Case Report

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Portal vein thrombosis as complication of romiplostim treatment in a cirrhotic patient with hepatitis C-associated immune thrombocytopenic purpura

Georg Dultz[1], Bernd Kronenberger[1], Alireza Azizi[2], Ulrike Mihm[1], Thomas J. Vogl[2], Ulrike Sarrazin[1], Christoph Sarrazin[1], Stefan Zeuzem[1], Wolf-Peter Hofmann[1,*]

[1]*Medizinische Klinik 1, Klinikum der J.W. Goethe-Universität, Frankfurt am Main, Germany;* [2]*Institut für Diagnostische und Interventionelle Radiologie, Klinikum der J.W. Goethe-Universität, Frankfurt am Main, Germany*

Background & Aims: Thrombopoietin receptor agonists are a new class of compounds licenced for the treatment of immune thrombocytopenic purpura. They are currently being studied for patients with thrombopenia in advanced liver disease or under therapy for hepatitis C. There are indications that the risk for development of portal vein thrombosis in patients with advanced liver cirrhosis might be increased under therapy with thrombopoietin receptor agonists. We report a case of a patient with Child class B liver cirrhosis with concurrent immune thrombocytopenic purpura that developed portal vein thrombosis under therapy with the thrombopoietin receptor agonist romiplostim.

Methods: A 50-year-old woman with hepatitis C virus associated immune thrombocytopenic purpura and Child class B liver cirrhosis presented in our emergency with rapidly evolving hydropic decompensation and general malaise. For immune thrombocytopenic purpura, the patient was started on the thrombopoietin receptor agonist romiplostim nine months ago.

Results: During hospitalization, the platelet count was measured above 330,000/μl and partial portal vein thrombosis was diagnosed by imaging studies. The thrombotic event was assumed to be associated with the romiplostim treatment for immune thrombocytopenic purpura via excessive elevation of platelet count. After anticoagulation with heparin and cessation of romiplostim treatment, complete recanalisation of the portal vein was achieved.

Conclusions: We conclude that romiplostim should be used with precaution in patients with hepatitis C-associated immune thrombocytopenic purpura and advanced liver cirrhosis as the risk for thrombotic complications may increase significantly.

© 2011 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Case report

A 50-year-old woman with Child class B liver cirrhosis due to chronic hepatitis C was admitted to the hospital in June 2010 with rapidly evolving hydropic decompensation and general malaise. The patient was on the waiting list for orthotopic liver transplantation and had a Model for End-Stage Liver Disease (MELD) score of 20. Abdominal ultrasound examination showed large amounts of ascitic fluid and a thrombus that had emerged in the extrahepatic portal vein and which obstructed approximately two third of the veins lumen. By doppler sonography, portal vein peak-flow was measured to be 22 cm/s. Liver veins showed no abnormalities. The diagnosis was confirmed by computed tomography which showed a localized thrombosis at the intersection of the superior mesenteric vein into the portal vein (Figs. 1 and 2). Previous abdominal CT scans and regularly performed abdominal ultrasound examinations had never documented an obstruction of the portal vein so that it was assumed to be a recent event.

The patient had HCV-associated immune thrombocytopenic purpura (ITP) and treatment with the thrombopoitin receptor agonist (TRA) romiplostim was started nine months ago. ITP had been diagnosed in March 2009 by the detection of IgM and IgG antibodies by platelet immunofluorescence test (PIFT). The antibodies were specified by simultaneous analysis of specific platelet antibodies (SASPA) such as IgG antibodies against GP (glycoprotein) IIb/IIIA, IX, Ia/IIA, CD32, CD62p, CD9, GPV, CD109, CD31, CD49e, CD36, and HLA-class I-attributes and IgM antibodies against GP IX. Pseudothrombocytopenia was excluded previously by blood smear examination. Bone marrow aspiration had shown increased megakaryopoiesis. As the patient experienced bleeding from esophageal varices in the past, coexisting ITP was considered as a major risk factor for re-bleeding although band ligation was performed previously and the patient was on prophylactic propranolol therapy. Therefore, ITP was treated by pulse therapy with glucocorticosteroids 2 mg/kg but no significant increase in platelet count could be observed. Glucocorticosteroids were ultimately stopped as the patient developed deterioration of blood glucose levels and hepatic encephalopathy. Since platelets dropped below 20,000/μl repeatedly, treatment with the TRA romiplostim 500 μg/week subcutaneously was initiated. Romiplostim is approved for patients with ITP in which steroids are not successful and in which splenectomy is not

* Corresponding author. Address: Medizinische Klinik 1, Klinikum der J.W. Goethe-Universität, Theodor-Stern-Kai 7, 60594 Frankfurt am Main, Germany. Tel.: +49 696301 5122; fax: +49 696301 83112.
E-mail addresses: hofmann@em.uni-frankfurt.de, Wolf-Peter.Hofmann@polikum.de (W.-P. Hofmann).

