Heparin-Induced Thrombocytopenia vs. Plasmapheresis-Induced Platelet Loss in a Case of Thrombotic Thrombocytopenic Purpura

Nils H. Thoennissen\textsuperscript{a} Claudia Baumann\textsuperscript{b} Reinhard Kelsch\textsuperscript{b} Oliver Albrecht\textsuperscript{a}
Carsten Müller-Tidow\textsuperscript{a} Walter Sibrowski\textsuperscript{b} Wolfgang E. Berdel\textsuperscript{a} Rolf Mesters\textsuperscript{a}

\textsuperscript{a}Department of Medicine, Hematology and Oncology, \textsuperscript{b}Department of Transfusion Medicine, University of Münster, Germany

Summary

Background: Thrombotic thrombocytopenic purpura (TTP) is a clinically heterogeneous syndrome associated with thrombocytopenia, microangiopathic hemolytic anemia, neurologic changes, renal impairment, and fever. The outcome was almost universally fatal until the use of plasma exchange therapy which has dramatically altered the course of disease. Case Report: Here, we report on a 30-year-old female patient suffering from TTP who experienced apheresis treatment resistance. Non-responding thrombocytopenia after initial improvement of neurological symptoms was noted while the patient continued to receive daily plasma exchange therapy (Sartorius-Haemoprocessor\textsuperscript{TM}). Neither increased volume of plasma exchange nor using cryosupernatant plasma instead of solvent detergent (SD) plasma nor high-dose glucocorticoids lead to a persisting platelet increment. Because of a positive anti-heparin/PF4 antibody gel test we suspected a heparin-induced thrombocytopenia type II (HIT II) that developed during plasma exchange therapy. A subsequent non-heparin plasma exchange therapy (COBE Spectra\textsuperscript{TM}) with centrifugation technique and citrate as anticoagulant was consequently applied, followed by an increment of the platelet count to normal levels. Additional investigations of the serum with HIT-specific ELISA tests and heparin-induced platelet activation assay (HIPA) turned out to be negative. Eventually it remains unclear to what extent the therapeutic plasma exchanges potentially reduced HIT antibodies and consequently sophisticated the test results. Obviously, the switch to a centrifugal plasmapheresis system using heparin-free anticoagulation was followed by therapeutic success. Conclusion: Platelet loss due to the applied plasmapheresis system as well as potential drug-induced immune thrombocytopenia due to heparin administration during plasma exchange may cause persistent thrombocytopenia in patients with TTP. This may be incorrectly interpreted as continuing active disease, potentially leading to inappropriate additional treatments.

Schlüsselwörter
Thrombotisch-thrombozytopene Purpura · TTP · Therapeutische Plasmamaustauschbehandlung · HIT II

Zusammenfassung
Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare entity with clinical symptoms such as thrombocytopenia, Coombs-negative microangiopathic hemolytic anemia and predominant central nervous system involvement. After initial endothelial cell injury unusually large von Willebrand factor (vWF) complexes can be found in the plasma due to a deficiency of the vWF-cleaving protease ADAMTS-13 in most of the patients [1]. Long Zheng et al. [1] and Vesely et al. [2] showed that in case of a highly decreased protease activity and a lack of protease antibodies there is a high chance to achieve a good and rapid response to plasma exchange therapy in non-hereditary sporadic TTP.

In TTP, plasma exchange against fresh frozen plasma is the therapy of choice. This treatment dramatically reduced the lethality in the past decades [3, 4]. Exacerbation of thrombocytopenia after initial recovery, while the patient still continues to receive daily plasma exchange therapy, signals increased disease activity and necessitates more intensive treatment. Daily plasma exchange is recommended until platelet counts increase, with the standard exchange fluid being fresh frozen plasma (FFP) or solvent detergent (SD) plasma in which vWF is largely removed [5]. In a literature review it has been postulated that cryosupernatant plasma from which the cryoprecipitate fraction is removed, has no advantage in the initial treatment of TTP, but apparently in patients who were refractory to FFP [5–7]. When using plasma exchange therapy, the thrombocytopenia typically requires several days before recovery begins. The intervals of apheresis can be extended after patient’s response to treatment as indicated by increasing platelet counts and decreasing hemolytic activity. In that context, the platelet count seems to be the most important variable on which to base treatment decision [5].

In this report, we describe one patient with TTP in whom primary refractory TTP unresponsive towards plasma exchange was initially suspected. Subsequently, a diagnostic workup revealed the suspected diagnosis of concomitant heparin-induced thrombocytopenia type II (HIT II), probably due to heparin application during the apheresis procedure with filtration technique.

Case Report

We report on a 30-year-old woman who presented with mild fever, malaise, dyspnoe, distal paresthesia, mild jaundice, hematuria, and petechial hemorrhage. On admission, the patient’s laboratory variables showed severe anemia with hemoglobin level of 5.5 g/dl, LDH of 2,238 U/l, and highly decreased platelet counts of 5/nl (fig. 1). Besides negative findings in a direct antiglobulin test, a high amount of red blood cell fragmentation was found in the differential blood count. A bone marrow aspiration showed features compatible with TTP like increased erythrocytosis and megakaryopoiesis and normal granulocytopoiesis. Diagnostic tests for an underlying malignancy with ultrasonographic and CT screenings were negative. The activity of the ADAMTS-13 protease was markedly decreased with <3% (normal value 30–120%), which provided further evidence for TTP. Antibodies against the protease were not detected.

