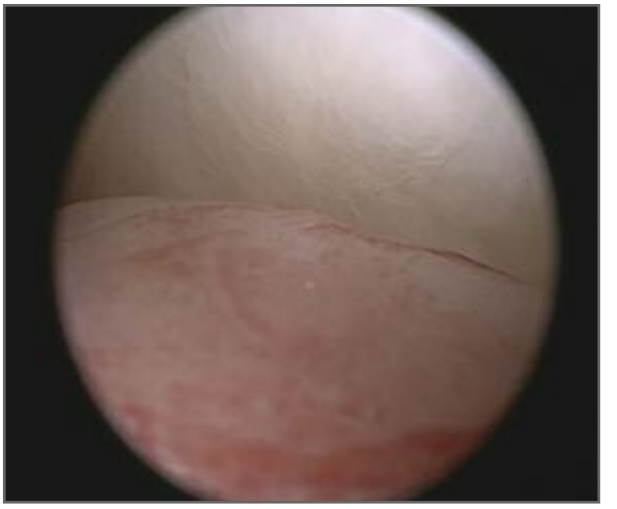

FIGURE 1. Retro-patellar space and granular synovitis

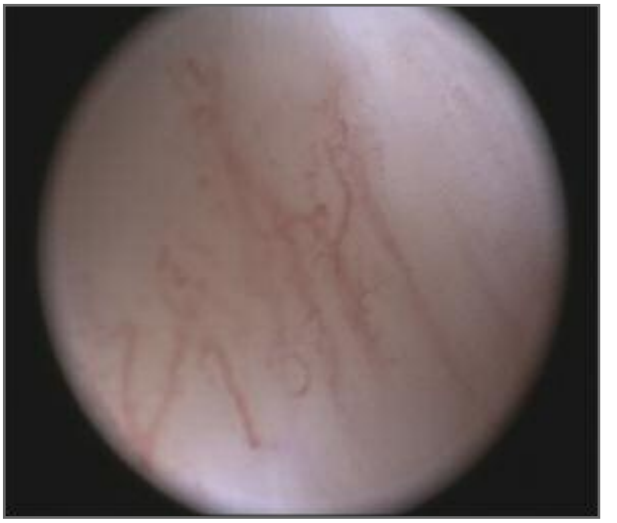

FIGURE 2. Increased vascularity with disorganized vessels covering approximately 50% of the proliferating synovium area

health status he had severe complications during hospital stay. At the 36th post-admission day, he developed an acute pancreatitis and was transferred to the Gastroenterology department, where he eventually died.

DISCUSSION

Although the total number of TB cases has decreased, the reduction of EPTB has been modest, resulting in a progressive increase of the proportion of cases with EPTB among all cases of TB. The reason for this pattern

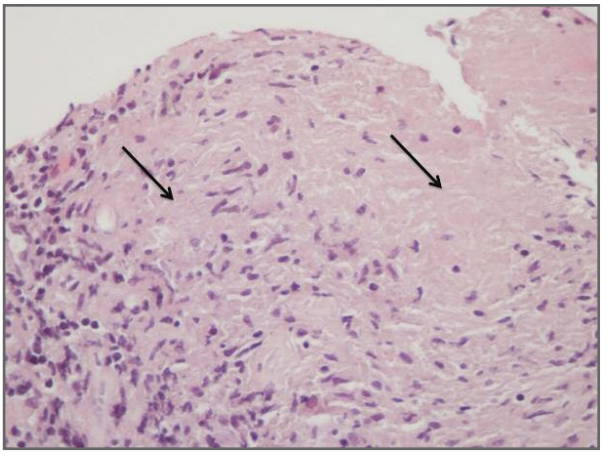

FIGURE 3. Section of the synovium showing granulomatous inflammation: epithelioid granulomas with extensive central caseation necrosis (black arrows) (H&E, X40 obj.)

change is not clear although some studies have suggested that older age, immigration from countries with high prevalence of tuberculosis, predominance of women in the population, underlying immune compromising diseases, among others, contribute to this fact[1,5]. Studies demonstrated that patients with hematologic neoplasms, as was the case of our patient, have tuberculosis rates of about 40 times greater than the current rate among the USA population[6]. Head and neck cancer were also associated with higher risk of developing TB[6]. Other causes of immunosuppression described as associated with EPTB are human immunodeficiency virus infection, diabetes mellitus, malnutrition, alcoholism, hemodialysis, exposure to immunosuppressive and cytotoxic drugs and other debilitating illnesses.

