Case report

Long term remission after treatment with Rituximab in a case of thrombotic thrombocythopenic purpura

Remisiune de durată după tratamentul cu Rituximab într-un caz de purpură trombotică trombocitopenică

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is caused in a majority of cases by auto-antibodies that inhibit the von Willebrand factor (vWF) multimer cleaving enzyme (ADAMTS13); the abnormal persistence of these vWF multimers determines disseminated aggregation of platelets, leading to disseminated thrombosis as well as hemorrhage through platelet consumption. The natural history of the disease is severe, but with plasmapheresis followed by massive plasma transfusions (plasma exchange) and immunosuppressive treatment, TTP can be cured in a majority of cases. RL, 50 years old presented in December 2010, at the emergency room with confusion associated with headache. The neurological examination revealed confusion, bradylalia, without any focal signs. Clinical examination showed marked cutaneo-mucous pallor, hepatomegaly 4-5 cm and splenomegaly 3 cm under the costal margin. The hematological examination showed normocytic anemia (Hb 6 g/dl), moderate thrombocytopenia (28 x10^9/L), reticulocytosis (13%) and the presence of schizocytes. Biochemically there was indirect hyperbilirubinemia, mild hepatocytolysis, elevated lactatedehydrogenase (LDH) at 2637 U/L, normal renal function. Based on the clinical and hematological data, a diagnosis of TTP was established and treatment with plasma exchange (PEX) was urgently initiated in association with dexamethasone 16 mg/day and antiplatelet treatment with aspirin 75 mg/day. The response to PEX was prompt with rapid normalization of platelet count and reticulocytes, and the gradual disappearance of schizocytes. About 6 weeks later, after the reduction of the corticosteroid dose, concomitantly with an episode of acute enterocolitis with Klebsiella spp, followed by acute pneumonia with Enterococcus faecalis and Klebsiella pneumoniae, the platelet count dropped to 35x10^9/L, with reappearance of schizocytes on the blood smear and reticulocytosis. Dexamethasone 16 mg/day and PEX were resumed; vincristine and cyclophosphamide were also associated but no significant response was observed. We decided therefore to associate rituximab 375 mg/m^2 (700 mg)/week. Four rituximab doses were administered, with a favourable outcome, with normalization of the platelet count and subsequent disappearance of schizocytes. Presently, the patient is in remission at 19 months after completing the treatment with rituximab. This case report illustrates the fact that in some TTP cases, classical treatment with plasma exchange and corticosteroids may not lead to lasting results. The association of B-cell specific immunosuppression anti-CD20 monoclonal antibodies (rituximab) may be an effective alternative.

Keywords: *thrombotic thrombocytopenic purpura, plasma exchange, rituximab, dexamethasone*

