Tuberculosis in rheumatoid arthritis patients: the difficulty in making the diagnosis of latent infection*

Tuberculose em pacientes com artrite reumatoide: a dificuldade no diagnóstico da forma latente

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Abstract

Since the beginning of the use of anti-TNF in the treatment of rheumatoid arthritis and other inflammatory diseases, cases of pulmonary tuberculosis and extrapulmonary tuberculosis have been reported in patients receiving such treatment. In most cases, the disease develops by the time the patient has received the sixth infusion. Every patient should be evaluated for latent tuberculosis infection prior to the use of a TNF inhibitor. However, the diagnosis of latent tuberculosis infection is a challenge. The tuberculin test, which was the only test available to detect latent tuberculosis infection for nearly a century, presents a number of limitations. Tests based on the detection of the in-vitro production of IFN-γ by mononuclear cells activated by specific antigens appear to be more accurate and have been studied in patients with rheumatoid arthritis.

Keywords: Tuberculosis, pulmonary; Arthritis, rheumatoid; Tumor necrosis factor-alpha; Infection.

Resumo

Desde o início do uso de drogas anti-TNF para o tratamento da artrite reumatoide e outras doenças inflamatórias, casos de tuberculose pulmonar e extrapulmonar vêm sendo notificados em pacientes submetidos a tal tratamento. Na maioria das vezes, a doença se desenvolve durante as seis primeiras infusões. Todo paciente deve ser avaliado para tuberculose latente antes do início do uso de um bloqueador de TNF; no entanto, o diagnóstico de tuberculose latente é um desafio. A prova tuberculínica, o único teste disponível para a detecção de tuberculose latente por quase um século, apresenta uma série de limitações. Testes baseados na detecção da produção de IFN-γ in vitro por células mononucleares ativadas por antígenos específicos parecem ser mais acurados e vêm sendo pesquisados em pacientes com artrite reumatoide.

Descritores: Tuberculose pulmonar; Artrite reumatoide; Fator de necrose tumoral alfa; Infecção.

Introduction

Worldwide, nearly 25,000 people develop tuberculosis every day and, in 2007, approximately 1.7 million died from this disease.[1] These numbers make tuberculosis the leading cause of death from a curable infectious disease in adults. In Brazil, the numbers are also alarming. A total of 81,660 new cases were reported in 2008. In 2005, the annual incidence reported in Brazil was 43.7 cases per 100,000 population, whereas the annual incidence reported in the state of Goiás was 17.35 cases per 100,000 population. It is estimated that 50 million Brazilians are infected with the tuberculosis bacillus.[2]

Approximately 5% of all individuals infected with *Mycobacterium tuberculosis* will develop active tuberculosis within the first two years after infection. Latent tuberculosis infection is defined as the period between the moment at which the bacilli enter the organism and the onset of active tuberculosis.[3] The remaining 95% of exposed individuals will prevent the development of the disease via an effective cellular immune response. Elements that can affect immunity, such as co-infection (e.g., with HIV), comorbidity (e.g., diabetes mellitus), age, use of immunosuppressants and nutri-

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tional status, promote the development of the disease. Rheumatoid arthritis (RA) is a comorbidity that has gained considerable interest in the last decade. In this period, biological agents, also known as new drugs that alter the course of the disease, have been introduced. Among the biological agents available in Brazil are TNF inhibitors (anti-TNF). Since the beginning of the use of anti-TNF, cases of pulmonary tuberculosis and extrapulmonary tuberculosis have been reported in patients receiving such treatment.[4]

The objective of the present article is to discuss the diagnosis of latent tuberculosis infection in RA patients, which allows the indication of treatment of the latent infection prior to the use of anti-TNF, thereby reducing the incidence of active tuberculosis in this population.

