

Case report

Acute thrombocytopenia from alteplase in a patient with stroke

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Abstract:

Alteplase, a recombinant tissue plasminogen activator (rtPA), is a standard thrombolytic therapy for acute ischemic stroke. Although generally safe, it can cause complications such as hemorrhagic transformation, intracranial hemorrhage, gastrointestinal hemorrhage, and angioedema. Acute thrombocytopenia has rarely been reported after rtPA administration. Awareness of this adverse reaction is essential for timely management.

In this case report, a 69-year-old Thai male with no known underlying diseases developed sudden-onset left hemiparesis, left upper motor neuron facial palsy, and dysarthria. At a general hospital, his non-contrast CT brain scan showed a hypodense lesion in the right frontoparietotemporal region with an Alberta stroke programme early CT score (ASPECTS) of 4. The diagnosis was right MCA infarction. Thrombectomy was not performed due to the poor ASPECTS. He received a standard dose of rtPA. His platelet count was 205,900/ μ L on admission, and his PT and PTT were normal. Forty-eight hours later, the patient developed an altered level of consciousness. A non-contrast CT brain was repeated, and the result showed progressive brain swelling without bleeding, so he was intubated and transferred to King Narai Hospital for decompressive craniectomy. Sixty-one hours after rtPA was administered (before surgery), his platelet count decreased to 25,000/ μ L and his PT and PTT were normal. He exhibited no signs of bleeding. Thrombocytopenia was confirmed on repeat evaluation using a citrate tube, with a platelet count of 42,000/ μ L without evidence of platelet clumping. Intermittent platelet concentrate transfusions were given. Eight days after rtPA administration, his platelet count returned to the normal range, and no further platelet transfusion was needed. The proposed mechanism of thrombocytopenia was drug-induced.

Keywords : ● Alteplase ● Stroke ● Thrombocytopenia ● Drug-induced thrombocytopenia

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รายงานผู้ป่วย

ภาวะเกล็ดเลือดต่ำเฉียบพลันหลังได้รับยา Alteplase ในผู้ป่วยโรคหลอดเลือดสมอง

กันต์ โรจนกิจ

แผนกอายุรกรรม โรงพยาบาลพระนารายณ์มหาราช

บทคัดย่อ

Alteplase ซึ่งเป็น recombinant tissue plasminogen activator (rtPA) เป็นยาละลายลิ่มเลือดมาตรฐานสำหรับโรคหลอดเลือดสมองตีบเฉียบพลัน แม้ว่าจะมีความปลอดภัยค่อนข้างสูง แต่อาจทำให้เกิดภาวะแทรกซ้อนที่สำคัญได้ เช่น การเปลี่ยนเป็นเลือดออกในเนื้อสมองหลังจากโรคหลอดเลือดสมองตีบ ภาวะเลือดออกในสมอง เลือดออกในระบบทางเดินอาหาร และภาวะบวมน้ำของทางเดินหายใจ ภาวะเกล็ดเลือดต่ำเฉียบพลันหลังได้รับยา rtPA เป็นภาวะแทรกซ้อนที่พบรายงานน้อยมาก อย่างไรก็ตาม การตระหนักรู้และการเฝ้าระวังภาวะแทรกซ้อนดังกล่าวมีความสำคัญต่อการรักษาอย่างทันท่วงที

