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Journal of Pharmacology & Clinical Toxicology

Case Report

Rituximab in a Case of Plasma Exchange Refractory Moschcowitz Syndrome

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Submitted: 23 May 2017

Accepted: 02 June 2017

Published: 05 June 2017

ISSN: 2333-7079

Keywords

- Moschcowitz
- Plasma exchange
- Relapse
- Rituximab

Abstract

A 32 year old female patient suffering from weakness and discomfort in both flanks associated with red urine was transferred to hospital. In addition the patient showed paralysis of the right body side and seizures. Laboratory test showed a severe haemolytic anemia and thrombocytopenia with elevated values for lactate dehydrogenase. Together with the finding of fragmentocytes the diagnosis thrombotic thrombocytopenic purpura (TTP - Morbus Moschcowitz) was secured. Later low levels of ADAMTS13 and high levels of anti-ADAMTS13-antibody were determined. Treatment was started with plasma exchange with fresh frozen plasma and citrate anticoagulation (double plasma volume was exchanged in every treatment session). After initial improvement a first relapse occurred in a treatment gap. Under continued plasma exchange (17 plasma exchange treatment sessions at all) a second relapse occurred. This relapse was successful treated with rituximab. Under this combined therapy a fast and persistent clinical and biochemical improvement was achieved.

CASE REPORT

A 32 year old female patient was admitted with severe pain in both flanks accompanied with weakness, discomfort and red urine since 4 days. An outpatient care center suspected pylonephritis with makrohaematuria and started treatment with oral norfloxacine.

However during the following 2 days the patient weakness, discomfort and paralysis of the right body side progressed. After the patient presented seizures, she was transfered to our emergency unit.

First laboratory tests showed a severe anemia (Hb 5.1 mmol/l, Hk 0,24), an elevated acitivity of lactate dehydrogenase (1022 IU/l), a decreased haptoglobin and increased values for creatinine (128µmol/l). A thrombocytopenia with 16 gpt/l was present. Therefore the diagnosis of Morbus Moschcowitz (thrombotic thrombocytopenic purpura) was suspected. Coombs test was negative and fragementocytes were detected, this confirmed the suspected diagnosis. Plasmapheresis (PF1000 plasmafilter (Gambro AG), Baxter BM 11/14, regional citrate anticoagulation) was started immediately. The double of the calculated plasma volume was exchanged with fresh frozen plasma during each session. Serum calcium levels have been controlled continuously, intravenous substitution was performed if necessary (ionised serum calcium levels lower than 1,0 mmol/l). In addition to the plasma exchange a prednisolone therapy (100 mg/d) was started.

Initially a fast recovery of the patient and platelet counts (raised up to 87 gpt/l) was the result. Due to near normalized platelet counts and a satisfying clinical picture after the second plasma exchange and problems with the central venous catheter (femoral vein) the plasma exchange was discontinued, despite the fact that a continuation of plasma exchanged was scheduled for two more days. Another three days later a relapse occurred with decreased haemoglobin value and platelet counts (25 gpt/l, followed by a further decrease to 5 gpt/l), with increased lactate dehydrogenase and recurrence of seizures. With the second course of plasma exchange therapy a short improvement of clinical signs and laboratory tests (platelets max. 119 gpt/l) was achieved, but this was followed by a second relapse during plasma exchange and prednisolone therapy (platelets 8 gpt/l).

Laboratory immunological tests confirmed the suspected case of a Moschcowitz syndrome, thrombotic thrombocytopenic purpura (TTP). The activity of the metalloproteinase ADAMTS13 was below 2% (normal 50-110%), ADAMTS13 antigen concentration was below 2% (normal 45-110%), ADAMTS13 antibody concentration was above 100 U/ml (normal <16 U/ml).

For this case of antibody mediated idiopathic form of TTP as an autoimmune disease with non-response to plasma exchange therapy, we decided to use rituximab (MabThera, Roche Registration Limited, Welwyn Garden City, UK) for additional immune suppression.

Under continuation of prednisolone and plasma exchange therapy, rituximab was given at 375 mg/m^2 body surface area once a week for 4 weeks at all. Plasma exchange was paused for 48 hours after rituximab administration in order to prevent washing

out. Three days later all laboratory test were normalized. Plasma exchange was continued for 2 more days. After the application of rituximab no more relapses occured, the patient recovered fast. 4 months after discharge and receiving one more dose of rituximab the patient was on well being, platelet counts and LDH were normal. Rituximab therapy was stopped (Figure 1).

