Case Report

Thrombotic thrombocytopenic purpura secondary to ABO group incompatible blood transfusion in a patient after cardiac surgery

Yalcin Solak, Nedim Yilmaz Selcuk, Abduzhappar Gaipov, Ramazan Ucar[1], Zeynep Biyik, Kadir Acar[2]

Abstract

The triggers of secondary thrombotic thrombopcytopenic purpura (TTP) include drug toxicity, radiation and high-dose chemotherapy, angioinvasive infections, surgery and acute graft versus host disease. TTP secondary to surgery have been reported in a number of cases. Most of the cases have been occurred after open heart surgery. Extensive endothelial damage is held responsible as the initiating mechanism in postoperative TTP cases. However, there is no report of secondary TTP describing development owing to ABO incompatible blood transfusion. Here, we describe a patient who developed TTP after transfusion of ABO incompatible blood during hospitalization for bypass surgery. We also propose a hypothesis which may account for the possible underlying mechanism.

Keywords: ABO incompatible, blood transfusion, coronary artery bypass grafting surgery, thrombotic thrombocytopenic purpura

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Introduction

ABO incompatible blood transfusions are rare, result in haemolytic transfusion reactions (HTR), and they can be fatal in 2 to 6% of cases.[1,2] It is enough to transfuse only 10-15 ml of ABO incompatible blood to cause following symptoms of acute HTR: Fever, hypotension, disseminated intravascular coagulation (DIC), complement-induced acute intravascular hemolysis and acute renal failure.[3,4]

In adults, thrombotic thrombocytopenic purpura (TTP) is idiopathic in approximately one-third of cases and in the remainder it is encountered in a variety of potentially triggering clinical situations (so-called secondary TTP), including pregnancy, malignancies, drugs, infection, auto-immune disorders and after haemopoietic stem cell transplantation.[5] Secondary thrombotic TTP is a life-threatening condition and is characterized by an aggressive course, it requires prompt treatment at the outset. In case of delayed or inadequate treatment mortality rate may be close to 100%.[6] To date, there is no report in the literature about secondary TTP caused by ABO incompatible blood transfusion. We present a case of TTP developed after a HTR in the setting of cardiac bypass surgery.

Case Report

A 64-year-old male patient developed nausea, vomiting and chills during red blood cell (RBC) suspension transfusion on the second day of coronary by-pass surgery. Transfusion was stopped immediately. Caring physicians recognized an error in labeling of the RBC suspension. With a preliminary diagnosis of ABO incompatible transfusion reaction, aggressive hydration was instituted. In the follow-up, hemoglobin values dropped and lactate dehydrogenase (LDH) and serum creatinine levels started to increase proportionally. Urine color was darkened with a gradual development of oligo-anuria and acute kidney injury (AKI). On the 7th day of transfusion, platelet count decreased and

From:
Departments of Nephrology, [1]Internal Medicine and [2]Hematology, Konya University Meram School of Medicine, Meram, Konya, Turkey

Correspondence:
Dr. Yalcin Solak, Konya University, Meram School of Medicine, Hemodialysis Unit, 42090, Meram, Konya, Turkey.
E-mail: yalcinsolakmd@gmail.com

LDH level increased significantly. In peripheral blood smear, polychromasia and abundant schistocytes were seen. TTP was diagnosed according to following criteria: Thrombocytopenia, microangiopathic anemia, increase in LDH level, and development of AKI. We started hemodialysis and plasmapheresis on the 8th day because of TTP and AKI. After 11 and 15 sessions of hemodialysis and plasmapheresis, respectively, platelet, LDH, urea, creatinine levels and urine output improved. Steroid therapy (1 mg/kg/day) was given simultaneously. The patient showed a dramatic improvement, and plasmapheresis and hemodialysis were stopped subsequently. On the 41th day of admission he had bloody diarrhea and C. Difficile toxin A was found to be positive in feces and vancomycin was administered for pseudo-membranous enterocolitis. On the 50th day, multiple infarctions were seen on cranial CT that was performed for the evaluation of confusion. Blood urea, creatinine and LDH levels increased, hemoglobin and platelet levels decreased again. In addition schistocytes were seen in blood smear. Plasmapheresis was performed because of recurrent thrombotic microangiopathy and hemodialysis was also started again. Thrombocytopenia persisted until the patient died eventually due to cardiac arrest. The pertinent laboratory data and major interventions are chronologically illustrated in [Table 1].

Discussion

Every 1 of 14000 blood transfusions are erroneous, and among them 1 of 13000 are ABO incompatible.[3] The pathogenesis of HTR is most likely related with activation of complement and hemostatic system, which leads to attachment of host antibodies to red blood cell antigens of incompatible donors blood.[4] As a result, it can modify the intravascular hemolysis and initiate symptoms such as nausea, vomiting, chills, fever and dark appearance of urine, which were evident in our patient during and after transfusion. In addition, studies presented relation between ABO groups, clearance of ultra large Von Willebrand factor multimers (ULVWF), deficiency of ADAMTS13 and risk of TTP development.[7] ADAMTS13 is a circulating zinc metalloprotease, responsible to cleave the ULVWF, thereby the multimers become progressively smaller due to cleavage by ADAMTS13. Deficiency of ADAMTS13 leads to a shift of plasma ULVWF multimers to larger sizes, adhesion with platelets and its aggregation, leading to endothelial injury with activation of thrombosis cascade.[8]

Data from Terrell *et al*.[9] demonstrated that blood group "O" is an independent risk factor for TTP associated with severe ADAMTS13 deficiency. Our patient had also "O" ABO blood group, but we could not documented the ADAMST13 deficiency due to unavailability of the lab technique at our institution at that time.

