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Post-operative thrombotic thrombocytopenic purpura: A review

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SUMMARY

Post-operative thrombotic thrombocytopenic purpura (TTP) is a recently recognised life-threatening clinical syndrome with considerable similarity to classic TTP in presentation and response to early treatment with plasma exchange. To date, 29 cases of TTP associated with surgery have been reported. The majority of cases have complicated vascular surgeries, with a few cases seen following gastrointestinal or orthopaedic procedures. Characteristically, patients develop microangiopathic haemolytic anaemia and consumptive thrombocytopenia 5 to 9 days following surgery with variable presence of fever, impaired renal function and altered mental status. The pathogenesis of post-operative TTP is speculative but may involve the release of large amounts of high-molecular-weight von Willebrand factor (vWF) multimers due to endothelial damage resulting from surgery in the setting of marginal levels of vWF-cleaving enzyme. The myriad of common post-surgical complications that may present with clinical manifestations similar to TTP may result in confusion with the potential for delay in the initiation of life-saving plasma-exchange therapy. It is important that physicians be alert to the phenomenon of post-operative TTP so that prompt recognition and treatment will prevent serious morbidity or mortality.

Keywords: Thrombotic; thrombocytic purpura; post-operative; thrombocytopenic

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening clinical syndrome presenting principally as thrombocytopenia and microangiopathic haemolytic anaemia. Other manifestations that are variably present include fever, impaired renal function and altered mental status (1–4). The original descriptions of the illness required all five manifestations without alternative explanation to establish the diagnosis (1,4). TTP was therefore a diagnosis of exclusion, and it was nearly uniformly fatal.

Over the past two decades, it has become well established that plasma exchange is often life-saving (5–9). Because early recognition and treatment are essential to prevent serious morbidity or mortality, it is now recommended that a diagnosis of TTP be assumed based on the presence of only thrombocytopenia and microangiopathic haemolytic anaemia in the absence of alternative cause (10,11).

Recently, the cause of classic TTP has been defined (12). It is due to the development of an autoantibody against von-Willebrand factor (vWF)-cleaving enzyme, which functions to hydrolyse high-molecular-weight vWF multimers into less active subunits. The resultant deficiency of the cleaving enzyme results in the abnormal circulation of high-molecular-weight vWF multimers, which activate platelets in association with endothelium in the microvasculature. The clinical manifestations of the illness are due to the removal of platelets from circulation, the fragmentation of red blood cells traversing partially occluded microvessels and the tissue ischemia resulting from the occlusions. The efficacy of plasma exchange now has an explanation, as the removal of the patient's plasma removes the offending autoantibody, while infusion of fresh plasma replaces the deficient vWF-cleaving enzyme. A familial, relapsing form of TTP has been described, and affected individuals are now known to inherit dysfunctional or deficient vWF (13,14).

A clinical presentation closely resembling classic TTP has been reported in association with certain infections, drugs, pregnancy, collagen vascular disease and malignancies. The pathogenesis of TTP in these settings remains unclear.

There have recently been a number of reports by us (15–20), and others (21–24), of a clinical syndrome resembling TTP occurring after surgical procedures. Characteristically, patients having a normal hemogram prior to surgery develop microangiopathic haemolytic anaemia and consumptive thrombocytopenia about 5–9 days following surgery. As in classic TTP, fever, impaired renal function and altered mental status are variably present. Because of the recent surgery, these manifestations are often attributed to other causes, such as blood loss, haemodilution, infection, disseminated intravascular coagulation (DIC) or heparin-induced thrombocytopenia.

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Because this event is life-threatening and responsive to plasma exchange, it is critical that post-operative TTP be promptly recognised and treated.

To date, 29 cases of post-operative TTP have been reported. The types of surgical procedures in which the complication has been observed are summarised in Table 1. The majority are cardiac or vascular surgeries, although some cases have followed gastrointestinal procedures. We have even observed a case following a knee replacement procedure (18).

The pathogenesis of post-operative TTP is unknown. Hypothetically, endothelial damage at the time of surgery may release high-molecular-weight vWF multimers in amounts sufficient to overwhelm available vWF-cleaving enzyme. It is possible that some cases may involve patients who have a marginal vWF-cleaving enzyme level before surgery due to heredity or other cause. This idea is supported by reports of patients suffering from a second episode of TTP following a subsequent surgical procedure (15,16). There are no reports of post-operative TTP patients relapsing with TTP in the absence of a surgical intervention.