Clinical case

We report the case of a 41-year-old female homemaker from the city of Piracanjuba, located in the state of Goiás, Brazil. The patient had previously been diagnosed with arterial hypertension and had been using enalapril for several years. In addition, she had been diagnosed with RA more than ten years prior. During that period, she was treated with various therapeutic regimens for RA. She had been under treatment prednisone (5 mg/day) and methotrexate. Since she continued to have many joint symptoms, adalimumab was also prescribed. After two months of adalimumab treatment, the patient began to have low fever almost daily, as well as mild dry cough and mild asthenia. She sought medical attention at an emergency room in the city of Goiânia, also located in the state of Goiás, and was diagnosed with pneumonia after a chest X-ray (Figure 1). The patient used azithromycin (500 mg) for five days, in accordance with a prescription. The patient initially presented a slight improvement, but the dry cough and fever returned after the medication was discontinued. Two months later, since her clinical profile remained the same, she sought medical attention again, at which point a ten-day course of levofloxacin (500 mg/day) was prescribed. Again, she presented a slight improvement but the symptoms reappeared after the end of the course.

The patient stated that she was not a smoker or an alcoholic. She reported that she had tested negative on a tuberculin skin test (TST) conducted before the initiation of adalimumab treatment, and that, according to the rheumatologist who treated her, a chest X-ray performed at the time was normal. After the use of azithromycin (three and half months prior), she also received an additional infusion of adalimumab. Physical examination revealed mild pallor and no palpable lymph node enlargement. There were fine rales in the upper third of the left hemithorax and coarse rales in the middle third of the right hemithorax, as well as scattered rhonchi. Her hands and feet had joint deformities. A chest X-ray revealed alveolar opacities in the left upper lobe, left lower lobe and middle lobe, as well as images suggestive of bronchogenic dissemination (Figure 2). A CT scan of the chest revealed tree-in-bud centrilobular opacities (Figure 3).

Another TST was performed, and the result was again negative (induration, 0 mm). Two consecutive sputum samples were smear-negative (Ziehl-Neelsen staining). The patient underwent bronchoscopy, which showed a whitish infiltrative lesion occluding 50% of the bronchial lumen of the left upper lobe as well as intense adjacent inflammatory reaction. The anatomopathological examination of the bronchial lesion revealed an extensive, chronic granulomatous inflammatory response with coagulative necrosis. There were no signs of malignancy. The bronchoalveolar lavage fluid tested positive for AFB in smear microscopy. The patient was diagnosed with pulmonary tuberculosis, and treatment with regimen 1 (rifampin/isoniazid/pyrazinamide) was instituted. She presented favorable evolution, showing improvement in the symptoms and in the radiological aspect thirty days later. The patient was discharged after six months of treatment, showing complete resolution of the respiratory symptoms and significant improvement in the chest X-ray results (Figure 4).

Inflammatory response in RA and in tuberculosis

It is known that RA is a chronic inflammatory disease, is autoimmune, has unknown etiology and affects all ethnic groups worldwide. Females are more often affected than are males (ratio = 2.5:1). Although the onset of RA can occur at any age, its incidence peaks between the fourth and fifth decades of life. The disease is clinically characterized by symmetrical

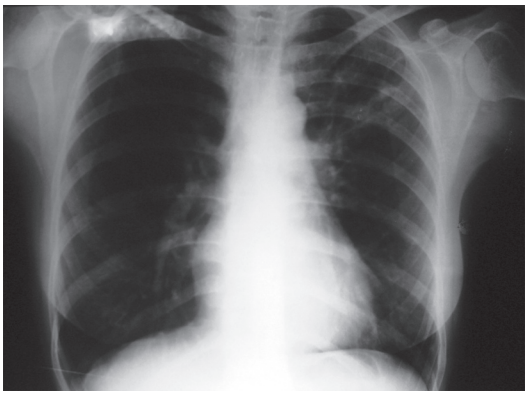

Figure 1 - Chest X-ray revealing alveolar opacity with apparent cavitation in the left upper lobe.