The initiating mechanism of secondary TTP include drug toxicity, radiation and high-dose chemotherapy, angioinvasive fungal or viral infections, surgery and acute graft versus host disease.[10] The exact underlying mechanisms of secondary TTP remain to be elucidated. Primary and Secondary TTP also appear to differ in their response to therapy. Primary or idiopathic form responds to plasmapheresis 80% of the cases whereas this rate is very low in secondary forms. Relapse rates are higher in secondary TTP depending on the initial event. The clinical course of our patient showed a severe relapse despite an initial complete biochemical and clinical response.[11]

Recently Canadian Apheresis Group conducted a phase II trial to test the beneficial effects of Rituximab in idiopathic TTP.[12] In this form of the disease, there is a severe and autoimmune deficiency of ADAMTS 13. Actually this

Table 1: Laboratory data and major clinical events and interventions during the course of the hospitalization

	Initial data	1 week (1-7 days)	2 week (8-14 days)	3-4 weeks (15-28 days)	5-7 weeks (29-49 days)	8 week (50-56 days)	9-10 weeks (57-69 days)
Symptoms		Nausea, chilling and vomiting			Diarrhoea	Mental confusion	Death
Urine output		1800→100 cc	500→1000 cc	1300-1700 cc	2000 cc	2000→600 cc	200 cc
Hb (g/dL)	12,8	→11,8	9,6-7,5	8,1→10,3	10,3-9,4	9,0-11,0	8,4→6,9
Plt (×10³/mm³)	158	→104	72-13	63→105	125-135	246→15	31→11
LDH (u/L)	-	→559	1442→3439	792→270	270-276	→1935	1214→283
Cr (mg/dL)	1,1	→1,7	2,5-5,1	6,3→3,7	3,4-1,6	1,5→3,4	3,8→1,4
Urea (mg/dL)	35	→43	98→126	170→59	72-21	27→118	156→78
ALT/AST (u/L)	-	68/36	224/119	43/25	16/18	108/107	61/64
Schistocytes		++	++++			+++	++
Diagnosis		HTR, AKI	TTP, AKI		Pseudo-membranous enterocolitis	Multiple cerebral infarction	TTP and AKI Relaps
Treatment interventions		CABG ABO-IBT	Haemodialysis ×15 and Plasmapheresis ×11			Plasmapheresis ×8 and Haemodialysis ×3	
			Vancomycin+imipenem		Vancomycin	Meropenem	Intubation

Hb: Haemoglobin; Plt: Platelets; LDH: Lactate dehydrogenase; Cr-serum creatinine; ALT/AST: Aminotransferase; HTR: Haemolytic transfusion reactions; AKI: Acute kidney injury; ABO-IBT: ABO incompatible blood transfusion; TTP: Thrombotic thrombocytopenic purpura

study was planned after reporting of many cases in which rituximab was shown to be beneficial.[13] And the authors concluded that autoimmune deficiency of ADAMTS 13 may be due to yet unidentified autoantibodies and while plasmapheresis clears circulating autoantibodies, treatment modalities such as rituximab precludes further antibody production via blockage of B cells.[12]

Postoperative TTP have been described after a number of surgical operations, most common of which is open heart surgery.[14] TTP developed after five to nine days after surgical operation in most of the case reports. The exact underlying mechanism is not known currently. However, it has been proposed that extensive endothelial damage during surgery may lead to release of high-molecular weight von Willebrand Factor (HMW-vWF) multimers in substantial amounts sufficient to overwhelm the capacity of the vWF-cleaving enzyme. However, despite thousands of CABG operations worldwide at each year, only a handful of cases have been reported. This may in part be related to presence of confounding factors such as blood loss, hemodilution, severe infection, DIC, and heparin induced thrombocytopenia commonly in the early course of CABG. Another explanation may be the rare patients who have genetically low levels of cleavage enzyme.

TTP secondary to ABO incompatible blood transfusion has never been reported in the literature to date. We hypothesize a potential mechanism which may account for the development of TTP in this setting. However, TTP developed in our patient in the setting of open heart surgery. After the ABO incompatible blood transfusion, DIC usually develops if sufficient amount of incompatible blood is transfused. One may argue that our case also developed DIC but not TTP. We know that DIC is self-limited provided that underlying inciting disease is well controlled. However, thrombocytopenia in our patient developed 1 week after the offending event and lasted for weeks despite normal coagulation tests (INR and aPTT), which is unusual in the setting of DIC. Another supporting finding in favor of TTP was a favorable response to plasmapheresis performed with fresh frozen plasma. The patient responded initially to plasmapheresis along with intermittent hemodialysis as needed. It is very difficult to discriminate whether transfusion of ABO incompatible blood or open cardiac surgery or the combination of the two actually initiated the process. Perhaps, both factors worked hand-in-hand. However, one clinical observation supports our hypothesis of blood transfusion as the initiating factor. None of the TTP cases secondary to surgery had relapsed unless the patient underwent a second operation.[14] However, this was not the case in our patient who developed a relapse after near complete improvement of laboratory and clinical parameters. Despite initial recovery, he developed a second bout which was complicated by multiple cerebral thrombi and subsequently died. Given the complex picture of early postoperative phase of CABG and the presence of potential confounders, many cases of postoperative TTP may have been missed. Prompt recognition is of utmost importance because of not only high mortality rate when left untreated but also to institute specific therapies. availability of efficient therapeutic maneuvers

Conclusion

To our knowledge, this is the first report of TTP secondary to ABO incompatible blood transfusion. We also proposed a putative pathophysiologic hypothesis based on this case.

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