Hepatitis B virus reactivation secondary to immunosuppressive treatment

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Abstract

Reactivation of hepatitis B virus (HBV) replication in patients undergoing immunosuppressive therapy may precipitate flare ups of chronic HBV infections. We present the case of a 57 year old female who had suffered six weeks of abdominal discomfort, dyspepsia, and joint paint. After three weeks of therapy with prednisolone, methotrexate and chloroquine, the patient developed ascites and increased serum levels of AST and ALT. Chronic hepatitis B infection was confirmed by liver biopsy.

Conclusion: Tests for hepatitis B should be conducted before immunosuppressive therapy is begun. Corticosteroids and other immune suppressors can reactivate hepatitis B and produce severe clinical symptoms and can put the patient's life at risk.

Key words

Hepatitis, immunological tolerance, viral activation.

INTRODUCTION

Approximately 5% of immunocompetent adults who become infected with hepatitis b virus (HBV) develop chronic infections. It is estimated that at this moment there are 350 million people in the world who are chronically infected with HBV.

The clinical course of chronic HBV infections is usually very slow. Symptoms such as arthralgia or fatigue are not specific to this disease along, so that only in very advanced stages of hepatic damage can the stigmata of chronic liver disease be recognized.

It is well known that viral reactivation can occur in these patients when they are exposed to treatment with immunosuppressants, to chemotherapy or to cytotoxic agents. Since 2007 the American Association for the Study of Liver Diseases (ASLD) has published guides for treating patients with chronic hepatitis B virus infections. They recommend testing for HBsAg, anti-HBc, anti-HBsAg and aminotransferases levels in patients who may be treated with chemotherapy or immunosuppressants so that complications from reactivation of the virus can be avoided.

We present the case of a patient whose hepatitis B virus was reactivated after beginning immunosuppression therapy.

CASE PRESENTATION

The patient was a 57 year old woman who had suffered epigastric pain, malaise, arthralgia and subjective weight loss for six weeks. She had consulted doctors on two occasions. They had prescribed treatment with omeprazole and aluminum hydroxide, but the patient had not improved.

The only relevant history was a diagnosis of hypothyroidism two years earlier. She received 50 micrograms of levothyroxine per day, but the patient had stopped taking the medication on her own initiative six months prior to development of symptoms. A physical examination showed that the patient was generally in good condition, although she

experienced mild pain upon deep palpation of the epigastrium. No jaundice or hepatosplenomegaly was found.

Paraclinical tests found a total leukocyte count of 2,600/mL, 46.3 % lymphocytes and 43% polymorphonuclear leukocytes (PMN); a hemoglobin count of 13.2 gr/dL; a platelet count of 98,000/mL; an aspartate transaminase (AST) level of 43 U/L (normal = 30 U/L); an alanine transaminase (ALT) level of 63 U/L (normal = 30 U/L); a total bilirubin level of 1.3 mg/dL (normal up to 1.1 mg/dL), a direct bilirubin level of 0.5 mg /dL, an alkaline phosphatase level of 145 U/L (VN= 120), a thyroid stimulating hormone (TSH) level of 4.3 uU/ml, a free triiodothyronine (T3) level of 2.1 pg/ml, a thyroxine (T4) level of 7.1 ug/dL, an antinuclear autoantibody (ANA) proportion of 1/320 with a nucleolar pattern , complement component C3 test result of 74.03 mg/dl (90 – 170). Complement Component C4 results of 9.76 mg/dl (12 – 36), lactate dehydrogenase (LDH) level of 521 UI (200- 400), polymerase chain reaction (PCR) test result of 4.7 mg/L, rheumatoid factor of 18.25 U/ml (normal measurement is less than 14 U/ml), fasting blood sugar level of 89 mg/dl, serum creatinine level of 0.9 mg/dl, and ureic nitrogen level of 12 mg/dl.