peripheral polyarthritis, which leads to deformity and destruction of the joints due to bone and cartilage erosion. Wrists, fingers, toes, knees and feet are most commonly affected. In addition, nonspecific constitutional symptoms, such as fatigue, nonrestorative sleep and weight loss, can occur.[5-7] The principal alterations in the synovial membrane of such patients are as follows: hyperplasia; vascular alterations, including microvascular injury, thrombosis and neovascularization; edema; and inflammatory cell infiltrate composed primarily of CD4+ T cells. Antigen-activated CD4+ T cells stimulate monocytes, macrophages and synovial fibroblasts to produce the cytokines IL-1, IL-6 and TNF-α, as well as to secrete metalloproteinases, through the surface markers CD69 and CD11 and through the release of soluble mediators, such as INF-γ and IL-17. In addition, the activated CD4+ T cells stimulate B cells to produce immunoglobulins, including the rheumatoid factor. The principal cytokines responsible for inflammation in RA are IL-1, IL-6 and TNF-α. The cytokines IL-1 and TNF-α stimulate the cells of the synovial membrane to produce collagenases and other proteases, as well as activating chondrocytes, stimulating them to produce proteolytic enzymes that can locally degrade cartilage. Finally, IL-1 and TNF-α can contribute to local demineralization through osteoclast activation.[5,8] Being an inflammatory cytokine, TNF-α plays an important and perhaps dominant role in rheumatoid synovitis. In a study of synovial cell cultures from RA patients, TNF-α inhibition by antibodies significantly reduced the production of IL-1, IL-6, IL-8 and GM-CSF. Therefore, it is likely that TNF-α inhibition has a more global effect on inflammation than does the inhibition of other cytokines that are present in high concentrations in the synovial liquid, such as IL-1.[8] The treatment of RA includes symptomatic medications for pain control: nonsteroidal anti-inflammatory drugs; glucocorticoids; and drugs that alter the course of the disease, such as hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, azathioprine and cyclosporine. In patients who continue to have significant joint symptoms, despite the use of combinations of these drugs, biological agents, among which is anti-TNF, are indicated.[6]

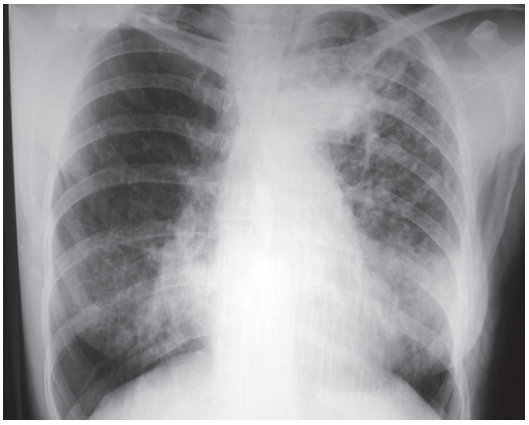

Figure 2 - Chest X-ray revealing alveolar opacities in the left upper lobe and bilaterally at the lung bases, as well as images suggestive of bronchogenic dissemination in the middle third of the left hemithorax.

Conversely, the effectiveness of the cellular immune response in tuberculosis depends, in part, on the ability to produce an appropriate cytokine profile, including TNF-α. Being involved in the increased capacity of macrophages to phagocyte and destroy mycobacteria, TNF-α is a pro-inflammatory cytokine with an important role in the pathogenesis of tuberculosis. In addition, the production and release of TNF-α are essential for the formation of granulomas that sequester mycobacteria and prevent their dissemination.[4]

TNF-α inhibitors and tuberculosis

Drugs that inhibit TNF-α have been developed and used in RA patients with the objective of neutralizing the deleterious effects of this inflammatory cytokine. To date, there are three drugs available to patients who are refractory to conventional treatments for RA, including

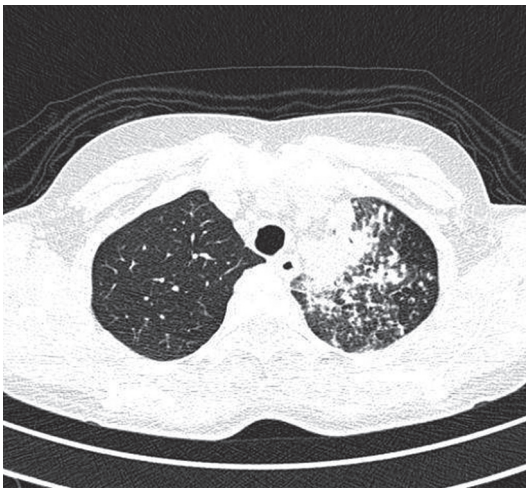

Figure 3 - Chest CT scan revealing tree-in-bud centrilobular opacities predominantly in the upper portions of the left lung.

