Utility of rotational thromboelastometry for the diagnosis of asymptomatic hyperfibrinolysis secondary to anaphylaxis

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We present a case of hyperfibrinolysis induced by oxaliplatin-derived anaphylactic shock, which was diagnosed with rotational thromboelastometry (ROTEM). A 57-year-old male patient underwent a second course of oxaliplatin (126 mg/m^2/course)-based chemotherapy for stage IV metastatic rectal cancer. Two minutes after the infusion of oxaliplatin, the patient lost consciousness and developed generalized urticarial lesions, followed by hemodynamic instability and respiratory insufficiency. He was diagnosed anaphylactic shock and transported to emergency department (ED) after intramuscular injection of 0.2 mg of adrenaline, an intravenous injection of 100 mg of hydrocortisone, and 500 mg of methylprednisolone. After arriving in the ED, the patient remained in shock and early resuscitation with administration of 5 mg of D-chlorpheniramine maleate and 20 mg of famotidine was performed. He recovered from his state of shock 30 min after the resuscitation. ROTEM findings showed fulminant hyperfibrinolysis with minimal changes in standard coagulation tests (SCTs) and no remarkable coagulopathy. Seven hours after the attack, he became asymptomatic and follow-up ROTEM revealed values within normal limits with the exception of sustained slight abnormalities of SCTs. He was discharged the next day without any signs of spontaneous bleeding and has continued his outpatient chemotherapy uneventfully. A review of the literature on anaphylaxis-induced hyperfibrinolysis and a discussion of the mechanism between anaphylactic shock and hyperfibrinolysis were performed. Although administration of tissue-type plasminogen activator can play a vital role in anaphylactic shock-induced hyperfibrinolysis, early effective resuscitation is imperative to prevent severe hemorrhagic complications. Therefore, ROTEM is a useful tool that can detect these dynamic changes faster and more accurately than SCTs. *Blood Coagul Fibrinolysis* 27:450–453

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Introduction

Anaphylaxis is a sudden onset, life-threatening allergic reaction, and is often mediated by adverse reactions to medications [1,2]. Oxaliplatin is a third-generation platinum derivative and frequently selected in the treatment of advanced colorectal cancer as part of the FOLFOX regimen [3]. The incidence of oxaliplatin-induced life-threatening severe allergic reaction, categorized type 1 allergy, is known to be low accounting for around 2% [4,5]. Although generalized urticarial rash with itching, hypotension, and bronchospasm are the most famous symptoms derived from anaphylactic shock, there are few reports on coagulation and anticoagulation abnormalities such as both bleeding and thrombotic tendency.

Recently, viscoelastic test devices such as rotational thromboelastometry (ROTEM) have been introduced as point-of-care testing. ROTEM can correctly show several aspects of coagulation and the thrombolytic cascade using human whole blood only in an hour. It is especially useful for detecting hyperfibrinolysis as its diagnosis by standard coagulation tests (SCTs) can be challenging [6,7].

Herein, we present a case of hyperfibrinolysis without bleeding complications induced by oxaliplatin-related anaphylactic shock detected with ROTEM. To the best of our knowledge, this is the first case report of anaphylactic shock-induced hyperfibrinolysis diagnosed with ROTEM.

Case report

A 57-year-old male with progressive stage IV metastatic rectal cancer status post a resection of the primary lesion underwent oxaliplatin-based chemotherapy (XELOX regimen). He had no history of drug or food allergy, and had a previous history of exposure to oxaliplatin-based chemotherapy without a remarkable allergic reaction 4 years prior. In both cases the oxaliplatin dosages were 126 mg/m^2/course and the patient developed anaphylaxis during the second course of chemotherapy. Two

