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CASE REPORT

Anaphylaxis Following Contrast-Enhanced CT with Iodixanol: A Case Report and Literature Review

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Background: Iodixanol-induced anaphylactic reaction is a well-known adverse event of contrast agents, which are generally well-tolerated and reversible. Serious and fatal reactions such as anaphylactic shock after computed tomography (CT) enhancement have been described. However, there is no data on these events in the literature.

Objective: This report describes a case of a serious anaphylactic reaction, possibly related to iodixanol and provides an overview of case reports.

Case Summary: A 47-year-old women who experienced persistent abdominal pain for more than one month, was proposed of hiatal hernia with CT images taken two weeks previously and was admitted to the gastrointestinal surgery department. The patient underwent contrast-enhanced abdominal CT for the evaluation of multiple intraperitoneal hemodynamic features. A few minutes after abdominal enhanced CT scan, the patient was pale, sweating, had muscle tension and trembling, even coma and profound hypotension with 90/43 mm Hg. Immediately she was supported with oxygen inhalation, was treated with adrenaline subcutaneously, dexamethasone intravenously, and rapid intravenous drip of compound sodium chloride. Ten minutes later, the patient was in respiratory and cardiac arrest and the pupils were dilated. CPR and intermittant static push of 1 mg adrenaline were immediately carried. After endotracheal intubation, the patient's spontaneous heart rate and pupils recovered, and her blood pressure recovered to 105/53 mm Hg. It was suggested that the patient was suffering from iodixanol-induced anaphylactic shock and nephropathy, and she was transferred to the intensive care unit. Despite immediate treatment, the patient died.

Conclusion: A 47-year-old female patient with no history of allergies developed severe fatal anaphylactic shock after receiving iodixanol. Although contrast agents induced anaphylactoid/anaphylactic reactions do not often occur, clinicians should be conscious of the potentially serious anaphylactic reaction, which could lead to a life-threatening or fatal event.

Keywords: radiocontrast media, iodixanol, anaphylaxis, shock, nephropathy

Introduction

Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems.[1] Despite common clinical features, the underlying mechanisms of anaphylaxis may vary. Nevertheless, some of the activated pathway may be common to different types of anaphylaxis reactions or be present simultaneously. Based on the involvement of IgE, anaphylaxis is subclassified into IgE-mediated and not IgE-mediated reaction. IgE-mediated anaphylaxis is considered the classic and most frequent. Tryptase, a neutral serine protease which is released from secretory granules of mast cells (MCs), is the gold standard laboratory test for the diagnosis of IgE-mediated anaphylaxis.[2] Non-IgE-mediated anaphylaxis is generally nonallergic hypersensitivity reactions resulting from nonspecific MC and/or basophil degranulation.[3] Anaphylactic shock is one of the most serious of all allergic reaction and even can be fatal. Although death from anaphylactic shock is uncommon and most episodes of anaphylaxis can generally be reversed by a single dose of epinephrine, severe anaphylactic shock accompanied with cardiovascular collapse can be resistant to treatment and can lead to death.[4]

The main cause of anaphylaxis is drugs, including radiographic contrast medium (RCM). With the widespread use of computed tomography (CT) scans, iodinated contrast medium (ICM) is used about 75 million times per year worldwide.[5]

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Compared to high-osmolality ionic contrast agents, low-osmolality ones are well-tolerated and have fewer cardiovascular and anaphylactic reactions.[6] However, serious and life-threatening adverse events such as anaphylactic shock and anaphylactic deaths still occur with RCM use.[7] Moreover, acute anaphylactic reactions, such as bronchospasm, profound hypotension, and severe urticarial have been reported to have occurred within minutes after RCM administration. RCM-related adverse reactions range from mild and self-limiting to severe and life-threatening events. Although other imaging can be used as an alternative test in RCM hypersensitivity patients, CT imaging has its own advantage and unavoidable in some clinical situations. RCM-induced anaphylactic shock is a rare complication of contrast-enhanced CT whose incidence is 1% or less. Antihistamines, corticosteroids, epinephrine have been used as preventive measures. However, RCM induced anaphylactic emergency, damage and death cannot be complete prevented.[8,9] Currently, there are no established guidelines on premedication for RCM induced anaphylaxis.[10] Furthermore, only a few cases of RCM-induced anaphylactic shock using iodixanol, an iso-osmolar non-ionic contrast agent, have been reported up to now.