to methotrexate: two humanized monoclonal antibodies—infliximab and adalimumab—and a fusion protein composed of two TNF p75 units hybridized to the Fc portion of human IgG1, which acts as a competitive TNF inhibitor—etanercept.[9] These three agents have been proven to be effective and safe in patients with initial or established disease, improving quality of life and minimizing the progression of radiological damage.[10,11] However, since the beginning of the use of anti-TNF-α, hundreds of cases of pulmonary tuberculosis and extrapulmonary tuberculosis have been reported in patients receiving such treatment. In a survey of all cases reported to the Food and Drug Administration up to May of 2001, it was observed that, among the 140,000 patients treated with infliximab, there were 70 reported cases of tuberculosis, 40 of which were cases of extrapulmonary tuberculosis. In most cases (98%), tuberculosis developed by the time the patient had received the sixth infusion.[12] Other studies have demonstrated an increased incidence of tuberculosis in patients treated with anti-TNF.[13] Therefore, patients receiving anti-TNF should be considered to be at risk for progression of a recently acquired infection to active tuberculosis or for reactivation of a remotely acquired infection.[4]

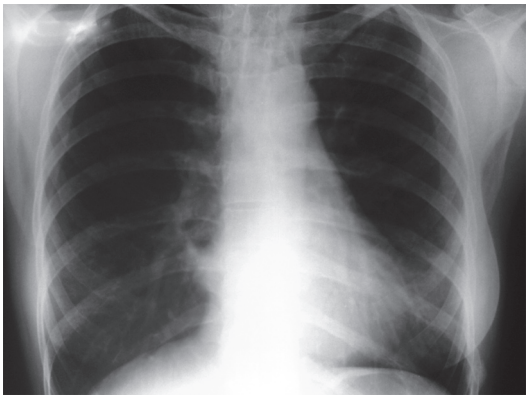

Figure 4 - Chest X-ray revealing significant improvement after the completion of tuberculosis treatment with regimen I.

Latent infection

Every candidate for anti-TNF treatment should be evaluated for latent tuberculosis infection prior to the initiation of such treatment.[3,4,6,7,14] The diagnosis of latent tuberculosis infection is a challenge. It is not possible to detect the presence of latent mycobacteria in the body directly. In general, patients do not have any clinical complaints or radiological abnormalities. In accordance with the III Brazilian Thoracic Association Guidelines on Tuberculosis, candidates for anti-TNF treatment who have a TST induration ≥ 5 mm should receive treatment for latent infection—isoniazid at a dose of 5-10 mg/kg of body weight (up to 300 mg/day) for 6 months—and anti-TNF treatment should be initiated only after at least one month of isoniazid treatment.[3] Patients with negative TST results but with a history of tuberculosis, without adequate treatment or a chest X-ray suggestive of sequelae of tuberculosis, would also be candidates for treatment of latent tuberculosis infection.[14,15]

A major complicating factor for the diagnosis of latent tuberculosis infection in RA patients is the abnormal cellular immune function observed in such patients. Patients with RA would have an inability to produce an adequate response to the TST even when infected with *M. tuberculosis*.[16]

The TST is the test that has been used the longest to diagnose latent tuberculosis infection. It is based on the cell reaction (accumulation of inflammatory cells) occurring in the skin 24-72 h after intradermal injection of PPD (a mixture of proteins of low molecular weight).[17] The TST, the only test available to detect latent tuberculosis infection for nearly a century, presents a number of limitations, some of which are of an operational nature (injection technique, reading

Chart 1 - Studies comparing rheumatoid arthritis patients and controls in terms of positive tuberculin skin test results.