Abbreviations: HCV, hepatitis C virus; ITP, immune thrombocytopenic purpura; MELD, model for end-stage liver disease; TRA, thrombopoietin receptor agonist; GP, glycoprotein.

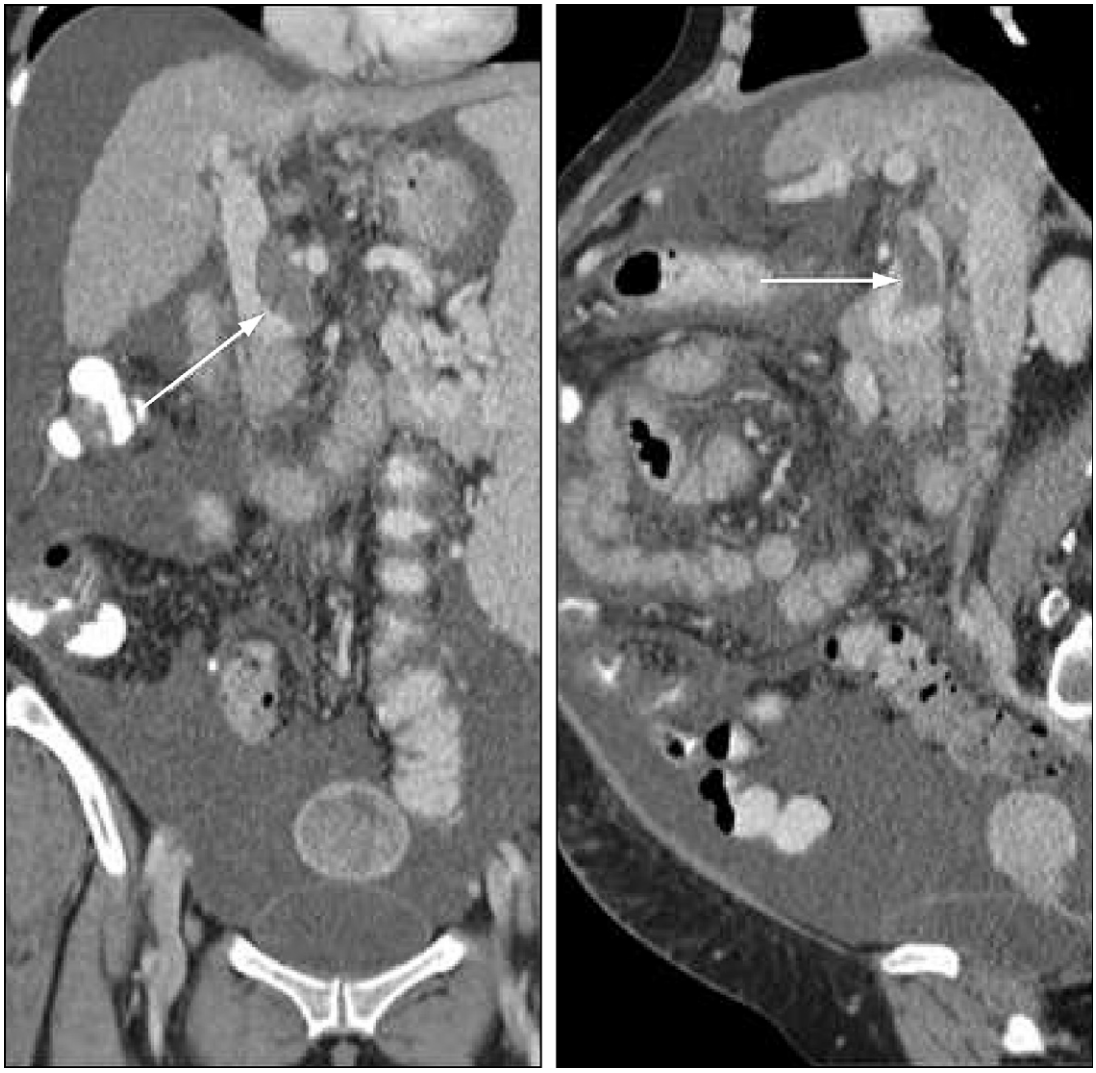

Fig. 1. The coronal and sagital view of a contrast enhanced CT in a 50-year-old female patient shows partial obstruction of the portal vein. The white arrow indicates narrowing and partial obstruction due to a huge thrombosis located in the extrahepatic portal vein.

recommended. At that time point, the patient had a Child class B cirrhosis with a MELD score of 16 without clinical signs of hepatic encephalopathy or hydropic decompensation. Weekly romiplostim injections resulted in a rapid increase in platelet count over 50,000/μl and were continued until hospital admission in June 2010.

