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Anaphylactic Shock Cased by Hemocoagulase *Agkistrodon*: A Case Report

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Abstract

Hemocoagulase Agkistrodon, a thrombin-like enzyme derived from the venom of the *Agkistrodon acutus* snake, has been employed in clinical practice as a hemostatic agent. Herein, we report a case of anaphylactic shock triggered by hemocoagulase *Agkistrodon*. A 32-year-old woman underwent diagnostic dilation and curettage with cervical tissue biopsy procedure under general anesthesia and experienced anaphylactic shock following the postoperative administration of hemocoagulase. Instances of hemocoagulase *Agkistrodon*-induced anaphylactic shock were rarely documented. Therefore, unexplained gastrointestinal symptoms and hypotension in patients receiving hemocoagulase *Agkistrodon* should prompt consideration of this possibility.

Keywords: Hemocoagulase *Agkistrodon*; Allergy; Anaphylactic Shock; Diagnostic dilation and curettage with cervical tissue biopsy procedure

Introduction

Hemocoagulase *Agkistrodon* (HCA), is a Thrombin-like Enzyme (TLE) isolated and purified from *Agkistrodon acutus* venom. Currently, TLE have been widely used to prevent and stop surgical bleeding [1]. In 2009, Hemocoagulase *Agkistrodon* for injection was approved to clinically prevent clotting in superficial wound bleeding during surgical procedures in China [2]. In a phase III clinical trial involving 432 consecutive adult patients conducted at multiple centers, the prospective, randomized, controlled, double-blind study demonstrated that HCA exhibits a robust capability for hemostasis and coagulation. It was observed to be a safe option for managing capillary hemorrhage during incisions in abdominal surgeries [3].

Anaphylaxis is a critical systemic hypersensitivity reaction known for its swift onset and potential lethality. Severe cases manifest as a life-threatening compromise in airway, breathing, and/or circulation, and may occur even in the absence of typical skin features or circulatory shock [4]. The most frequent elicitor groups worldwide are food, insect venom, and drugs [4]. HCA, being an animal-venom, has been associated with reported instances of hypersensitive reactions following its use [5,6]. In this paper, we report a case of anaphylactic shock induced by hemocoagulase *Agkistrodon*. The incident occurred following uterine conization under general anesthesia, with the administration of hemocoagulase postoperatively to address hemorrhage. This patient experienced classic gastrointestinal symptoms along with manifestations of shock.

Case Presentation

A 32-year-old woman was admitted to the hospital due to experiencing lower abdominal distension accompanied by increased vaginal discharge for the past 3 months. The patient underwent diagnostic dilation and curettage with cervical tissue biopsy procedure under general anesthesia without intubation due to chronic cervicitis on January 15th, 2024. The patient entered the operating room at 11:45, where intravenous access was established in the cephalic vein at the wrist, and lactated Ringer's solution infusion was initiated. Anesthetic induction began at 12:00, with the administration of 80 μg of fentanyl and 100 mg of propofol. The surgical procedure commenced at 12:05 after the patient lost consciousness. The surgery concluded at 12:10, and the patient regained consciousness at 12:13. During the perioperative period, vital signs remained stable, and there were no adverse events. The patient returned to the ward from the operating room at 13:00. Twenty minutes later, the administration of HCA commenced, dissolved in 100 ml of 0.9% sodium chloride

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Table 1: Blood gas analysis.

Project	13:38 (During Anaphylaxis)	14:11 (Post Anaphylaxis)
PH value	7.26	7.42
Arterial partial pressure of oxygen, PaO_2 (mmHg)	39	219
Arterial partial pressure of carbon dioxide, $PaCO_2$ (mmHg)	38.6	25.2
Hematocrit, HCT (%)	47	40
Sodium, Na^+ (mmol/L)	138.0	135.0
Potassium, K^+ (mmol/L)	3.05	3.70
Chloride, Cl^- (mmol/L)	104	103
Calcium, Ca^{2+} (mmol/L)	1.93	1.17
HCO_3^- (mmol/L)	16.7	15.9
Actual base excess, ABE (mmol/L)	-9.5	-6.8
Standard Base Excess, SBE (mmol/L)	-9.0	-7.8
Anion Gap, AG (mmol/L)	16.7	16.8
Fraction of inspiration O_2, FiO_2 (%)	21	45
Lactic acid (mmol/L)	3.9	2.1

