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Hepatitis B Surface Antigen Seroconversion Developed with Tenofovir Disoproxil Fumarate: HIV/HBV Case Report and Literature Review

Tenofovir Disoproksil Fumarat ile Gelişen Hepatit B Yüzey Antikoru Serokonversiyonu: HIV/HBV Olgu Sunumu ve Literatürün İrdelenmesi

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ABSTRACT

Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) coinfections are important health problems worldwide and in our country. While acute HBV infections are relatively rare in patients with HIV infection, the chronicity rate is more prevalent in HIV-HBV co-infections. A 49-year-old male patient who was admitted with acute HBV symptoms is presented in this case. During the investigation of the cause of hepatitis, HIV infection was also detected, and emtricitabine + tenofovir disoproxil fumarate + dolutegravir treatment was initiated. While the patient developed a virological and immunological response to HIV infection, hepatitis B surface antigen seroconversion also occurred. This case report aimed to draw attention to HIV-acute HBV coinfection and analyze HBV reactivation and immune reconstruction syndrome in HIV-positive individuals. It is obvious that there is a need for research on the prevalence, risk factors, and prognosis of co-infection in our country.

Keywords: HIV, acute HBV, prognosis, coinfection, HBsAg seroconversion

ÖZ

Hepatit B virüsü (HBV) ve insan immün yetmezlik virüsü (HIV) koenfeksiyonları dünyada ve ülkemizde önemli sağlık sorunudur. HIV enfeksiyonlu olgularda akut HBV enfeksiyonları nadir görülmesine karşın, HBV enfeksiyonunun kronikleşme oranı HIV-HBV koenfeksiyonlarında daha sıktır. Bu olguda 49 yaşında, akut HBV kliniği ile başvuran erkek hasta sunulmuştur. Hepatit etiyoloji araştırılırken HIV enfeksiyonu da saptanmış ve emtrisitabin + tenofovir disproksil + dolutegravir başlanmıştır. Hastada HIV enfeksiyonunda virolojik ve immünolojik yanıt alınırken, hepatit B yüzey antikoru serokonversiyonu da gelişmiştir. Bu olgu sunumu ile HIV-akut HBV koenfeksiyonuna dikkat çekmek istenirken, HIV-HBV reaktivasyon ve HBV ilişkili immün rekonstitüsyon inflamatuar sendromu ilişkisi de irdelenmiştir. Ülkemizde koenfeksiyonun sıklık, risk faktörleri ve prognozunu ortaya koyan araştırmalara ihtiyaç bulunmaktadır.

Anahtar Kelimeler: HIV, akut HBV, prognoz, koenfeksiyon, HBsAg serokonversiyonu

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Introduction

The prevalence of hepatitis B surface antigen (HBsAg) is 4.57%, and the most commonly affected group is between the ages of 25 and 34 (6.36%) in our country (1). In addition, there are 39437 individuals living with human immunodeficiency virus (HIV), most frequently in the 25-29 age group (18%) (2). HIV/hepatitis B virus (HBV) coinfection is found at a rate of 5.8-7% (3,4). The exact number of HIV/acute HBV cases is not precisely known. Acute HBV is rarely seen in individuals living with HIV. For example, only 18 individuals among 3,098 HIV (+) individuals developed acute HBV during 18 years of follow-up in Spain (5).

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Since hepatitis B was not included in the routine vaccination program in our population before 1998, acute HBV is observed more frequently in older individuals (1). Besides, the fact that HIV and HBV infections are often seen in the same age groups and the transmission routes of the two infections being similar, indicates that HIV/acute HBV co-infection will increase over time, especially in older individuals. As in the present case, HIV infection may be manifested by acute HBV in middle-aged or elderly individuals.

Currently, national and international guidelines recommend; screening patients diagnosed with HIV for chronic, acute, or occult HBV infection, including HBV-effective agents in the antiretroviral therapy (ART) plan in chronic or occult HBV, as well as vaccination of susceptible individuals (6,7).

In this article, a case of HIV infection diagnosed while investigating the etiology of acute hepatitis is reported. The HIV course and prognosis of acute HBV, HBV reactivation that can be seen in HIV (+) patients, HBV-related IRIS and HIV-HBV relationships are discussed.

Case Report

A 49-year-old male patient with complaints of widespread body pain and weakness persisting for a month was redirected to our outpatient clinic because of elevated transaminase level detection. The patient was admitted to our clinic with a prediagnosis of acute hepatitis. There was also no evidence of secondary hepatotropic viral or bacterial infection, and the patient had no symptoms of primary HIV infection. The patient's medical history revealed previous diabetes mellitus, hypertension, chronic obstructive pulmonary disease, hyperlipidemia, and coronary artery disease, whereas there was no drug, substance, or alcohol abuse other than medications for chronic diseases. It was noted that the patient, who is heterosexual, underwent a coronary bypass operation two years prior in which he received blood transfusion during and had suspicious sexual contact within the last 6 months of admission. On physical examination, the patient's general condition was good, consciousness was clear, oriented, and cooperative, and no icterus or organomegaly was detected. The results of the tests performed on admission were as follows: alanine aminotransferase, 531 U/L, aspartate aminotransferase: 220 U/L, total bilirubin: 1.1 mg/dL, delta bilirubin: 0.35 mg/dL, gamma-glutamyl transferase: 657 U/L, laktat dehidrogenaz: 182 U/L, alkaline phosphatase: 170 U/L. There was no abnormality in the lung or abdominal radiological examinations performed for control. Serologic tests showed HBsAg, hepatitis B core antibody (anti-HBc) IgM, hepatitis B e antigen (HBeAg), anti-HBe, and anti-HIV positivity. Anti-hepatitis A virus (HAV) IgM and anti-hepatitis C virus were negative, anti-HAV IgG was positive, and the other results were; HBV-DNA: $1.2x10^7$ IU/mL, HIV-RNA: 2350000 copies/mL, CD4+ T lymphocytes: 338 hc/uL, CD8+ T lymphocytes: 734 hc/uL.

