RHEUMATOLOGY RESEARCH JOURNAL

Vol. 8, No. 3, July ,2023
Webpage: http://rheumres.org
Email: rheumres@gmail.com
ISSN:2476-5856
doi: 10.32592/RR.2023.8.3.107

Case Report Open Access

Tuberculosis reactivation in patients with rheumatoid arthritis on tumor necrosis factor-alpha-blockers: A case report

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Tumor necrosis factor-alpha-blockers have revolutionized the treatment of rheumatoid arthritis. They do, however, increase the risk of latent tuberculosis (TB) reactivation. In many countries, including Iran, TB skin tests and chest radiography are used to assess this risk. The interferon-gamma release assay test is a secondary test used to rule out the potential risk of latent TB reactivation but is not required. In this report, we present a 67-year-old female rheumatoid arthritis patient who was on tumor necrosis factor-alpha-blockers (Adalimumab) and manifested severe symptoms of TB infection in our service eight months after taking the initial treatment. In this case, the TB skin test and chest radiography were negative at initiating the remedy. Following a timely diagnosis and TB treatment, the patient was cured. Mandatory double-checking with TB skin test and interferon-gamma release assays test is recommended before tumor necrosis factor-alpha-blocker prescription in rheumatoid arthritis patients to prevent the risk of fatal tuberculosis reactivation.

Keywords: Rheumatoid arthritis; Anti-tumor necrosis factor-alpha blocker; Tuberculosis; Interferon-gamma

Introduction

Because all TNF-alpha-inhibitors increase the risk of tuberculosis (TB) [1, 2], patients are routinely checked with TB skin tests and chest radiography when initiating treatment. The granulomatous response is used by the host to defend itself against mycobacteria. TNF-alpha is required for granuloma function. The rate of TB is higher among patients receiving Adalimumab (144 events per 100,000) or infliximab than in patients receiving etanercept (39 per 100,000). Extrapulmonary TB is more frequent (62%) [2]. In this report, we present an RA patient who was on Adalimumab and manifested severe TB symptoms despite a negative TB skin test and chest radiography.

Case presentation

A 67-year-old female RA patient was admitted to Fasa's Valiasr hospital ten days ago with chief complaints of fever and abdominal pain. The patient was on Adalimumab for eight months. Before starting Adalimumab, the patient had a Negative TB skin test and a normal chest radiography. She was febrile in the hospital (temperature: 39.7°C). Her pulse

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Received:28 October 2022; **Accepted:**04 May 2023

rate was 90 per minute, and her blood pressure was 110/70 mmHg. Lab tests were Hb: 11.4 g/dl, platelet count: 187000/mL, white blood cell count: 4700/mL, erythrocyte sedimentation rate: 45 mm/h, CRP: +, serum Iron: 11 µg/dl (normal 33-149), total iron binding capacity: 135 µg/dl. Calcium: 8 mg/dl, phosphor: 3.6 mg/dl, CA125: 485 U/L (normal ≤ 35), CA19-9: 36.7 (normal ≤ 35), CEA: 2.12 (positive ≥ 10), TSH: 2.42 mIU/ml, stool occult blood: negative, urinalysis was normal. Urine culture: no growth after 24 hrs, blood gas: normal (PH: 7.38, PCO2: 43.8 mmhg, HCO3: 26.2 mmol/L), wright and 2ME: negative, BUN: 6 mg/dl, Cr: 1.1 mg/dl, Glucose: 93 mg/dl, PT: 14.5 sec and INR: 1.21).

Her abdominal cavity was found to have ascites. On abdominal fluid analysis, albumin: 2.5 g/dL, LDH: 468 units/dL, glucose: 199 mg/dL, total protein: 4.7 g/dL, WBC count: 4830 (90% mononuclear cells; 10% multinucleated cells) and adenosine deaminase: 25 IU/L (normal = 15) were reported. Abdominal fluid gram staining was negative. Serum laboratory tests revealed Alb: 3.1 g/dl, protein: 6.5 g/dl, SGOT: 28 U/L, SGPT: 14 U/L and ALP: 204 U/L. The Serum–Ascites Albumin Gradient (0.6) was less than 1.1 g/dl. The level of adenosine deaminase in the abdominal fluid was relatively high. Other lab tests were unremarkable. Chest x-ray was normal. Abdominopelvic sonography revealed moderate free fluid in the abdomino-pelvic cavity. Endoscopy revealed reflux esophagitis grade A and erosive gastritis, while colonoscopy revealed no abnormalities. With intravenous and oral contrast, abdominal computated tomography revealed moderate to severe free fluid, a few para-aortic, peri-portal, and peri-pancreatic small lymph nodes, and mesenteric fat edema. In this period, the patient was febrile. She was suffering from mild abdominal pain and anorexia. Malignancy and TB were considered in the differential diagnosis because the ascetic fluid gradient was less than 1.1 g/dl. On the seventh day of her admission, she had a diagnostic laparoscopy and a peritoneal biopsy.