ผู้ป่วยชายไทยอายุ 69 ปี ไม่มีประวัติโรคประจำตัว มีอาการอ่อนแรงครึ่งซีกซ้ายเฉียบพลันร่วมกับอัมพาตเส้นประสาทใบหน้าชนิด upper motor neuron ซีกซ้าย และภาวะพูดลำบาก ภาพถ่ายเอกซเรย์คอมพิวเตอร์สมอง (CT brain) แบบไม่ฉีดสารทึบรังสีที่โรงพยาบาลทั่วไปแห่งหนึ่งพบรอยโรคความหนาแน่นต่ำบริเวณสมองส่วน frontoparietotemporal ด้านขวา โดยมีคะแนน ASPECTS เท่ากับ 4 ได้รับการวินิจฉัยว่าเป็นโรคหลอดเลือดสมองตีบที่ middle cerebral artery ด้านขวา ผู้ป่วยไม่ได้รับการทำ thrombectomy เนื่องจากคะแนน ASPECTS ต่ำ ผู้ป่วยได้รับ rtPA ขนาดมาตรฐาน ผลการตรวจเลือดก่อนให้ยาพบว่าเกล็ดเลือดมีค่า 205,900/ μ L ค่า PT และ PTT อยู่ในเกณฑ์ปกติ หลังได้รับ rtPA 48 ชั่วโมง ผู้ป่วยมีระดับความรู้สึกลดลง จึงได้รับการตรวจ CT brain ซ้ำ พบภาวะสมองบวมเพิ่มขึ้นโดยไม่พบเลือดออก ผู้ป่วยได้รับการใส่ท่อช่วยหายใจและส่งต่อมายังโรงพยาบาลพระนารายณ์มหาราชเพื่อทำการผ่าตัดลดความดันในกะโหลกศีรษะ ที่เวลา 61 ชั่วโมงหลังได้รับ rtPA (ก่อนการผ่าตัด) พบเกล็ดเลือดต่ำ 25,000/ μ L โดยที่ค่า PT และ PTT อยู่ในเกณฑ์ปกติ ผู้ป่วยไม่มีอาการเลือดออก การตรวจยืนยันโดยใช้หลอด citrate ได้ค่าเกล็ดเลือด 42,000/ μ L และไม่พบภาวะ platelet clumping ทำให้ยืนยันภาวะเกล็ดเลือดต่ำได้ ผู้ป่วยได้รับการให้เกล็ดเลือดเป็นระยะ หลังได้รับ rtPA ไปแล้วครบ 8 วัน ค่าเกล็ดเลือดกลับสู่ระดับปกติและไม่จำเป็นต้องให้เกล็ดเลือดเพิ่มเติม กลไกที่น่าจะเป็นสาเหตุของภาวะนี้คือภาวะเกล็ดเลือดต่ำที่เกิดจากยา (drug-induced thrombocytopenia)

คำสำคัญ : ● Alteplase ● โรคหลอดเลือดสมอง ● ภาวะเกล็ดเลือดต่ำ ● ภาวะเกล็ดเลือดต่ำจากยา

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2569;36:225-30.

Introduction

Thrombocytopenia is one of the most frequent causes for hematologic consultation, and may be life-threatening.¹ Although the normal platelet count in humans (150,000 to 400,000/ μ L) far exceeds the minimal level required to avoid pathologic hemorrhage (< 50,000/ μ L), a number of medical conditions can increase the destruction of platelets or reduce their production, enhancing the risk of bleeding.¹

Alteplase is a recombinant tissue plasminogen activator (rtPA) that converts plasminogen to plasmin, a serine protease that breaks down fibrin, the major component of blood clots. Thrombolysis, traditionally with alteplase, is the standard of care for ischemic stroke and is indicated within 4.5 hours after symptom onset.²

Although rtPA administration can achieve revascularization, it also carries a risk of treatment-related complications, such as hemorrhagic transformation, intracranial hemorrhage, gastrointestinal hemorrhage, and angioedema.^{3,4} Thrombocytopenia following rtPA administration has rarely been reported. The mechanism remains unclear, but drug-induced thrombocytopenia is suspected. This case report reviews the causes, clinical presentation, and management of drug-induced thrombocytopenia.

Case report

A 69-year-old Thai male, with no known underlying diseases and no history of alcohol consumption and smoking developed sudden-onset left hemiparesis, left upper motor neuron facial palsy, and dysarthria. At a general hospital, his non-contrast CT brain scan showed a hypodense lesion in the right frontoparietotemporal region with an ASPECTS of 4. The diagnosis was right MCA infarction, and thrombectomy was not performed due to the poor ASPECTS. He received a standard dose of rtPA (68.86 mg). His platelet count was 205,900/ μ L on admission, and his PT (9.8 seconds) and PTT (20.6 seconds) were within normal limits. Twenty-four hours after rtPA administration, his non-contrast CT brain scan