In the course of an epidemiological survey of tuberculosis in Gironde (France), pulmonary tuberculosis was detected in 63% of the cases and 37% had EPTB. The most frequent localizations of EPTB were: lymph nodes (32%), pleural (28%), genito-urinary (12%) and osteo-articular localizations (7%). This survey showed that EPTB was more frequent in patients younger than 20 or over 60 years old, and in HIV infected patients[7].

OAT most often involves the spine, followed by tuberculosis arthritis in weight-bearing joints, the knee or hip being the most commonly affected[1,4]. OAT is typically the result of a direct hematogenous spread of TB bacilli from a primary focus. The clinical presentation of TB arthritis is characterized by a slowly progressive mono-arthritis of the hip or knee, although it can virtually affect any joint. Presentation is indolent with pain, joint swelling and decreased range of motion while systemic symptoms are usually absent[1,4]. Although not observed in our patient, chest radiography shows concomitant pulmonary disease in one half of patients with OAT[1].

A significant delay has been noted between the first symptoms and the treatment of tuberculosis arthritis. A median time to diagnosis of 13 weeks with a range from 4 days to 104 weeks has been reported[8]. Patients with TB arthritis can receive a misdiagnosis of pyogenic arthritis, bone tumor or other inflammatory arthritis. Given the vast list of possible differential diagnosis, the early diagnosis of tuberculosis arthritis is dependent on a high index of clinical suspicion that would be prompted particularly by knowledge of an infectious contact, or documenting conversion of a tuberculin skin test. The tuberculin skin test is used to identify individuals with previous sensitization to mycobacterial antigens. False negative results may occur in the setting of immunosuppression or natural waning of immunity, as in our clinical case. Tuberculin skin test has more diagnostic value in countries with low rate of tuberculosis infection and that are not performing universal Bacillus Calmette–Guérin vaccination.

Typical imaging features include severe juxta-articular osteoporosis, marginal erosions and gradual joint space narrowing (Phemister triad). Para-articular soft--tissue calcifications and abscesses can also be found. Routine biochemistry does not show any specific changes. The average synovial white cell count in OAT commonly ranges from 10000 to 20000 cells and polymorphonuclear leukocytes predominate. However cell counts can be as high as those seen in case of pyogenic arthritis[9]. The normal glucose level in synovial fluid is usually less than 10 mg/dL lower than serum levels of glucose in the fasting state. Joint disorders caused by infectious agents have usually a large decrease in synovial fluid glucose[9,10], as seen in the present clinical case. In spite of this, synovial fluid glucose levels are neither sensitive nor specific for septic arthritis and therefore results must be interpreted cautiously. Synovial fluid adenosine deaminase level, has been correlated with the diagnosis of TB arthritis, with a high sensitivity and specificity (83.3% and 96.7% respectively)[11], but this laboratorial exam was not available for our patient. Septic arthritis can coexist with crystal arthropathy; therefore, the presence of crystals does not preclude a diagnosis of septic arthritis, as it was found in this case.

Reliable diagnostic methods include synovial fluid cultures, which are positive for MT in almost 80% of

proven cases, but only about one-fifth of the patients will have a positive synovial fluid smear for acid-fast tubercular bacillii[9]. Synovial biopsy, demonstrates granuloma in more than 90% of specimens[9], which may not be synonymous of TB, given the existence of other diseases that show synovial granulomas. Fungal joint diseases, sarcoidosis, erythema nodosum, traumatic fat necrosis, brucellosis, Crohn's disease and foreign body giant cell reaction are other possible causes of granulomatous synovitis[9,10]. Of remark, culture of synovial tissue may be positive even when blood and synovial fluid cultures have been negative[8]. PCR, as a method for diagnosing tuberculosis, has shown to be sensitive for rapid detection of MT with a mean detection time of less than one day, compared with the average 13 days for diagnosis by radiometric method BACTEC[12]. The PCR result for our patient allowed a rapid diagnosis and supported the implementation of anti-tuberculosis treatment.

Arthroscopy is a minimally invasive procedure that facilitates the diagnosis of infectious arthritis, including TB, by allowing direct visualization of intra-articular space and enabling adequate sampling of synovial membrane. Furthermore this technique brings additional benefits for the treatment of septic arthritis due to an efficacious joint lavage and removal of debris[13]. Early arthroscopic lavage at initial stages of infection can influence the outcome, as a shorter time between the first symptoms and the lavage is a known factor of better prognosis[14]. Because tuberculosis presentation often mimics other systemic diseases, arthroscopy and synovial membrane biopsy should be promptly performed when the diagnosis of a monoarthritis is not clear or treatment established for other etiologies is not efficacious, as in our case. This arthroscopy was performed by a rheumatologist, in an outpatient minimal invasive techniques room, under local anesthesia and according to previously published recommendations[15]. The easy access to this technique by a rheumatologist allowed a rapid diagnosis and early initiation of a specific therapy. The herein case therefore highlights that arthroscopic guided synovial biopsy is an important tool in the diagnostic algorithm of a monoarthritis of unknown etiology.

