A case of gynecomastia due to entecavir

Entekavir'e bağlı jinekomasti vakası

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Hepatitis B is an important health problem all over the world as well as in our country. Entecavir is a nucleoside analog used in the treatment of chronic hepatitis B. We present a case of a 55-year-old male patient who developed unilateral gynecomastia while under treatment with entecavir. Physical examination was unremarkable except for minimal hepatomegaly. Laboratory examination revealed: HbsAg: positive, HBeAg: negative, anti-HBe: positive, HBV DNA: 800,000 copies/ml, total anti-HDV: negative, and alanine aminotransferase: 105 U/L (normal range: 0-41). The treatment was started with pegylated interferon. During the follow-up, transaminases did not regress and HBV DNA was found to still be highly positive at the sixth month evaluation. Pegylated interferon treatment was stopped and entecavir was started at a dose of 0.5 mg/day. Six months after the initiation of entecavir treatment, the patient presented with a painful swelling in the right breast. On physical examination, there was painful gynecomastia on the right side, which was confirmed with mammography and ultrasound of the breast tissue. The patient was not taking any drug that may have caused gynecomastia. Hormonal status of the patient was normal. Laboratory values were normal. We considered that this unilateral gynecomastia might be an adverse effect of entecavir. Since the patient had a rapid viral and biochemical response to entecavir, the drug was continued under close follow-up and there was no further progression of the gynecomastia.

Key words: Chronic hepatitis B, antiretroviral treatment, nucleoside analogs, entecavir, gynecomastia

Hepatit B tüm dünyada olduğu gibi ülkemizde de önemli bir sağlık sorunudur. Entekavir kronik B hepatiti tedavisinde kullanılan bir nükleosid analoğudur. Biz entekavir tedavisi altında gelişen tek taraflı jinekomasti olgusunu sunacağız. 55 yaşında erkek hasta. Fizik muayenesinde minimal hepatomegali dışında bir özellik yok. Laboratuvar incelemesinde HbsAg pozitif, HBe-Ag negatif, Anti-HBe pozitif, HBVDNA: 800.000 kopya/mL, Anti-HDV total negatif, alanine aminotransferase 105 U/l (normal aralık: 0-41) bulundu. Pegile interferon tedavisi başlandı. Takiplerinde transaminaz değerleri azalmadı ve tedavinin 6. ayında bakılan HBVDNA seviyesi aynı düzeyde bulundu. İnterferon tedavisi kesildi ve entecavir 0.5 mg/gün başlandı. Entekavir tedavisi başlandıktan altı ay sonra hastanın sağ memesinde ağrılı şişlik başladı. Fizik muayenede saptanan sağ taraftaki ağrılı jinekomasti, mamografi ve ultrason ile doğrulandı. Hasta jinekomastiye neden olabilecek ilaç veya toksik bir madde kullanmıyordu. Hormon profili normaldi. Laboratuvar değerlerinde bir özellik yoktu. Biz bu tek taraflı gelişen jinekomastinin entekavire bağlı bir yan etki olduğunu düşündük. Hastada entekavir ile hızlı bir biyokimyasal ve viral cevap alındı. Bu nedenle tedavi kesilmeden hasta takip edildi ve jinekomastide herhangi bir ilerleme gözlenmedi.

Anahtar kelimeler: Kronik hepatit B, antiretroviral tedavi, nükleozid analogları, entekavir, jinekomasti

INTRODUCTİON

Hepatitis B is an important health problem all over the world as well as in our country. It is known that more than 400 million people are infected with hepatitis B virus (HBV). In Turkey, 3.5 million people are infected with HBV. Chronic hepatitis B can be treated with interferons and antiviral agents. Entecavir is a nucleoside analog used in the treatment of HBV. We present a case who developed unilateral gynecomastia while under treatment with entecavir.

CASE REPORT

A 55-year-old male patient presented because of septal deviation to the Ear, Nose and Throat (ENT) clinic, and during the initial evaluation for the operation, it was noted that he had elevated transaminases and a positive HBsAg. The patient had a history of hypertension and had been regularly taking perindopril terbuthylamine 10 mg plus indapamide 1.25 mg/day for two years.

