Severe Bleeding Tendency due to Excessive Fibrinolysis in Two Patients With Aortic Disease: Role of Tranexamic Acid in Non-Surgical Candidate

Pui Lun Yipa, b, Sze Man June Laua, Tsui Yin Jaime Leea

Abstract

Disseminated intravascular coagulation (DIC) is characterized by systemic activation of coagulation pathway which can lead to thrombosis and bleeding. Chronic DIC associated with aortic aneurysm or dissection commonly presents with bleeding symptoms with variable severity due to enhanced fibrinolysis. Patients with unexplained bleeding diathesis with DIC should include aortic disease as one of the differential diagnoses. This paper reports two patients with severe hemorrhagic complications due to aortic disease. Long-term prophylactic treatment is recommended if the underlying aortic disease cannot be surgically managed. Tranexamic acid is a potentially safe option to relieve bleeding tendency.

Keywords: Bleeding; Fibrinolysis; DIC; Aortic disease

Introduction

Disseminated intravascular coagulation (DIC) is characterized by systemic activation of coagulation system, resulting in consumption of clotting factors and platelets. Activation of fibrinolysis also occurs together with coagulation, but the degree of fibrinolysis depends on the underlying disease [1]. In patients with suppressed fibrinolytic DIC, widespread microthrombi are formed, leading to small vessels occlusion and organ dysfunction. In contrast, the enhanced fibrinolytic type DIC is associated with significant fibrinolysis resulting in bleeding diathesis. Uncommonly, chronic DIC secondary to aortic aneurysms or vascular malformation can be the underlying cause of enhanced fibrinolysis [2]. In patients with aortic dissection, the chronic coagulation activation due to exposure of collagen tissue and tissue factor in the false lumen locally leads to consumption of clotting factors and secondary fibrinolysis. Subsequent depletion of platelets, clotting factors and fibrinogen may result in systemic bleeding tendency [3].

Case Reports

Case 1

A 78-year-old male patient had history of hypertension, diabetes mellitus, stage IV chronic kidney disease and infra-renal abdominal aortic aneurysm (AAA) with endovascular stent. Type II Endo-leak was noted at the level of bifurcation on follow-up computed tomography (CT) scan after stenting. He experienced easy bruising after the operation but did not seek medical attention until 4 years later, when he presented to orthopedics with right knee non-traumatic hemarthrosis. Initial blood tests revealed mild thrombocytopenia (platelets 99 × 10^9/L), prothrombin time (PT) 13.8 s (reference range (RR): 10.7 - 13.1 s) and activated partial thromboplastin time (APTT) 27.1 s (RR: 25.8 - 33.8 s). He had a second episode of spontaneous right knee hemarthrosis 6 months later. Hemarthrosis subsided with regular use of tranexamic acid. Fibrinogen level rose to 3.16 g/L after a few days of regular tranexamic acid and it was then stopped. Three months following the second episode of hemarthrosis, he presented to the emergency department with sudden onset of unconsciousness without any trauma, and his blood pressure was well-controlled. Urgent CT scan of head showed extensive intraventricular hemorrhage. The patient passed away 2 days after admission.