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Rezumat

Purpura trombotică tombocitopenică (PTT) este cauzată în majoritatea cazurilor de apariţia de autoanticorpi care inhibă enzima de clivare a multimerilor factorului vonWillebrand (vWF), ADAMTS13; persistenţa exagerată a multimerilor de vWF determină agregarea diseminată a trombocitelor, cu apariţia unui tablou clinic caracterizat prin tromboze diseminate şi hemoragii prin trombocitopenie de consum. Evoluţia naturală a bolii este gravă, dar prin plasmafereză urmată de transfuzii masive de plasmă (plasma exchange) şi tratament imunosupresiv se poate obţine vindecarea în majoritatea cazurilor. RL, 50 ani se prezintă în decembrie 2010 la Serviciul de Urgenţă pentru apariţia bruscă a unei stări confuzive importante asociată cu cefalee. La examenul neurologic pacienta este confuză, cu bradilalie, dar nu se evidenţiază semne de focar. Examenul obiectiv relevă paloare marcată cutaneo-mucoasă, hepatomegalie la 4-5 cm şi splenomegalie la 3 cm sub rebordul costal. Hematologic se decelează anemie normocromă, normocitară (Hb 6g/dl), trombocitopenie moderată (28 x 10^9/L), reticulocitoză (13%) şi prezenţa de schizocite. Biochimic se remarcă hiperbilirubinemie indirectă, uşoară hepatocitoliză şi LDH mult crescut (2637 U/L), funcţie renală normală. Pe baza criteriilor clinice şi hematologice s-a stabilit diagnosticul de PTT şi s-a initiat de urgenţă tratament cu plasma exchange (PEX) în asociere cu imunosupresie cu dexametazonă 16 mg/zi şi tratament antiplachetar cu aspirină 75 mg/zi. Raspunsul iniţial la PEX a fost prompt cu normalizarea valorii trombocitelor şi a reticulocitelor, dispariţia schizocitelor şi a splenomegaliei. Aproximativ după 6 săptămâni, concomitent cu reducerea dozei de corticoizi, în condiţii de enterocolită acută cu Klebsiella spp, urmată de pneumopatie acută cu Enterococcus faecalis şi Klebsiella pneumoniae se observă scăderea trombocitelor la 35x10^9/L, reapariţia schizocitelor şi creşterea reticulocitelor, moment în care se reia corticoterapia cu Dexametazonă 16 mg/zi, se reiau sedinţele de PEX şi se asociază alcaloizi de vinca şi ciclofosfamidă. Având în vedere recidiva precoce la reducerea dozei de corticoid se decide asocierea de rituximab 375 mg/m^2 (700 mg)/săptămâna. Se administrează 4 perfuzii cu rituximab, evoluţia pacientei fiind favorabilă, cu normalizarea valorii trombocitelor şi disparitia schizocitelor. La momentul actual, pacienta este în remisiune, la 19 luni de la terminarea tratamentului cu rituximab. Cazul prezentat subliniază faptul că în unele cazuri de PTT, tratamentul clasic cu plasma exchange şi corticosteroizi nu este eficient pe termen lung. Asocierea imunosupresiei specifice cu anticorpi monoclonali anti-CD20 (rituximab) poate fi eficientă.

Cuvinte cheie: *purpura trombotica trombocitopenica, plasmafereza, rituximab, dexametazona*

Received: *16h August 2012;* ***Accepted:*** *14th November 2012;* ***Published:*** *29 November 2012.*

Introduction

Acquired thrombotic thrombocytopenic purpura (TTP) is an acute, life-threatening illness characterized by thrombocytopenia, disseminated thrombosis, microangiopathic hemolytic anemia (MAHA), and often signs of organ dysfunction—typically neurologic, cardiac, renal, or abdominal symptoms. Often the symptomatology is undulatory, sometimes with transient spontaneous symptom remission and recurrence over a few hours. Severe deficiency of the von Willebrand factor (vWF) cleaving protease ADAMTS13 is present in most cases of acquired TTP because of the presence of antibody, primarily IgG, to ADAMTS13. The mainstay of treatment remains plasma exchange (PEX) and steroids which are effective in 60-80% of patients. However, about 30-40% of patients experience relapses or never reach complete remission and PEX-independence. In such refractory/relapsing TTP patients, further immunosuppressive therapy may be required, such as cyclosporine, cyclophosphamide, or vincristine (1, 2). One alternative, increasingly used lately, is to combine PEX with specific B-cell targeted immunosuppression with the anti-CD20 monoclonal antibody (moAb), rituximab (3-5). We hereby present a case of relapsed/refractory TTP successfully treated with PEX and rituximab.

Case Report

R.L., female, 50 years old, was admitted in the emergency unit with severe headache and confusion of sudden onset. Neurological examination revealed confusion, bradylalia, without any focal signs. Physical examination

