Journal of Cardiothoracic Surgery

CASE REPORT Open Access

A case of anaphylactic shock to human fibrinogen infusion during cardiac surgery

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Abstract
Human fibrinogen (FIB) has been clinically proven to be considerably effective for the treatment of postoperative bleeding, with reported cases of allergic reactions to human FIB being rare. Here, we report a case of an anaphylactic shock in 27-year-old patients with rheumatic heart valve disease who received a human FIB infusion during mitral valve replacement, aortic valve replacement, and tricuspid valve-shaping surgery. The patients showed generalised profuse sweating, a barely noticeable skin rash, faint pulse, systolic pressure < 50 mmHg, and a heart rate of 71 beats/min. We share insights from a case of severe allergy to human FIB infusion during cardiac surgery, through which we have gained experience in the processes of diagnosing and treating. This report aims to provide a preliminary summary of the characteristics of this case to serve as a reference for fellow clinicians.

Keywords Cardiac surgery, Human fibrinogen infusion, Severe allergic reaction

Introduction

Anaphylactic reactions are potentially serious systemic responses, either immunologic or nonimmunologic, that are typically rapid in onset, of variable severity, responsive to the timely administration of epinephrine, and rarely cause death [1]. Severe anaphylaxis is characterised by the compromise of breathing and/or circulation and most often, but not always, progresses from and is preceded by milder signs/symptoms [2]. There is some genetic tendency and individual distinction involved in these reactions [3]. Human fibrinogen (FIB) preparations are derived from the plasma of healthy individuals through a process that includes separation, purification, viral inactivation, and lyophilisation. The infusion of human FIB corrects hypofibrinogenemia and improves coagulation function disorder [4]. However, sporadic instances of adverse allergic reactions to it have been documented. Detailed below is such a case, marked by a severe allergic reaction precipitated by human FIB infusion.

Medical records

The patient was a 27-year-old woman at 30+weeks of gestation complicated with heart disease who underwent a caesarean section under spinal anaesthesia. The operation was successful, and a live baby boy weighing 3.5 kg was born. Postoperative intensive care unit care was given to the patient to adjust heart function and regular follow-ups were conducted after discharge. She was readmitted to hospital half a month after undergoing the caesarean section for further treatment. The patient had no history of allergic reactions to any medication or food and no history of a blood transfusion. Physical examination: The patient weighed 51.8 kg and was 162.5 cm tall, with an American Society of Anesthesiologists classification of III. Her body temperature was 36.6 °C, heart rate 117 times/min, respiration 19 times/min, and blood pressure 120/76 mmHg (1 mmHg=0.133 kPa). Laboratory

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examination: white blood cells, 20.14×10^{9}/L, red blood cells 5.15×10^{12}/L, and haemoglobin (Hb) 173 g/L; coagulation, liver, and kidney function, as well as electrolyte levels were generally normal. Five months previous, the patient had sought treatment for 'coughing for 15 days and having chest discomfort for 6 hours'. Check echocardiography tips: The left atrium was significantly enlarged (left and right diameters 98 mm, upper and lower diameters 90 mm, left atrium area approximately 70 cm^2), the left ventricle was enlarged, the right atrioventricular diameter was within normal range. Mitral valve: the anteroposterior diameter of the mitral annulus is 40 mm and the left and right diameters are 34 mm. The mitral lobe thickens, contracts, calcifies and increases echo, especially the obvious valve tip, junctional adhesion, the open diameter is about 7 mm, and the subvalvular tendon cord is thickened. Based on the limited nature of the valve opening, this area was estimated to be approximately 1.6 cm^2 using the cartography method, and the closure was seriously incomplete, as seen in Fig. 1. Tricuspid valve: no abnormality in morphology and structure, good opening, poor closure. Tricuspid valve: no abnormality in morphology and structure, good opening poor closure. Aortic valve: thickened lobe, good opening, open diameter 8 mm, poor closure, ring diameter 18 mm, sinus diameter 24 mm, sinus junction diameter 19 mm, ascending aorta diameter 28 mm. Pulmonary valve: structure, opening and closing are generally normal. In the systolic period, the forward flow velocity of the aortic valve increased, where Vmax=1.9 m/s, PGmax=15mmHg; a low-medium regurgitation signal was detected in the diastolic period, and the contractile part was 3.5 mm. In the diastolic period, the forward mitral flow velocity increased, the estimated valvular orifice area MVA (P1/2t)=1.2 cm^2, and the systolic probing and probing and a large number of regurgitation signals, with a regurgitation area of 24.4 cm^2. Systolic detection