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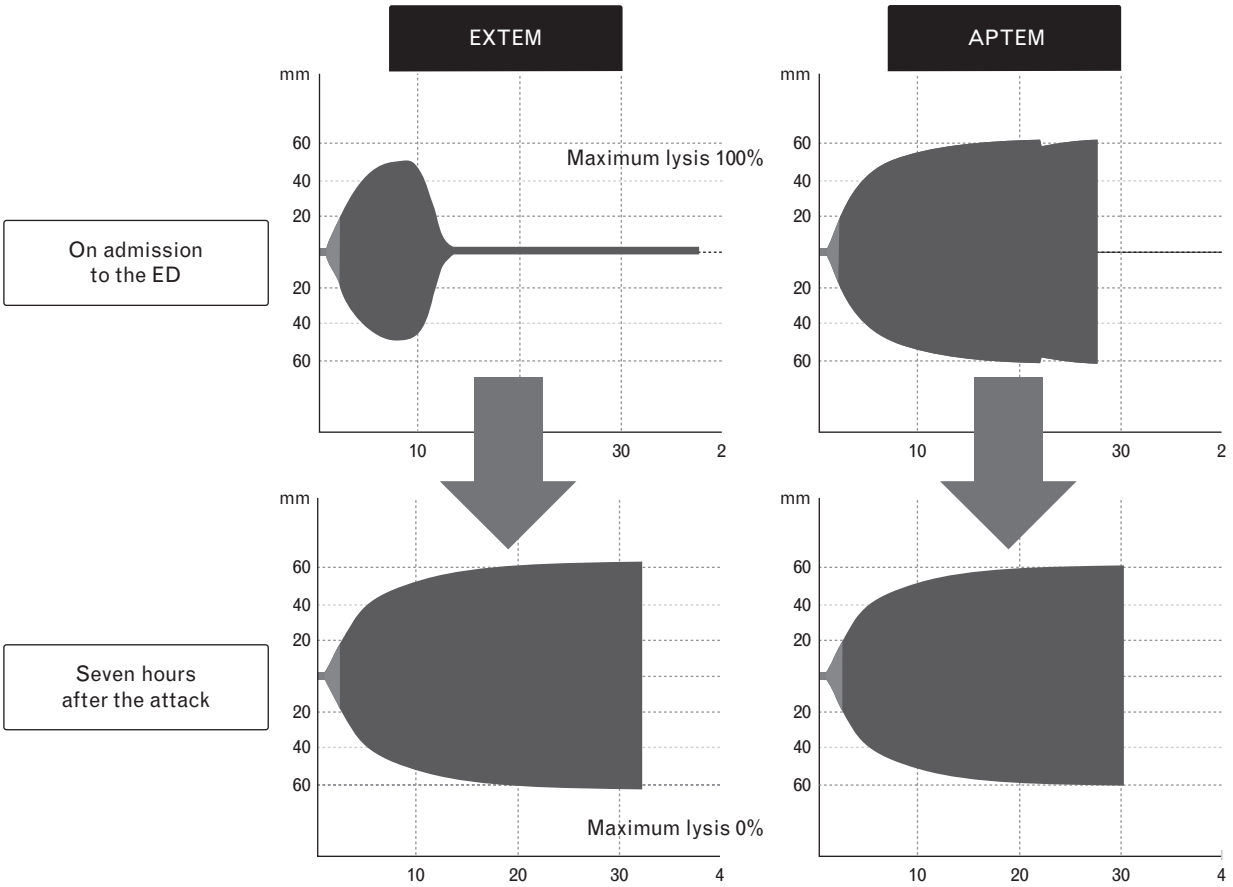
Fig. 1



Rotational thromboelastometry [ROTEM (EXTEM and APTEM)] findings on admission to the emergency department (ED) and seven hours after the attack. On admission to the ED, the patient's thromboelastometric analysis revealed fulminant hyperfibrinolysis in spite of only a few changes of standard coagulation tests. Seven hours after the attack, the follow-up ROTEM showed complete normal findings. ED, emergency department.

minutes after the infusion of oxaliplatin, he lost consciousness and developed generalized urticarial lesions. He recovered consciousness immediately after oxygen administration and fluid resuscitation. He subsequently complained of dyspnea and generalized itching. His hemodynamic collapse (blood pressure 61/36 mmHg, heart rate 145 bpm) and respiratory insufficiency (respiratory rate 33 breaths/min, arterial O_2 saturation 86%) in addition to his aforementioned general symptomatology indicated that the patient was in anaphylactic shock. He was then transported to the emergency department (ED) after an intramuscular injection of 0.2 mg of adrenaline and intravenous injection of 100 mg of hydrocortisone followed by administration of 500 mg of methylprednisolone intravenously.

On admission to the ED, blood samples were collected while the patient remained hemodynamically unstable. Two peripheral intravenous lines were placed and physiological saline was injected rapidly followed by administration of 5 mg of D-chlorpheniramine maleate and 20 mg of famotidine. The patient recovered from his shock state 30 min after the initiation of resuscitation. Although the patient's dyspnea and eruption were improved in a few hours, he was admitted to the emergency care unit for monitoring of his vital signs and symptoms of anaphylaxis.

Thromboelastometric analysis revealed fulminant hyperfibrinolysis, although very few changes were seen in SCTs including D-dimer at 1.41 μg/ml (normal limit <1.0 μg/ml) (Fig. 1, Table 1). Platelet, prothrombin time (PT), activated partial thromboplastin time, and fibrinogen were all within normal limits. There were no signs of increased bleeding tendency.