Review of the platelet count during hospitalization revealed a peak of 331,000/μl whereas platelet count ranged between 50,000/μl and 100,000/μl during several weeks before admission (Fig. 3). Hence, coincidence of exceeding increase in platelet count and onset of portal vein thrombosis suggests a causative role of romiplostim leading to immediate discontinuation of romiplostim treatment. Thrombophilia screening including antiphospholipid antibodies, factor II/V mutations and Jak 2 genotyping did not show any abnormalities. Continuous intravenous administration of unfractionated heparin was initiated and the clinical condition of the patient improved constantly. The beneficial antithrombotic effect of heparin treatment was evaluated by intra-arterial digital subtraction angiography (DSA) of the celiac trunk and superior mesenteric arteries nine days later. Fortunately, complete recanalization of the portal vein was achieved (Fig. 4). Celiac trunk and inferior vena cava were shown to be free of thrombotic material. The patient was discharged two weeks after the diagnosis of portal vein thrombosis and low molecular weight heparin was administered subcutaneously thereafter. Finally, the patient received a liver graft in August 2010. Histologic examination of the patient's explanted liver revealed advanced cirrhosis without evidence of hepatocellular carcinoma.

Discussion

Chronic HCV infection is associated with a variety of extrahepatic manifestations including lymphoproliferative hematologic diseases as well as a wide range of immune-related disorders [1,2]. Recent reports emphasize that the incidence rate of ITP in patients with chronic hepatitis C is higher than previously

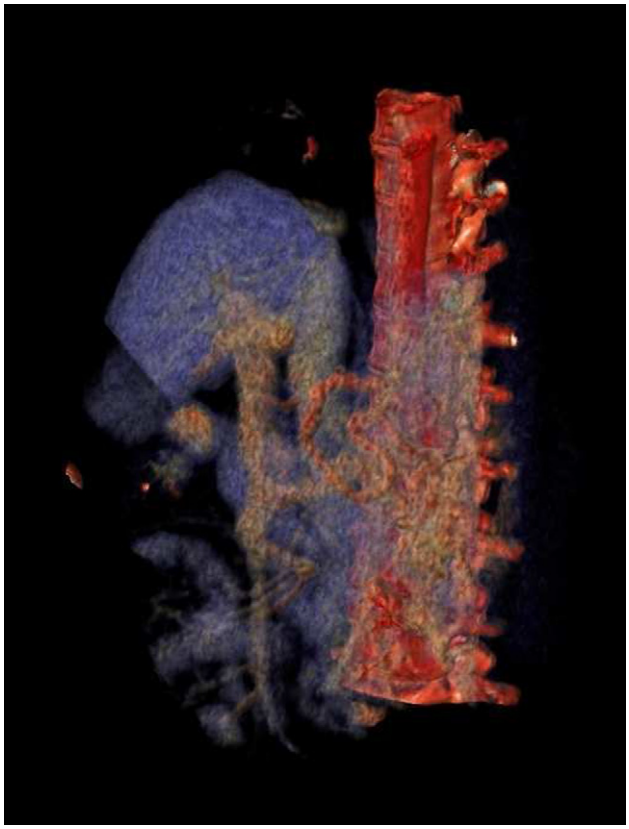

Fig. 2. The 3D reconstruction of the contrast enhanced CT shows the region of partial obstruction of the portal vein. The reconstruction was done as an attempt to localize the exact level of obstruction which was the region of intersection of the superior mesenteric vein into the portal vein.

