RESOLUTION OF IMMUNE THROMBOCYTOPENIA ASSOCIATED WITH CHRONIC HEPATITIS B VIRUS INFECTION IN A PATIENT TREATED WITH ANTIVIRAL THERAPY

Fuat ERDEM, İlhami KİKİ, Mehmet GÜNDOĞDU, Refik Ali SARI

Atatürk Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı, Hematoloji Bilim Dalı (FE,İK,MG) ve İmünoloji Bilim Dalı (RAS), Erzurum

Özet

Trombositopeni, kronik karaciğer hastalığı olan hastalarda görülen en sık hematolojik bozukluklardan biridir. Kortikosteroid yada immünglobulin verilmeden sadece anti-viral tedavi ile trombosit sayısı düzelen kronik immun trombositopenik purpura (ITP) ve kronik hepatit B virus (HBV) enfeksiyonu olan 65 yaşında bir bayan hastayi sunduk.

Anahtar kelimeler: Kronik hepatit B virus enfeksiyonu, İmmun trombositopenik purpura, Anti-viral tedavi

Summary

Thrombocytopenia is one of the most frequent haematological disorders in patients with chronic liver disease. We present a case of a 65-year-old woman who referred to our outpatient of haematology for chronic hepatitis B virus (HBV) infection and chronic Immune thrombocytopenic purpura (ITP). A sustained normalization of platelet count was observed during antiviral therapy without of administration corticosteroid or immunoglobulin.

Key words: Chronic hepatitis B virus infection, Immune thrombocytopenic purpura, Anti-viral therapy
Introduction

ITP is an acquired hematologic disorder by immune-mediated thrombocytopenia, which may be asymptomatic or result in bruising or mucocutaneous bleeding. The incidence of ITP in the adult population has been estimated at 60 cases per 1 million persons per year (1,2). ITP has been classified as primary or secondary and as acute or chronic. Adult-onset ITP is generally chronic, the onset is often insidious, and approximately females are affected twice as much as males (3). Secondary forms of ITP have been reported in association with infections, including human immunodeficiency virus and hepatitis C virus, as well as systemic lupus erythematosus, antiphospholipid syndrome, lymphoproliferative disorders (chronic lymphocytic leukemia and lymphoma, large granular lymphocytic leukemia) and therapy with drugs such as heparin and quinidine (3,4-10). Chronic hepatitis B is a common and frequently severe form of liver disease that affects at least 1 million Americans and 300 million people worldwide (11). Several extrahepatic manifestations are associated with chronic HBV infection, many with significant morbidity and mortality. The cause of these extrahepatic manifestations is generally believed to be immune mediated (12).

Case Report

Our case is a 65 year-old woman without a remarkable medical history until the 63 year of life, when she had been diagnosed chronic ITP. After 1 year, liver biopsy had been done after platelet count was increased by intra venous immunoglobulin. The chronic active infection of HBV had been diagnosed in basing on the clinicopathological findings, administration of alpha-interferon has been in another hospital. She was admitted to our hospital in october 2003. In the course therapy of interferon, her haematological and biochemistrical profile were both normal. After 1 month cessation of interferon therapy, she was readmitted to outpatient of haematology because of absence of thrombocytopenia in duration associated with Hepatitis B virus was considered as sequestration and destruction of platelets in the enlarged and congested spleen with an impaired ability of bone marrow to compensate by increasing platelet production (15). It has also been hypothesized that increased platelet associated immunoglobulins may play a role in the pathogenesis of thrombocytopenia in chronic liver disease (15). However, It has been reported that IFN may induce or exacerbate several autoimmune abnormalities because of its immunomodulatory properties (16). Also, Lamivudine-associated thrombocytopenia has been reported (17). In our patient, platelet count has been normalized due to the clearance of serum HBV-

