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Adalimumab-Induced Pulmonary Adverse Event In A Patient With Ankylosing Spondylitis: A Case Report.

Estela Louro[1,2], Simone Tomás Gonçalves[1,2], Rodrigo Aparecido Silva[2], Ricardo Alexandre Spironello[3],Francielli Maria Souza Silva-Comar[3], Paulo Roberto Donadio[4], and Roberto Kenji Nakamura Cuman[3]*.

[1]Department of Pharmacy, StateUniversityof Maringá, Maringá, Paraná, Brazil.
[2]Graduate Program in Health Science, State University of Maringá, Maringá, Paraná, Brazil.
[3]Department of Pharmacology and Therapeutics, State University of Maringá, Maringá, Paraná, Brazil, Brazil.
[4]Department of Medicine, State University of Maringá, Maringá, Paraná, Brazil.

ABSTRACT

Adalimumab, a tumor necrosis factor alpha antagonist, is widely used to treat autoimmune diseases such as ankylosing spondylitis. However, this drug is associated with both infectious and non-infectious pulmonary adverse events, including a reactivation of latent tuberculosis. We report and discuss the case of a 49-year-old patient with ankylosing spondylitis, treated with Adalimumab, who presented dyspnea, fever, night sweats, fatigue, general malaise and cough with discharge. On physical examination, presence of ventilatory movements with crackles in the left lung base. Laboratory and imaging tests with hematological and biochemical parameters and chest computed tomography with normal pattern. The symptoms ceased when treatment with Adalimumab was stopped, but after one year latent tuberculosis was evidenced. The diagnosis of bronchopneumonia was interpreted as an adverse reaction to Adalimumab. With the subsequent results of positive tuberculin tests and a history of previous exposure to tuberculosis prior to treatment with an immunobiological agent, we can consider that the respiratory manifestations could already be symptoms of latent tuberculosis reactivation. This case shows the importance of considering the possibility of diagnosing drug-induced lung disease, including tuberculosis, in patients treated with Adalimumab.

Keywords: adalimumab; ankylosing spondylitis; tumor necrosis factor-α; tuberculosis.

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Corresponding author

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INTRODUCTION

Adalimumab, an antagonist of tumor necrosis factor alpha (anti-TNFα), similar to other drugs in this class, is widely used in the treatment of inflammatory processes and autoimmune diseases, such as: spondyloarthritis, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease and systemic sclerosis. However, intensive monitoring must be maintained in patients who use these drugs due to infectious and non-infectious pulmonary adverse events, such as: pneumonitis, broncheolitis obliterative, interstitial lung disease and reactivation of pre-existing infections caused by fungi and mycobacteria [1]. In this paper, we present a case report of a patient being treated for ankylosing spondylitis with Adalimumab who developed pulmonary adverse events.

CASE REPORT

Female patient, 49 years old, brown, non-smoker and sedentary, diagnosed with fibromyalgia and ankylosing spondylitis (AS), HLA-B27 negative, presenting axial and peripheral symptoms since 2016. Before the diagnosis, she had used Pregabalin and Gabapentin, prescription replaced by Prednisone, Hydroxychloroquine and Cyclobenzaprine. In July 2016 there was a change in medication due to worsening pain, for Sulfasalazine, Ibuprofen and Duloxetine. After two weeks, the patient presented severe epigastric pain, the medication use was suspended and a new prescription included Naproxen+Omeprazole and Amitriptyline, maintained until February 2017. Due to the worsening of the joint inflammation process and severe arthralgia, she underwent the protocol tests for use of immunobiological drugs and started treatment with Adalimumab, Indomethacin and Amitriptyline. During the investigation, non-reactive tuberculin test (PPD) and chest X-ray with normal parameters. After 6 months of treatment with the anti-TNFα drug, the patient showed improvement in pain symptoms, but began to develop pulmonary complications, with dyspnea, fever, night sweats, fatigue, general malaise and cough with discharge. On physical examination, he presented ventilatory movements with crackles in the left lung base. Laboratory and imaging tests, hematological and biochemical parameters and chest computed tomography, all within normal limits. However, due to the worsening of the pulmonary respiratory condition, the patient was hospitalized and diagnosed with unspecified bronchopneumonia. Adalimumab and other medications were discontinued, and treatment with Ceftriaxone was carried out for 3 days. The patient started home treatment with Amoxicillin for another seven days and Gabapentin. Six weeks after discontinuing Adalimumab, dyspnea and other pulmonary symptoms improved. Cardiovascular and pulmonary problems were ruled out after expert assessment. During the investigation, she reported that her husband had undergone treatment for tuberculosis in 2003, with a recurrence in 2006. With active AS, she presented intense pain in the sacroiliac region and difficulty in movement, worsening when walking, sitting and lying down and BASDAI score 9.5, treatment with Adalimumab was restarted. After the second dose of the drug, the patient presented a relapse of the respiratory condition, suggesting an adverse reaction to Adalimumab, being definitively withdrawn in December 2017 and starting treatment with Naproxen, Loratadine and nebulization with Phenoterol and Ipratropium. In March 2018, with the improvement of the pulmonary condition, but still presenting intense disseminated pain, treatment with Etanercept was started. The tuberculin test (PPD) performed showed a negative result (< induration of 5 mm). The patient continued on medication for 9 months with AS and fibromyalgia under control. From then onwards, the patient returns to intense pain in the pelvis, ecchymosis in the hip and lower limbs, otalgia and pain in the right eye, and the same pulmonary symptoms described above. Right eye uveitis was diagnosed. New PPD featured induration of 10 mm. Etanercept was suspended, starting treatment with Prednisone, Methotrexate, Folinic Acid and Isoniazid as per protocol for the treatment of latent tuberculosis. Thirty days of treatment, he returned for consultation with pain worsening in the lumbar and pelvic region and edema in the lower limbs. She presented with dry cough, dyspnea and ventilatory-dependent pain in the rib cage (pain on inspiration). The medication was continued, with the addition of Gabapentin, Amitriptyline, and Ketoprofen. The result of the PPD performed after 60 days of treatment indicated an induration of 16 mm, presenting intense lumbar and pelvic pain and generalized joint pain in wrists, fingers, elbows, knees and ankles, in addition to edema and hyperemia in the right elbow joint and ankles. She reported improvement in her ulveitis and pulmonary status, normal chest X-ray and, on physical examination, free lungs, with no adventitious sounds. Followed treatment with Etanercept.

