Renal Replacement Therapy

CASE REPORT Open Access

Spontaneous iliopsoas muscle hematoma secondary to disseminated intravascular coagulation caused by nafamostat mesilate allergy: a case study

Kunihisa Nezu[1], Takashi Yoshioka[2*], Hiromichi Katayama[1], Taro Fukushi[3] and Atsushi Kyan[1]

Abstract

Background: A spontaneous iliopsoas muscle hematoma is relatively rare and often associated with abnormal coagulation. Nafamostat mesilate is an anticoagulant agent that is sometimes used to treat hemodialysis patients at high risk of bleeding. Although severe drug allergy caused by nafamostat mesilate was previously reported, spontaneous iliopsoas muscle hematoma secondary to disseminated intravascular coagulation caused by nafamostat mesilate allergy has not yet been reported.

Case presentation: Severe nafamostat mesilate allergy occurred in a 78-year-old male patient with a 2-year history of hemodialysis. During hospitalization, disseminated intravascular coagulation occurred followed by a progressive iliopsoas muscle hematoma a few days later. Emergent transarterial lumbar artery embolization was successfully performed.

Conclusion: For dialysis patients, a detailed medical history including repeated nafamostat mesilate use and considering an allergy to nafamostat mesilate in differential diagnosis are critical. In addition to early diagnosis, when an iliopsoas hematoma occurs, early intravascular treatment is important.

Keywords: Spontaneous iliopsoas muscle hematoma, Nafamostat mesilate, Hemodialysis, Disseminated intravascular coagulation

Background

Spontaneous iliopsoas muscle hematoma is a relatively rare disease. It is related to abnormal coagulation in a patient or oral administration of the anticoagulant. Although radiological examination enables early diagnosis of the condition and interventional radiologic techniques have progressed, spontaneous iliopsoas muscle hematoma has a high mortality rate [1, 2]. In Japan, patients on hemodialysis who are at high risk of bleeding are sometimes treated with nafamostat mesilate because of its short half-life. Some allergic reactions to nafamostat mesilate, including severe conditions, such as anaphylactic shock, have been reported in recent years [3, 4]. Patients with hemodialysis are generally at high risk of bleeding because of the usage of anticoagulant drugs during hemodialysis, and some case reports showed cases of iliopsoas hematoma for patients in hemodialysis [5–10]. Here, we report a rare case of spontaneous iliopsoas muscle hematoma with disseminated intravascular coagulation (DIC) due to severe allergy caused by repeated administration of nafamostat mesilate.

Case presentation

A 78-year-old male with established end-stage renal disease secondary to operation for aortic dissection who had been on hemodialysis for 2 years was hospitalized due to high fever and hypotension after dialysis. On the day prior to admission, we had changed the anticoagulation agent administered during hemodialysis from

* Correspondence: yoshioka.takashi.52a@kyoto-u.jp
[2]Center for Innovative Research for Communities and Clinical Excellence (CiRC2LE), Fukushima Medical University, 1 Hikarigaoka, Fukushima-shi, Fukushima-ken 960-1295, Japan
Full list of author information is available at the end of the article

Table 1 Clinical parameters of the patient on admission

Vital signs	
Body temperature (°C)	38.8
Blood pressure (mmHg)	63/38
Heart rate (bpm)	90
Physical examination	
Appearance	Pale and chilly
Chest and abdominal examination	Within normal limits
Others	Hands, warm and sweaty
Medication	
Bisoprolol fumarate 2 .5 mg/day, febuxostat 10 mg/day, vonoprazan fumarate 10 mg/day, furosemide 80 mg/day, levetiracetam 500 mg/day	
Hematological examination	
White blood cell (/μL)	1800
Platelet (/μL)	73,000
Hemoglobin (g/dL)	9.7
Neutrophils (/μL)	1670
Eosinophils (/μL)	30
Biochemical examination	
AST (IU/μL)	21
ALT (IU/μL)	11
γ-GTP (IU/μL)	24
Total bilirubin (mg/dL)	0.66
Total protein (g/dL)	6.3
C-reactive protein (mg/dL)	0.26
BUN (mg/dL)	17.3
Creatinin (mg/dL)	3.25
Sodium (mEq/L)	140
Potassium (mEq/L)	3.1
Calcium (mg/dL)	8.7

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen

intravenous heparin to intravenous nafamostat mesilate because of mild oral bleeding during dialysis.

