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Ankylosing Spondilitis in a Patient with Hepatitis Reactivation Treated with Anti-tumor Necrosis Factor Alpha: A Case Report

Anti Tümör Nekroz Faktörü Alfa ile Tedavi Edilirken Hepatit Reaktivasyonu Gelişen Ankilozan Spondilit Hastası: Olgu Sunumu

Emine Unkun Kandemir, Nilgün Mesci, Berna Günay, Duygu Geler Külcü

Health Sciences University Turkey, Haydarpaşa, Numune Training and Research Hospital, Department of Physical Medicine Division of Rehabilitation Clinic, İstanbul, Turkey

Abstract

Ankylosing spondylitis (AS), a type of spondyloarthropathy, is an autoimmune disease characterized by inflammation that mostly affects soft tissues, such as the axial skeleton, sacroiliac joint, tendons, and ligaments. The aims of AS treatment are to restore spinal flexibility, improve posture, relieve symptoms, prevent limitations in range of motion, and decrease complications. In medical treatment steps, patients with high disease activity despite treatment with non-steroidal anti-inflammatory drugs are recommended to be treated with biologic agents, including anti-tumor necrosis factor-alpha and interleukin-17 inhibitors. The risk of serious infection should be considered in patients treated with biologic agents. Anti- tumor necrosis factor (TNF)- agents administered without appropriate antiviral prophylaxis in patients with chronic hepatitis-B virus infection have been shown to induce viral reactivation. Therefore, they should be used in combination with antiviral therapy. However, rare cases of hepatitis reactivation although antiviral prophylaxis are reported in the literature. We aimed to present a case of hepatitis-B reactivation despite the use of a prophylactic antiviral drug with an anti-TNF- agent.
Keywords: Hepatitis-B infection, spondyloarthropathy, ankylosing spondylitis, hepatitis reactivation, anti-tumor necrosis factor-alpha

Öz

Spondiloartropatinin bir türü olan ankilozan spondilit (AS), esas olarak aksiyel iskelet, sakroiliak eklem, tendonlar ve bağlar gibi yumuşak dokuları etkileyebilen enflamasyonla karakterize otoimmün bir hastalıktır. AS tedavisinin amaçları omurga esnekliğini geri kazandırmak, postürü iyileştirmek, semptomları hafifletmek, fonksiyonel kısıtlamaları önlemek ve komplikasyonları azaltmaktır. Farmakolojik tedavi basamaklarında, non-steroid anti-enflamatuvar ilaçlarla tedaviye rağmen yüksek hastalık aktivitesi olan hastaların anti-tümör nekroz faktörü (TNF)-alfa ve interlökin-17 inhibitörlerini içeren biyolojik ajanlarla tedavi edilmesi önerilmektedir. Biyolojik ajanlarla tedavi edilen olgularda ciddi enfeksiyon riski göz önünde bulundurulmalıdır. Kronik hepatit B enfeksiyonu olan hastalarda uygun antiviral profilaksi olmadan verilen anti-TNF-alfa ajanlarının viral reaktivasyonu indüklediği gösterilmiştir. Bu nedenle, antiviral tedavi ile birlikte kullanılmaları önerilmektedir. Ancak literatürde antiviral profilaksiye rağmen hepatit reaktivasyonunun görüldüğü nadir vakalar bildirilmiştir. Biz de anti TNF-alfa ajanının profilaktik bir antiviral ilaç ile birlikte kullanılmasına rağmen hepatit-B reaktivasyonu gelişen bir olguyu sunmayı amaçladık.
Anahtar kelimeler: Hepatit-B enfeksiyonu, spondiloartropati, ankilozan spondilit, hepatit reaktivasyonu, anti tümör nekroz faktör alfa

Introduction

Ankylosing spondylitis (AS), a type of spondyloarthropathy, is an autoimmune disease characterized by inflammation which can mostly affect soft tissues such as the axial skeleton, sacroiliac joint, tendons and ligaments. This inflammation may lead to fibrosis and calcification, leading to loss of flexibility and fusion of the spine in some severe cases (1). AS is a rheumatological disease that usually occurs in the third decade of life and rarely after the age of 45, and its prevalence is assumed to be between 0.1% and 1.4% worldwide, based on studies (2). The goals of AS treatment are to restore spinal flexibility, improve posture, relieve symptoms, prevent range of motion limitations, and decrease complications. In medical treatment steps, patients with high disease activity despite treatment with non-steroidal anti-inflammatory drugs (NSAIDs) are recommended to be treated with biologic agents including anti-tumor necrosis factor (TNF)-alpha and interleukin- 17 inhibitors. The risk of serious infection should be considered in cases treated with biologic