During clinical examination tuberculosis arthritis is often overlooked. High index of suspicion, synovial membrane biopsy and appropriate microbiologic testing are fundamental to avoid diagnostic delay.

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CORRESPONDENCE TO

Sílvia Carina Teotónio Fernandes
Avenida Professor Egas Moniz, 1649-035 Lisboa
E-mail: silvia_tfernandes@yahoo.com

REFERENCES

1. Pigrau-Serrallach C, Rodríguez-Pardo D. Bone and joint tubercu. losis. Eur. Spine J. Off. Publ. Eur. Spine Soc. Eur. Spinal Deform. Soc. Eur. Sect. Cerv. Spine Res. Soc. 2013;22 Suppl 4:556-566.
2. Portugal – Infeção VIH, SIDA e Tuberculose em números - 2014. www.dgs.pt/estatisticas-de-saude/estatisticas-de-saude/publicacoes/portugal-infecao-vih-sida-e-tuberculose-em-numeros-2014.aspx Accessed in December 8th 2014
3. Fiske CT, de Almeida AS, Shintani AK, Kalams SA, Sterling TR. Abnormal immune responses in persons with previous extrapulmonary tuberculosis in an in vitro model that simulates in vivo infection with Mycobacterium tuberculosis. Clin. Vaccine Immunol. CVI. 2012;19:1142-1149.
4. Jutte PC, van Loenhout-Rooyackers JH, Borgdorff MW, van Horn JR. Increase of bone and joint tuberculosis in The Netherlands. J. Bone Joint Surg. Br. 2004;86:901-904.
5. García-Rodríguez JF, Álvarez-Díaz H, Lorenzo-García MV, Mariño-Callejo A, Fernández-Rial Á, Sesma-Sánchez P. Extrapulmonary tuberculosis: epidemiology and risk factors. Enfermedades Infecc. Microbiol. Clínica. 2011;29:502-509.
6. Kamboj M, Sepkowitz KA. The risk of tuberculosis in patients with cancer. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2006;42: 1592-1595.
7. Daucourt V, Petit S, Pasquet S, Portel L, Courty G, Dupon M, et al. [Comparison of cases of isolated pulmonary tuberculosis with cases of other localizations of tuberculosis in the course of an active surveillance (Gironde, 1995-1996)]. Rev. Médecine Interne Fondée Par Société Natl. Francaise Médecine Interne. 1998;19:792--798.
8. Bresnihan B. Are synovial biopsies of diagnostic value? Arthritis Res. Ther. 2003;5:271-278.
9. Wallace R, Cohen AS. Tuberculous arthritis: A report of two cases with review of biopsy and synovial fluid findings. Am. J. Med. 1976;61:277-282.
10. Saraiva F, Canas DA Silva J, Jaime Branco. Silva J, Gaião L, Viana Queiroz M. tuberculose osteo-articular - apresentação de sete casos e revisão da literatura. Acta Reumatológica Portuguesa. 1990;XV:147-165.
11. Foocharoen C, Sarntipipattana C, Foocharoen T, Mahakkanukrauh A, Paupairoj A, Teerajetgul Y, et al. Synovial fluid adenosine deaminase activity to diagnose tuberculous septic arthritis. Southeast Asian J. Trop. Med. Public Health. 2011;42: 331--337.
12. Negi SS, Khan SFB, Gupta S, Pasha ST, Khare S, Lal S. Comparison of the conventional diagnostic modalities, bactec culture and polymerase chain reaction test for diagnosis of tuberculosis. Indian J. Med. Microbiol. 2005;23:29-33.
13. Stutz G, Kuster MS, Kleinstück F, Gächter A. Arthroscopic management of septic arthritis: stages of infection and results. Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA. 2000;8: 270--274.
14. Vispo Seara JL, Barthel T, Schmitz H, Eulert J. Arthroscopic treatment of septic joints: prognostic factors. Arch. Orthop. Trauma Surg. 2002;122:204-211.
15. Van de Sande MGH, Gerlag DM, Lodde BM, van Baarsen LGM, Alivernini S, Codullo V, et al. Evaluating antirheumatic treatments using synovial biopsy: a recommendation for standardisation to be used in clinical trials. Ann. Rheum. Dis. 2011;70: 423-427.