DISCUSSION

Morbus Moschcowitz [1], is characterised by microangiopathic hemolytic anemia (coombs negative), thrombocytopenia, renal failure, CNS changes (seizures) [2]. Laboratory test show low hemoglobin levels, low platelet counts, elevated serum lactate dehydrognase and sometimes elevated serum creatinine and urea. Due to hemolysis, haptoglobin is decreased. A specific sign for microangiopathic diseases is the presence of fragementocytes. The pathophysiological principle of the disease is the lack of the metalloproteinase ADAMTS13 or a decreased activity of this enzyme. ADAMTS13 (also known as von Willebrand factor-cleaving protease) is an enzyme that cleaves large von Willebrand multimers [3]. A heredetary form is the Upshaw-Schülman-Syndrome. Patients with this rare inherited ADAMTS13 deficiency show only a mild clinical course but severe exacerbation during acute illness. The secondary TTP (40% of all cases) is often associated with cancer, pregnancy, medication (e.g. clopidogrel, ticlopidine, quinine, mitomycin, tacrolimus), infection with HIV, Bartonella or bone marrow transplantation. The primary or idiopathic form of TTP is characterized by a decreased activity of ADAMTS13 due to the evidence of antibodies.

The decreased activity of ADAMTS13 [4], leads to a decreased cleaving of large von Willebrand multimers. This cause thrombosis and lowering of thrombcytes with neurological symptoms as well as hemolysis.

Standard therapy for TTP is prednisolone (1,5 mg / kg body weight) and plasma exchange therapy. The decreased activity of ADAMTS13 can be replaced by fresh frozen plasma (FFP). In mild cases the amount of ADAMTS13 infusion of FFP is sufficient.

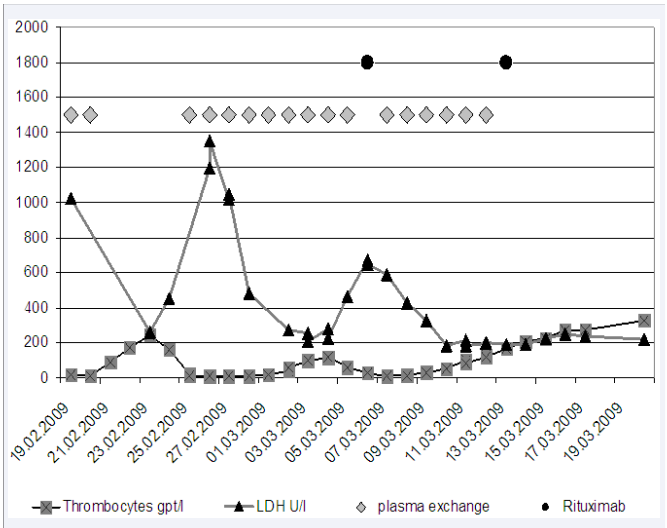

Figure 1 Time course of treatment.

During PE not only ADAMTS13 is substituted, circulating anti-ADAMTS13 antibodies are also removed. Transfusion of platelets should be avoided [5].

A review of the literature shows case reports and uncontrolled reporting use of vincristin [6], and other immunosuppressive substances (cyclosporin, immunglobulins) [7]. Before PE became the therapy of choice, splenectomy was performed especially in chronic forms. Neither amount nor frequency of plasma exchange have been investigated in detail. Mostly accepted is the daily exchange of single or double plasma volume for at least two days once the platelet counts and the LDH have been normalized.

First case reports of rituximab in the treatment of TTP were found [8-13]. Rituximab as a anti-CD 20 antibody suppresses B-lymphocytes and the production of antibodies. A short review of use of rituximab in TTP led to the decicision to use rituximab in this case

CONCLUSION

The application of rituximab in this case was a successful treatment of a TTP which had been refractory to standard therapy based on prednisolone and plasma exchange therapy. The increasing number of case reports with ineffective treatment of TTP shows the need of better treatment options for this disease. Rituximab seems to be such an option, especially in cases with relapses despite prednisolone and plasma exchange therapy. Another aspect of this case is the fast relapse after stopping plasma exchange therapy too early.

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Cite this article

Koball S, Führer A, Mitzner S (2017) Rituximab in a Case of Plasma Exchange Refractory Moschcowitz Syndrome. J Pharmacol Clin Toxicol 5(4):1082.