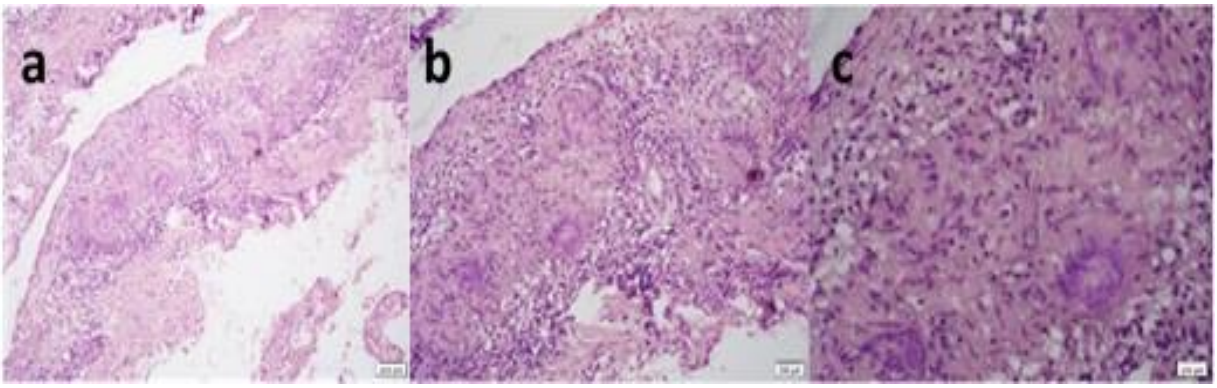

Figure 1: Multiple non-caseating granulomas with the aggregate of epithelioid histiocytes and Langhan's type multinucleated giant cells in peritoneal membrane section (Magnification: X100 (a), X200 (b), X400 (c) Hematoxylin & Eosin or H. & E. stained).

The pathology report indicated granulomatous inflammation with no evidence of malignancy (Figure 1). Polymerase chain reaction (PCR) was positive for mycobacterium TB. Anti TB therapy was started for her and continued for 9-months. Her fever subsided after one week, and she was feeling better. Abdominal sonography didn't show any evidence of ascites six months after treatment, and she was well.

Discussion

There have been case reports of fatal TB infections following TNF–alpha blocker usage. Two cases died from disseminated TB infection despite having negative TB skin tests and interferon-gamma (IGRA) test before initiation of TNF-alpha-blocker [3]. Another case was reported in Poland in 2020, involving a 52-year-old man with psoriasis who was on Adalimumab [4]. Cases of TB that occur shortly

after initiating TNF-alpha-blockers are likely to represent the reactivation of latent TB. In contrast, those that occur later may be either delayed reactivation or newly acquired TB infection progressing directly to active disease. In a UK study, the median time to event for infliximab (5.5 months) was lower than for Adalimumab (18.5 months) [1,2].

In Iran, before starting TNF-alpha-blockers, a TB skin test and chest radiography are routinely performed to rule out latent TB. According to the most recent studies, screening should include a careful history of identifying potential epidemiologic risk factors for TB exposure, a physical examination, a tuberculin skin test, or IGRA. A chest radiograph is also recommended in patients with a positive tuberculin skin test or IGRA or a history and physical examination suggestive of TB [5, 6]. Data suggest that using a single screening test does not identify all patients at risk for TB because false-negative results are more common in immunocompromised individuals [7]. According to the most recent recommendations in UP.DATE 2023, if the patient has any risk factor for TB exposure, such as birth, residence, or travel (for more than 3 months) to a TB–endemic area (IRAN is in a TB endemic area), a dual testing strategy is recommended by the American College of Rheumatology as well as some public health agencies [5, 6, 8, 9].

Conclusions

As mentioned in the discussion, Iran is in a TB endemic area [10]. Therefore dual testing is required to rule out latent TB. However, there have been reports of TB reactivation in patients who have undergone the dual test. Even if the TB screening test is negative, we should be concerned about the patient's use of TNF-alpha-blockers.

Acknowledgment

Not applicable.

Conflict of interest

None

Funding

No funds.

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