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【 CASE REPORT 】

Risk of Heparin-induced Immediate-type Hypersensitivity during Arteriovenous Fistula Placement

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Abstract:
Heparin is commonly used to prevent clotting; however, severe hypersensitivity reactions during vascular access (VA) placement are rarely but occasionally reported. A 49-year-old man experienced a heparin-induced hypersensitivity reaction during VA placement. Severe side effects may occur even while placing the VA; therefore, we reconsidered the routine use of heparin, as the side effects are unpredictable. Physicians should be aware of the risk of heparin-induced hypersensitivity and be ready to effectively manage it during VA placement.

Key words: heparin-induced hypersensitivity, end-stage renal disease, vascular access placement

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Introduction

Heparin is widely used as an anticoagulant. Some nephrologists use heparin in the process of arterio-venous fistula (AVF) placement in order to prevent clotting of arteries during clumping.

Despite its widespread application in daily clinical practice, hypersensitivity reactions to heparin are rare. Furthermore, in contrast to delayed-type hypersensitivity, immediate-type anaphylactic reactions after heparin administration are extremely rare.

We herein report a case of a 49-year-old patient who developed a hypersensitivity reaction after the intravenous administration of heparin during AVF placement. This is a rare report that focuses on a heparin-induced hypersensitivity reaction during AVF placement.

Case Report

A 49-year-old man with end-stage renal disease caused by diabetic nephropathy was admitted to our hospital for AVF surgery prior to starting hemodialysis (HD). His medical history included hypertension and chronic heart failure (CHF). CHF was caused by ischemic cardiomyopathy with hypoperfusion in the inferior-posterior myocardial region proven by pharmacological stress myocardial scintigraphy. Echocardiography revealed a poor left ventricular function with an ejection fraction (EF) of 35% and diffuse hypokinesis (Fig. 1). His family history was unremarkable, and he had no history of allergies. His medication included olmesartan, perindopril, amlodipine, carvedilol, furosemide, iron sulfate, and sennosides. He had never been administered heparin. A physical examination performed at admission showed a height of 1.66 m, a body weight of 77.0 kg, a body mass index of 28.0 kg/m^2, a temperature of 36.7℃, a pulse of 109 beats/min with regular rhythm, a blood pressure of 121/79 mmHg, an oxygen saturation of 99% (room air), and significant pitting edema of both legs. The findings of the chest, heart, and abdomen were unremarkable. The laboratory examination revealed severe renal dysfunction (Table). Chest radiography performed on admission (Fig. 2A) showed an increased cardio-thoracic ratio without congestion in both lung fields. Electrocardiogram (ECG) showed sinus tachycardia and P mitrale in lead V_1 on admission. Given his low EF, we decided to place the AVF as peripheral as possible in order to avoid acute heart failure after AVF placement. We selected an end-to-side anastomosis between the cephalic vein and the radial artery.

On day 2 after admission, the patient walked into the operating room (OR) with no complaints. On the initial physical examination, his pulse was 80 beats/min with regular

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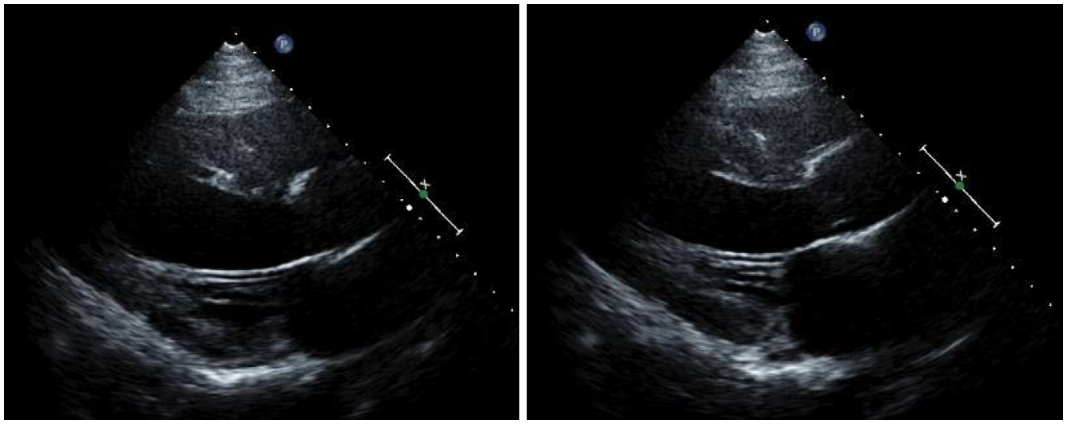