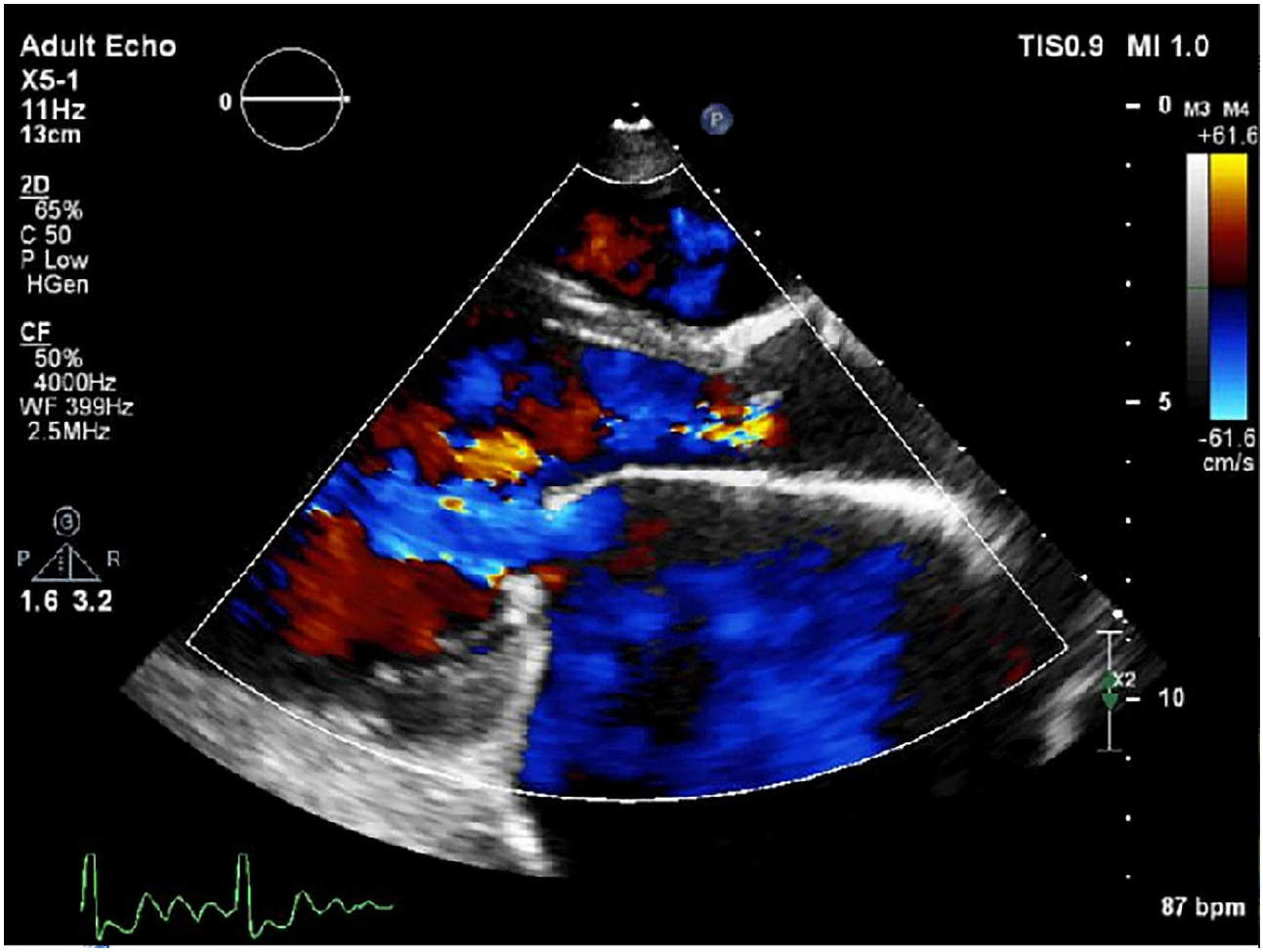

Fig. 1 Preoperative ultrasound diagnosis (mitral insufficiency). The anteroposterior diameter of the mitral ring was 40 mm, the left and right diameters were 34 mm, the lobe was thickened, contracture, calcification, and enhanced echo, especially with obvious valve tip, junction adhesion, open diameter about 7 mm, and thickened subvalvular tendinous cords. Due to the limited opening, the area of the valve opening was estimated to be about 1.6 cm^2 by the cartography method, and the closure was seriously unclosed

and a low tricuspid regurgitation signal, regurgitation area of 4.0 cm^2.