injection. At 13:30, the patient described feeling nauseous with the urge to vomit, abdominal pain, and accompanying numbness in the lips. Simultaneously, the monitoring system indicated a decrease in blood pressure from the initial 113/70 mmHg to 80/45 mmHg, with the heart rate increased from 75 beats per minute to 120 beats per minute (bpm), saturation of peripheral oxygen was 90%, and displaying a continuous worsening trend. Promptly proceed with arterial blood gas analysis (Table 1) and bedside Electrocardiogram (ECG) examination. At that moment, the physician considered the reflex induced by cervical traction, subsequently opting for the intravenous injection of 10 μg of norepinephrine twice. However, the situation did not ameliorate; the blood pressure persisted in declining to 60/40 mmHg, accompanied by a rapid heart rate of 160 bpm (Figure 1). At this juncture, the patient exhibits an altered level of consciousness, accompanied by episodes of vomiting and skin flushing. At 13:52, epinephrine (0.2 mg) was administered, and additional intravenous access points were established: One for the administration of promethazine (25 mg) and the other for Ringer's solution (500 mL). Despite these interventions, the patient's blood pressure did not normalize. Auscultation detected crackles and wheezing in both lung fields. A second dose of epinephrine (0.2 mg) was administered at 13:58. The patient's vital signs gradually stabilized.

Blood gas analysis indicated an elevation in her lactic acid level to 3.9 mmol/L. Preoperative routine examinations revealed the patient's cardiac function to be satisfactory. Hematological parameters, such as creatine kinase-MB and troponin I, were within normal limits (Table 2), thus ruling out cardiogenic shock. After her circulation stabilized, she remained under observation for an additional day without displaying any abnormalities. The child remained without sequelae after being discharged home with instructions for allergy monitoring.

Discussion

Anaphylactic shock caused by drug reactions is not uncommon and can be triggered by various substances such as analgesics, antibiotics, biologics, and contrast media, among others [4,7]. The patient involved in this case was a 32-year-old woman, characterized as a young individual with no prior history of cardiopulmonary

Table 2: Serological index.

Project	January 11 (Pre-operation)	January-15 (Post Anaphylaxis)
White blood cell count, WBC (× 10^9/L)	6.56	7.52
Neutrophil count (× 10^9/L)	3.78	3.19
Lymphocytes count (× 10^9/L)	2.30	4.06
Monocyte count (× 10^9/L)	0.39	0.24
Eosinophil count (× 10^9/L)	0.07	0.03
Basophil count (× 10^9/L)	0.02	0.0
Percentage of Neutrophil (%)	57.6	42.4
Percentage of Lymphocytes (%)	35.0	54.0
Percentage of Monocyte (%)	6.0	3.20
Percentage of Eosinophil (%)	1.1	0.4
Percentage of Basophil (%)	0.3	0.0
Red blood cell count, RBC (× 10^{12}/L)	4.06	3.98
Hemoglobin (g/L)	123.0	124.0
Hematocrit, HCT (%)	37.4	37.3
Platelet count (× 10^9/L)	284.0	257.0
Myoglobin (ng/ml)	-	15.06
Creatine Kinase isoenzymes, CK-MB (ng/ml)	-	<1.5
Troponin I (ng/ml)	-	0.01

diseases. And the patient had no prior history of atopy, asthma, or allergic reactions to either drugs or food. The preoperative physical examination revealed no notable findings. Serological tests and an ECG were performed during the episode of anaphylactic shock, confirming the absence of hemodynamic instability associated with cardiac issues. In contrast to conventional understanding, an elevation in both the quantity and percentage of lymphocytes in the serum was observed, accompanied by decreased percentage of eosinophils (Table 2). The administration of HCA infusion commenced one hour after the operation for the patient. The decrease in blood pressure and the elevation in heart rate induced by propofol and fentanyl can be mitigated. HCA (1 Unit) was dissolved in 100 ml of 0.9% sodium chloride injection. The instructions for HCA usage specify dissolving it with water for injection and administering it *via* slow intravenous injection. In practical clinical applications, a common approach involves using 0.9% sodium chloride injection for the preparation of HCA for injection [5,8]. There were rarely any reports of allergic reactions caused by 0.9% sodium chloride injection.