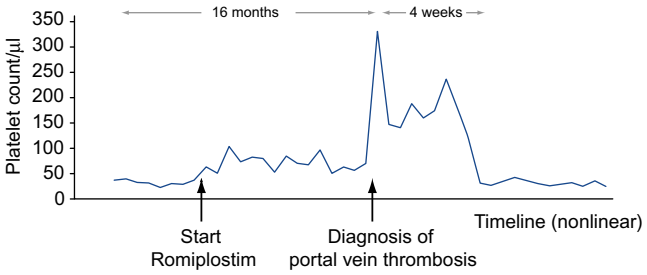

Fig. 3. Development of platelet count from diagnosis to start of romiplostim therapy and detection of portal vein thrombosis.

expected [3]. ITP can either occur *de novo* as primary ITP or secondary due to other underlying conditions, such as pharmacotherapy, autoimmune diseases, or chronic viral infections including HCV [4]. About 20% of ITP patients have serologic evidence of HCV infection. Thus, routine screening for HCV in patients with ITP is now recommended [5].

ITP is characterized by thrombocytopenia (<100,000/µl) due to the formation of autoantibodies against platelet surface antigens. Pathophysiology involves exceeding platelet destruction due to accelerated elimination of antibody-coated platelets by macrophages and dendritic cells in the spleen. Additionally, autoantibodies seem to directly impair platelet production in the bone marrow. Furthermore the thrombopoietin blood level in

Fig. 4. Digital subtraction angiography of the patient after cessation of romiplostim and treatment with heparin for 9 days. The vascular anatomy of the inferior mesenteric artery and completely recanalized portal venous system are shown. Notice the large portal vein due to portal hypertension and the absence of the huge thrombosis previously shown on the CT.

ITP patients seems to be low in relation to the depressed platelet numbers (relative thrombopoietin deficiency) [6]. In patients with liver disease, platelet count may be diminished further by exceeding sequestration of platelets in the enlarged spleen.

To allow the diagnosis of ITP, a low platelet count is obligatory (<100,000/µl) and other secondary causes should be excluded. In 60–80% of cases platelet-bound antibodies can be detected [7] and specified as antibodies against platelet surface antigens (e.g. GP IIb/IIIa, GP Ib/IX, GP Ia/IIa) with highly sensitive and specific tests. The detection of specific platelet bound antibodies confirms the immunologic cause for the low platelet count, but determination between primary and secondary ITP is not possible. Bone marrow aspiration shows activation of megakaryopoiesis [8].

The therapeutic strategy is determined by bleeding complications and platelet count. ITP patients with platelet counts over 30,000/µl without bleeding complications do not require therapy, whereas ITP patients with serious bleedings (requiring transfusion) should receive treatment regardless of the number of platelets. Due to complications of portal hypertension, the risk of bleeding in our patient was considered even higher as in otherwise healthy individuals with ITP. First line therapy for ITP are steroids given in a dosage of 1–4 mg/kg (predniso[lo]ne) for 1–2 weeks and subsequent dose reduction or alternatively, dexamethasone 40 mg/d for 4 days repeatedly every 14–28 days. Initial responses are over 70%, but sustained response is reached in 10–50% only. In the acute bleeding situation iv immunoglobulins are added to the therapy regime. The second line therapy includes splenectomy with a sustained response in about 60% of patients [9].

Newer approaches for refractory ITP therapy include, rituximab, a CD20 receptor antibody that alters B cell response and antibody formation, thus leading to a response in 30–50% of patients. Nevertheless it is not yet approved for ITP [9].

The idea that thrombocytopenia is not singularly caused by increased platelet destruction but also by impaired platelet formation and relative thrombopoietin deficiency led to the development of agents that directly stimulate the thrombopoietin receptor. Two drugs have been approved for the treatment of refractory ITP: (1) eltrombopag, an organic molecule administered orally once daily, and (2) romiplostim, a protein of 60 kDa where the thrombopoietin binding domain is linked to the Fc portion of IgG, which is administered by subcutaneous injection once a week [10]. In the first randomized controlled phase III study about 80% of ITP patients showed a platelet response under romiplostim treatment in comparison to less than 10% in the placebo group [10]. Comparable results were seen in a recent phase III study testing eltrombopag [11]. In August 2008 romiplostim was approved in the US for patients with ITP lacking sufficient response to other treatments. The most frequent side effects associated with romiplostim treatment are headache, arthralgia, and myalgia. After abrupt termination of treatment, the platelet count can temporarily drop under the initial value. In some patients an increase in bone marrow reticulin has been reported. That is why bone marrow examination of treated patients before and during therapy should be considered [12].

