Original Research Paper

Volume - 13 | Issue - 06 | June - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

General Medicine

AN INTERESTING CASE OF EXTRA PULMONARY TUBERCULOSIS IN RHEUMATOID ARTHRITIS

Dr. Rakesh Kumar*	Post Graduate Resident, ESI PGIMSR, New Delhi. *Corresponding Author
Dr. Maduri Vankayalapati	Ex Senior Resident, ESI PGIMSR, New Delhi.
Dr Priyank Rastogi	Associate Professor Medicine Deptt, ESI PGIMSR, New Delhi.
Dr Rajesh Chetiwal	Professor & Head of the Deptt, Medicine, ESI PGIMSR, New Delhi.

ABSTRACT The treatment of Rheumatoid Arthritis has been revolutionized ever since the advent of biologicals in treatment armamentarium. One of such drugs, Etanercept, a TNF-α antagonist is used as immunomodulatory drug in Rheumatoid Arthritis since 2002. It is usually considered as an effective drug in treatment of Rheumatoid Arthritis. However, there remains safety issues like occurrence of tuberculosis in patients on treatment with the drug. Although usual site of involvement with tuberculosis is pulmonary, but extra-pulmonary Tuberculosis can also be seen in patients receiving Etanercept. Here we report a case of 53 year old female patient of Rheumatoid Arthritis, Type-2 Diabetes mellitus and Hypothyroidism on Etanercept treatment who developed disseminated extra-pulmonary Tuberculosis in the form of Tubercular Pleural Effusion along with Pericardial effusion and Mediastinal lymphadenopathy.

KEYWORDS : TNF-α antagonist, Kochs' Disease.

INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by progressive joint destruction. If the disease is not treated properly, it leads to progressive pain, deformity and loss of function which is often accompanied by worsening quality of life and increasing mortality (1).

Tumour necrosis factor alpha (TNF-α) is a significant cytokine in RA as it mediates inflammation (2). Introduction of TNF-α inhibitors has revolutionized RA treatment options and had high efficacy in modifying the disease course and preventing the morbidity and mortality caused with the disease (3). Although TNF-α inhibitors have good clinical efficacy in Rheumatoid Arthritis, but there have been concerns regarding increased predisposition for Tuberculosis in patients receiving this medication. As per a study conducted in the United States in 2008, the estimated Tuberculosis incidence rate in Etanercept treated cases of RA reported to the FDA was 28 cases/100,000 patients (4). Most of the cases of TB are of pulmonary origin, however few cases have been reported with extra pulmonary TB in patients receiving Etanercept.

Here, we report a case of Rheumatoid Arthritis with Type 2 Diabetes Mellitus, Hypothyroidism on etanercept treatment for one year with disseminated extra-pulmonary Tuberculosis in the form of Pleural effusion, Pericardial effusion and Mediastinal lymphadenopathy who responded well to anti-tubercular treatment.

Case Report:

A 53 years old female patient arrived in casualty department of our institution with came with chief complaints of moderate fever on and off for three months with evening rise of temperature, progressive difficulty in breathing of grade 3/4 Modified Medical Research Council (mMRC) scale and bilateral lower limb swelling for 1 week. There was a prior history of Rheumatoid arthritis, T2DM and Hypothyroidism for which patient was on regular treatment. There was no complaint of chronic cough, cold, loose stools or history of joint swelling or stiffness in past 8 months. There was no past history of Tuberculosis.

On General Examination, patient was normotensive, tachypnoeic and tachycardia was present with oxygen saturation of 95 % on room air, JVP was raised and bilateral pitting oedema was present with facial puffiness. On systemic examination, heart sounds were of decreased intensity. On respiratory system examination, there was decreased air entry in bilateral lungs in inframammary, infra-axillary and infra-scapular areas; and the findings were more pronounced on towards right lung. Central nervous system and abdominal system examination were normal.

Patient was subjected to relevant evaluation and investigations. Haematological tests revealed mild anaemia of Normocytic Normochromic type with normal Liver and kidney function tests. Fever profile was negative for malaria, dengue, and typhoid. ESR was raised at 40 mm in 1st hr.