Physical examination was unremarkable except for minimal hepatomegaly. Peripheral signs of

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chronic liver disease were absent. Laboratory examination demonstrated: HbsAg: positive, HBeAg: negative, anti-HBe: positive, HBV DNA: 800,000 copies/ml, total anti-HDV: negative, anti-HAV IgG: positive, anti-HCV: negative, and anti-human immunodeficiency virus (HIV): negative. Biochemical evaluation revealed: glucose: 92 mg/dl (normal range: 76-110), creatinine: 0.87 mg/dl (normal range: 0.7-1.2), cholesterol: 166 mg/dl (normal range: 50-200), triglycerides: 76 mg/dl (normal range: 1-200), aspartate aminotransferase (AST): 70 U/L (normal range: 0-38), alanine aminotransferase (ALT): 105 U/L (normal range: 0-41), alkaline phosphatase (ALP): 70 U/L (normal range: 0-129), γ-glutamyl transpeptidase (GGT): 51 U/L (normal range: 11-49), albumin: 4.3 g/dl (normal range: 3.4-4.8), gamma globulin: 1.4 g/dl (normal range: 0.7-1.6), total bilirubin: 0.85 mg/dl (normal range: 0.0-1.1), prothrombin time (PT): 14.3 seconds, international normalized ratio (INR): 1.11 (normal range: 0.82-1.2), and alpha-fetoprotein: 3.35 ng/ml (normal range: 0-7). Blood count was unremarkable. The patient refused liver biopsy.

The treatment was started with pegylated interferon alpha-2a 180 μg (once a week, subcutaneously) in June 2007. During the follow-up, transaminases did not regress and HBV DNA was found to still be highly positive at the sixth-month evaluation. Interferon treatment was stopped in January 2008 because of primary nonresponse, and entecavir was started at a dose of 0.5 mg/day in January 2008. At this time point, the physical examination of the patient was normal, with a height of 175 cm, weight of 90 kg, glucose: 99 mg/dl, creatinine: 0.99 mg/dl, cholesterol: 144 mg/dl, triglycerides: 84 mg/dl, AST: 108 U/L, ALT: 162 U/L, ALP: 50 U/L, GGT: 40 U/L, albumin: 4.2 g/dl, gamma globulin: 1.5 g/dl, total bilirubin: 1.08 mg/dl, PT: 14.6 seconds, INR: 1.21, and alpha-fetoprotein: 4.25 ng/ml. Three months after the initiation of entecavir treatment, transaminases were in normal range (AST: 37 U/L, ALT: 32 U/L). Six months after the initiation of entecavir treatment, the patient presented with a painful swelling in the right breast and at this time, AST was 36 U/L and ALT was 35 U/L, with a 2 log decrease in HBV DNA (HBV DNA: 5,300 copies/ml). Physical examination revealed painful gynecomastia on the right side, which was confirmed with mammography and ultrasound of the breast tissue. Hormonal status of the patient was as follows: follicle-stimulating hormone (FSH): 5.80 mIU/ml (normal range: 0.7-11.1), luteinizing hormone (LH): 7.57 mIU/ml (normal range: 0.8-7.6), testosterone: 677.8 ng/dl (normal range: 280-800), dehydroepiandrosterone sulfate: 108.9 ug/dl (normal range: 70-490), progesterone: 0.244 ng/ml (normal range: 0.2-1.5), estradiol: 38.12 pg/ml (normal range: <56), prolactin: 6.66 pg/ml (normal range: 2.5-17), beta-human chorionic gonadotropin (hCG): <0.100 mIU/ml (normal range: <-2.7), thyroid stimulating hormone: 3.36 uIU/ ml (normal range: 0.270-4.2), free T3: 4.34 pmol/L (normal range: 2.99-6.8), and free T4: 12.95 pmol/L (normal range: 12-22). Blood glucose level was 96 mg/dl, creatinine: 0.87 mg/dl, sodium: 140.8 mEq/L (normal range: 133-150), potassium: 4.46 mEq/L (normal range: 3.3-5.1), chloride: 105.6 mEq/L (normal range: 95-115), cholesterol: 148 mg/dl, and triglycerides: 87 mg/dl. Blood count and sedimentation rate were normal. Dual energy X-ray absorptiometry scan T-score was normal (>-1 SD).