Thrombotic events under eltrombopag and romiplostim have been reported but clear evidence of an increased risk during romiplostim therapy is lacking [12]. However, recently there has been an alarming communication about an increased number of portal vein thromboses in patients with advanced liver disease receiving eltrombopag in a randomized controlled trial [http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm211796.htm). Since thrombocytopenia in patients with advanced liver disease is common and platelet administration may be necessary prior to invasive procedures, this study was initiated to evaluate the efficacy of eltrombopag in cirrhotic patients. Eltrombopag was administered 14 days before an elective invasive procedure. In May 2010, a drug alert was issued and the study was terminated by the sponsor as portal vein thrombosis had been detected in 4% of patients receiving eltrombopag in comparison to only 1% in the placebo arm. All except one patient experienced the portal vein thrombosis at platelet counts above 200,000/μl.

The data are in line with the case described for our patient since a high platelet count coincided with the development of portal vein thrombosis. Patients with liver disease per se have an increased risk for portal vein thrombosis. The prevalence is 1% in early stages of liver cirrhosis and 30% in candidates for liver transplantation [13]. It can be assumed that treatment with TRAs is an additional risk factor for portal vein thrombosis, at least, if an uncontrolled elevation of the platelet numbers in patients with precipitating risk factors like advanced liver disease is induced.

Currently, new indications for TRAs in patients with liver disease are being investigated.

In patients with advanced chronic hepatitis C (including Child class A) in whom platelet counts below 90,000/μl to 100,000/μl are present, treatment with pegylated interferon alfa2a or 2b should be initiated with caution according to the package inserts. Furthermore, treatment with pegylated interferon alfa and ribavirin frequently requires dose reductions due to bone marrow toxicity which negatively affects sustained virologic response rates [14]. Early clinical trials have been published or are currently under way to evaluate the efficacy of eltrombopag and romiplostim to enable antiviral treatment in patients with advanced chronic hepatitis C and thrombocytopenia [15], (and www.clinicaltrials.gov). So far, no increased frequency of thrombotic events has been reported to our knowledge in patients with compensated Child class A liver cirrhosis, however, the present case illustrates the potential risks.

In conclusion, treatment with the TRA romiplostim for ITP was associated with portal vein thrombosis in our patient with advanced Child class B liver cirrhosis due to chronic hepatitis C. A careful risk-benefit analysis is recommended prior to the initiation of TRA therapy in patients with advanced liver disease and platelet counts should be monitored regularly in short intervals.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Zignego A, Giannini C, Ferri C. Hepatitis C virus-related lymphoproliferative disorders: an overview. World J Gastroenterol 2007;13:2467–2478.
[2] Landau D, Saadoun D, Calabrese LH, Cacoub P. The pathophysiology of HCV induced B-cell clonal disorders. Autoimmun Rev 2007;6:581–587.
[3] Chiao EY, Engels EA, Kramer JR, Pietz K, Henderson L, Giordano TP, et al. Risk of immune thrombocytopenic purpura and autoimmune hemolytic anemia among 120 908 US veterans with hepatitis C virus infection. Arch Intern Med 2009;169:357–363.
[4] Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168–186.
[5] Liebman HA, Stasi R. Secondary immune thrombocytopenic purpura. Curr Opin Hematol 2007;14:557–573.
[6] Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Blood 2009;113:6511–6521.
[7] Meyer O, Agaylan A, Bombard S, Kiesewetter H, Salama A. A novel antigen-specific capture assay for the detection of platelet antibodies and HPA-1a phenotyping. Vox Sang 2006;91:324–330.
[8] Matzdorff A, Giagounidis A, Greinacher A, Hiller E, Kiefel V, Müller-Beissenhirtz H, et al. Diagnosis and therapy of autoimmune thrombocytopenia. Recommendations of a joint Expert Group of DGHO, DGTI, DTH. Onkologie 2010;33:2–20.
[9] Stasi R. Immune thrombocytopenic purpura: the treatment paradigm. Eur J Haematol Suppl 2009;71:13–19.
[10] Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet 2008;371:395–403.
[11] Cheng G, Saleh MN, Marcher C, Vasey S, Mayer B, Aivado M, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet 2010.
[12] Kuter DJ. Thrombopoietin and thrombopoietin mimetics in the treatment of thrombocytopenia. Annu Rev Med 2009;60:193–206.
[13] Ponziani FR, Zocco MA, Campanale C, Rinninella E, Tortora A, Di Maurizio L, et al. Portal vein thrombosis: insight into physiopathology, diagnosis, and treatment. World J Gastroenterol 2010;16:143–155.
[14] McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology 2002 Oct;123 (4):1061–1069.
[15] McHutchison JG, Dusheiko G, Shiffman ML, Rodriguez-Torres M, Sigal S, Bourliere M, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. N Engl J Med 2007;357:2227–2236.