CRP level was more than 5mg/L which is positive. DAS28-ESR score was 2.6 points and DAS28CRP score was 2.10 points indicating low disease activity of RA. Thyroid profile was normal. Sputum was sent for Acid Fast Bacilli staining which came out as negative. Chest X-ray was suggestive of pleural effusion in bilateral lungs in lower zone more towards right with cardiomegaly and diagnostic pleural tap revealed raised TLC with lymphocytic predominance and raised ADA and protein levels. Mantoux test was positive with 10mm induration.

CECT chest and abdomen suggested of collapse present in Right middle lobe and inferior lingular segment with bilateral pleural effusion, pericardial effusion with necrotic mediastinal lymph nodes. Electrocardiogram showed low voltage QRS complexes and T-wave inversions chest lead V2- V6. Echocardiography suggested loculated moderate pericardial effusion, LVEF 60% with Right Ventricular and Right Atrial diastolic collapse. On basis of above investigations, a diagnosis of Disseminated Extrapulmonary Tuberculosis was made and anti-tubercular treatment was started.

After completing intensive phase of anti-tubercular treatment for 2 months, patient showed considerable improvement in her functional capacity. The patient was able to perform daily activities with minimal discomfort and dyspnoea improved from grade 4 to grade 2 mMRC scale.

Cardiac size was normal in Chest X ray done after 2 months and repeat echocardiography a demonstrated no traces of pericardial effusion.

DISCUSSION:

Despite having excellent efficacy, there have always been some safety concerns with anti- TNF therapy. The various anti TNF agents approved by US FDA have been tabulated in table 1 (5). There has been evidence from pharmacovigilance studies that anti-TNF therapy increases the risk of Tuberculosis, with a possible differential risk between the three anti-TNF drugs: Infliximab (INF) and Adalimumab (ADA) (both monoclonal antibodies) having a higher risk than Etanercept (ETA), a soluble TNF receptor (6-9). The RATIO registry reported the SIRs (Systemic Inflammatory Response Syndrome) for individual anti-TNF-α agents as 18.6 (95% confidence interval [CI], 13.4– 25.8) for Infliximab, 29.3 (95% CI, 20.3–42.4) for Adalimumab and 1.8 (95% CI, 0.7–4.3) for Etanercept (10).

Table 1: TNF-α inhibitors in Rheumatoid Arthritis treatment (5)

S.no	Name of drug	Year of approval	FDA	Mechanism of action	
1	Etanercept	1998		Soluble TNF-α receptor	
2	Infliximab	1999		Monoclonal antibody	anti-TNF-α
3	Adalimumab	2002		Monoclonal antibody	anti-TNF-α
4	Certolizumab	2009		Monoclonal antibody	anti-TNF-α
5	Golimumab	2009		Monoclonal antibody	anti-TNF-α

The postulated mechanism for risk of Tuberculosis with Etanercept therapy is due to TNF-α blockers having soluble TNF-α p-75 receptors competing with TNF-α cell membrane receptors and blocking the biological activity of the cytokine. Because TNF-α is a cytokine that has been shown to be essential for an effective immune response to mycobacterial infection, blocking of TNF-α may lead to tubercular infection (new onset or activation).

A study evaluated the tuberculosis cases in patients receiving etanercept where only 12.5% patients developed disseminated extrapulmonary tuberculosis. In the study, eleven (46%) of the 24 patients with a reported clinical manifestation had pulmonary tuberculosis exclusively, but 13 (54%) had a diagnosis of extrapulmonary disease which was disseminated in 3 patients (12.5%). The postulated mechanism for risk of Tuberculosis with Etanercept therapy is due to TNF-α blockers having soluble TNF-α p-75 receptors competing with TNF-α cell membrane receptors and blocking the biological activity of the cytokine. Because TNF-α is a cytokine that has been shown to be essential for an effective immune response to mycobacterial infection, blocking of TNF-α may lead to tubercular infection (new onset or activation). The median interval between the receipt of the first dose of etanercept and the diagnosis of TB in the study was 11.5 months (11). However, in the present case study, the time interval was greater as the patient received first dose of etanercept more than one year before the diagnosis of Tuberculosis.