The patient was diagnosed with 'rheumatic heart valve disease: moderate mitral stenosis with severe insufficiency, moderate aortic valve insufficiency, severe tricuspid insufficiency, severe pulmonary artery hypertension, class-II cardiac function, and atrial fibrillation'. The patient was scheduled to undergo 'mitral valve replacement, aortic valve replacement, and tricuspid valve-shaping surgery'. Preoperative routine abstinence from drinking and eating was instigated, and communicate fully with patients before anesthesia to inform them of the nature of the surgery and the risks of surgery. Anaesthesia was induced using remimazolam at 6 mg/kg/h, remifentanil at 0.25 μg/kg/min, and rocuronium at 0.85 mg/kg. Remimazolam was adjusted by 1 mg/kg/h after loss of consciousness. A 7-cm midline chest skin incision was made. A sternal saw was used to perform a partial sternotomy from the right second intercostal space down to the xyphoid process. A 7-mm soft-flow aortic cannula was placed on the ascending aorta. Bicaval venous cannulation was performed using 22 Fr cannulas. The patient was placed on cardiopulmonary bypass with vacuum-assisted venous return. An aortic cross-clamp was placed, and cardiac arrest was achieved by cold-blood antegrade cardioplegia. Over 3 h into the surgery and 12 min after effecting cardiopulmonary bypass, an initial 'test dose' of 10 mg protamine was administered. The patient had no adverse reactions, and an injection of 400 mg protamine was used to neutralise heparin, and 1 g of human FIB (Jiangxi Boya Biopharmaceutical Group Co., Ltd., Lot No.: RX20211054) was dissolved in 50 mL of normal saline over 15 min by intravenous infusion. Roughly 2 min post-infusion, the patient experienced severe anaphylactic shock, with profuse generalised sweating, pale face, a barely noticeable skin rash, faint pulse, systolic pressure < 50 mmHg, and a heart rate of 71 beats/min. The FIB infusion, intravenous anesthesia and and the inhalation of anaesthetics were immediately stopped, as well as rapid infusions of crystalloid solution (compound electrolyte solution, 700 mL) and colloid (Polygeline, 200 mL) were administered, in addition to increasing the infusion rate of dopamine (from 0.5 to 1 μg/kg/min) and decreasing the infusion rate of milrinone (from 1.56 to 0.9 mg/h) during resuscitation. However, haemodynamics did not significantly improve. The cardiovascular collapse was initially considered to have had a surgical cause; however, no complex intracardiac complications were found upon examination by the surgeon at the surgical table or through postoperative transoesophageal echocardiography. Examination of the patient revealed skin flushing and swelling in the head and facial area; the anaesthesia machine showed an increase in peak airway pressure from 13 to 21 cm HO_2, and urgent venous blood gas analysis indicated pH 7.3, pCO2 42 mmHg, PaO2 47 mmHg, haematocrit 45%, Hb 16.2 g/dl, and base excess −5.7 mmol/L. A diagnosis of anaphylactic shock was immediately made, with adjustments to increase oxygen concentration and oxygen flow. Concurrently, 40 mg of methylprednisolone was administered intravenously, as well as 1 mg of adrenaline (Shanghai Hefeng Pharmaceutical Co., Ltd., Lot No.: 10,210,406), diluted with normal saline to 10 ml, at a concentration of 0.1 mg/ml by intravenous injection. The infusion speed was accelerated, and an additional 500 mL of Polygeline was administered. Approximately 20 min later, circulation was comparatively stabilised. During surgery, the patient was administered a total of 2,440 mL of fluids, with a blood loss of 600 mL and urine output of 1,780 mL. Post-surgery, the patient was transferred to the intensive care unit. The tracheal cannula was removed on the first day after the operation and the patient was discharged successfully on day 8. One month later, during a follow-up visit, her condition was found to be generally good. Apart from protamine, no other drugs that could cause allergies had been used before the allergic reaction. A residual heparin effect was found by conducting viscoelastic tests, and no allergic reaction occurred after using 100 mg protamine again, approximately 40 min post-correction of the anaphylactic shock. Therefore, we attribute the allergic reaction to FIB. To diagnose the allergic reaction to FIB more accurately, FIB immunoglobulin E (IgE) antibody was tested one week after the incident, and the result was positive. This case report was approved by the Ethics Committee of our hospital and the patient signed an informed consent form.