Seven hours after the attack, the patient completely recovered from shock and became asymptomatic. The follow-up ROTEM revealed completely normal findings with exception to his SCTs, which showed a slightly prolonged PT at 13.2 s (normal limit <13.0), a high fibrinogen and an increased fibrin degradation products level at 12.9 μg/ml (normal limit <5.0 μg/ml) and a high

Table 1 Standard coagulation tests and rotational thromboelastometry (EXTEM) findings on admission to the emergency department and 7 h after the attack

	Normal range	On admission to the ED	Seven hours after the attack
Plt ($10^4/\mu l$)	13.1–36.2	21.4	14.7
PT (s)	10.0–13.0	12.4	13.2
INR	0.90–1.10	1.07	1.12
aPTT (s)	25.0–40.0	32.0	27.7
Fib (mg/dl)	200–400	320	312
FDP (μg/ml)	0.0–5.0		12.9
D-dimer (μg/ml)	0.00–1.00	1.41	5.72
ATIII (%)	80.0–130.0		64.9
Clotting time (s)	38–79	49	47
Alpha (°)	63–83	73	75
CFT (s)	34–159	84	93
MCF (mm)	50–72	50	63
Maximum lysis (%)	<15	100	0

aPTT, activated partial thromboplastin time; ATIII, antithrombin III; CFT, clot formation time; ED, emergency department; FDP, fibrinogen and fibrin degradation products; Fib, fibrinogen; INR, international normalized ratio of prothrombin time; MCF, maximum clot firmness; Plt, platelet; PT, prothrombin time.

D-dimer of 5.72 μg/ml. On the second day of his hospitalization, the patient remained stable without any signs of spontaneous bleeding and subsequently discharged from the hospital. He continues his outpatient chemotherapy regimen without further complication.

Discussion

The use of chemotherapeutic agents is not a common cause of anaphylaxis, even though 44% of anaphylactic reactions occur iatrogenically [1]. According to the latest chart reviews in Asian countries, allergic reactions caused by oxaliplatin accounted for up to 15% of all patients who received the FOLFOX regimen [4,5]. Oxaliplatin-related hypersensitive reaction mediated by IgE antibodies leads to hypotension, bronchospasm, sweating, and generalized edema with flushing [8–10]. However, severe cases of anaphylaxis with thrombotic or bleeding tendency had not been reported until now.

There are two major mechanisms of fibrinolysis: primary and secondary, which depend on the presence of the stimulation of fibrin generation which is activated by tissue factors [11]. Primary fibrinolysis is characterized as a thrombin-independent increase in tissue-type plasminogen activator secreted by endothelial cells, which convert plasminogen to plasmin followed by an initiation of fibrinolysis [12]. Secondary fibrinolysis is caused by fibrin generation. This phenomenon keeps the blood vessels patent by resolving redundant clot [13]. Hyperfibrinolysis occurs when the fibrinolytic (anticoagulation) pathway is activated more than fibrin generation, and causes excessive bleeding which can occur after a variety of major surgical procedures [6,12,14,15]. Unfortunately, publications concerning hyperfibrinolytic activity in patients with anaphylaxis have not been reported frequently.

We searched the PubMed database and three articles dealing with hyperfibrinolysis due to an anaphylactic shock diagnosed by standard blood test were obtained. Although severe coagulopathy such as prolonged PT, activated partial thromboplastin time, and markedly decreased fibrinogen levels were observed in two of three patients, these coagulation disorders were normalized within 2 days [16,17]. Interestingly, no bleeding tendency was identified during the courses for all patients and these disorders resolved spontaneously. On the contrary, Mazzi *et al.* [16] emphasized the importance of distinction between primary and secondary hyperfibrinolysis because the treatment of each conditions differs. However, it is difficult to clinically diagnose the pattern of fibrinolysis by routine laboratory coagulation test.

In the present case report, we detected hyperfibrinolysis using ROTEM in a patient undergoing anaphylactic shock within only a few hours, whereas abnormal findings of SCTs were confirmed after the recovery of hyperfibrinolysis by ROTEM. We identified seven additional articles on hyperfibrinolysis diagnosed by thromboelastography. Oozing from the wound surface was observed in one patient reported by De Souza *et al.* [18], whereas no bleeding complications were found in the other reports. Although four patients in whom the hyperfibrinolysis occurred during surgery were administered tranexamic acid and fresh frozen plasma intraoperatively, hyperfibrinolysis of the other three patients was resolved spontaneously within a few hours. There are no other case reports on hyperfibrinolysis diagnosed by ROTEM. In the present case, although coagulation abnormality diagnosed by SCTs was mild on admission, ROTEM findings showed remarkable hyperfibrinolysis. Moreover, hyperfibrinolysis findings in ROTEM were normalized 7 h later, whereas prolonged prothrombin activity and higher fibrin degradation product and D-dimer of SCTs were still confirmed. These results suggest that ROTEM analysis was able to detect hyperfibrinolysis due to an anaphylactic shock faster and more accurately than SCTs. Interestingly, the dynamic shift in coagulation/ anticoagulation system in patients with anaphylactic shock

without bleeding tendency appeared in a much shorter period of time.

Our case report demonstrates that the activation of plasmin is discontinued in response to early effective resuscitation before severe hemorrhagic complications arise. Moreover, ROTEM can detect these hemodynamic changes, which have been undetected by SCTs. Further research is needed to elucidate the pathophysiological mechanism of hyperfibrinolysis and evaluate the indication of tranexamic acid administration for patients with anaphylactic shock.

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Conflicts of interest

There are no conflicts of interest.

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