The question whether to withhold Etanercept and start ATT or continue etanercept after starting ATT needs further research. In previous studies, the grounds for initiating anti-TNF medication 1 month after beginning preventive TB chemotherapy in participants with positive LTBI (Latent tubercular bacterial infection) were not obvious in the case of active Tuberculosis (12). In the present study, Etanercept was discontinued and patient was maintained on other disease modifying drugs like Methotrexate and Hydroxychloroquine. For clinicians managing RA, severe illness flares in patients being treated for active TB can be a significant issue. Resuming a biologic after completing at least a 6-month course of active TB therapy, according to specialists, is recommended (13, 14). Nonetheless, it is uncertain what to do if the anti-TNF-therapy must be restarted urgently and the answer needs to be explored in further studies.

CONCLUSION:

RA patients receiving Etanercept therapy should be routinely screened for evidence of activation of Tuberculosis. Although common site for Tuberculosis in such patients is pulmonary involvement, but pleural effusion and pericardial effusion may also seen in patients. Therefore, regular careful clinical evaluation for early diagnosis, investigations and workup including echocardiography study may be done in suspected cases. Further studies need to be conducted to shed light on whether biological therapy should be continued in conjunction with anti-tubercular treatment in the patients who develop active disease.

REFERENCES

1. Nanke Y, Kotake S, Akama H, Kamatani N. Alkaline phosphatase in rheumatoid arthritis patients: possible contribution of bone-type ALP to the raised activities of ALP in rheumatoid arthritis patients. Clin Rheumatol. 2002;21:198–202.
2. Fütterer A, Mink K, Luz A, Kosco-Vilbois MH, Pfeffer K. The lymphotoxin beta receptor controls organogenesis and affinity maturation in peripheral lymphoid tissues. Immunity. 1998;9:59–70.
3. Kleinert S, Tony HP, Krause A, et al. Impact of patient and disease characteristics on therapeutic success during adalimumab treatment of patients with rheumatoid arthritis: data from a German noninterventional observational study. Rheumatol Int. 2012;32:2759–2767.
4. Wallis, R.S. Mathematical modeling of the cause of tuberculosis during tumor necrosis factor blockade. Arthritis & Rheumatism. 2008;58: 947-952. https://doi.org/10.1002/art.23285
5. Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB et al. The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. Int J Mol Sci. 2021 Mar 8;22(5):2719. doi: 10.3390/ijms22052719. PMID: 33800290; PMCID: PMC7962638
6. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumour necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345:1098–104.
7. Mohan AK, Cote TR, Block JA, et al. Tuberculosis following the use of etanercept, a tumour necrosis factor inhibitor. Clin Infect Dis 2004;39:295–9.
8. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associated with tumour necrosis factor antagonists. Clin Infect Dis 2004;38:1261–5.
9. Shergy WJ, Isern RA, Cooley DA, et al. Open label study to assess infliximab safety and timing of onset of clinical benefit among patients with rheumatoid arthritis . J Rheumatol 2002;29:667–77.
10. Tubach F, Salmon D, Ravaud P, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum. 2009;60:1884–94.
11. Mohan AK, Coté TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis. 2004;39(3):295-299. doi:10.1086/421494
12. Cantini F, Prignano F, Goletti D. Restarting biologics and management of patients with flares of inflammatory rheumatic disorders or psoriasis during active tuberculosis treatment. J Rheumatol Suppl. 2014;91:78-82. doi:10.3899/jrheum.140106.
13. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625–39.
14. Denis B, Lefort A, Flipo RM, Tubach F, Lemann M, Ravaud P, et al. Long-term follow-up of patients with tuberculosis as a complication of tumour necrosis factor (TNF)-α antagonist therapy: safe re-initiation of TNF-α blockers after appropriate anti-tuberculous treatment. Clin Microbiol Infect 2008;14:183–6.