showed a large, ill-defined hypodense lesion involving the right frontoparietotemporal region without evidence of hemorrhagic transformation or intracranial hemorrhage. Forty-eight hours after rtPA administration, the patient developed an altered level of consciousness, and his non-contrast CT brain scan showed progressive brain swelling with a 0.7-cm midline shift to the left, without hemorrhagic transformation or intracranial hemorrhage. He was intubated, given intravenous mannitol, and transferred to King Narai Hospital for decompressive craniectomy. Sixty-one hours after rtPA was administered (before surgery), his platelet count decreased to 25,000/ μ L, while hemoglobin was 16.7 g/dL, hematocrit 50.2% and white blood cell count 10,630/ μ L with neutrophil predominance. No abnormal leucoerythroblastic blood picture, no evidence of microangiopathic hemolytic anemia, no blast cells, and no platelet clumping were observed. His PT (12.3 seconds) and PTT (23.6 seconds) were within normal limits. His liver function test showed: AST 39 U/L, ALT 18 U/L, ALP 64 U/L, total protein 6.04 g/dL, albumin 3.16 g/dL, globulin 2.88 g/dL, total bilirubin 0.79 mg/dL, and direct bilirubin 0.46 mg/dL. His physical examination revealed no cutaneous stigmata of chronic liver disease, no hepatosplenomegaly and no palpable lymphadenopathy. He exhibited no signs of bleeding, but the surgeon required his platelet count to be maintained above 100,000/ μ L. Thrombocytopenia was confirmed on repeat evaluation using a citrate tube, with a platelet count of 42,000/ μ L and no evidence of platelet clumping. No other causes of thrombocytopenia such as sepsis or other suspected drugs (aspirin, atorvastatin, milk of magnesia, omeprazole, amiodarone, atropine and mannitol) were noted. Intraoperatively, the patient received 6 units of platelet concentrate. One hour after platelet transfusion, CBC was repeated, and the platelet count was 58,000/ μ L. The one-hour corrected count increment (1-hr CCI) was 19,200 (using platelet counts of 25,000/ μ L and 58,000/ μ L). On that day, eight more units of platelet concentrate were transfused, and the platelet count increased to 118,000/ μ L.