On day 1 after admission, treatment was initiated with 100 mg intravenous prednisone and therapeutic plasma exchange treatment with one volume exchange daily. Initially, we used the Sartorius Haemoprocessor™ (Göttingen, Germany) with a membrane filtration system (Bellico, Vineland, NJ, USA). The plasma will be filtered continuously through the membrane pores. The use of larger veins or a double lumen catheter in one larger vein usually allows to maintain a high enough flow to avoid clotting of the system. In this system, unfractioned heparin is the standard anticoagulation regime to prevent coagulation activation within the extracorporeal circuit [8].

After two sessions of plasma filtration, the patient clinically responded with an improvement of her neurological symptoms. But even though the patient recovered rapidly from her symptoms with continuation of daily plasma exchanges, the platelet count did not increase (fig. 1). On day 10 after admission, we intensified the treatment by increasing the daily plasma exchange volume from initially 1,700 to 3,000 ml on average. Moreover, we increased the dose of immunosuppressive therapy up to 350 mg intravenous prednisone. Nevertheless, the thrombocytopenia remains unaffected. Furthermore, we tried to use cryosupernatant plasma instead of SD plasma to treat the refractory TTP since day 17. On days 19, 20, 26, and 27 we had to use SD plasma intermittently because of unavailability of cryosupernatant plasma over weekends. The usage of cryosupernatant plasma induced only a slight, nonpersistent platelet increment (fig. 1).

On day 31, we screened for a potentially underlying HIT II by performing a rapid semi-quantitative anti-heparin/PF4 antibody gel test (DiaMed-ID PaGIA, Diamed Medizintechnik, Cologne, Germany) [9] which was found to be positive. Since day 32, we then used regularly a centrifugal apheresis system (COBE Spectra®, Gambro BCT, Lakewood, CO, USA) (fig. 1) in which a heparin-free anticoagulation, i.e. a combination of sodium citrate, citric acid and glucose (ACD-A), is the regimen of choice [5]. This apheresis system uses centrifugal forces to achieve a stable steady state of the cellular blood components and a separation of the plasma. Therefore, the separation and plasma exchange can be performed continuously, with a lower potential risk of damage and loss of cellular blood components compared to devices working discontinuously [8].

Subsequent to the implementation of the centrifugal apheresis system, an improvement of thrombocytopenia was detected, and the platelet count started to increase constantly and stabilized at normal levels (fig. 1). Remarkably, before screening for HIT II we intermittently switched to the centrifugal apheresis system because of organizational reasons, and a significant increment of the platelet count could be noted on days 21–25 which was followed by a platelet drop after returning to the filtration apheresis system (fig. 1).

A further semi-quantitative anti-heparin/PF4 antibody gel test was done on day 41. Again, it was positive. However, to verify the result we repeated the test with serially diluted plasma. The dilution titer of 1 made the diagnosis of HIT II unlikely [10]. Now, additional assays such as sensitive enzyme-linked immunosorbent assay (ELISA) and the specific heparin-induced platelet activation assay (HIPA) were performed which turned out to be negative.

While continuing centrifugal plasmapheresis, the ADAMTS-13 protease activity was shown to reach a normal value of 39% on day 50. Finally, the intervals of apheresis were increased, and the patient was discharged for a regular follow-up in our outpatient facility.

Discussion

The only case with simultaneous occurrence of TTP and HIT II published so far is a cardiac surgery patient described by Benke and Moltzan [11]. In this patient, HIT II was diag-
nosed because of initial thrombocytopenia with pulmonal embolus, positive heparin-PF 4 ELISA and a confirmatory serotonin release assay. Later on, the patient additionally developed TTP-like symptoms with a reduced ADAMTS-13 activity. In general, the HIT II diagnosis is primarily based on clinical criteria and should be confirmed by laboratory testing. Therapeutic decisions must often be made before reliable laboratory results become available. In our case, HIT II was not primarily investigated because of an initial TTP diagnosis. The laboratory rapid tests of HIT II showed repetitive positive results but discrepant confirmatory and functional tests for heparin-dependent antibodies. Daily performed TPA possibly had a lasting lowering effect on the antibody titer in the patient’s serum. Therefore, it remains unclear whether HIT II was of additional importance in this case of TTP. After all, we could not completely exclude the presence of HIT II in our patient.

The pros and cons of different plasmapheresis techniques have been vigorously debated. Currently, there is no randomized controlled trial comparing different methods of plasmafiltration with respect to mortality or at least the potential plasmapheresis-induced platelet loss in TTP patients. A disruption of thrombocytes in the pores of the membranes forced by a high transmembrane gradient frequently has been suggested as one possible underlying reason for therapeutic resistance. In a large trial comparing plasma exchange via the centrifugal technique with plasma infusion alone in the treatment of TTP, Rock et al. [12] showed an improvement in mortality when using plasma exchange by centrifugation. Moreover, Perdue et al. [13] could show that the platelet loss is only minimal when using the COBE Spectra centrifugal system. In our case, the patient may suffer from a subliminal loss of platelets to various extents, depending on the gravity level during centrifugal plasmapheresis.

In conclusion, in our case it remains unclear whether the reason for therapeutic resistance in TTP was a coexistent HIT II or a significant platelet loss due to the plasmapheresis system. In patients with TTP refractory to plasma exchange therapy, alternative etiologies of the underlying thrombocytopenia should be considered. Future clinical research should include the evaluation of the role of plasmafiltration compared to centrifugation.

References

Heparin-Induced Thrombocytopenia vs. Plasmapheresis-Induced Platelet Loss in a Case of Thrombotic Thrombocytopenic Purpura