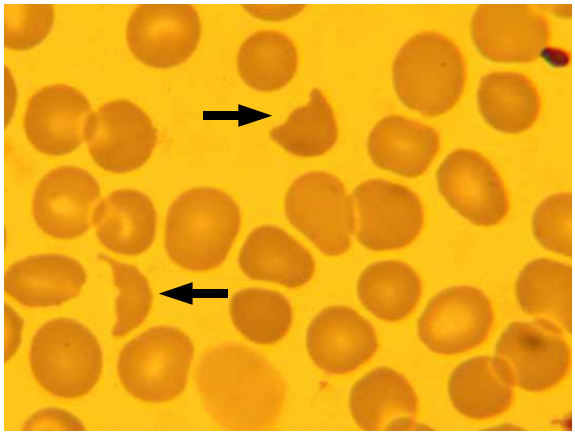

Figure 1. The presence of schizocytes (fragmented red cells) on the peripheral smear

showed marked cutaneo-mucous pallor, mild scleral jaundice, hepatomegaly 4-5 cm and splenomegaly 3 cm under the costal margin. The hematological exam showed normocytic anemia with hemoglobin (Hb) level at 6 g/dl, moderate thrombocytopenia with a platelet count of 28 $x10^9$/L, reticulocytosis 13% and abundant schizocytes on the peripheral smear (*Figure 1*). Biochemically, there was increased indirect bilirubin (2.3mg/dl), mild hepatocytolysis (ASAT-52U/L, ALAT-64U/L) and elevated lactate dehydrogenase (LDH) at 2637 U/l, normal creatinine (1.05mg/dl) and urea (36mg/dl). Virological screening tests for hepatitis B virus (AgHBs), hepatitic C virus (anti-HCV) and human immunodeficiency virus (anti-HIV) were negative. Based on the clinical and hematological data, a diagnosis of TTP was established. We were not able to determine ADAMTS13 or high-molecular weight vWF multimer levels. Treatment with plasmapheresis followed by massive fresh frozen plasma (FFP) infusion (4 liters of FFP/session) – plasma exchange (PEX) - was urgently initiated in association with dexametasone 16 mg/day and antiplatelet treatment with aspirin 75 mg/day. The response to PEX was prompt with disappearance of neurological symptoms after the first session, and normalization of platelet count after three PEX sessions. Soon afterwards, we observed the normalization of reticulocyte count, and the gradual disappearance of schizocytes. Two more PEX sessions were performed after platelet normalization (a total of five PEX sessions were initially done). Coricosteroids were continued at a dosage of 64 mg methylprednisolone for another 2 weeks, and then slowly tapered over the next 4 weeks. About 6 weeks after the last PEX session, after the reduction of the corticosteroid dose, concomitantly with an episode of acute enterocolitis with *Klebsiella* spp, followed by acute pneumonia with *Enterococcus faecalis* and *Klebsiella pneumoniae*, the platelet count dropped to $35x10^9$/L, with reappearance of schizocytes on the blood smear and reticulocytosis. Dexamethasone 16 mg/day and PEX were resumed; vincristine and cyclophosphamide were also associated but no significant response was observed. We decided therefore to associate rituximab 375 mg/m2 (700 mg)/week. Four rituximab doses were administered, with a favorable outcome, with rapid normalization of the platelet count and subsequent disappearance of schizocytes (*Figure 2*). PEX were stopped after the second rituximab administration and corticosteroids were tapered and stopped two weeks after the last rituximab dose. At present, the patient is in remission at 19 months after completing the treatment with Rituximab, with a normal clinical and hematological picture.

Discussion

The majority of acute acquired TTP cases (> 70%) are now recognized as being autoimmune and antibody mediated, primarily IgG to ADAMTS13. The efficacy of PEX treatment is well established. As it is an autoimmune disease, it seems logical that immunosuppression should play a role in the management of TTP. However, besides the routine administration of corticosteroids, there are limited data clearly demonstrating the utility of other im-

munosuppressive therapies in the management of TTP. Several small patient series describe various therapies, such as vincristine, cyclophosphamide, cyclosporine or splenectomy (1).