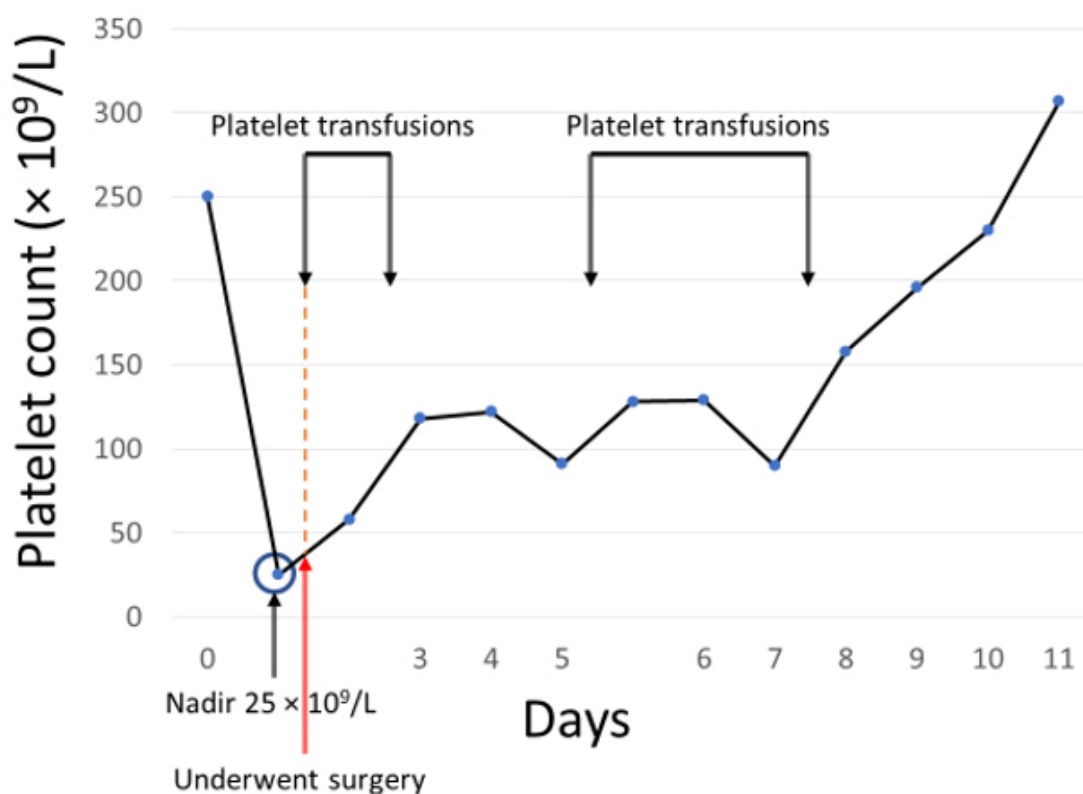


Figure 1 Trend of platelet count after rtPA administration

Five days after rtPA administration, the platelet count decreased to $91,000/\mu L$, so the patient received four units of platelet concentrate. One hour after the transfusion, the platelet count increased to $128,000/\mu L$, and 1-hr CCI was 32,291. The patient developed a decreased level of consciousness, the right pupil measured 3.5 mm and the left 4 mm, both with slightly reactive responses to light. A repeat non-contrast CT brain scan was performed, revealing progressive brain edema with a small hemorrhagic transformation in the right thalamic region, along with increased right subfalcine and bilateral uncal herniation. The management was conservative. Seven days after rtPA administration, the platelet count decreased to $90,000/\mu L$. Five units of platelet concentrate were transfused, and the following day the repeated platelet count was $158,000/\mu L$ (eight days after rtPA administration). Daily follow-up platelet counts were obtained, and the results were 196,000, 230,000, and $307,000/\mu L$, respectively (Figure 1). The patient underwent a tracheostomy and was referred to the general hospital for supportive care.

Discussion

Drugs may cause thrombocytopenia either by immune or nonimmune mechanisms.⁵ Nonimmune thrombocytopenia results in suppression of platelet production by general myelotoxicity (e.g., chemotherapy), dose-dependent myelosuppression (e.g., linezolid) or interference with specific megakaryocyte function (e.g., bortezomib).⁵ Immune-mediated thrombocytopenia results in accelerated platelet destruction by drug-dependent platelet antibodies that cause platelet clearance (e.g. quinine and quinidine) or platelet activation (e.g., heparin).⁵ Dose-dependent myelosuppression and immune destruction of the platelets are two well-known causes.¹

In this case, the proposed mechanism was drug-induced thrombocytopenia. Immune-mediated thrombocytopenia is likely, given the onset of thrombocytopenia sixty-one hours after rtPA administration, although the mean delay in onset of immune-mediated thrombocytopenia is typically reported to be one to two weeks following exposure to an offending immunogenic drug, and the 1-hr CCI was successful.⁶⁻⁸ The time course of drug-