Case 2

A 63-year-old woman had no medical problems apart from being a hepatitis B carrier. She was admitted for sudden onset of severe chest pain. CT revealed type A aortic dissection extending distally from the aortic root to the left common iliac artery. She developed pulseless electrical activity just prior to skin
incision due to cardiac tamponade. Emergency resection and replacement of ascending thoracic aorta was performed. She managed to have a good recovery without neurological sequelae. She presented 6 months after discharge with generalized spontaneous bruises. Her hemoglobin dropped from 11.1 to 8.4 g/dL and her platelets count was 90 × 10^9/L. Clotting profile was normal except for mild prolongation of APTT 14.5 s and elevated D-dimer > 5,000 ng/mL. She experienced hematuria and managed conservatively. Four months after the first episode of bruises, she suffered from extensive bruises over her limbs. Laboratory data indicated anemia, thrombocytopenia (hemoglobin 5.7 g/dL, thrombocytopenia 90 × 10^9/L) and abnormal clotting profile (APTT 38.5 s, PT 16.5 s, fibrinogen 0.5 g/L and D-dimer > 5,000 ng/mL) (Fig. 1). Clotting factors and von Willebrand assays as performed in case 1 were all normal. The International Society on Thrombosis and Hemostasis (ISTH) DIC score was 6, consistent with overt DIC. In view of the development of bleeding tendency after aortic dissection, thrombocytopenia, chronically elevated D-dimer and low fibrinogen, DIC with excessive fibrinolysis secondary to aortic dissection was suggested. Bleeding tendency was stopped by cryoprecipitate to replenish fibrinogen together with regular tranexamic acid. Follow-up CT scan showed aortic dissection of similar extent - both true and false lumens were patent, with slower perfusion over false lumen. The option of surgical repair was discussed with the surgeons to ameliorate the chronic DIC and bleeding tendency, but the surgical risk was deemed to be too high for the patient. Therefore, long term tranexamic acid (750 mg daily) was prescribed to control the fibrinolysis. Eight months after taking regular tranexamic acid, the previously reduced level of fibrinogen recovered to 2.7 g/L and the platelets count improved to 144 × 10^9/L. She did not experience any recurrence of bruises or bleeding symptoms.

Discussion

Fibrinolysis is activated in parallel with coagulation to regulate and limit clot formation. In some clinical conditions (e.g., severe trauma, post-partum hemorrhage, uncontrolled acute promyelocytic leukemia, etc.), excessive fibrinolysis predominates and results in bleeding tendency. A study involving 76 pre-operative patients with aortic aneurysms showed elevation of fibrin-degradation products in 39% of the patients, while clinically overt DIC occurred in up to 4% [4]. Nevertheless, it could be difficult for clinicians to establish the association of DIC, bleeding and vascular disease if they were unfamiliar with the condition, and particularly if patients had remote history of aortic surgery. Both cases 1 and 2 showed bleeding complications and laboratory findings of markedly elevated level of D-dimer, thrombocytopenia and hypofibrinogenemia. DIC-related bleeding should be considered as a potential cause of unusual bleeding in patients with aortic disease or after aortic surgery. Apart from aortic dissection and stenting with endoleak, there were no other identified causes that triggered coagulopathy in our patients. There is no single gold standard laboratory diagnostic test for DIC with enhanced fibrinolysis. Investigations usually show elevated levels of D-dimer (or fibrin and fibrinogen degradation product), plasmin-alpha 2-plasmin inhibitor complex and thrombin-antithrombin complex coupled with hypofibrinogenemia. Fibrinogen level and clinical symptoms responded to treatment quickly as shown in case 2, hence fibrinogen could be used as a marker for monitoring the activity of DIC-fibrinolysis.

Figure 1. Clinical course of treatment and improvement of DIC-related parameters in patient 2. DIC: disseminated intravascular coagulation. Dotted line denote platelet count, solid line denote fibrinogen.
cient clotting factors and platelets is the mainstay of treatment. Both of our cases have the bleeding tendency drastically ame-
liorated by normalizing the fibrinogen level. Antifibrinolytic
agents such as tranexamic acid, is generally not recommend-
ed for patient with DIC due to the risk of thromboembolism. However, it could be a reasonable option for severe bleeding
patients with DIC and hyperfibrinolysis [5]. When surgical or
endovascular intervention for the aortic disease is not possi-
bile, long term medical treatment would be needed to control
the chronic DIC and fibrinolysis. There is no standard systemic
therapy for aortic enhanced fibrinolysis-DIC; anticoagulation
[6], antifibrinolics [7], or a combination of both [8] have been
reported to be successful in halting the consumption of coagu-
lation factors. The main purpose of anticoagulation is to inhibit
thrombus generation, thereby the cycle of thrombus forma-
tion and destruction would be interrupted. On the other hand,
tranexamic acid inhibits the enzymatic breakdown of fibrin by
plasmin, thus reducing the activity of fibrinolysis. In case 2,
coagulopathy as measured by fibrinogen level was quickly re-
versed by tranexamic acid and she remained free from bleeding
complications for more than 8 months. We believed that the
long-term use of tranexamic acid is reasonable in view of her recurrent spontaneous bleeding diathesis. This approach of
using long term tranexamic acid has been reported to success-
fully control DIC with excessive fibrinolysis in a patient with
chronic renal failure [9]. As shown in case 1, who suffered from
spontaneous intracranial hemorrhage after discontinuation of
tranexamic acid, bleeding complications can recur if medical
treatment is not maintained. Long-term treatment is therefore
essential to ensure that bleeding tendency is controlled if the
underlying aortic disease cannot be surgically managed.