Rituximab (MabThera^{R}, Roche Pharmaceuticals) is a monoclonal anti-CD20 antibody that specifically depletes B lymphocytes. Rituximab has been used for the past decade with considerable success in the treatment of B-cell malignant lymphoproliferative diseases. It was also proven beneficial in several non-malignant autoimmune diseases, such as immune thrombocytopenic purpura, autoimmune hemolytic anemia, acquired hemophilia, rheumatoid arthritis, multiple sclerosis (6,7). Several small case series have successfully and safely used rituximab, usually as salvage therapy in patients with acute TTP who failed to respond to standard daily PEX and steroids or in relapsed acute idiopathic TTP patients (3-5). A recently published prospective study on 32 patients reported the results of rituximab as initial treatment in newly diagnosed TTP, as adjuvant treatment to PEX; a comparison with historical controls in which PEX alone was used showed a significantly lower rate of relapse at 12 months in the patients treated upfront with rituximab (8). It is still too early to tell if this initial benefit will translate into a longer lasting benefit, once the B-cell depleting effect of rituximab disappears.

In our patient, at the time of TTP relapse, the classical PEX and corticosteroid approach did not lead to significant improvement of the platelet counts. Furthermore, apparently, the relapse was precipitated by a string of infectious events, possibly related to prolonged corticosteroid treatment. Only after rituximab was added there was a steady increase of platelets. The effect has so far been lasting, 19 months after stopping any TTP directed treatment. It is also notable that despite

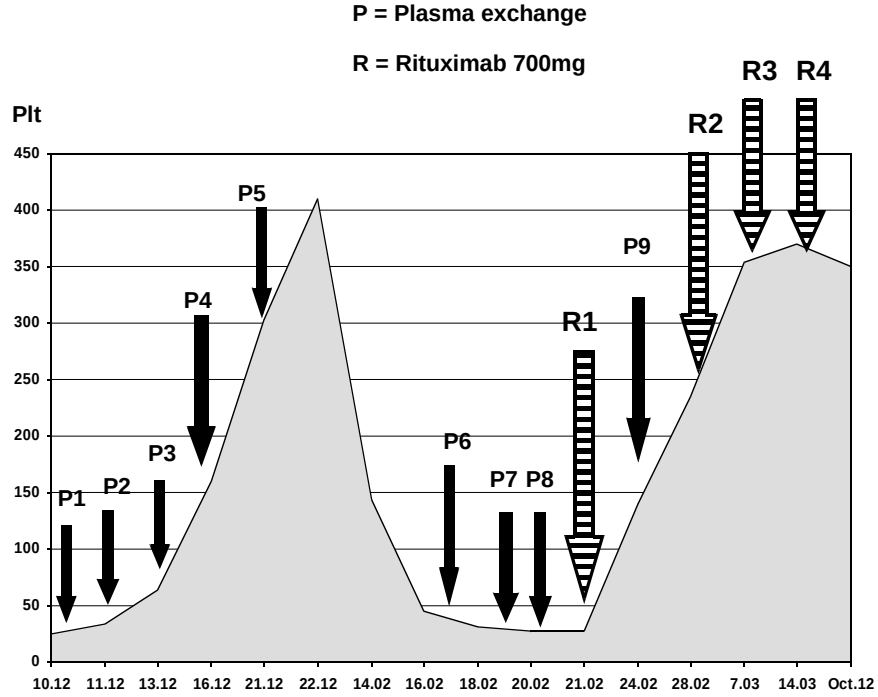

Figure 2. The effect of plasma exchange (P) and rituximab (R) treatment on the platelet count of patient R.L. with relapsing TTP. The patient was diagnosed on the 10th of December 2010. The last rituximab dose was given on the 14th of March 2011. The latest follow-up visit was in October 2012.

its anti-B-cell effect, rituximab treatment was not associated with further infectious complications, or any other adverse effects for that matter. The rapid effect of rituximab also allowed us to wean the patient as soon as possible from the prolonged corticosteroid treatment.

Conclusions

This case report illustrates the fact that in some TTP cases, classical treatment with plasma exchange and corticosteroids may not lead to lasting results. The association of B-cell specific immunosuppression with anti-CD20 monoclonal antibodies (rituximab) may be an effective alternative, leading to fewer relapses and longer-lasting responses. According to our knowledge, this is the first TTP patient successfully treated with rituximab in Romania.

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