The patient's clinical parameters on admission are shown in Table 1. According to these test results, septic shock was strongly suspected. Therefore, we examined two sets of blood culture and started intravenous administration of noradrenaline (0.06 μg/kg/min) and meropenem (0.5 g/day). On the second day of hospitalization, liver dysfunction and coagulation were observed. The patient's biochemical and coagulation examination results were white blood cell count, 13,300/μL; platelet count, 71,000/μL; AST, 266 IU/L; ALT, 166 IU/L; γ-glutamyl transpeptidase (γ-GTP), 125 IU/L; fibrinogen degradation products (FDP), 225 μg/mL; fibrinogen, 89 mg/dL; and prolongation of prothrombin time, 7.9 s. According to the International Society on Thrombosis and Haemostasis criteria, the total DIC score was 7 points. Based on these findings, we diagnosed the patient with DIC.

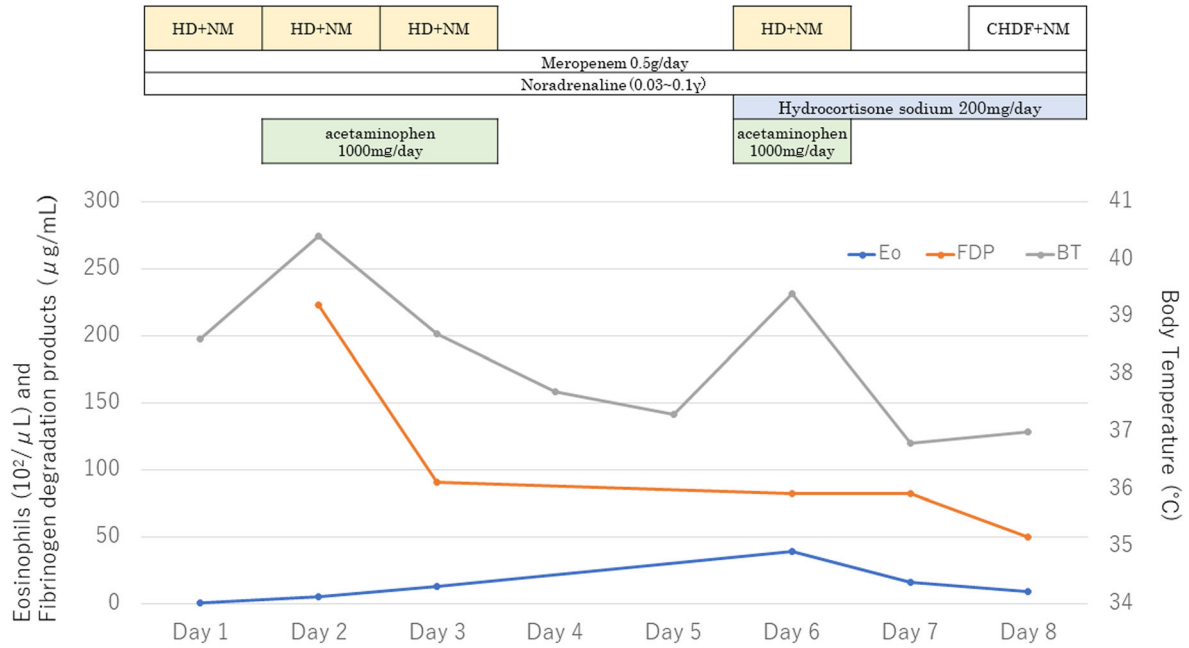
On the day 6 of hospitalization, hematological examination revealed elevated eosinophils (3870 μ/mL) and procalcitonin (126 ng/mL). In addition to this, the patient's febrile condition and hypotension presented only during hemodialysis. The blood cultures performed at admission were all negative. These findings indicated that not sepsis but some kind of severe allergic reaction had occurred. Furthermore, the only drug introduced during the clinical course was nafamostat mesilate. Therefore, we diagnosed the patient with DIC secondary to severe allergy to nafamostat mesilate. We stopped the administration of antibiotics, started intravenous administration of hydrocortisone sodium succinate (200 mg), and changed the anticoagulant administered during dialysis from nafamostat mesilate to low molecular weight heparin. However, his drug-induced lymphocyte stimulation test (DLST) results were negative.