Address for Correspondence/Yazışma Adresi: Emine Unkun Kandemir, Health Sciences University Haydarpasa, Numune Training and Research Hospital, Department of Physical Medicine Division of Rehabilitation Clinic, İstanbul, Turkey
E-mail: unkunemine@gmail.com **ORCID ID:** orcid.org/0009-0003-8204-5260
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agents. While determining the indications and contraindications of biologic agents, the comorbidities of the patients should be evaluated in detail (3). Hepatitis-B virus (HBV) infection is a global health problem and one of the main causes of liver diseases. The Global Hepatitis Report published in 2017 revealed that 257 million people worldwide were living with HBV in 2015 (4). In a study conducted in Turkey in AS patients, the prevalence of HBV infection was found to be 5.7%(5). The updated American Association for the Study of Liver Disease guideline for the prevention, diagnosis, and treatment of chronic hepatitis-B defined HBV reactivation in HBsAg and anti-HBc positive patients as follows: 100- fold IU/mL increase in HBV-DNA compared to baseline level, In a patient whose HBV-DNA positivity could not be detected before, at least 1000-fold U/mL increase in HBV DNA or at least 10,000-fold IU/mL increase if the initial HBV-DNA value was not present (6). Anti TNF-alpha therapy is effectively used in the treatment of many chronic inflammatory rheumatic diseases. It is recommended to combine anti-TNF-alpha agents with antiviral treatments in rheumatology patients with chronic hepatitis-B infection (7). It has been shown that anti-TNF-alpha agents administered without convenient antiviral prophylaxis can contribute to viral reactivation in patients with chronic hepatitis-B infection. However, rare cases of hepatitis reactivation despite antiviral prophylaxis have been reported in the literature (7) We aimed to present a case of hepatitis-B reactivation despite using a prophylactic antiviral drug with an anti TNF-alpha agent.

Case Report

A 49-year-old male patient has been diagnosed with AS for 25 years, and was followed up in an external center for 5 years with Sulfasalazine 2x2 and NSAIDs treatment after the first diagnosis.He has been followed up in our rheumatic diseases outpatient clinic since 2016. When the patient applied to us, he was being treated with NSAIDs and had not responded to treatment recently; visual analogue scale (VAS) (0-10) pain score: 5, Bath AS Disease Activity Index (BASDAI) score: 6.3, Bath AS Functional Index (BASFI) score:4.2, HLA-B 27: Negative, sacroiliac magnetic resonance imaging showed unilateral sacroiliitis (Figure 1).

When blood values were examined, acute phase reactants were normal. Systemic examination was unremarkable. Modified schober: 5 cm, occiput wall distance: 5 cm, tragus wall distance: 14 cm, sacroiliac tests were negative, inflammatory low back pain was described. The patient was being followed up in the gastroenterology department with the diagnosis of chronic hepatitis B. Anti-TNF treatment was planned for the patient, the gastroenterology clinic was consulted for antiviral agent before the treatment and Lamivudine was recommended to be started. Etanercept 50 mg/wk treatment was started by us in the first month of lamivudine treatment. In the 3rd month of etanercept treatment, the patient's VAS pain score: 1 BASDAI score: 0.9 BASFI score regressed to 1 values. The patient was being followed in remission with etanercept and lamivudine treatments for the last 5 years. In his routine examinations 2 months ago; alanine aminotransferase (ALT): 371 U/L (<33), aspartate aminotransferase (AST): 147 U/L (<32), Sedimentation (ESR): 26 mm/h (2-20), C-reaktif protein: 6.68 mg/L (0-5) levels. Etanercept use was discontinued because ALT and AST were more than 3 times higher, and the patient was referred to the gastroenterology clinic. In the examinations made in gastroenterology; HBsAg:2027S/CO, HBV-DNA:8055491 IU/mL, considering hepatitis reactivation, (the patient's HBV-DNA value was higher than 105 IU/mL before etanercept treatment) antiviral agent lamivudine used by the patient was discontinued and Tenofovir treatment was started instead. After the decrease in ALT and AST levels in the first month of tenofovir use, the patient's condition was evaluated as resistance to lamivudine treatment and we were informed that etanercept treatment could be continued. Etanercept treatment was started again for the patient and in the 2nd week of the treatment; AST:16, ALT: 19, ESR:16 mm/hr, VAS: 2, BASDAI:1.5, BASFI:0.8. The disease activity of the patient is in remission and he is being followed up by our clinic with etanercept and tenofovir treatment. Patient's consent has been obtained.

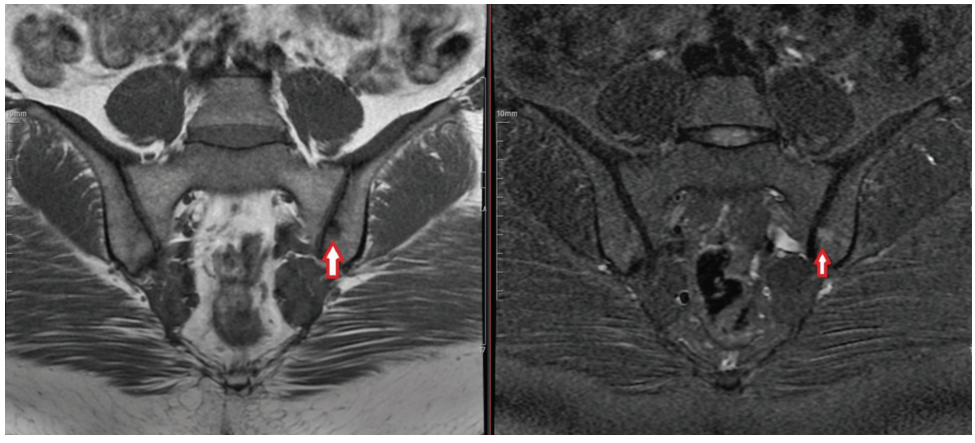

Figure 1. There is an increase in STIR signal consistent with sacroiliitis on the left sacroiliac joint 1/2 inferior iliac face

