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Case Report

Severe candida laryngitis in a patient with rheumatoid arthritis treated with adalimumab

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Abstract

Rheumatoid arthritis is a chronic erosive rheumatic disease that can present with polyarticular involvement. Anti-TNF-alpha drugs are used in cases that are resistant to traditional disease-modifying antirheumatic drugs (DMARDs). Anti-TNF-alpha drugs are groundbreaking drugs, the efficacy of which has been proven in the treatment of rheumatoid arthritis. However, the data concerning safety remain limited and contradictory. The risk of tuberculosis reactivation, various infections, as well as lymphoproliferative disease and/or secondary malignancy is a matter of discussion. In this report, we report a 52-year-old male patient using adalimumab for active rheumatoid arthritis who presented to our polyclinic with generalized mouth and throat sores, hoarseness, and swallowing difficulty. Candida laryngitis was detected in the laryngoscopy and culture samples. Adalimumab was discontinued, and the infection was controlled with anti-fungal treatment.

Key words: Rheumatoid arthritis, candida laryngitis, adalimumab

Introduction

Rheumatoid arthritis is a chronic inflammatory disease that can be in the form of destructive and erosive arthritis and can also present with extra-articular involvement. The purpose of treatment is to control disease activity, ensure full remission, and prevent radiological progression. To this end, groundbreaking anti-TNF-alpha drugs have been used recently, in addition to the traditional disease-modifying antirheumatic drugs (DMARDs), which have been used for many years. Many proinflammatory cytokines are involved in the pathogenesis of rheumatoid arthritis (RA). The most important one of them is TNF-alpha, which acts like an orchestra conductor. TNF-α is a proinflammatory cytokine that plays a significant role in the pathogenesis of many inflammatory diseases by stimulating the release of inflammatory cytokines, such as IL-1 β (interleukin 1 beta), IL-6, and IL-8. TNF-α inhibition is used effectively in the treatment of many rheumatic and systemic autoimmune diseases. The most important side effects of the anti-TNF-α drugs used for the treatment of rheumatoid arthritis include the development of viral, bacterial, and fungal infections, primarily tuberculosis (1-3). Therefore, in patients receiving anti-TNF-α therapy, caution should be exercised for opportunistic infections, like fungal infections (4). Fungal infections are most commonly associated with infliximab (80%), followed by etanercept (5-9). Data on the use of adalimumab are not adequate. In a review based on the screening of publications made, it was found that 80% of cases developing invasive fungal infections associated with anti-TNF-α were associated with infliximab, 16% was associated with etanercept, and 4% were associated with adalimumab; 30% of these fungal infections were found to be cases of histoplasmosis, 23% was candidiasis, and 23% was aspergillosis, and they most commonly involved the lungs (10). The information on fungal infections associated with the use of anti-TNF-α drugs is limited to case reports or a few patient series. In this report, a case of candida laryngitis developing in an RA patient due to adalimumab use is reported.

Case Presentation

A 52-year-old male patient presented to the rheumatology clinic around 6 years ago with complaints of pain, swelling, and morning stiffness in the wrists and metacarpophalangeal (MCF) and proximal interphalangeal (PIF) joints. He was diagnosed with rheumatoid arthritis following laboratory, serological, and radiological analyses and was started on methotrexate (MTX) 15 mg/week, sulfasalazine 2 g/day, methylprednisolone 4 mg/day, and hydroxychloroquine (HQ) 200 mg/day. After using these drugs and returning for regular control visits, the patient presented to our rheumatology polyclinic 6 months ago upon the worsening of his complaints of pain, swelling, and more than 1 hour of morning stiffness in the wrists and MCF, PIF, and knee joints. Physical examination revealed findings of synovitis in both wrists, the MCF and PIF joints, as well as both knee joints. Laboratory analyses revealed the following: WBC: 10,000/uL, Hgb: 12.6 g/dL, Htc: 39.4%, Plt: 485,000/uL, urea: 24 mg/dL, creatinine: 0.1 mg/dL, SGOT: 35 U/L, SGPT: 43 U/L,

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Figure 1. White-grey plaque formation against a hyperemic background on the posterior pharyngeal wall

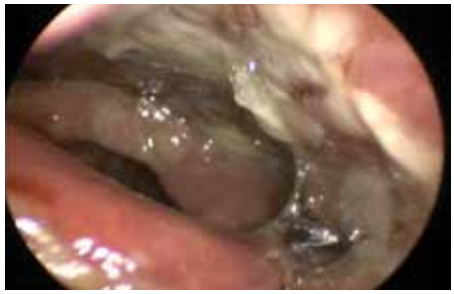
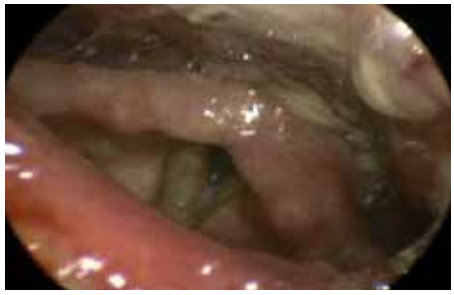