Discussion

Current strategies for treating hepatitis B focus on clearance of active HBV infection through suppression of viral replication. Interferon-α and nucleoside analogs (lamivudine and adefovir) are currently approved for treatment of chronic hepatitis B (14). Thrombocytopenia is one of the most frequent haematological disorders in patients with chronic liver disease. The pathogenetic mechanisms leading to this disorder are sequestration and destruction of platelets in the enlarged and congested spleen with an impaired ability of bone marrow to compensate by increasing platelet production (15). It has also been hypothesized that increased platelet associated immunoglobulins may play a role in the pathogenesis of thrombocytopenia in chronic liver disease (15). However, It has been reported that IFN may induce or exacerbate several autoimmune abnormalities because of its immunomodulatory properties (16). Also, Lamivudine-associated thrombocytopenia has been reported (17). In our patient, platelet count has been normalized due to the clearance of serum HBV-

Case Report

Her haematological profile was as follows: haemoglobin 13 g/dl, haematocrit 40%, white blood cells count 8.5x10⁹/l and platelet count 10x10⁹/l. The peripheral blood film revealed decreased but megathrombocytes. Erythrocyte sedimentation rate was 35 mm/1h. Serum biochemistry revealed glucose 103 mg/dl, BUN 16.5 mg/dl, uric acid 5 mg/dl, creatinine 0.8 mg/dl, SGOT 80 IU, SGPT 86 IU, GGT 20 IU, ALP 95 UI, LDH 300 UI. Serological tests were as follows: HBsAg; positive, HBeAg; positive, HBV-DNA: 100.000 copy/ml. Results of the immunological tests (anti-dsDNA antibodies, antinuclear antibodies) and coagulation parameters (activated partial thromboplastin time, prothrombin time, plasma fibrinogen, D-dimer) were normal. Platelet-associated immunoglobulin G was not assessed, since it was not recommended as a diagnostic measure in recent guidelines (13). Bone marrow aspiration was normal except for increased megakaryocytes. She refused control liver biopsy. Initially, thrombocytopenia associated with Hepatitis B virus was considered because of absence of thrombocytopenia in duration of Interferon therapy. But, bone marrow aspirate and good response to intra venous immunoglobulin were suggestive of immune thrombocytopenia. Because of the above biochemical and serological tests, appropriate treatment for chronic hepatitis B infection with lamivudine (100 mg/day) was started. On follow-up, platelets and liver function tests (SGOT, SGPT) were found to be 50x10⁹/l, normal (<40IU/L), respectively, after 4 weeks of therapy. Physical examination revealed no petechiae and ecchymoses. On the third month, her platelets and HBeAg, HBV-DNA were 180X10⁹/L, negative, 10.000 copy/ml respectively. We therefore decided to continue lamivudine at a dose of 100 mg/day. After 6 months of lamivudine therapy, the platelet count was still normal.
DNA during IFN/lamivudine therapy. It has been shown that hepatitis C virus (HCV) can replicate extrahepatically, specifically in the bone marrow (18). Replication of HCV in the bone marrow may contribute to the etiology of thrombocytopenia observed in HCV-infected patients. A high prevalence of HCV positivity has been reported in several series of patients with ITP (19,20). Moreover, it has been shown that thrombocytopenia in HCV-infected patients is reversed after treatment with IFN-α monotherapy (20-22). Since the patient displayed severe thrombocytopenia and both good response to intra venous immunoglobulin and antiviral therapy, we speculated that immune thrombocytopenic purpura in this case was attributed both to the production of autoimmune antibodies against platelets and to bone marrow inhibition by hepatitis B virus infection. A significant increase in platelet count during treatment with interferon-alpha or lamivudine monotherapy in patient with chronic hepatitis B virus infection constitute clinical evidence supporting the hypothesis that HBV may have a direct pathogenic role in the process leading to thrombocytopenia. To our knowledge, the improvement of HBV-associated ITP due to IFN-α or lamivudine therapy has not been reported. Further investigation is warranted to determine the mechanisms.

References

Yazıma adresi: Yrd.Doç.Dr.Fuat ERDEM
Atatürk Üniversitesi Tıp Fakültesi
İç Hastalıkları Anabilim Dalı,
Hemotoloji Bilim Dalı, Erzurum