Discussion

The management of patients with chronic hepatitis-B infection with AS is complex and requires the attention and care of specialists from various fields. Since it is known that immunosuppression treatments to be applied in AS may lead to HBV reactivation, HBV serology should be checked before the treatment and the patient should be re-evaluated according to these results (8). There is a consensus in the literature which whole patients who start immunosuppressant therapy should be tested for HBsAg, anti-HBs and anti-HBc total. This is a measure to protect patients against hepatitis reactivation (9). Prophylactic treatment in patients who will receive anti TNF-alpha therapy; provided by nucleoside analogues such as lamivudine, adefovir, tenofovir, and entecavir. Entecavir (0.5 mg/day) is the first-line treatment for prophylaxis in hepatitis-B patients with inflammatory rheumatic disease. This indication is a conclusion of entecavir's strong antiviral effect, low resistance ratios, and its relationship with rheumatic drugs in long-term studies (10). When evaluated for HBV reactivation, HBsAg positive patients are at higher risk for HBV reactivation but the highest risk is in patients with HBV-DNA higher than 105 IU/mL copies (11). The case we presented also had HbsAg positivity, and the HBV-DNA value was higher than 105 IU/mL copies before anti-TNF-alpha treatment and had the risk factors for HBV reactivation in the literature. In the literature, it has been seen that lamivudine is the most commonly used antiviral drug prophylactically together with anti TNF-alpha. (12). One study showed that prophylactic usage of an oral antiviral agent can preserve from HBV reactivation in the majority (>90%) of patients with chronic HBV infection treated with an anti-TNF-alpha agent. In this study, viral reactivation developed in just one patient (7%) because of a Lamivudine-resistant strain during anti-TNF-alpha therapy (7). In another study, it was shown that the probability of developing resistance to lamivudine is higher compared to other antivirals. For this reason, treatment with drugs that are less likely to develop resistance to antivirals such as entecavir and tenofovir is recommended in suitable patients (13). In a meta-analysis evaluating the efficacy of antiviral prophylaxis compared to no treatment, it was shown that HBsAg positive patients benefited more from antiviral treatment (14). In our case, viral reactivation developed despite prophylaxis with lamivudine and contrary to the literature, although HbsAg was positive, it did not benefit from prophylactic treatment. In the literature, infliximab has been associated with a higher ratio of induced liver disease (elevated transaminase levels, viral reactivation, and acute liver failure) compared to etanercept (15). Between TNF-alpha inhibitors, reactivation has been reported more with infliximab and adalimumab than with etanercept (16). Although etanercept was preferred as an antiviral agent in our case, reactivation developed. When anti-TNF-alpha agents are used alone without antiviral prophylaxis, the risk of reactivation varies between 1% and 10%, depending on the hepatitis B serology of the patient (16). Lamivudine has been used in 90% of reported HBsAg positive cases treated with anti TNF-alpha agents. Up-to-date international guidelines for the management of HBV infection offer that lamivudine alone should be sufficient for patients taking immunosuppressive therapy for less than 6 months. In our case, lamivudine was started by gastroenterology considering the current guidelines. However, it remains unclear whether lamivudine provides benefit in patients requiring long-term immunosuppressive therapy, as is generally the case with anti-TNF-alpha therapy. Longer-term lamivudine prophylaxis has been associated with the occurrence of lamivudine resistant HBV strains (17). Most of the cases reported in the literature are HBV reactivations that develop in patients who do not use antiviral prophylaxis together with anti-TNF-alpha agents (16,18). Expert opinions are that antiviral therapy should be started 1 month before anti-TNF-alpha therapy is given to chronic HBV patients (19). Our case is HBV reactivation that developed despite using antiviral prophylaxis.

Conclusions

In patients with a diagnosis of chronic HBV and using anti-TNF-alpha, liver enzymes should be monitored at regular intervals. It should be kept in mind that hepatitis reactivation may develop in patients followed up with anti-TNF-alpha therapy despite receiving antiviral prophylaxis. This case reinforces the importance of current recommendations for periodic monitoring of chronic HBV patients receiving anti-TNF-alpha therapy and planning appropriate therapy.

Ethics

Informed Consent: Patient's consent has been obtained.

Footnotes

Authorship Contributions

Concept: E.U.K., N.M., Design: B.G., D.G.K., Data Collection or Processing: E.U.K., N.M., B.G., D.G.K., Analysis or Interpretation: E.U.K., N.M., B.G., D.G.K., Literature Search: E.U.K., N.M., B.G., D.G.K., Writing: E.U.K.

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