To gather relevant information, a comprehensive search was independently conducted in databases including PubMed, Medline, Embase, and the Cochrane Library (latest update as of January 28th, 2024), with two reports of allergies caused by HCA [5,6]. A case of severe anaphylactic shock occurred in a 5-year-old child undergoing scheduled surgery for the removal of a right femoral intramedullary nail [5]. Within 5 min of the intravenous bolus injection of 1 unit of HCA, the patient developed a widespread transient diffuse erythema on the anterior chest. Subsequently, after 20 min, a sudden and profound cardiovascular collapse ensued. In this case, HCA was administered between anesthesia induction and skin incision, however, other potential causes and drug-induced allergies, particularly narcotics, cannot be ruled out. Another report presented a case of a 41-year-old woman who experienced anaphylactic shock attributed to HCA prior to undergoing surgery for colon cancer [6]. The patient refrained

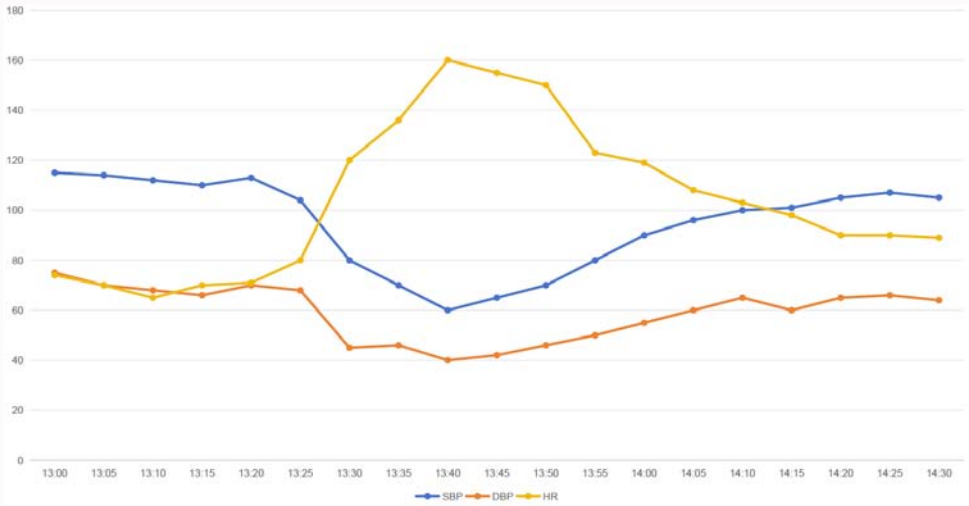

Figure 1: Blood pressure and heart rate during shock. The minimum blood pressure recorded was 60/40 mmHg, with a heart rate of 160 bpm, observed approximately 20 minutes after the initiation of HCA infusion during the shock.

from using any medications prior to the procedure. However, shortly after the administration of 2 units of HCA over a span of 3 min, the patient encountered a sudden onset of anaphylactic shock. It has been reported that the patient exhibited symptoms of shock following the administration of HCA eight minutes, resembling those we previously reported (ten minutes). The initial symptoms observed in the patient we reported were gastrointestinal, including nausea, abdominal colic and vomiting. Indicators of anaphylaxis include gastrointestinal symptoms (severe crampy abdominal pain, repetitive vomiting), especially following exposure to non-food allergens. Treatment is warranted without the condition having to persist, aligning with the grading system for allergic reactions employed by the U.S.-based Consortium of Food Allergy Research [9].

When the patient experienced anaphylactic shock, a venous blood test was conducted. Compared to four days before the operation, the blood routine examination indicated an increase in both lymphocyte count and percentage, coupled with a decreased percentage of eosinophils (Table 2). Relative lymphocytosis, characterized by a rise in lymphocytes exceeding 40% with a normal absolute white blood cell count in adults [10,11], can serve as an indicator of various conditions. It may denote infection, such as acute viral or bacterial infections, as well as be indicative of inflammation, or associated with connective tissue disorders [10]. Subsequent studies have demonstrated the involvement of eosinophils and lymphocytes in the development of atopic dermatitis [12,13]. The patient's lymphocyte levels were within the normal range preoperative, and the subsequent rise in both proportion and count did not rule out the possibility of infections. In patients referred for uncontrolled asthma, blood measures of eosinophils exhibited variability with distinct patterns [14], only the proportion of eosinophils increased in this patient we reported.

Conclusion

When patients using HCA experience unexplained abdominal symptoms, they should remain vigilant for the possibility of allergic reactions. Detailed clinical manifestations and history, along with laboratory findings, will provide clues for the diagnosis of this disease. Attention should be focused on potential Adverse Drug Reactions (ADRs). Additional research and alternative clinical prophylactic measures should be explored to prevent ADRs and ensure patient safety.

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