After a thorough review of the patient's medical records, it was observed that HBsAg and anti-HIV tests were negative in the preoperative examinations, but the tests were not repeated for any reason in the following period. No anti-HBc IgG analysis was performed.

The patient was hospitalized for a period of 12 days with a diagnosis of acute HBV and HIV infection. Because liver function tests regressed and symptoms improved, the patient was discharged with a diagnosis of HIV infection, and treatment with emtricitabine + tenofovir disoproxil fumarate (TDF) + dolutegravir was initiated.

The patient was monitored at regular intervals, and the initial 3-month follow-up revealed that transaminases reached normal limits and the CD4+ T lymphocyte count was 700 hc/uL. HIV-RNA levels that had long been low positive dropped to undetectable levels after approximately 12 months. After 20 months, the patient was HBsAg negative and the anti-HBs titer was >1000 mIU/mL.

Discussion

Although the rate varies from region to region, chronicization develops in 7.7-11% of HIV (+) patients after acute HBV (5,8). In addition, HBV-DNA levels tend to be higher in people living with HIV, and the risk of progression to end-stage liver disease, cirrhosis, and hepatocellular cancer is higher. In addition, reactivation is more frequent in HIV (+) in conjunction with CD4+ T lymphocyte count (9).

Our patient was started on ART, including TDF, in accordance with guideline recommendations because of the negative effect of HIV on HBV (6,7). In contrast to the high expectation of chronicization in the literature, HBV infection resolved with cure in our patient (5,8). Depending on the genotype of the study group or the length of follow-up, the frequency of HBsAg clearance can range from 3.7-18% (10,11). Audsley et al. (12) conducted a follow-up of 92 HIV-HBV patients treated with ART including TDF for 5 years and found HBsAg clearance in 11 patients (12%) after a mean treatment duration of 48 months (range 3-88 months), and in only 4 of these patients, anti-HBs became concurrently positive. Yang et al. (10) have shown that HBsAg seroclearance correlates with ART duration; while the clearance rate was 1.8% between 2 and 4 years, increasing to 29.4% up to 10 years. Our patient achieved HBsAg seroconversion in a considerably shorter time (20 months).

A study conducted in China revealed that older age, high CD4+ T lymphocyte level, and initial HBeAg positivity ease HBsAg clearance in HIV/HBV coinfections using ART containing TDF (13). The development of HBsAg seroconversion in this study supports the facilitation of these factors.

Although the prognosis for HBV in this study was favorable, the late suppression of HIV-RNA was remarkable. However, CD4+ T lymphocytes increased rapidly. The effect of HBV over the course of HIV treatment has not yet been fully clarified. While some studies have shown that HBV decreases CD4+ T lymphocyte levels and increases the risk of progression to AIDS (14,15), there are also studies that have reached the contrary results (16). More data are required for certainty on this aspect.

Hepatic exacerbation observed in HBsAg-positive individuals living with HIV after ART initiation is called HBV-related IRIS. There is an immunopathogenesis implicated in HBV-specific CD8+ T lymphocytes and non-HBV-specific mononuclear cells that is believed to be associated with reconstruction, but this has yet to be fully clarified. There is no widely recognized definition for the diagnosis of HBV-related IRIS; therefore, the diagnosis is made

by first excluding other causes and demonstrating HBV-related hepatic exacerbation on liver biopsy. HBV-related IRIS can generally be managed by maintaining current ART without worsening the patient's general condition (17). Because acute hepatitis symptoms started before ART, IRIS was not considered in this study.

In addition to IRIS, in HIV (+) patients, occult HBV reactivation occurring after cessation of ART, which is proven to be effective against HBV, may also lead to transaminase elevation. A similar situation may also occur in HIV (+) patients on ART without HBV efficacy. HBV reactivation is identical in terms of clinical and laboratory findings to the process experienced in HIV (-) individuals who are started on immunosuppressive therapy for various reasons. In these patients, switching to an ART effective against HBV is considered sufficient to obtain desired outcomes; however, HBsAg seroconversion may develop again (18). No anti-HBc IgG result was observed in our patient's medical history. However, our case was not considered reactivation because there was no ART experience.

Conclusion

It is rare that our case has resulted in a good prognosis in a short time despite being HIV (+). In addition, this patient is a robust reminder that HIV infection should be investigated together with acute HBV in age groups in which the risk of acute HBV persists. It should also be noted that HBV reactivation and HBV-related IRIS can develop in patients with HIV. This case also highlighted the fact that there are not enough data on HIV/HBV at the national level. Our country requires studies to determine the incidence, risk factors, and prognosis of HIV-acute HBV coinfection and to evaluate IRIS or reactivation processes.

Ethics

Informed Consent: Informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: Z.K., E.D., C.B., A.Y., Concept: Z.K., E.D., C.B., A.Y., Design: Z.K., E.D., C.B., A.Y., Data Collection or Processing: Z.K., E.D., C.B., A.Y., Analysis or Interpretation: Z.K., E.D., C.B., A.Y., Literature Search: Z.K., E.D., C.B., A.Y., Writing: Z.K., E.D., C.B., A.Y.

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