After changing the treatment, the patient's fever soon subsided (Fig. 1). On the eighth day of hospitalization, he complained of pain in his left thigh. Contrast-enhanced computed tomography (CECT) showed an iliopsoas hematoma with extravasation from a lumbar artery (Fig. 2b). We chose a noninvasive treatment for this condition, beginning with an intravenous transfusion of 8 units of fresh frozen plasma (FFP) and 2 units of red blood cell concentrate (RBC). For several days, the patient's condition remained stable. On the 15th day, the size of the hematoma appeared almost unchanged, as evaluated by non-contrast CT.

On the 24th day of hospitalization, we observed a sudden drop in his hemoglobin level from 9.7 to 6.7 g/dL; platelet count, 73,000/μL; AST, 17 IU/L; ALT, 6 IU/L; γ-GTP, 125 IU/L; FDP, 99.2 μg/mL; fibrinogen, 185 mg/dL; and prolongation of prothrombin time, 41.8 s. CECT showed that the iliopsoas muscle hematoma had considerably increased in size. In addition, extravasation from the lumbar arteries was observed (Fig. 2c). We determined that an invasive treatment was critical, and he subsequently underwent an emergent selective transarterial embolization of collapsed lumbar arteries (Fig. 3). On the 44th day of hospitalization, all drug treatment was discontinued and the patient started rehabilitation. On the 108th day, he was discharged from the hospital.

Discussion

In this case, we encountered a spontaneous iliopsoas muscle hematoma due to DIC caused by severe allergy to nafamostat mesilate. Spontaneous iliopsoas muscle hematoma is a relatively rare disease where the etiology is a collapse of the small arteries. The disease can occur in patients at high risk of bleeding. According to



Eo = eosinophils, FDP = fibrinogen degradation products, BP = body temperature, HD = hemodialysis, CHDF = continuous hemodiafiltration, NM = nafamostat mesilate, LMWH = low-molecular-weight heparin.

Fig. 1 Clinical course of the patient after admission. Eo eosinophils, FDP fibrinogen degradation products, BP body temperature, HD hemodialysis, CHDF continuous hemodiafiltration, NM nafamostat mesilate, LMWH low molecular weight heparin

previous reports, the mortality rate is as high as 30–34% [1, 2]. Popov et al. [3] classified intraperitoneal and intramuscular hematomas into three types and three subtypes: type I—no active bleeding in a patient in a hemodynamically stable condition, type II—active bleeding and no muscular fascia rupture, and type III—active bleeding and muscular fascia rupture; subtypes: type II-a—type II with no contraindication to cessation of anticoagulation, type II-b—type II with contraindication to cessation of anticoagulation, and type II-c—type II with no anticoagulation therapy or antiplatelet therapy. Although there are some case reports of iliopsoas hematoma in hemodialytic patients [5–10, 11], there are still no reports with spontaneous iliopsoas hematoma secondary to severe allergic DIC due to nafamostat mesylate. The review of literature on PubMed for iliopsoas