This report describes a case of an anaphylactic shock that manifested as acute bronchospasm, profound hypotension, and pulmonary edema. That was considered to probably non-IgE-mediated anaphylaxis related to iodixanol administration. The report also reviewed the literature from reported cases of iodixanol-induced adverse reaction to find whether others has experienced the same serious events.

Case Report

A 47-year-old woman was hospitalized suffering from persistent abdominal pain for nearly a month. The patient had suffered from calculus of intrahepatic duct and gallbladder prior to admission and underwent a CT scan two weeks previously. The patient was suffering from a hiatal hernia in most of the stomach and the beginning of the duodenum and mesangium located above the diaphragm and part of the intestinal wall was slightly thickened.

To evaluate the causes of abdominal pain, the content of esophageal hiatal hernia into the thoracic cavity and ischemic necrosis of abdominal content, a contrast enhanced CT of the abdomen was performed. For this procedure, the patient received a total of 70 mL of iodixanol intravenously (Visipaque 320, GE Healthcare, Cork, Ireland). The result showed that the patient had an esophageal hiatal hernia with gastric turnover, a left inguinal hernia, increased mesangial lymph nodes in ileocecal region and calcification in the left lateral lobe of the liver or intrahepatic bile duct stones. However, after 5 minutes of the procedure, the patient became pale with sweating, muscle tension and trembling followed by complaining of general numbness, she subsequently developed hypotension (BP 90/43 mm Hg), dyspnea and cardiac respiratory arrest. The patient was immediately treated with delivery of oxygen, received adrenaline 1 mg subcutaneously and further treatment with dexamethasone 5 mg, and rapid intravenous drip of compound sodium chloride. After BP value up to 117/68 mmHg, the patient was urgently transferred from the CT scan room to the ward. However, the patient was reanimated again with dilated pupils and cardiac arrest. Finally, she had not yet recovered consciousness and was transferred to the intensive care unit (ICU).

The patient remained unconscious and was given endotracheal intubation and ventilator to assist breathing (FiO2, 100%) in the ICU. Electrocardiogram (ECG) monitoring result showed that her heart rate (HR) was 63 bpm, the lowest BP value was 58/38 mm Hg and SpO2 was 100%. Both pupils were equal in size and circle, with a diameter of 1.5 mm, and the light reflection was disappeared. The respiratory sound of the lungs was thick, no rales were heard, the heart rate was fast, the heart sounds were unequal, and the rhythm was uneven. The muscle strength test of limbs showed no response, and there was no edema in the lower limbs. Analysis of arterial gas indicated: pH 7.06, PO_2 599mmHg, PCO_2 28mmHg, Na^+ 127 mmol/L, K^+ 2.9 mmol/L, Lac 11.6 mmol/L, HCO^{3-} 7.9 mmol/L. With the consent of family members, right femoral vein catheterization was performed under local anesthesia. After active rehydration, pressor, anti-shock and anti-allergy (norepinephrine pump 8 mL/h, 10 mg/50 mL and pituitary vasopressin pump 1 mL/h, 30U/50 mL), BP value of the patient was 118/80 mmHg, HR was 80 bpm, SpO2 was 96%, and the patient still remained coma. Laboratory evaluation showed a white blood cell count of 13,720/μL with 88.3% neutrophils. Aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) were 47 U/L (normal ≤ 32 U/L) and 499 U/L (normal 135–214 U/L). The level of serum tryptase was 5.38 ng/mL (<20 ng/mL). Serum potassium concentration of the patient decreased to 3.06 mmol/L. The patient was treated with adding alkali based on blood pH and correcting electrolyte turbulence. Contrast-induced nephropathy (CIN) is a serious complication of angiographic procedures and results from administration of RCM.[11]