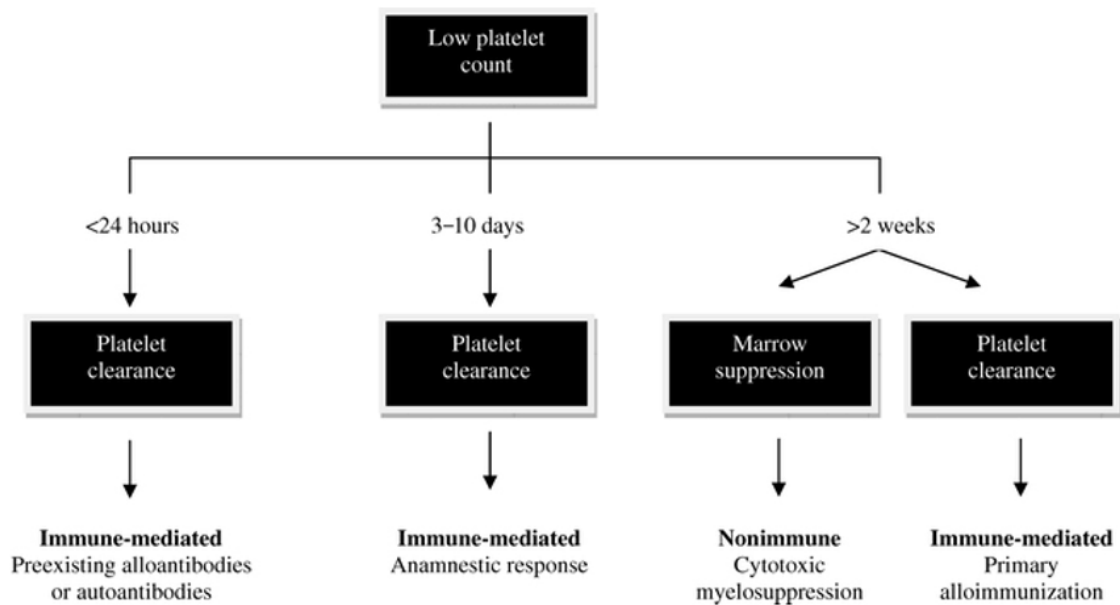


Figure 2 Categorization of drug-induced thrombocytopenia by time of onset of thrombocytopenia

induced thrombocytopenia related to marrow suppression is generally slow, often for several weeks, reflecting the time required to deplete the megakaryocyte population, which was unlikely in this case (Figure 2).⁶

Two explanations have been proposed for rare cases of drug-induced thrombocytopenia occurring within 24 hours.⁶ The first is that the patient has been exposed to the offending drug (even if undocumented) and that the acute drop represents a response to pre-existing alloantibodies.⁶ An explanation for patients with rapid-onset, drug-induced thrombocytopenia, without prior drug exposure, is that they have pre-existing, "naturally occurring" antibodies.⁶

Most patients experience moderate to severe thrombocytopenia (platelet count less than 50,000/ μ L), with the majority reaching nadir levels below 20,000/ μ L.⁶ To help establish the likelihood that a particular drug was the cause of the thrombocytopenia, several clinical scoring systems have been developed.⁵ In 1982, Hackett, et al. proposed the following criteria: (1) thrombocytopenia developed while the patient was taking the drug, resolved once the drug was stopped and did not recur while the patient was off the drug; (2) other causes of thrombocytopenia were excluded; (3) thrombocytopenia recurred upon re-administration of the drug; and (4)

an in vitro test for drug-dependent platelet antibodies was positive.⁵ A positive re-challenge or a positive laboratory test was sufficient to confirm the diagnosis.⁵ Unfortunately, drug-dependent platelet antibodies were not tested in this case due to limited resources.

Management involves discontinuing the offending medication because, in immune-mediated cases, the mechanism is drug-dependent and antibody binding is partly linked to the presence of the drug. The time frame for platelet count recovery to greater than 100,000/ μ L is generally within one to ten days, with a median of about seven days.⁶ Platelet transfusions may be required to treat patients with severe thrombocytopenia and bleeding and other supportive measures including high dose IVIG and a brief course of corticosteroids may be reasonable.⁵ Drug-dependent platelet antibodies can persist for many years; thus, patients with a confirmed diagnosis should be counseled to avoid future exposure to the drug.⁵

In another study conducted in 1994, thrombocytopenia developed after administering thrombolytic therapy among patients with acute myocardial infarction.⁹ The authors stated that it most likely constituted a multifactorial phenomenon, e.g. heparin-induced thrombocytopenia or complication of intra-aortic balloon pump.⁹ This case

appears to be one of the first case reports to demonstrate thrombocytopenia following thrombolytic therapy without other suspected drugs and without signs of bleeding except for hemorrhagic transformation, which can occur on its own in acute large cerebral infarction.

Conclusion

Alteplase is a standard thrombolytic therapy for acute ischemic stroke. This case highlights thrombocytopenia as a complication of rtPA. Although the mechanism is unclear, awareness of thrombocytopenia is important, as it can increase the risk of bleeding, particularly hemorrhagic transformation and intracerebral hemorrhage. Further studies are needed to evaluate the mechanism and to determine which cases should undergo follow-up complete blood count monitoring.

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