DISCUSSION

Gynecomastia is described as glandular tissue growth in the male breast. Breast tissue consists of glandular ductal epithelium and periductal connective tissue. Gynecomastia starts initially with symptoms of pain and tenderness and is seen as a swelling. Histologically, it is characterized with hyperplasia of the ductal epithelium, infiltration of periductal tissues with inflammatory cells and an increased subareolar fat tissue. It might be seen together with liver cirrhosis, during adolescence, in elderly or obese people, and in hyperthyroidism. Gynecomastia might also occur secondary to drugs like spironolactone, digital glycosides, cimetidine, enalapril, amiodarone, and some illicit drugs like heroin, marijuana, amphetamine and alcohol. A decrease in the androgen and estrogen ratio or an increased tissue sensitivity to estrogen play a role in the pathogenesis (1-3). The initial step in the diagnosis of gynecomastia is the description of enlarged breast tissue or mass on the physical examination. The increase of subareolar fat tissue without a glandular tissue enlargement in the breast is defined as pseudogynecomastia or lipomastia. The differential diagnosis of gynecomastia and pseudogynecomastia can be made with physical examination. The differentiation of gynecomastia from breast cancer is important and can be done with breast ultrasound and mammography (1).

Entecavir is a guanosine nucleoside analog for the treatment of HBV. It is recommended as first-line treatment because of its high antiviral potency and low resistance profile (4-6). Adverse effects like asthenia, anaphylactoid reactions, skin lesions, gastrointestinal disturbances, and central nervous system problems have been reported with entecavir. It is also known that it might cause hyperglycemia and an increase in lipase levels (7). However, there is no data in the literature indicating that it might cause gynecomastia.

Highly active antiretroviral treatment is used in the treatment of HIV infections and has led to an improvement in the prognosis of the disease. In this treatment, there is a triple or quadruple combination of nucleoside or nonnucleoside reverse transcriptase inhibitors and protease inhibitors. This multidrug regimen has many adverse effects and side effects like hepatotoxicity and metabolic or mitochondrial disturbances. Highly active antiretroviral treatment can cause gynecomastia. The prevalence of gynecomastia due to highly active antiretroviral treatment in HIV infection is reported to be 2-3% (2, 3). There are some hypothetic physiopathological mechanisms on how antiretroviral agents can cause gynecomastia. Some authors suggest that antiretroviral agents have direct mammotrophic effect on estrogen and progesterone receptors in breast tissue. Others suggest that highly active antiretroviral treatment improves cytokine response in T-helper cells and increases especially interleukin-2 production. It is shown that interleukin-2 increases proliferation of human breast cancer cells in vitro. Interleukin-6 also increases estrogen and stimulates breast growth. Immune reconstitution can increase estrogen in breast tissue and cause real gynecomastia (3).

The patient had been followed for almost 18 months and the gynecomastia, which was confirmed by breast ultrasound and mammography, developed at the sixth month of the entecavir treatment. At the initial presentation, before, during and after the treatment with interferon and before the treatment with entecavir, the patient was examined many times and there was no gynecomastia. We carefully discussed with the patient all the drugs, herbal remedies, alcohol or illicit drugs that might cause gynecomastia. The patient was taking perindopril terbuthylamine 10 mg plus indapamide 1.25 mg/day regularly for hypertension. However, the patient had been using this medication for many years, and it is well known that these drugs do not cause gynecomastia.

For the differential diagnosis, blood glucose level, cholesterol and triglycerides were examined and were within normal limits. Dual energy X-ray absorptiometry scan was normal. The patient was not obese, with a body mass index of 29.4 kg/m^2. With these findings, we excluded the lipodystrophic syndrome. Sex hormone levels were normal and there were no symptoms of hypogonadism. Thyroid dysfunction was excluded, and alpha-fetoprotein and beta-hCG were normal. Abdominal ultrasound revealed hepatomegaly and grade I hepatosteatosis. With the help of all these physical and laboratory values, we excluded testicular tumor, adrenocortical tumor, lung cancer, gastric cancer, hepatocellular cancer, and renal cell cancer.

In the evaluation prior to starting entecavir, the patient had no peripheral findings of chronic liver disease. There was neither splenomegaly nor cytopenia or portal hypertension findings on Doppler ultrasonography of the portal system. Gastroscopy revealed no esophageal or gastric varices or portal hypertensive gastropathy. Albumin, bilirubin, gamma globulin, and PT were normal. In addition, the patient had no clinical or biochemical signs of cirrhosis.

We considered that this unilateral gynecomastia and mastodynia might be an adverse effect of entecavir. The patient had a rapid viral and biochemical response to entecavir. Therefore, we did not stop the drug but followed the patient closely, and the gynecomastia showed no progression.

In the literature, there are case reports of gynecomastia after retroviral treatment in HIV infection. With the use of entecavir, which is a nucleoside analog, gynecomastia might develop via the same mechanism.

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