Table 1 Summary of Case Reports of Anaphylactic Reactions and Organ Damage Related Iodixanol

Report	Age, y	Sex	Patient Characteristics	Iodixanol Injection/Onset of Adverse Reaction	Presentation	Outcome
Tokiyoshi et al (2002)[21]	79	F	Right recurrent nerve plasy	50 seconds after contrast medium bolus injection	Apneic, fatal anaphylactoid shock, marked laryngeal edema and extensive mast cell infiltration	Cardiopulmonary resuscitation, but died
Won-Wook et al (2004)[22]	45	M	Substernal pain, cardiac catheterisation	5 minutes after iodixanol to the left coronary	Itching, dizziness, urticarial, cyanosis, hypotension	Fluid resuscitation and vasopressors, recovered 1 hour later
Alcoceba et al (2009)[23]	61	M	Thoracic pain, cardiac catheterisation	300 mL of iodixanol, 5 minutes after receiving iodixanol	Itching, heat, dyspnea and cardiac respiratory arrest	Hospitalized in ICU, improved at 48 hours
Emiliano et al (2011)[24]	76	F	Coronary artery disease, recurrent transient ischemic attacks		Aphasia, stupor, and full hemiparesis	Anti-edema drugs, recovery within 48 hours
Jun et al (2017)[25]	58	F	Multiple intracranial aneurysms, hypertension, hypothyroidism, peripheral, arteryocclusive disease	220 mL of iodixanol, a few hours after procedure	Fever, sulcal obliteration of right cerebral hemisphere, left hemiparesis involving face, arm and leg (grade 3/5), sensory loss, and left-sided neglect with drowsy mentality	Hydration with enough fluid, and intravenous dexamethasone, mannitol and anticonvulsant, recovered on day 6

Abbreviations: F, female; M, male; NR, not report; ICU, intensive care unit.

The laboratory investigation showed significant reduction of radioactive drug uptake in kidneys and iodixanol-related nephropathy.

The patient was hospitalized in ICU for improving. After the patient's symptoms were relatively stable, she was transferred to the ward and changes to her condition were closely observed. During hospitalization, the patient underwent acute heart failure, arrhythmia, multiple bacterial infections of the lungs, encephalopathy, electrolyte disturbances. Finally, sudden cardiac arrest occurred after cardiopulmonary resuscitation and the patient died three months later.

Literature Review

In general, an allergic reaction to iodixanol is uncommon, but in rare cases it can be life-threatening. We performed a literature review to find whether other patients had experienced the same serious symptom, including anaphylactic reactions. Literature searches written in English were conducted through PubMed and Google scholar between 2002 to 2022. Finally, 6 articles (with a total of 6 cases) reporting iodixanol-associated anaphylaxis were found. Detailed information on the dose of iodixanol, the time period between iodixanol administration and anaphylactic reactions, clinical manifestations and outcomes of these reaction was available in 6 case described in case reports and is summarized in Table 1.

Discussion

Anaphylaxis is an unexpected, sudden, and sometimes lethal event, usually induced by exposure to drugs, nutrients and contrast media in this case. The number of cases of anaphylactic reactions are increasing rapidly[12] and 75% of cases have no previous history of allergy.[13] The study of Korean tertiary care hospital has shown that RCM was the most commonly anaphylaxis involved drug.[14] Currently, high-osmolality ionic contrasts have been replaced by low-osmolality non-ionic ones, which contributes to the decreased incidence of RCM-related adverse events, but anaphylactic death still occurs. Anaphylactic shock is the most severe form of RCM induced hypersensitivity and can be life-threatening if combined

with profound hypotension. However, the clinical characteristics and risk factors for the development of anaphylaxis accompanied by hypotension (anaphylactic shock) are not clearly elucidated.