Figure 1. Cardiac ultrasonography findings. Left ventricular contraction is moderately deteriorated with diffuse hypokinesis, although the regional left ventricular wall motion is normal. The left atrium and left ventricle are dilated. No valvular dysfunction is found. Aortic diameter: 23 mm, left atrial dimension: 44 mm, interventricular septum thickness: 13 mm, posterior wall thickness: 14 mm, left ventricular end-diastolic diameter: 54 mm, left ventricular end-systolic diameter: 45 mm, end-diastolic volume: 141 mL, end-systolic volume: 92 mL, systolic volume: 49 mL, ejection fraction: 35%, fractional shortening: 17%, E wave 770 mm/s, A wave 879 mm/s, E/A 0.9, E/e' med 15.3, E/e' lat 14.9.

rhythm, blood pressure was 150/80 mmHg, and oxygen saturation was 95% (room air). In the supine position, his oxygen saturation remained 95% (room air); therefore, supplemental oxygen was provided (3 L/min via mask). Monitoring included electrocardiographic lead II, blood pressure, and oxygen saturation. We injected 1% lidocaine into the right forearm for local anesthesia at 9:32 AM, and AVF surgery was started at 9:33 AM. Cefazolin 1 g was administered as antibiotic prophylaxis. The oxygen saturation remained at 95% on oxygen 3 L/min, and he had no complaints at 10:06 AM. We cut the cephalic vein at the peripheral end of the operating field and expanded the vein by injecting saline containing heparin. Before the administration of intravenous heparin, no adverse events with hemodynamic or respiratory alternations were observed, and no skin reaction of any type, even after antibiotic prophylaxis, was noted. We injected heparin at 1,500 units (1,000 units per mL) into the vein and clumped 2 points on the radial artery at 10:15 AM. When we anastomosed the vessels, the patient suddenly complained of dyspnea at 10:23 AM. His oxygen saturation dropped to 91%, so the oxygen flow rate was increased to 5 L/min. Although no cyanosis of the face and skin was noted, the patient became restless and tried to stand up on the operating table. Anesthesiologists were called at 10:24 AM to maintain his respiratory condition. Despite oxygen administration via mask ventilation in the sniff position, his dyspnea was exacerbated at 10:25 AM. His pulse was 100 beats/min with regular rhythm, blood pressure was 160/100 mmHg, and oxygen saturation was 95% with mask ventilation. Because ventilation was difficult, we decided to use mechanical ventilation. Sevoflurane and dexmedetomidine hydrochloride were prescribed for sedation, and patient was intubated at 10:38 AM. Mechanical ventilation was adjusted to maintain normal oxygen saturation. His peak airway pressure was high (33 mmHg), but after the intravenous administration of methylprednisolone 500 mg, his peak airway pressure gradually decreased with good oxygenation maintained (arterial oxygen partial pressure: 248 mmHg). After maintaining this condition, AVF placement was completed at 11:12 AM.

The anesthesiologist noticed a large amount of foamy sputum from the tracheal tube and auscultated tracheal stenosis sounds and wheezes in both lungs. On a laboratory examination, the levels of cardiac biomarkers were not elevated. Chest radiography demonstrated pulmonary edema (Fig. 2B), but electrocardiographic monitoring and ECG showed no changes, and an arterial blood gas analysis revealed no acid-base disturbance or electrolyte imbalance. We speculated that the patient's pulmonary edema was a result of an anaphylaxis reaction to the heparin and managed him in the intensive-care unit (ICU). Methylprednisolone 500 mg and antihistamines (famotidine 10 mg/day and chlorpheniramine 5 mg/day) were administered in the ICU. His respiratory condition improved soon after the administration of these drugs, and the partial pressure of arterial oxygen (PaO_2)/fraction of inspiratory oxygen (FiO_2) ratio improved from 258.3 to 480. Neither the ECG findings nor the cardiac biomarker levels changed. The findings of a drug-induced lymphocyte stimulation test (DLST) were negative: the simulation index (SI) was 1.2 (reference values: S.I. <1.6, negative test; S.I. 1.6-1.8, false positive test; S.I. >1.8, positive test).