An esophagogastroduodenoscopy showed a duodenal ulcer of approximately 5 mm wide with no signs of bleeding

A diagnosis of systemic lupus erythematosus (SLE) and a duodenal ulcer without complications was established. Treatment began with 50 mg of prednisolone, 400 mg of chloroquine, and 80 mg esomeprazole daily, plus 7.5 mg of methotrexate per week. Anti native DNA antibodies, anti SM, anti-RO, and anticardiolipin antibodies tests were conducted. Results received one week later were all negative. Three weeks after initiation of triple therapy for SLE, the patient presented significant clinical deterioration with vomiting and confinement to bed.

A complete abdominal ultrasound was performed. Its only relevant finding was the presence of free fluid in the pelvic area located at the bottom of the posterior fornix. A new biochemical profile showed an AST level of 177 U/L, an ALT level of 127 U/L, and a serum albumin level of 2.9 gr/dL. Because of these results and the clinical deterioration of the patient, an abdominal CAT scan was requested. It showed the presence of abundant ascitic fluid but showed no other relevant findings.

Other lab tests results showed that the patient was HBsAg Positive, but negative for antibodies against hepatitis c virus. Her HIV and VDRL tests were also negative. She had an HBV-DNA viral load of 2,410,000 UI /ml (limit of detection under 19 UI/ml). Alpha-fetoprotein (AFP) and alpha 1-antitrypsin levels were normal, and anti-mitochondrial antibodies (AMA) were negative.

EVOLUTION

It was decided to suspend all treatment for lupus and to begin treatment with 0.5 mgs of entecavir, 80 mg of furosemide and 100 mg of spironolactone per day by the oral route. After four weeks of the new treatment the patient felt better. She had recovered her appetite completely, her abdominal pain had disappeared, and her ascites was resolved.

Later a laparoscopic procedure to obtain a hepatic biopsy was performed. The biopsy showed a cirrhotic liver with a macronodular macroscopic pattern. The microscopic examination of the hepatic tissue with hematoxylin eosin staining, Masson's trichrome and PAS showed extensive fibro-connective tissue bands with chronic inflammatory infiltration breaking through the limiting plate as well as isolated centers of necrosis. Some hepatocytes show binucleation (See Figures 1 and 2).

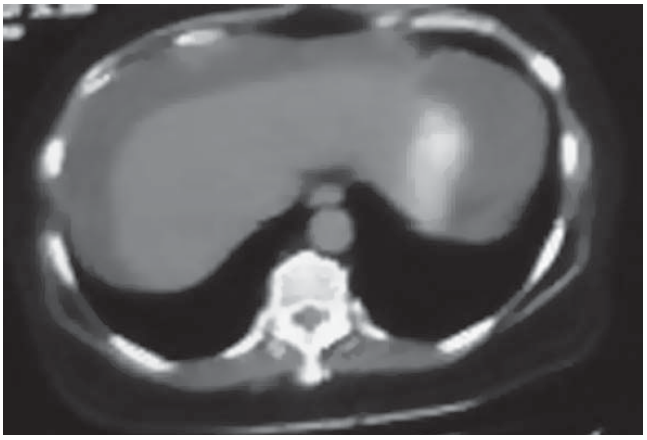

Figure 1. Abdominal tomography showing ascetic liquid.

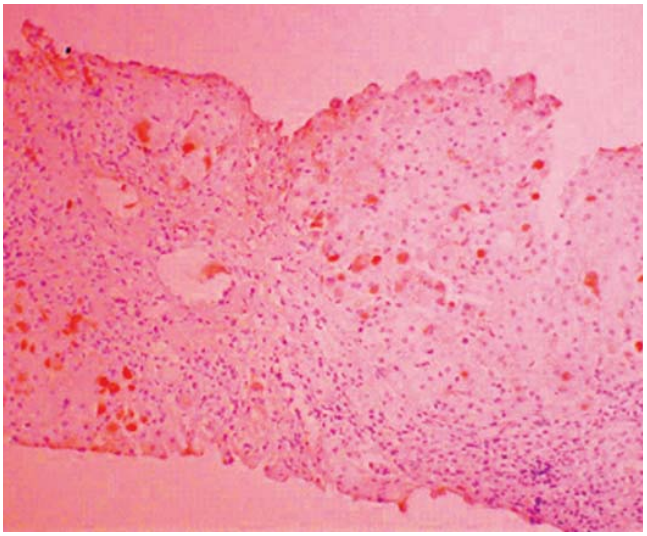

Figure 2. Immunohistochemistry exam showing HBsAg in the liver.