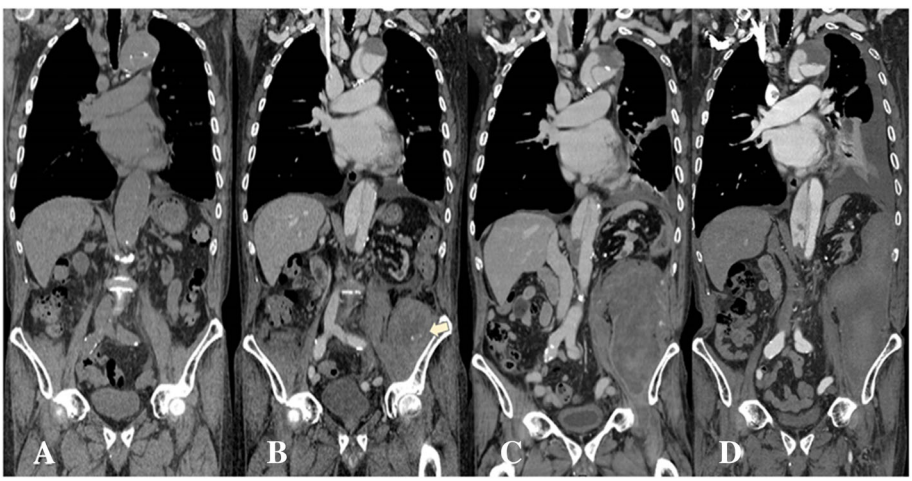


Fig. 2 Abdominal computed tomography showed an iliopsoas hematoma. **a** Day 7, non-CECT revealed no obvious findings. **b** Day 8, CECT revealed an iliopsoas hematoma (5 × 3 × 6 cm) with active contrast extravasation (arrow). **c** Day 24, CECT revealed an extremely enlarged hematoma (10 × 16 × 8 cm). **d** Day 46, CECT revealed that the hematoma had stabilized and had not enlarged (7 × 20 × 5 cm)

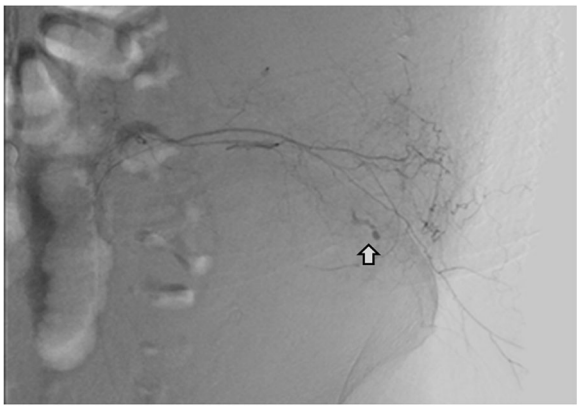


Fig. 3 Arteriography of the lumbar arteries. Active bleeding from the second to fourth branches of the left lumbar arteries (arrow). Selective transarterial embolization was performed

hematoma in chronic hemodialysis patients is shown in Table 2.

In general, noninvasive treatment is the first choice; however, when a noninvasive treatment does not improve the patient's condition, minimally invasive surgery, i.e., interventional radiology (IVR), is a better treatment option [1]. Although there are no defined criteria for selection of treatment, Popov et al. recommended type II-b, type II-c, and type III as indications for IVR [12]. In this case, when the patient complained of pain in his left thigh, the hematoma had spread to the outside of the iliopsoas muscle fascia. Thus, the iliopsoas hematoma was classified as type III at the first diagnosis based on the classification of Popov et al. Although a type III hematoma is an indication for IVR, we initially chose a noninvasive treatment, which resulted in IVR treatment. While the patient survived, we should have selected immediate IVR at the first diagnosis of iliopsoas hematoma because the patient was not discharged until after more than 100 days.