The patient's respiratory condition recovered well, and he was extubated on day 4 after admission. HD was started with a temporary catheter from day 6 after admission; heparin was replaced with a saline-replenishing catheter and with mesilate nafamostat as an anticoagulant. On day 22, a DLST to heparin showed positive results (S.I. 2.6). Throughout the

Table. **Laboratory Tests on Admission.**

blood tests	value	continue	
WBC	6,700 /μL	AST	16 IU/L
neutrophils	68.3 %	ALT	12 IU/L
lymphocyte	17.8 %	γGTP	13 IU/L
monocyte	7.7 %	ALP	316 IU/L
eosiophils	5.6 %	T-Bil	0.2 mg/dL
basophils	0.6 %	CK	975 IU/L
RBC	274×10^4 /μL	CRP	1.09 mg/dL
Hb	8.5 g/dL	urinarysis	value
Ht	25.5 %	protein	3+
MCV	93.1 fL	glucose	250
MCH	30.9 pg	gravity	1.016
MCHC	33.2 %	pH	6.5
Plt	21.5×10^4 /μL	urobilinogen	±
TP	6.5 g/dL	bilirubin	-
Alb	2.9 g/dL	ket	-
BUN	53 mg/dL	WBC	2+
Cr	7.4 mg/dL	nitrate	-
eGFR	7.1 mL/min/1.73m^2	occult blood	2+
UA	4.9 mg/dL	RBC	30-49 /hpf
Na	140 mEq/L	WBC	50-99 /hpf
K	6.2 mEq/L	epitherial casts	1+
Cl	112 mEq/L	TP	672 mg/dL
Ca	5.8 mg/dL	Cr	65.7 mg/dL
iP	6.6 mg/dL	venous blood gas	Value
LDH	289 IU/L	HCO_3^-	17.6 mmol/L

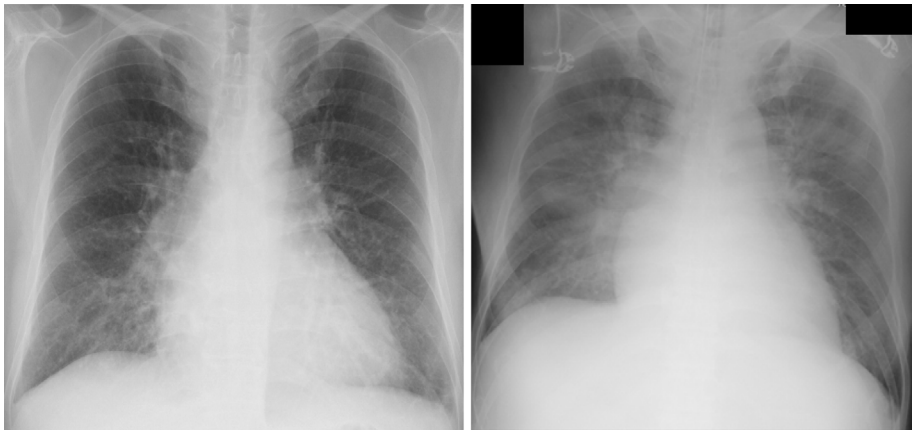
Hb: hemoglobin, Ht: hematocrit, Plt: platelet, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cr: serum creatinine, eGFR: estimated glomerular filtration rate, UA: uric acid, LDH: lactic acid dehydrogenase, AST: asparate aminotransferase, ALT: alanine aminotransferase, γGTP: γ-glutamyl transpeptidase, ALP: alkaline phosphatase, T-Bil: total bilirubin, CK: creatine kinase, CRP: C-reactive protein

patient's hospitalization, we observed no reactions against other allergens. In fact, a DLST performed for cefazolin and lidocaine at the same time as the second test for heparin showed negative results. The patient's clinical course was uneventful, and he was discharged on day 23 after admission. The patient now attends an outpatient HD clinic without any problems and also avoids heparin.