We also performed an immunohistochemistry study of the hepatic tissue for antibodies directed specifically against antigens of the hepatitis b virus. This study had a strong positive result.

A year after initiating treatment with entecavir, furosemide and spironolactone, the patient is in good general condition. There have been no signs of hepatic failure, and her HBV-DNA viral load is undetectable. Her thyroid profile tests continue to be normal and a new test for ANAs was negative. An endoscopic check up of her upper digestive tract showed healing of the duodenal ulcer. No esophageal varices were found.

DISCUSSION

Patients with chronic hepatitis B virus infections can experience outbreaks of viral reactivation when they are exposed to immunosuppression therapy. The natural course of these outbreaks varies. The great majority of cases are asymptomatic and are accompanied by elevated aminotransferases (ALT) and DNA viral loads. However, Calabrese et al. also describe cases of patients who develop jaundice, hepatic decompensation, fulminant hepatic failure including some cases which lead to the patients deaths (1).

Reactivation of HBV is more frequent when corticosteroids are included within the immunosuppression protocol. More recently Ostuni et al. and Bruno Roche and Didier Samuel have described reactivations and severe histories of hepatitis with the use of other immunomodulators/immunosuppressants such as rituximab, infliximab and other anti-TNFs used to treat rheumatologic diseases or intestinal inflammatory disease (2, 3).

Corticosteroids directly stimulate transcription of viral DNA. Vassilopoulos and Calabrese have shown that a significant increase in viremia levels can occur within two weeks of initiation of therapy. Since corticosteroids' direct immune suppressing effects favor viral replication without any kind of opposition, their use favors increased viremia (4).

The case that we have reported is a patient with a chronic hepatitis b virus infection with severe cirrhotic histological damage, but without any signs of decompensation at the time her first consultations. Once therapy with corticosteroids started, the patient decompensated and developed ascites, and increased aminotransferases. Her hepatitis b viral load was very high at the time of diagnosis.

Tests for previously existing hepatitis b infection were not conducted at the beginning of this patient's treatment. It is probable that her base viral load was low, but increased with immunosuppression therapy in the same way that her aminotransferase levels increased. The diagnosis of chronic HBV infection should have been made before starting immunosuppression therapy.

As Barzila points out, under ideal conditions a patient like ours should also have been evaluated for severity of hepatic damage in order to define whether she should have been treated with antiviral medications or with prophylactic therapy to avoid reactivation of the virus (5).

Antiviral prophylaxis is recommended for patients with chronic infections who are inactive carriers or who have hidden forms of the hepatitis b virus. These patients are characterized by negative HBsAg test results, but positive anti-HBsAg and/or anti-Core HBV test results. The medication recommended for prophylaxis of these cases of viral reactivation is lamivudine.

Patients with chronic hepatic disease, who have serious histological damage and a history of HBV reactivation, as was the case of our patient, must be treated with powerful antiviral medications with high genetic barriers that prevent the appearance of resistance. These characteristics are present in nucleoside analogs such as entecavir or tenofovir.

In this case the patient also tested positively for ANAs. These auto antibodies are induced by the hepatitis B virus and can generate confusion by simulating autoimmune diseases.

The mechanism by which the hepatitis B virus causes the creation of auto antibodies is unknown, although crossed reactivity between autoantigens and viral proteins has been suggested.

It has been demonstrated that up to 50% of patients who are seropositive for hepatitis B present auto antibodies, antinuclear antibodies and anti smooth muscle antibodies.

Patients chronically infected with HBV can become over-infected with the hepatitis delta virus and develop decompensation that is clinically indistinguishable from reactivation of HBV. In our case no serologic tests for hepatitis delta were performed.

Conflicts of interest

None of the authors has any conflict of interest that could affect the presentation of this case.

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