Study	RA patients	Controls	RA patients presenting positive TST results	Controls presenting positive TST results
(place)	n	n	%	%
Ponce de Leon et al.[18] (Lima, Peru)	112	96	29.4	70.8
Provenzano et al.[15] (Palermo, Italy)	69		8.7[a]	
Marques et al.[21] (Pernambuco, Brazil)	48	48	14.6[a]	33.3
Greenberg et al.[20] (Nova York, USA)	61	42	21.3	11.9
Sezer et al.[19] (Antalya, Turkey)	58	69		39
	35[b]/23[c]		20[b]/31[c]	

RA: rheumatoid arthritis; and TST: tuberculin skin test. [a]Overall diagnosis of latent tuberculosis in 24.6% (history of tuberculosis or TST induration > 5 mm or chest X-ray consistent with previous tuberculosis: calcified nodule; apical fibrosis; or pleural thickening). [b]Patients without a history of treatment for RA. [c]Patients with a history of treatment for RA, candidates for the use of anti-TNF.

technique and need for two visits to the laboratory) and some of which are of an immunological nature (booster effect, low specificity in individuals who have been vaccinated with BCG, cross-reaction with other mycobacteria and low sensitivity in immunocompromised patients).

In a study of 112 RA patients and 96 controls conducted in Lima, Peru, it was observed that 70.6% of the RA patients had negative TST results, in comparison with 26% of the controls. All patients received prednisone at doses lower than 7.5 mg/day, which are recognized as having no immunosuppressive effect.[18]

More recently, in a study of 149 individuals (35 untreated RA patients, 23 RA patients, 22 patients with ankylosing spondylitis who were receiving immunosuppressants and were candidates for treatment with biological agents and 69 healthy individuals), it was observed that the untreated RA patients had significantly smaller TST indurations than did the RA patients who were receiving immunosuppressants, the patients with ankylosing spondylitis and the controls, suggesting a direct effect of RA on TST results.[19]

In a study of 69 RA patients, 10 patients with ankylosing spondylitis and 6 patients with psoriatic arthritis conducted in Italy, it was observed that 8.7% of the patients had positive TST results, whereas, overall, 24.6% of the patients were diagnosed with latent tuberculosis infection based on a history of tuberculosis, positive TST results or radiological lesions consistent with sequelae of tuberculosis. The data obtained suggest that the TST is not sensitive enough to diagnose latent tuberculosis infection in RA patients and patients with other spondyloarthropathies.[15]

In a recent study of 96 individuals (48 RA patients and 48 healthy controls) conducted in Pernambuco, Brazil, it was observed that 14.6% of the RA patients had positive TST results (induration ≥ 5 mm), in comparison with 33.3% of the patients in the control group (induration ≥ 10 mm).[20]

A result that is in disagreement with previous findings was observed in a study conducted in the city of New York (USA). Considering that a positive TST result was defined as an induration ≥ 10 mm, 16.4% of the RA patients tested positive, in comparison with 11.9% of the controls. Using a TST cut-off point of 5 mm in the RA patients, 21.3% tested positive.[21]

In addition, it is relevant to mention the study in which the use of treatment for latent tuberculosis infection in patients who would receive anti-TNF was based only on the TST results, there being 4 cases of active tuberculosis among the 43 patients included.[22]

With the exception of the study conducted in New York, the other studies described showed a significantly lower percentage of positive TST results among RA patients (even when defining a positive TST result as an induration ≥ 5 mm) than among healthy controls, therefore suggesting that the TST has limited ability

to identify latent tuberculosis infection in the former group of patients (Chart 1).

New tests for the diagnosis of latent tuberculosis infection

The development of alternative tests for the diagnosis of latent tuberculosis infection has been the subject of numerous studies. The identification of regions of the *M. tuberculosis* genome that are absent from BCG and environmental bacteria has allowed the development of new diagnostic tools. Two proteins encoded by the region of difference 1 (ESAT-6 and CFP-10), which is deleted during the transformation of *M. bovis* for the production of BCG vaccine, are used as specific antigens. These proteins induce a strong T cell immune response in experimental models, leading to the production of INF-γ, which is quantified by the tests.[23] Two commercial tests for quantifying INF-γ have been used in studies. The first uses ELISA technology and measures the concentration of INF-γ released after incubation of whole blood with the specific antigen (QuantiFERON-TB-Gold®; Cellestis Inc., Valencia, CA, USA). The other employs the enzyme-linked immunospot (ELISPOT) assay using peripheral blood mononuclear cells that produce INF-γ in response to the stimulation with the specific antigens (T-SPOT.TB®; Oxford Immunotec, Abingdon, United Kingdom).