Conclusions

In conclusion, DIC with enhanced fibrinolysis should be con-
sidered as the underlying cause of abnormal bleeding in pa-
tients with aortic disease. The risk of bleeding persists in pa-
tients without surgical correction, therefore long-term medical
treatment is warranted. Tranexamic acid can be used in acute
bleeding episodes to stop bleeding, and it can also be a feasible
option for maintenance therapy.

Acknowledgments

None to declare.

Financial Disclosure

No funding was received. None of the authors have disclosures
relevant to this manuscript.

Conflict of Interest

None to declare.

Informed Consent

The manuscript has been sufficiently de-identified to protect
the patient. Patient 1 has since died and is unable to provide in-
formed consent. Written informed consent was obtained from
the patient 2 for publication of this case report.

Author Contributions

Pui Lun Yip, Sze Man June Lau and Tsui Yin Jaime Lee treated
the patients, wrote and approved the manuscript.

Data Availability

The authors declare that data supporting the findings of this
study are available within the article.

References

1. Asakura H. Classifying types of disseminated intravas-
cular coagulation: clinical and animal models. J Intensive
Care. 2014;2(1):20.
2. Levi M, Scully M. How I treat disseminated intravascular
coagulation. Blood. 2018;131(8):845-854.
3. Thompson RW, Adams DH, Cohen JR, Mannick JA,
Whittemore AD. Disseminated intravascular coagula-
tion caused by abdominal aortic aneurysm. J Vasc Surg.
1986;4(2):184-186.
4. Fisher DF, Jr., Yawn DH, Crawford ES. Preoperative
disseminated intravascular coagulation associated with
aortic aneurysms. A prospective study of 76 cases. Arch
Surg. 1983;118(11):1252-1255.
5. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for
the diagnosis and management of disseminated intravas-
cular coagulation. British Committee for Standards in
Haematology. Br J Haematol. 2009;145(1):24-33.
6. Kawano H, Hata T, Uda A, Maemura K. Use of rivar-
oxaban for the effective management of disseminated in-
travascular coagulation associated with abdominal aortic
aneurysm. Intern Med. 2015;54(20):2625-2628.
7. Uzuka T, Nakamura M, Kuroda Y, Watanabe N. The use
of an anti-fibrinolytic agent to reduce endoleak following
endovascular repair of multiple aortic aneurysms. Interact
Cardiovasc Thorac Surg. 2015;21(2):266-268.
8. Ontachi Y, Asakura H, Arahata M, Kadohira Y, Maekawa
M, Hayashi T, Yamazaki M, et al. Effect of combined ther-
dapy of danaparoid sodium and tranexamic acid on chronic
disseminated intravascular coagulation associated with
abdominal aortic aneurysm. Circ J. 2005;69(9):1150-
1153.
9. Kimura SI, Odawara J, Aoki T, Yamakura M, Takeuchi M,
Watanabe Y, Matsue K. Use of tranexamic acid for dissem-
inated intravascular coagulation with excessive fibrinolysis
associated with aortic dissection in a patient with chronic
renal failure. Int J Hematol. 2009;89(4):549-552.