Figure 2. Edematous appearance of the vocal cords and arytenoids



T. protein: 7.3 g/dL, serum albumin: 3.8 g/dL, BG: 110 mg/dL, ESR: 76 mm/h, CRP: 8.3 mg/dL, RF: 52 IU/mL, anti-CCP: 220 IU/mL, and ANA: negative. The lung X-ray and abdominal USG were normal. Hand and wrist X-rays were taken, and findings consistent with RA were detected. The case was evaluated as active RA resistant to traditional therapy (DAS28>5.6), and anti-TNF-alpha was planned. The patient was scanned for TBC, and adalimumab 2x40 mg/month s.c. was started after obtaining his informed consent. Marked regression was seen in the clinical and laboratory assessment made at Month 2 of therapy (ESR: 23 mm/h, CRP: 0.5 mg/ dL). Nearly 3 months after therapy, the patient presented to the rheumatology polyclinic with complaints of generalized lesions and white plaque in the mouth, swallowing difficulty, and hoarseness. Laboratory analyses revealed the following: WBC: 9500/uL, Hgb: 12.9 g/dL, Htc: 39.8%, Plt: 385,000/uL, FBG: 110 mg/dL, urea: 14 mg/dL, creatinine: 0.82 mg/dL, SGOT: 26 U/L, SGPT: 32 U/L, T. protein: 7.1 g/dL, and albumin: 4.3 g/dL. C-reactive protein was 2.1 mg/dL (normal: 0-0.5 mg/dL), and ESH was 34 mm/h (normal: <30 mm/h). Routine urinalysis was normal. Serological tests were made, and cytomegalovirus IgM/IgG, EBV IgG/IgM antibodies, anti-HCV, HBsAg, and anti-HIV were found to be negative. Thyroid function tests were normal. Serum immunoglobulins (IgA, IgG, IgM) were found to be normal. Lung X-ray and abdominal USG were normal. Dermatology and ENT were consulted for the lesions in the mouth. Laryngoscopic imaging showed white-grey plaque formation and an edematous appearance against a hyperemic background (Figure 1, 2). There was Candida albicans growth in the samples obtained during the laryngoscopic examination. The patient was started on systemic (fluconazole 2g/day) and local antifungal therapy; the anti-TNF-drug was stopped. Marked regression was observed in the patient's complaints, and the infection was controlled after nearly 1 month of antifungal therapy. Low-dose corticosteroid, MTX 7.5 mg/day, and HQ were used for RA. The patient's disease is in remission, and he is being followed up with polyclinic controls.

Discussion

It has been shown with information from the literature that a higher rate of infection develops in patients with inflammatory rheumatic diseases receiving anti-TNF-α therapy (11-13). Susceptibility towards tuberculosis, as well as viral, bacterial, and fungal infections, is seen during anti-TNF-α treatment. After exposure to fungal antigen, naïve T cells differentiate into T helper cells, and the T helper 1 (TH1) response is regulated by interferon gamma (IFN-γ). TNF-α stimulates the release of IFN-γ and inflammatory cytokines, leading to increases in a series of chemokines. Also, TNF-α is a potent activator of endothelial adhesion molecules. Since IFN-γ plays a role in the phagocytosis and destruction of intracellular pathogens, anti-TNF-α drugs decrease the IFN-γ levels, compromising the cellular immune response and increasing the susceptibility to fungal infections (14, 15).

Infections developing in patients receiving anti-TNF-α therapy usually occur in the first months of therapy; the most common fungal pathogens include histoplasmosis (30%), followed by Candida and Aspergillus infections (8-10).

Since multiple immunosuppressive agents are used in the majority of cases receiving anti-TNF-α therapy, it is difficult to reach a definite conclusion based on case reports and case series (7, 9, 16). While the exact mechanism of these diseases is not known, the cytokine imbalance caused by anti-TNF-α therapy or suppression of the cells that suppresses autoimmune cells might be responsible. In addition, since granuloma formation with macrophages and lymphocytes and TNF-α, which maintains these cells, play a role in the host defense against mycobacterial and fungal infections, anti-TNF-α drugs are expected to compromise the granuloma structure and result in susceptibility to such infections (1). While adalimumab is expected to be less immunogenic than infliximab and etanercept, since it is a completely humanized monoclonal antibody, it is considered that the cellular immunity altered due to TNF-α blockage can be responsible for the side effects that occur (17). It was reported in a study that the incidence of infection increased twice in a series of 928 patients receiving anti-TNF-α therapy compared to the control group, and infections often tended to involve the upper and lower respiratory tract, urine tract, and soft tissues (18). The case reported here also had an upper respiratory tract infection. TNF-α inhibitor therapies are contraindicated in cases with active bacterial, mycobacterial, and fungal infections. In some cases, classical findings of infection may not occur, or infections may present with atypical findings due to systemic immunosuppression. In the literature, increased mortality rates were observed in life-threatening fungal infections in patients receiving anti-TNF-α therapy in endemic regions and in animal studies (8, 16, 19).

In conclusion, in light of this information, patients receiving anti-TNF-α therapy should be monitored closely for serious and opportunistic infections. More specific and detailed studies including larger patient series are warranted in treatment with these drugs, since they influence the course of the disease when administered early, prevent the complications of conventional therapy, and provide an alternative for cases that are resistant to treatment.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from the patient.

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