The ELISA-based method presents high specificity in healthy individuals vaccinated with BCG (over 98% vs. 35.4% on the TST).[24] Studies of the correlation between the ELISA method and the TST show very different results in areas where tuberculosis is endemic than in areas where it is not. These results might be affected by the low specificity of the TST in populations vaccinated with BCG and by false-negative results obtained by the ELISA method, since the antigens used in the test are not the only ones responsible for the antigenicity of *M. tuberculosis*.[25]

The use of the ELISA method for the diagnosis of latent tuberculosis infection in RA patients has been the subject of various studies in the last three years. In a study conducted in Lima, Peru, where tuberculosis is endemic (the estimated prevalence of latent tuberculosis infection is 68%), the use of the TST and the ELISA method in 101 RA patients and in 93 controls (patients with non-inflammatory rheumatic diseases) was compared. A positive TST result was defined as an induration ≥ 5 mm in RA patients and an induration ≥ 10 mm in controls. The number of patients with positive ELISA results was comparable between the RA group and the control group (44.6% and 59.1%, respectively), whereas the number of patients with positive TST results for latent tuberculosis infection was significantly lower in the RA group than in the control group (26.7% vs. 65.6%).[26]

In a study of a population in which there was low tuberculosis endemicity—142 patients with rheumatic diseases (57 with spondyloarthropathies, 40 with RA and 45 with other diseases)—poor concordance was observed between the TST results and the results of the determination of INF-γ. Positive ELISA results were more strongly associated with the presence of risk factors for latent tuberculosis infection and more weakly associated with BCG vaccination than were positive TST results (OR = 0.74; 95% CI: 0.15-1.47 vs. OR = 2.44; 95% CI: 0.74-8.01; p = 0.025). A history of BCG vaccination affected the TST results but not the ELISA results.[27]

In a study of 398 patients with autoimmune diseases conducted in Rome, Italy, good concordance was observed between the TST and the ELISA method (87.7%). That was a population in which tuberculosis was not endemic, and only 4% of the patients studied had been vaccinated with BCG.[28]

The other method for quantifying INF-γ, the ELISPOT assay, has also been studied in RA patients. In a study of patients with autoimmune disease conducted in France, 68 patients were classified as either having latent tuberculosis infection (n = 35) or not having latent tuberculosis infection (n = 33), in accordance with clinical and radiological criteria and based on positive TST results (induration ≥ 10 mm), during the investigation of latent tuberculosis infection prior to the use of anti-TNF-α agents. After the ELISPOT assay was performed with antigens specific for tuberculosis, the number of positive results in the group of patients classified as having latent tuberculosis infection increased (p = 0.05). Of the 13 patients with latent tuberculosis infections regardless of the TST, 38.5% had negative TST results and 15.4% had negative ELISPOT results, demonstrating a greater sensitivity of the ELISPOT assay in relation to the TST.[29]

In a recent study conducted in the state of Pernambuco, Brazil, the ELISPOT assay and the TST were performed in 48 RA patients and 49 healthy controls. Of the RA patients, 25% had positive ELISPOT results, whereas 14% had positive TST results. In the control group, 35% had positive TST results and 18% had positive ELISPOT results. Using different models for the identification of latent tuberculosis infection (positive TST results; positive TST results and chest X-ray abnormalities; positive TST results and household contact with active tuberculosis; positive TST results and radiological alteration; and household contact with active tuberculosis), a high specificity and a high negative predictive value were observed in the RS group, suggesting that, in that sample, the ELISPOT assay was more useful in identifying false-negative TST results (12 positive ELISPOT results vs. 7 positive TST results). In addition, that study demonstrated the ability of the ELISPOT assay to confirm, with a high degree of certainty, that, in cases of negative TST results, latent tuberculosis infection is really absent. Those authors concluded that, for the RA patients in that population, positive TST results did not need to be confirmed by the ELISPOT assay, and that treatment for latent tuberculosis infections should be indicated. In contrast, in cases with negative TST results and chest X-ray abnormalities or in those with household contact with active tuberculosis, false-negative results could be confirmed by the ELISPOT assay.[30]

