wjpmr, 2021, 7(6), 41-43

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Case Report

ISSN 2455-3301

WJPMR

LYMPH NODE TUBERCULOSIS ASSOCIATED WITH ANTI-TUMOR NECROSIS FACTOR ALPHA TREATEMENT FOR RHEUMATOID ARTHRITIS: A CASE REPORT

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Article Received on 30/03/2021 **Article Revised on 20/04/2021** **Article Accepted on 10/05/2021**

ABSTRACT

Anti-tumor necrosis factor alpha (TNF-α) are biological agents that have been widely used for treating rheumatic diseases such as rheumatoid arthritis. Because of its immunosuppressive activity, it appears to further increase the risk of latent tuberculosis infection reactivation or causing de novo infection with Mycobacterium tuberculosis.

We present a case of lymph node tuberculosis in a 53-year-old woman with rheumatoid arthritis who has been treated with two TNF-α inhibitors adalimumab and etanercept separately.

KEYWORDS: Rheumatoid arthritis, Anti-TNF agents, lymph node tuberculosis.

BACKGROUND

The development of biologic drugs, especially anti TNF-α therapy, has changed dramatically the prognosis of rheumatoid arthritis (RA). However, TNF-α is also a key cytokine in host defence against intracellular infection, such as mycobacterium tuberculosis.

Thus all patients must be screened carefully for possible active or latent tuberculosis infection before treatment. A medical history of TB, a chest X-ray, and interferon-gamma assay are important to take account of the prophylaxis use of anti-TB drug, isoniazid (INH) before giving TNF-α inhibitors.[1]

CASE REPORT

A 53-year-old Moroccan woman with a history of 15-year-seropositive rheumatoid arthritis was seen in the outpatient department. She used several different disease-modifying anti-rheumatic drug (DMARD) regimens until 2015.

She received one anti CD20 (Rituximab) in 2015 without any improvement, followed by adalimumab for nine months without a major improvement, then we switched to etanercept for nine months with remarkably great results. The patient did not have a personal history of tuberculosis nor did she have any known exposure to persons with active tuberculosis, however interferon-gamma assay (QuantiFERON) was positive before both anti-TNF-α administrations. Isoniazid prophylaxis 200 mg per day has been started one month before treatment and was given for 9 months.

The articular symptoms improved gradually after the etanercept injections (25 mg, twice weekly) combined with methotrexate (10mg weekly) and prednisone (5mg per day). The serial laboratory tests showed improvement during the use of etanercept. However, one month before admission, the patient presented with a painless unilateral axillary mass on the left side measuring 5 centimetres of soft consistency.

On physical examination, she was hemodynamically stable, body temperature at 37.1C, heart rate at 82 beat/min and arterial blood pressure at 130/70 mm Hg. She had no tender or swollen joint. Passive and active range of movement was limited in the two wrists. Neurological and vascular examinations were normal and so was the respiratory system examination.

Initial laboratory investigations revealed mild anemia (Hemoglobin: 11.8 gr/dL), no leukocytosis (55% lymphocyte), slightly elevated C-reactive protein (CRP) (12.6 mg/dL) and erythrocyte sedimentation rate (ESR) (31 mm/h).

The chest X-ray was normal. With these findings, we suggested the following diagnosis: Metastatic cancer, lymphoma and lymph node tuberculosis.

An ultrasound has showed a large heterogeneous hypoechoic left axillary formation which appears to have a peripheral shell measuring 33, 26, and 32 mm with small satellite lymphadenitis.

Thorax and abdomen CT scan revealed the presence of three triangular nodes in the lateral segment of the median lobe and the posterior segment of the right upper lobe of 5 mm each. And a well-defined left axillary fluid mass of 40 by 31 mm in favour of necrotic adenopathy magma, which suggested active tuberculosis.

A surgical biopsy was performed and it allowed the evacuation of 100cc of fluid, the cytobacteriological analysis was normal but the anatomopathologic result showed a polymorphic inflammatory granulation tissue that contains in some places epithelial and giant cellular granulomas with caseous necrosis.

In light of these findings, our final diagnosis was lymph node tuberculosis, which was related to the previously given biological treatment. Anti-tuberculosis treatment was prescribed for six months.