This study was approved by the Research Ethics Committee of the State University of Maringá, Maringá, Paraná, Brazil (CAAE: 44715321.1.0000.0104).

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DISCUSSION

AS is a rheumatic disease with the involvement of tumor necrosis factor alpha (TNFα) in the pathogenesis of inflammatory lesions. TNFα is a pro-inflammatory cytokine secreted by monocytes, macrophages and T lymphocytes during the inflammatory response, it also plays an important role in the immune response against infectious agents, including Mycobacterium tuberculosis [2,3].

The use of anti-TNFα in the treatment of AS is highly effective in reducing disease activity, improving clinical signs and symptoms and inhibiting radiographic progression [4]. Adalimumab is a recombinant human monoclonal antibody that blocks TNFα and may or may not be associated with other anti-inflammatory drugs to treat AS and other rheumatic diseases. As with Adalimumab, drugs of the same class such as: Etanercept, Infliximab, Golimumab and Certolizumab, can cause pulmonary adverse events [5,6]. The mechanism of these reactions is not well established, but it may be related to a combination of pathophysiological factors, including macrophage blockade and cytokine recruitment, increasing the risk of infections and triggering an inflammatory cascade that leads to pneumocyte proliferation and fibrosis [7, 8].

There is a need to control the appearance of opportunistic diseases in immunocompromised patients, as the use of immunotherapy can promote the appearance of latent or non-latent opportunistic diseases, requiring changes in drug therapy. Thus, polypharmacy can occur, increasing the risk of the appearance of adverse drug events, medication errors, drug interactions and adverse drug reactions.

In patients with AS, the differential diagnosis is very important to distinguish pulmonary events caused by an extra-articular manifestation of AS, exacerbation of pre-existing lung disease, heart failure, atypical infection caused by fungi and mycobacteria due to drug immunosuppression or interstitial lung disease caused by Adalimumab [9,10]. Anti-TNFα can lead to reactivation of latent TB by up to 250% [11] and further spread of the disease. Therefore, a differential diagnosis is necessary when the patient presents respiratory symptoms during treatment with these drugs [6].

Recommendations and protocols have been developed to reduce cases of TB reactivation in patients treated with immunobiological drugs [12]. However, there are differences between endemic countries and regions regarding the risk of exposure and different strategy can be established. In Brazil, due to the high endemic prevalence (31.6 per 100,000 inhabitants) [13] and the risk of reactivation of latent TB infection in patients with spondyloarthritis, the identification of high-risk patients and their treatment are essential before the onset of use or when there is a change of immunobiological [14,15].

In this clinical case presented, there is strong evidence that Adalimumab was responsible for the respiratory condition presented by the patient, because when the drug is definitively withdrawn, there was an improvement in symptoms. When applying the Naranjo Algorithm, the reaction was classified as proven for causality [16], reinforcing the established diagnosis. In addition, a probable latent tuberculosis infection was observed, since, despite the initial tests being negative, the use of Adalimumab when the AS condition worsened may have been the trigger for the reactivation of tuberculosis. There are reports that in the immunosuppressed patient, inadequate T cell response or skin anergy can lead to a false negative result for TB [14,17]. The clinical history must be carefully investigated, as despite the report of previous contact with TB, the diagnosis was not established at the onset of symptoms.

CONCLUSION

In the case presented, at first, the diagnosis of pneumonia was interpreted as an adverse reaction to Adalimumab. However, with the subsequent results of positive tuberculin tests and a history of previous exposure to TB prior to treatment with Adalimumab, we can concur that the respiratory manifestations could already be symptoms of latent TB reactivation. The presence of laboratory and imaging tests with atypical results makes the diagnosis difficult. However, the healthcare team must always be aware of the clinical history and adverse events during the use of anti-TNFα, especially those that may suggest a condition of TB and start treatment as soon as possible.

Conflicts of interest

The authors declare no conflict of interest with regards to this study.

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