RECOGNITION

As in classic TTP, post-operative TTP is a diagnosis of exclusion. Pertinent discriminating laboratory studies are summarised in Table 2. Thrombocytopenia and anaemia will be present, occurring 5–9 days following surgery. Fever, impaired renal function and altered mental status may occur in variable degrees. It is important to review a peripheral blood smear early in the evaluation. In addition to thrombocytopenia, the presence of fragmented red cells (schistocytes) is the cardinal abnormality associated with TTP, although this may be less prominent in post-operative TTP than in classic TTP. Schistocytes are not specific to TTP, as they may also be observed in DIC. A review of the peripheral smear may also provide clues to alternative causes for laboratory and clinical manifestations such as pseudothrombocytopenia (platelet clumping in laboratory tube anti-coagulant) or toxic granulation suggestive of infection. Infection should be excluded by evaluating likely sources (lung, urine and surgical wound) and obtaining appropriate cultures. Coagulation parameters should be assessed. The prothrombin time (PT)-, partial thromboplastin time (PTT)- and fibrin-split products or D-dimer will be abnormal in DIC but are usually normal in TTP. Evidence of haemolysis should be sought by obtaining a reticulocyte count, serum lactate dehydrogenase and haptoglobin. Medications should be reviewed to assess their possible contribution to haematologic abnormalities (heparin-induced thrombocytopenia, immune haemolysis and thrombocytopenia due to quinidine, certain antibiotics, etc.). Drugs known to be associated with the development of a TTP-like illness, such as ticlopidine (25,26) and quinine (27), should obviously be stopped. If renal insufficiency is present, volume depletion or urinary tract obstruction should be excluded as causes. Finally, in the presence of thrombocytopenia and microangiopathic haemolysis without other clear explanation, TTP should be assumed and plasma-exchange therapy should be initiated.

TREATMENT

Plasma exchange can be life-saving in TTP due to all causes (1–4). Results are best if the condition is recognised and treatment is begun before severe ischemic organ system

Table 1 Surgical procedures reported to be complicated by TTP

Procedure	*Number of cases*	*Postoperative day of onset*	*Treatment*	*Outcome (alive/dead)*	*Reference*
Cardiac surgery					
CABG alone	12	4–12	PE	11/1	(15,21)
CABG + valve surgery	2	8–19	PE	1/1	(15)
Non-CABG cardiac surgery					
Repair of foramen ovale	1	3	PE	0/1	(16)
Resection of myocardial sarcoma	1	10	None	0/1	(15)
Aortic valve replacement	1	7	PE	1/0	(15)
Pericardial window	1	5	PE	1/0	(15)
Vascular surgery					
Repair of aortic aneurysm	1	13	None	0/1	(22)
Femoropopliteal bypass graft	1	5	PE	1/0	(15)
Aortofemoral bypass graft	1	4	PE	1/0	(15)
Arteriovenous fistula formation	1	9	None	0/1	(15)
Injured neck vessel repair	1	17	None	0/1	(15)
Gastrointestinal surgery					
Bowel resection	4	3-11	PE	1/3	(16,17,23,46)
Cholecystectomy	1	3	None	0/1	(16,17)
Orthopaedic surgery					
Knee replacement	1	2	None	1/0	(18)

CABG, coronary artery bypass graft; PE, plasma exchange; TTP, thrombotic thrombocytopenic purpura.

Table 2 Distinguishing TTP from DIC

Laboratory test	*TTP*	*DIC*
CBC	Anemia and thrombocytopenia	Anemia and thrombocytopenia
Blood smear	Schistocytes	Schistocytes
LDH/retic count	Elevated	Elevated
Haptoglobin	Low	Low
PT/PTT	Normal	Elevated
Fibrinogen	Normal	Normal or low
FDP	Normal	High
D-dimer	Normal	High
Factors V and VIII	Normal	Low

CBC, complete blood count; DIC, disseminated intravascular coagulation; LDH, lactate dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time; TTP, thrombotic thrombocytopenic purpura.

damage is manifest (coma, advanced renal failure, digital gangrene and acute respiratory distress syndrome). Plasma exchange should be initially performed daily until clinical manifestations improve. The platelet count and serum lactate dehydrogenase (as an indicator of ongoing haemolysis) are useful markers of disease activity and should be followed closely. Initially, most patients require five to 10 daily plasma exchanges. If improvement has occurred, the frequency of exchange may then be reduced to every other day for 1–2 weeks, followed by twice a week for 2 weeks, then weekly for 1–2 months (28,29). Corticosteroids and anti-platelet agents are sometimes used as adjuvant treatments, but their contribution to overall benefit is uncertain. Platelet transfusions are not recommended as routine, because some reports have suggested that they might be detrimental to outcome (30–33). However, platelet transfusion should be considered to treat clinically serious bleeding, as the benefit in that situation may outweigh the risk. Failure of plasma exchange to result in benefit should prompt a re-evaluation for an alternative explanation for clinical manifestations. If none is found, subsequent treatments are largely based on anecdotal reports and include cytotoxic agents such as vincristine (34–36) or cyclophosphamide (37,38), immunomodulation with high-dose γ-globulin (39–41) or cyclosporin (42), or splenectomy (43–45).

In summary, post-operative TTP is a recently recognised life-threatening clinical syndrome with considerable similarity to classic TTP in presentation and response to early treatment with plasma exchange. The pathogenesis of post-operative TTP remains speculative but may involve the release of large amounts of high-molecular-weight vWF multimers due to endothelial damage resulting from surgery in the setting of marginal levels of vWF-cleaving enzyme. The myriad of more common post-surgical complications that may present with clinical manifestations similar to TTP may result in confusion with the potential for delay in the initiation of life-saving plasma-exchange therapy. It is important that physicians be alert to the phenomenon of post-operative TTP so that prompt recognition and treatment will prevent serious morbidity or mortality.

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