Nafamostat mesilate is a serine-decomposing enzyme inhibitor that results in anticoagulation through inhibition of the coagulation-fibrinolytic, complement, and platelet aggregation systems [13]. Nafamostat mesilate is sometimes used to treat hemodialysis patients at high risk of bleeding because of its short half-life. Some allergic reactions to nafamostat mesilate, including severe conditions such as anaphylactic shock, have been reported in recent years [3, 4]. The diagnostic criteria for an allergic reaction to nafamostat mesilate are not yet established. However, Mise et al. [3] proposed the following three diagnostic criteria: (1) Symptoms appear during hemodialysis when nafamostat mesilate is administered as an anticoagulant, and no symptoms are observed during treatment with other anticoagulants. (2) The possibility of allergic reactions to other drugs can be excluded. (3) The possibility of allergic reactions associated with diseases can be excluded. Additionally, Mise et al. reported that the frequency of allergy to nafamostat mesilate is about 1–2% among patients who have been re-administered with nafamostat mesilate. In our case, we diagnosed the patient with a severe allergy to nafamostat mesilate based on three observations. First, we observed elevated eosinophil levels and a febrile condition only on the days when the patient received hemodialysis, for which nafamostat mesilate was

Table 2 Review of literature for iliopsoas hematoma in chronic hemodialysis patients

No.	Author	Years	Country	Age	Sex	Etiology of ESRD	Time on dialysis	Antiplatelets	Anticoagulants	Laterality	Treatment	Outcome	Reference
1	Delorme MA	1993	Canada	68	M	CGN	6 years	None	None	ND	ND	ND	[5]
2	Inoue T	2001	Japan	76	F	ND	ND	ND	ND	L	Conservative	Death	[6]
3	Halak M	2001	Israel	72	F	ND	ND	None	Heparin	L	Endovascular Tx	Survival	[7]
4	Malek-Marín T	2010	Spain	76	M	ADPKD	18 years	None	Warfarin	R	Conservative	Survival	[8]
5	Fan WX	2012	China	67	F	DMN	2 weeks	Ozagrel	Heparin	L	Conservative	Survival	[11]
6	Li J	2016	Hong Kong	72	M	ND	5 years	Aspirin, clopidogrel	LMWH	R	Endovascular Tx	Survival	[9]
7	Hwang NK	2017	Korea	43	M	ND	ND	ND	Heparin	L	Endovascular Tx	Survival	[10]
8				69	F	ND	ND	Aspirin, clopidogrel	Heparin	L	Endovascular Tx	Death	
9				48	M	ND	4 months	Aspirin, clopidogrel, pletaal	LMWH	R	Endovascular Tx	Survival	

ESRD end-stage renal disease, *ND* not documented, *L* left, *R* right, *CGN* chronic glomerulonephritis, *Tx* treatment, *ADPKD* autosomal dominant polycystic kidney disease, *LMWH* low molecular weight heparin

administered. Second, the discontinuation of nafamostat mesilate and administration of a steroid drug relieved the clinical symptoms. Third, infectious diseases such as iliopsoas muscle abscess were not suspected based on the clinical course. Because the abnormal coagulation continued even after DIC treatment, the patient was diagnosed with a hematoma. Nakajima et al. indicated that the residual dissection after surgical treatment of Stanford type A aortic dissection will decrease coagulation, which is a risk for DIC development [14]. Although the coagulation test results were not examined before hospitalization, the platelet counts were ≤ 100,000/μL for 2 years. Therefore, it seems that DIC caused by nafamostat mesilate was prolonged by chronic aortic dissection in this case.

Although we diagnosed anaphylaxis due to nafamostat mesilate, his DLST results were negative. According to the report of Ito et al., the sensitivity of DLST is only 60%; therefore, it might not be necessary for diagnosing an allergy [4]. In this case, the DLST was considered to be false negative. However, blood pressure decreased within several hours after administration of nafamostat mesilate, which met the diagnostic criteria of anaphylaxis suggested by Simons et al. [15]. In addition, anaphylaxis is a type 1 allergic reaction, and the involvement of type 1 allergy and DIC were suspected in this case. Although the pathway from a type 1 allergy to DIC has not been fully elucidated, it might be related to mast cell and eosinophil mediators such as platelet-activating factor [16–18]. Takeda et al. described the possibility of causing DIC by eosinophil cationic protein, and a few complications of eosinophilia and DIC have been reported [19]. In this case, eosinophilia was increased and might have been an important factor in drug-induced DIC.