DISCUSSION

TNF-α is a key component of host defences against Mycobacterium tuberculosis.[2] It influences the course of an infection by promoting the influx of cells into the infected area to control the inciting agent; in addition it stimulates the production of proinflammatory cytokines and influences the maturation of inflammatory cells.[3]

TNF-α directly activates macrophages, which engulf and kill the mycobacterium. TNF-α induces apoptosis and therefore helps to limit the extent of damage and maintaining granuloma formation.[4] However, in the presence of a TNF-α inhibitor these functions may be disturbed, making the host vulnerable to tuberculosis.[4,5]

TNF-α inhibitors have been implicated in the reactivation of tuberculosis or in the progression of recently acquired tuberculosis. In a recent report, Mohan et al.[6] reviewed 25 cases of tuberculosis in patients who were treated with etanercept. Thirteen (54%) patients were diagnosed with extrapulmonary tuberculosis, including three cases of disseminated disease, two of lymphadenitis and one with articular tuberculosis. These atypical clinical presentations may result in a delay of diagnosis and treatment.

Extrapulmonary TB usually accounts for a small percentage of TB infections, but during TNF inhibitor treatment, more than half of TB infections are due to extrapulmonary TB.[7]

Four types of TNF-α inhibitors are commonly used in Morocco: infliximab, etanercept, adalimumab and recently golimumab. These agents have been recommended as treatment for RA in patients who are not adequately controlled by at least two other disease modifying anti-rheumatic agents.[8] Etanercept is a fusion protein that consists of two soluble p75 TNF-α receptors linked to an immunoglobulin Fc domain. It functions as a soluble receptor of TNF-α, competing with TNF-α on the cell membrane receptors and blocking the biological activity.[9,10] Its efficacy is demonstrated within the first week of treatment and tends to be sustained throughout the duration of therapy. Several side effects have been reported, including injection site reactions, headache, demyelinating disorders, lupus, and infections.[11]

The risk of TB infection differs according to each drug. In studies in England and France comparing 3 TNF inhibitors: Etanercept, infliximab and adalimumab, the incidence of TB was lowest with etanercept.[1213] One of the reasons for differences in the risk of infection is differences in their mechanism of action, etanercept, in the absence of rheumatoid factor, will itself not induce apoptosis of TNF-expressing cells. Compared to infliximab and adalimumab, because of weaker inhibition of granuloma formation, the risk of TB infection is lower with etanercept but these infections may be more severe if they do develop.[14]

Precautionary measures are necessary, in particular screening for latent TB infection that usually consists of a personnal or family medical history of tuberculosis and imaging studies.

The tuberculin skin test is easy, but false-negative and false-positive results are a problematic issue. Therefore it has been replaced with a blood interferon-gamma assay (QuantiFERON®TB second generation), which is very useful for TB diagnosis and is not affected by BCG vaccination.[15]

The present patient was initially evaluated for possible latent TB and had a chest X-ray before starting TNF inibitors that showed no abnormalities, there was no prior history of TB or contact with another person who had TB. However, the interferon-gamma assay was positive. In such cases with latent TB infection, the risk of recurrence is high; therefore INH prophylaxis was given for nine months. The diagnosis of active tuberculosis was established by histological findings of the granuloma. The use of multiple biological drugs might explain the TB infection that had occurred despite the INH prophylaxis.

The French drug agency (Afssaps) has issued guidelines for the prevention and management of tuberculosis occurring under anti TNF alpha agent, The prophylactic treatment of these latent TB infections includes 3 patterns possible: either rifampicin and isoniazid for 3 months (Rifinah® 2 / d), or rifampicin and pyrazinamide for 2 months or isoniazid alone for 9 months. The latter pattern is an alternative in case of liver toxicity or for very old or cirrhotic subjects.[16]

Gómez-Reino et al. recommended that, in patients with a suspected prior history of TB infection based overall from the medical history, tuberculin skin test, and imaging findings, INH 5 mg/kg (maximum 300 mg) should be given orally for at least 1 month prior to starting a TNF inhibitor. In such patients who received

INH as prophylaxis for a total of 9 months, they reported no occurrence of TB.[17]

CONCLUSION

As the use of TNF-α inhibitors becomes more widespread, additional cases of tuberculosis associated with TNF-α inhibitor treatment are expected. If infection does develop, early detection and appropriate treatments are mandatory to obtain a good outcome.

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