Discussion

Human FIB is a plasma glycoprotein synthesised and secreted by the liver and extracted from the blood of healthy individuals. It mediates platelet aggregation and participates in the late stage of the coagulation process. Thrombin converts FIB into fibrin monomer and forms fibrin polymers under the action of factor VIII, thus achieving biological haemostasis in surgeries [5]. The physiological haemostatic function of FIB is carried out through its conversion to fibrin by the action of thrombin [6]. Lasky et al. [7] reported the efficacy of human FIB concentrate in treating bleeding events and perioperative haemostasis in ≥97% of minor surgeries and ≥98.5% of major surgeries. During cardiopulmonary bypass heart surgery, the patient's blood comes into contact with a large number of non-physiological surfaces and the blood components are destroyed, resulting in abnormal clotting function, especially when the deep hypothermia stops blood circulation and consumes a large number of blood cells, clotting factors and platelets [8]. Prolonged cardiopulmonary bypass can damage plasma FIB content and

activity, increase perioperative blood leakage, and often require large numbers of allograft transfusions. Due to the limited reserve of FIB in the body, its level decreases to 1.5–2.0 g/L, which impairs coagulation function and increases the possibility of bleeding complications. In the present study, a normal saline solution pre-warmed to 30℃–37℃ was used to make a transparent solution after re-dissolution, which was mainly administered to treat FIB reduction or deficiency by intravenous infusion through an infusion set equipped with a filter. The patient suffered from blood damage and FIB deficiency due to the application of extracorporeal circulation during surgery, which aligned with the indications in the drug instructions, and the dosage was also in accordance with the requirements.

Allergic reactions or fever do not often occur in adult patients when human FIB is used; such adverse reactions in children and neonates are even fewer, with only one reported case of an allergic reaction in a newborn after receiving human FIB [9]. Compared to fresh frozen plasma and cryoprecipitates, FIB is considered safer for achieving haemostasis and presents a lower risk of fluid overload and pathogen transmission [10].

In this adult case, no adverse reactions associated with the infusion of the blood product prothrombin complex concentrate were observed. However, significant allergic reactions occurred after the transfusion of human fibrinogen, characterised by a drop in blood pressure, increased heart rate, hypoxemia, and swelling of the head and face. Without timely intervention, this can swiftly progress to life-threatening conditions such as laryngeal oedema and severe bronchospasm. Anaphylactic shock is a severe systemic hypersensitivity reaction with a rapid onset that can be life-threatening or fatal [11]. Such conditions result from the interaction between certain specific antigens and sensitised IgE antibodies, which subsequently abnormally activate mast cells and basophils, leading to disorder of the neurohumoral regulatory system. Laboratory testing conducted during or shortly after the acute event can help to support the clinical diagnosis of anaphylaxis and can help in the differential diagnosis of anaphylaxis, for example, severe asthma or myocardial infarction. In addition, these tests may provide evidence for anaphylaxis as a cause of death. Available tests for the detection of the following mast cell and basophil mediators are available: tryptase (serum/plasma), histamine (plasma), the histamine metabolite, N-methylhistamine (urine), leukotrienes, LTC4 metabolite, and LTE4 (urine) [12]. The severity of allergic reactions is related to genetic predispositions, the properties of the allergen, the route of entry into the body, T-helper cells, and the involvement of cytokines [13]. During the occurrence and progression of allergic diseases, extensive capillary leakage is one of the main factors leading to disease progression and various severe complications. It is now believed that this capillary leakage is a result of pathological responses mediated by the inflammatory cells and mediators involved in allergic inflammation, which damage the integrity of the vascular endothelial barrier. The therapeutic strategies for allergic reactions and anaphylactic shock mainly include the elimination of allergens, dynamic monitoring of vital signs, anti-shock treatment (adrenaline, fluid resuscitation, blood pressure control), and anti-allergy treatment. After a systemic allergic reaction, plasma extravasation can account for up to a 35% loss of total circulating blood volume within only 10 min, leading directly to hypovolemic shock and further potential damage to organ systems throughout the human body [14]. In conclusion, enhanced management should be performed when using FIB clinically, particularly in the first 30 min following its administration. Early detection and treatment of allergic responses are crucial. A thorough medical history should be gathered before surgery, and particular caution is warranted when using FIB in patients with an allergic constitution.

Acknowledgements
Not applicable.

Author contributions
Conception and design of the work: Xu C; Data collection: Wang WP; Analysis and interpretation of the data: Xu C, Wang WP; Drafting the manuscript: Xu C; Critical revision of the manuscript: all authors; Approval of the final manuscript: all authors.

Funding
The authors have received no financial support for the research, authorship, or publication of this manuscript.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This case report was approved by the Ethics Committee of Shanghai DeltaHealth Hospital and the patient signed the informed consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 23 April 2024 / Accepted: 30 June 2024
Published online: 05 August 2024

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