Discussion

This case confirmed two important clinical issues. First, heparin may cause severe hypersensitivity reactions during vascular access (VA) placement. Delayed reactions to subcutaneously injected heparin are commonly seen, and the work-up includes patch tests and intradermal tests. In contrast, to our knowledge, immediate-type hypersensitivity reactions to systemically administered heparin are very rare. Anaphylaxis to heparin has been linked to allergies to porcine products (1). Several cases of immediate-type reactions after intravenously injected heparin were eventually confirmed to be non-allergic anaphylaxis due to contaminants (2). Among the contaminants, oversulfated chondroitin sulfate (OSCS) can directly activate the contact system and induce the *in vitro* generation of C_3a and C_5a anaphylatoxins. Furthermore, OSCS activates kallikrein *in vivo* and can induce a profound hypotensive response in pigs, thus providing a potential biologic link between the contaminant and the anaphylactoid reactions seen in affected patients. The finding that hypotension did not develop in all animals treated with OSCS-contaminated heparin, even at a relatively high dose, is consistent with the observation that most patients who received contaminated heparin did not experience adverse events (2). Consequently, many physicians remain unaware of anaphylaxis to heparin (3).

Regarding the probability of hypersensitivity to heparin, some may contest that the present patient more likely experienced heart failure exacerbation than an allergic reaction. Indeed, his risk of acute heart failure was high due to the presence of several cardiovascular risk factors, such as CHF, chronic kidney disease, diabetes mellitus, and hypertension. However, the following three reasons exclude this possibility: First, acute heart failure typically develops due to acute coronary syndrome or arrhythmia with a sudden onset; the cardiopulmonary surveillance in this patient did not show any abnormalities. Second, dyspnea was exacerbated shortly after heparin administration. The time course between the



(A) (B)

Figure 2. A comparison between chest radiography performed at admission (A) and that performed after the anaphylaxis reaction (B). Both (A) and (B) show an increased cardio-thoracic ratio. In addition, (B) shows bilateral hilar expansion and congestion in both lung fields.

heparin injection and dyspnea onset therefore prompted us to suspect an allergic reaction. Furthermore, a CDC report on acute allergic-type reactions among patients undergoing hemodialysis (4) supports this condition as a probable allergic-type reaction. Finally, the patient's respiratory condition recovered soon after the methylprednisolone administration. If he had suffered from heart failure, his respiratory condition would not have improved soon after steroid administration. The rationale for our administering steroid therapy was based on its anti-inflammatory effect, and a previous study reported the use of steroid medications for the management of allergic reactions (5). In addition, the possibility of stress cardiomyopathy was excluded because of his ventricular wall motion.

The second important clinical issue of note is that physicians should avoid the routine use of heparin, as hypersensitivity to heparin cannot be predicted and we cannot anticipate which patients may develop shock. In addition, confirming heparin-induced allergic hypersensitivity is difficult. If a DLST is performed soon after the onset of anaphylaxis, then the number of false negative results has been reported to increase (6). Therefore, we cannot deny any possible allergic reaction to heparin using the currently available tests. In this case, we first obtained negative result for heparin on a DLST, but verified the allergic reaction later. However, we did not identify any association between immediate-type hypersensitivity and a positive result of DLST at the second exam, even though heparin would likely affect the patient either prior to admission or after the start of intravenous injection. The allergological work-ups of immediate-type hypersensitivity reactions to heparin rely on skin prick and intradermal heparin testing, with readings after 15 to 20 minutes (7). However, since this test represents delayed reactions to subcutaneously injected heparin, we theoretically cannot evaluate immediate hypersensitivity reactions to systemically administered heparin. While the basophil activation test (BAT) has been proposed as a complementary method for the *in vitro* diagnosis of heparin allergy (8), researchers with experience in the field of heparin allergy repeatedly failed to detect heparin sensitization by BAT (7). As a result, no test able to prove allergic reactions to heparin is currently available. Therefore, it is important to understand the basis for these clinical events and to predict future occurrences.

In conclusion, heparin injection can cause a severe allergic hypersensitivity reaction during VA placement, and physicians should reconsider the routine use of heparin because it is impossible to anticipate which patients will develop hypersensitivity to heparin. Physicians should consider the risk of heparin-induced hypersensitivity and be ready to effectively manage it during VA placement, especially in outpatient settings.

The authors state that they have no Conflict of Interest (COI).

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