Anaphylaxis is a severe immediate systemic hypersensitivity reaction with a trigger, and is characterized by life-threatening airway, breathing, and/or circulatory problems and may cause death. It remains a clinical diagnosis and the World Allergy Organization (WAO) published diagnostic criteria based on clinical parameters.[1] The current gold standard laboratory test involves measurement of serum total tryptase during an acute phase (ideally within 1–2 h, but up to 4 h) followed by a baseline measurement (≥24 h after the event).[15] Although a rise in serum total MCs tryptase is diagnostic, this is not seen in all cases of anaphylaxis. There are cases of IgE-mediated anaphylaxis where no significant tryptase increase is present, such as the case in our report. Furthermore, based on the involvement of IgE, anaphylaxis is subclassified into IgE-mediated and not IgE-mediated reaction. The allergic IgE-mediated mechanism of anaphylaxis has been continuously discussed for decades. IgE antibodies play an important role in anaphylaxis and other allergic diseases. IgE is found at much higher levels in patient with anaphylaxis than in healthy subjects. However, IgE levels alone do not explain a subject's susceptibility to anaphylaxis. In fact, a considerable percentage of patients who experience anaphylaxis do not present with any evidence of IgE-mediated activation of MCs.[3] Indeed, in the absence of IgE, anaphylaxis can still develop in mouse models. Taken together, the presence of antigen-special IgE antibodies cannot indicate that the patient necessarily will exhibit clinical reactivity, and anaphylaxis may exist with undetectable levels of circulating IgE in other potential mechanism pathways.[16]

Intravenous and arterial ICM is used to enhance the visibility of blood vessels and is considered as invaluable tools in the diagnosis of anatomic lesions. After administration, the RCM in the body is mainly excreted through the kidneys.[17] Hypersensitivity reaction to ICM have been reported to occur in a frequency of about 0.5–3% of patients receiving ICM. The diagnosis and management vary among guidelines published by various national and international scientific societies, with recommendations ranging from avoidance or premedication to drug provocation test.[18] It is suggested that fewer than 10% of cases evaluated after having an immediate reaction after ICM administration are finally confirmed as having hypersensitivity.[19] Although many question remained unclear, recently reported cases highlight that pharmacological premedication is not safe to prevent ICM hypersensitivity in patients with previous severe reactions. In general, if a patient has a previous hypersensitivity reaction to ICM, the culprit preparation should be avoided and a new contrast test needs to be performed. In case of a positive reaction, a skin test-negative product should be chosen by testing a panel of several different ICM. The presence of IgE-mediated ICM allergy has been long debated, yet the identification of specific anti-ICM IgE in the sera of patient, positive basophil activation tests, and immediate skin test positivity are arguments. A recent study demonstrates that skin testing for suspected ICM mediated hypersensitivity reaction is useful and can identify safe alternatives for further real-life setting injections of ICM.[20] These data support approaches based on clinical history and skin testing to guide ICM re-exposure.

Conclusion

Our reports and literature show that even iodixanol, an iso-osmolar non-ionic contrast agent, can cause contrast-induced non IgE-dependent anaphylactic shock without a significant increase in serum tryptase. The administration of ICM should be avoided in patients who have experienced a reaction to any agent. Although skin testing for suspected ICM-mediated hypersensitivity reaction could be useful, physicians should not rely on the result of skin test or the efficacy of premedication, and the attendant to the radiology department and the hospital emergency response team must be adequately prepared to handle these emergencies as they occur.

Consent for Publication

The authors certify that they have obtained all written patient consent forms from the spouse of deceased patient. In the form, the patient's spouse gave consent for clinical information to be reported in the journal. The case details are open access and can be browsed without institutional approval.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the

current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work the work and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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