The patient's procalcitonin level on day 6 of hospitalization was abnormally high. In this case, both blood cultures yielded negative results, and CECT did not show any infectious source. Therefore, anaphylactic shock was strongly suspected. It is possible that the non-infectious pathway of procalcitonin increased due to increased oxidative stress after the administration of acetaminophen for hepatic injury caused by DIC [20–22].

This case of iliopsoas muscle hematoma from DIC secondary to allergy to nafamostat mesilate resulted in two clinically important conclusions. First, nafamostat mesilate allergy should be considered in the differential diagnosis of febrile patients with a repeated history of nafamostat mesilate treatment. Second, iliopsoas muscle hematoma with active bleeding in patients on hemodialysis is always classified as type II-b because anticoagulant drugs are generally administered during hemodialysis. Therefore, IVR may be considered a first-line treatment option. In Japan, nafamostat mesilate is often used as an anticoagulant in patients on hemodialysis who are at high risk of bleeding, and these findings may help us to achieve both early diagnosis and early treatment intervention when spontaneous iliopsoas hematoma occurs.

Conclusions

We encountered a patient with iliopsoas muscle hematoma from DIC secondary to allergy to nafamostat mesilate. In Japan, nafamostat mesilate is sometimes used to treat patients on hemodialysis who are at high risk of bleeding. For dialysis patients, recording medical history of repeated nafamostat mesilate use and consideration of an allergy to nafamostat mesilate are critical. In addition to early diagnosis, when iliopsoas hematoma occurs, early intravascular treatment should be considered.

Abbreviations

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CECT: Contrast-enhanced computed tomography; DIC: Disseminated intravascular coagulation; DLST: Drug-induced lymphocyte stimulation test; IVR: Interventional radiology

Acknowledgements

We would like to thank Editage (www.editage.jp) for English language editing.

Funding

The authors received no funding in relation to this manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KN, HK, and AK provided the discussion and treatment of the patient. KN, TY, TF, and HK reviewed and revised the manuscript. All authors read and approved the final manuscript and agree with the submission to the journal.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Author details

[1]Department of Urology, Shirakawa Kosei General Hospital, Shirakawa-shi, Japan. [2]Center for Innovative Research for Communities and Clinical Excellence (CiRC2LE), Fukushima Medical University, 1 Hikarigaoka, Fukushima-shi, Fukushima-ken 960-1295, Japan. [3]Division of Blood Purification, Tohoku University Hospital, Sendai-shi, Japan.

Received: 30 November 2018 Accepted: 8 March 2019
Published online: 19 March 2019