Final considerations

In summary, studies of tests for quantifying INF-γ in the specific group of RA patients are still scarce. In addition, results vary significantly if we consider populations with different prevalences of latent tuberculosis infection. A great difficulty in evaluating the performance of such tests is the lack of a gold standard to identify true cases of latent tuberculosis infection, which makes it difficult to compare results among studies using different definitions. Another difficulty is the lack of standardization of the TST cut-off point in the studies, a positive result being defined as 5 mm by some authors and as 10 mm by others.

In the case reported here, testing for latent tuberculosis infection was carried out in accordance with the current Brazilian guidelines, by surveying the history of contacts and performing chest X-rays and TSTs. This case illustrates the possibility that RA patients can present active tuberculosis after the use of TNF inhibitors even without having latent infection, as identified by the methods currently used in Brazil. In addition, it demonstrates the delay in correctly diagnosing tuberculosis, a common situation even in a country with a high incidence of the disease. Therefore, the present case draws attention to the need for developing new diagnostic and management tools for this group of patients and, principally, to the need for monitoring patients for symptoms suggestive of active tuberculosis after starting treatment.

References

1. World Health Organization [homepage on the Internet]. Geneva: World Health Organization Global [cited 2009 Sep 5]. Global Tuberculosis Control - A short update to the 2009 report. Available from: http://www.who.int/tb/publications/global_report/en
2. DATASUS [homepage on the Internet]. Brasília: Ministério da Saúde [cited 2009 Sep 5]. TUBERCULOSE - Casos confirmados notificados no Sistema de Informação de Agravos de Notificação - Sinan Net. Available from: http://dtr2004.saude.gov.br/sinanweb/tabnet/dh?sinannet/tuberculose/bases/tubercbrnet.def
3. Conde MB, de Melo FA, Marques AM, Cardoso NC, Pinheiro VG, Dalcin Pde T, et al. III Brazilian Thoracic Association Guidelines on tuberculosis. J Bras Pneumol. 2009;35(10):1018-48.
4. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis. 2003;3(3):148-55.
5. Lipski PE. Artrite reumatóide. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al, editors. Harrison: Princípios de Medicina Interna. Rio de Janeiro: McGraw-Hill; 2006. p. 2064-73.
6. Bértolo MB, Brenol CV, Schainberg CG, Neubarth F, Lima FAC, Laurindo IM, et al. Atualização do consenso brasileiro no diagnóstico e tratamento da artrite reumatóide. Rev Bras Reumatol. 2007;47(3):151-9.
7. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002;46(2):328-46.
8. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med. 2001;344(12):907-16.
9. Toussirot E, Wendling D. The use of TNF-alpha blocking agents in rheumatoid arthritis: an update. Expert Opin Pharmacother. 2007;8(13):2089-107.
10. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999;130(6):478-86.
11. Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, et al. Randomised double-blind comparison

of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet. 1994;344(8930):1105-10.
12. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001;345(15):1098-104.
13. Wallis WJ, Burge DJ, Sabath D, Gardiner M. Tuberculosis reports with etanercept (Enbrel) therapy [abstract]. Arthritis Rheum. 2001;44 Suppl 9:S78.
14. British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. Thorax. 2005;60(10):800-5.
15. Provenzano G, Ferrante MC, Simon G. TB screening and anti-TNF alpha treatment. Thorax. 2005;60(7):613.
16. Sezer I, Kocabas H, Melikoglu MA, Arman M. Positiveness of purified protein derivatives in rheumatoid arthritis patients who are not receiving immunosuppressive therapy. Clin Rheumatol. 2009;28(1):53-7.
17. Teixeira HC, Abramo C, Munk ME. Immunological diagnosis of tuberculosis: problems and strategies for success. J Bras Pneumol. 2007;33(3):323-34.
18. Ponce de León D, Acevedo-Vásquez E, Sánchez-Torres A, Cucho M, Alfaro J, Perich R, et al. Attenuated response to purified protein derivative in patients with rheumatoid arthritis: study in a population with a high prevalence of tuberculosis. Ann Rheum Dis. 2005;64(9):1360-1.
19. Sezer I, Kocabas H, Melikoglu MA, Arman M. Positiveness of purified protein derivatives in rheumatoid arthritis patients who are not receiving immunosuppressive therapy. Clin Rheumatol. 2009;28(1):53-7.
20. Marques CD, Duarte AL, Lorena VM, Souza JR, Souza W, Gomes YM, et al. Resposta atenuada ao PPD no diagnóstico de infecção tuberculosa latente em pacientes com artrite reumatóide. Rev Bras Reumatol. 2009;49(2):121-5.
21. Greenberg JD, Reddy SM, Schloss SG, Kurucz OS, Bartlett SJ, Abramson SB, et al. Comparison of an in vitro tuberculosis interferon-gamma assay with delayed-type hypersensitivity testing for detection of latent Mycobacterium tuberculosis: a pilot study in rheumatoid arthritis. J Rheumatol. 2008;35(5):770-5. Erratum in: J Rheumatol. 2008;35(5):943.
22. Chen DY, Shen GH, Hsieh TY, Hsieh CW, Lan JL. Effectiveness of the combination of a whole-blood interferon-gamma assay and the tuberculin skin test in detecting latent tuberculosis infection in rheumatoid arthritis patients receiving adalimumab therapy. Arthritis Rheum. 2008;59(6):800-6.
23. Andersen P, Munk ME, Pollock JM, Doherty TM. Specific immune-based diagnosis of tuberculosis. Lancet. 2000;356(9235):1099-104.
24. Mori T, Sakatani M, Yamagishi F, Takashima T, Kawabe Y, Nagao K, et al. Specific detection of tuberculosis infection: an interferon-gamma-based assay using new antigens. Am J Respir Crit Care Med. 2004;170(1):59-64.
25. Kang YA, Lee HW, Yoon HI, Cho B, Han SK, Shim YS, et al. Discrepancy between the tuberculin skin test and the whole-blood interferon gamma assay for the diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country. JAMA. 2005;293(22):2756-61.
26. Ponce de Leon D, Acevedo-Vasquez E, Alvizuri S, Gutierrez C, Cucho M, Alfaro J, et al. Comparison of an interferon-gamma assay with tuberculin skin testing for detection of tuberculosis (TB) infection in patients with rheumatoid arthritis in a TB-endemic population. J Rheumatol. 2008;35(5):776-81.
27. Matulis G, Jüni P, Villiger PM, Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a Mycobacterium tuberculosis antigen-specific interferon gamma assay. Ann Rheum Dis. 2008;67(1):84-90.
28. Bartalesi F, Vicidomini S, Goletti D, Fiorelli C, Fiori G, Melchiorre D, et al. QuantiFERON-TB Gold and the TST are both useful for latent tuberculosis infection screening in autoimmune diseases. Eur Respir J. 2009;33(3):586-93.
29. Sellam J, Hamdi H, Roy C, Baron G, Lemann M, Puéchal X, et al. Comparison of in vitro-specific blood tests with tuberculin skin test for diagnosis of latent tuberculosis before anti-TNF therapy. Ann Rheum Dis. 2007;66(12):1610-5.
30. Marques CD, Duarte AL, de Lorena VM, Souza JR, Souza WV, de Miranda Gomes Y, et al. Evaluation of an interferon gamma assay in the diagnosis of latent tuberculosis infection in patients with rheumatoid arthritis. Rheumatol Int. 2009. Epub 2009 Apr 11.

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