References

1. Jawhari R, Chevallier O, Falvo N, d'Athis P, Gehin S, Charles PE, et al. Outcomes of transcatheter arterial embolization with a modified N-butyl cyanoacrylate glue for spontaneous iliopsoas and rectus sheath hematomas in anticoagulated patients. J Vasc Interv Radiol. 2018;29:210–7.
2. Llitjos JF, Daviaud F, Grimaldi D, Legriel S, Georges JL, Guerot E, et al. Iliopsoas hematoma in the intensive care unit: a multicentric study. Ann Intensive Care. 2016;6:8.
3. Mise N, Shimizu H, Nishi T, Kyono T, Masaki K, Nishio K, et al. Allergic reaction to nafamostat mesilate in hemodialysis patients. Nihon Toseki Igakkai Zasshi. 2004;37:65–70.
4. Ito K, Fukushima T, Nakashita H, Tamai R, Kiwaki S, Abe Y, et al. Two cases of allergic reaction induced by nafamostat mesilate during maintenance of hemodialysis, and analysis of 35 cases reported previously. Nihon Toseki Igakkai Zasshi. 2007;40:913–8.
5. Delorme M, Saeed N, Sevcik A, Mitchell L, Berry L, Johnston M, et al. Plasma dermatan sulfate proteoglycan in a patient on chronic hemodialysis. Blood. 1993;82:3380–5.
6. Inoue T, Okada H, Shioda K, Takahira S, Kanno Y, Sugahara S, et al. A case of myeloma kidney complicated by extramedullary plasmacytoma with massive bleeding. Nihon Jinzo Gakkai Shi. 2001;43:347–50.
7. Halak M, Kligman M, Loberman Z, Eyal E, Karmeli R. Spontaneous ruptured lumbar artery in a chronic renal failure patient. Eur J Vasc Endovasc Surg. 2001;21:569–71.
8. Malek-Marin T, Arenas D, Gil T, Moledous A, Okubo M, Arenas JJ, et al. Spontaneous retroperitoneal hemorrhage in dialysis: a presentation of 5 cases and review of the literature. Clin Nephrol. 2010;74:229–44.
9. Li J, Chan YC, Qing KX, Cheng SW. Spontaneous retroperitoneal hematoma simulating ruptured infrarenal aortic aneurysm in a patient with end-stage renal disease. Int J Angiol. 2016;25:e43–8.
10. Hwang NK, Rhee H, Kim IY, Seong EY, Lee DW, Lee SB, et al. Three cases of spontaneous lumbar artery rupture in hemodialysis patients. Hemodial Int. 2017;21:e18–21.
11. Fan WX, Deng ZX, Liu F, Liu RB, He L, Amrit B, et al. Spontaneous retroperitoneal hemorrhage after hemodialysis involving anticoagulant agents. J Zhejiang Univ Sci B. 2012;13:408–12.
12. Popov M, Sotiriadis C, Gay F, Jouannic AM, Lachenal Y, Hajdu SD, et al. Spontaneous intramuscular hematomas of the abdomen and pelvis: a new multilevel algorithm to direct transarterial embolization and patient management. Cardiovasc Intervent Radiol. 2017;40:537–45.
13. Fujii S, Hitomi Y. New synthetic inhibitors of C1r, C1 esterase, thrombin, plasmin, kallikrein and trypsin. Biochim Biophys Acta. 1981;661(2):342–5.
14. Nakajima T, Kin H, Minagawa Y, Komoda K, Izumoto H, Kawazoe K. Coagulopathy associated with residual dissection after surgical treatment of type A aortic dissection. J Vasc Surg. 1997;26:609–15.
15. Simons FER, Ardusso LRF, Bilò MB, El-Gamal YM, Ledford DK, Ring J, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J. 2011;4:13–37.
16. Tchougounova E, Pejler G. Regulation of extravascular coagulation and fibrinolysis by heparin-dependent mast cell chymase. FASEB J. 2001;15:2763–5.
17. Choi IH, Ha TY, Lee DG, Park JS, Lee JH, Park YM, et al. Occurrence of disseminated intravascular coagulation (DIC) in active systemic anaphylaxis: role of platelet-activating factor. Clin Exp Immunol. 1995;100:390–4.
18. Guilarte M, Sala-Cunill A, Luengo O, Labrador-Horrillo M, Cardona V. The mast cell, contact, and coagulation system connection in anaphylaxis. Front Immunol. 2017;8:846.
19. Takeda H, Nishikawa H, Tsumura T, Sekikawa A, Maruo T, Okabe Y, et al. Prominent hypereosinophilia with disseminated intravascular coagulation as an unusual presentation of advanced gastric cancer. Intern Med. 2014;53:563–9.
20. Tschiedel E, Assert R, Felderhoff-Muser U, Kathemann S, Witzke O, Hoyer P, et al. Undue elevation of procalcitonin in pediatric paracetamol intoxication is not explained by liver cell injury alone. Ann Hepatol. 2018;17:631–7.
21. Hinson JA, Roberts DW, James LP. Mechanisms of acetaminophen-induced liver necrosis. Handb Exp Pharmacol. 2010;196:369–405.
22. Raddant AC, Russo AF. Reactive oxygen species induce procalcitonin expression in trigeminal ganglia glia. Headache. 2014;54:472–84.