



A case of gadobenate dimeglumine-induced anaphylactic shock: a case report

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Abstract: A 70-year-old man was admitted to our hospital due to “liver cirrhosis; grade 3 hypertension; pulmonary infection”. On May 27, 2019, during upper abdomen plain and enhanced magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP), the patient experienced anaphylactic shock, manifested as sudden unconsciousness and lack of response, after intravenous administration of gadobenate dimeglumine (Multihance[®]). Gadobenate dimeglumine is a paramagnetic contrast used during diagnostic MRI. It has hepatobiliary specificity with very good imaging performance. A small amount is absorbed by normal liver cells after intravenous injection and excreted via the bile ducts while maintaining the chemical structure of gadobenate dimeglumine. It allows the visualization of local angiogenesis and perfusion, which reflect the hepatic blood supply and recent liver function, thereby providing a reference for clinical diagnosis. Gadobenate dimeglumine intravenous injection may cause adverse reactions such as nausea, dizziness, and anaphylactic shock. Anaphylactic shock is a known serious adverse reaction of gadobenate dimeglumine injection. In this paper, we report a case of gadobenate dimeglumine-induced anaphylactic shock based on the temporal relationship between the onset of symptoms and the injection. The patient received chest compressions and balloon-assisted ventilation in addition to rehydration and volume expansion and vasoactive drugs to maintain blood pressure, etc. The patient died despite treatments. In the clinical, physicians, nurses, and clinical pharmacists should closely monitor patients and promptly discontinue drug administration and provide symptomatic care in case of adverse reactions.

Keywords: Magnetic resonance imaging (MRI); gadobenate dimeglumine; anaphylactic shock; case report

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Introduction

In modern medicine, precise diagnosis and treatment increasingly depends on imaging. As an imaging technique, magnetic resonance imaging (MRI) is advancing rapidly and has become widely used in recent years. Gadobenate dimeglumine is a commonly used contrast in enhanced MRI that helps clarify the number of lesions, identify lesions that may be missed on plain scans, distinguish tumors and surrounding edema, and facilitate qualitative diagnosis. Gadobenate dimeglumine is clinically indicated for the

differential diagnosis of liver cancer and cholangiocarcinoma (1-4), but attention must be paid to its safety as it has been reported to induce anaphylactic shock (5). In this paper, we will report a case of gadobenate dimeglumine-induced anaphylactic shock. Unfortunately, the patient, who had cirrhosis, died despite treatment. Healthcare professionals should closely monitor patients for serious adverse reactions associated with gadolinium contrast agents.

We present the following article in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/apm-21-1076>).

Case presentation

A 70-year-old man visited the local hospital in April 2019 for unexplained fatigue and cough. He had no chest tightness, shortness of breath, chest pain, heart palpitations, skin or sclera jaundice, anorexia, abdominal distension, vomiting of blood, or black stools. Laboratory tests showed white blood cells (WBCs) $4.24 \times 10^9/L$, hemoglobin 115 g/L, platelets $53 \times 10^9/L$, total bilirubin 36.7 $\mu\text{mol/L}$, albumin 32.9 g/L, alanine aminotransferase 31 U/L, aspartate aminotransferase 51 U/L, and prothrombin time (PT) 14.9 s. Computed tomography (CT) showed liver cirrhosis and splenomegaly. His symptoms improved after liver-supporting and jaundice-reducing care. On May 15, 2019, the patient was admitted to the Department of Infectious diseases at our hospital for “liver cirrhosis; grade 3 hypertension; pulmonary infection”. He had a history of hepatitis E with successful treatment and a history of chronic hypertension. In April 2019, he was considered to have type 2 diabetes as laboratory tests performed at the local hospital showed elevated blood glucose. He had no known history of infectious diseases, such as tuberculosis, hepatic distomiasis, or schistosomiasis; chronic diseases, such as coronary heart disease or kidney disease; blood transfusion or blood transfusion reactions; major trauma and surgery; or allergies to food or drugs. A physical examination performed at admission showed that he was conscious and able to appropriately respond to questions, with normal orientation and numeration ability. He had no pale or yellow complexion. Additional exams showed palmar erythema (+), spider nevi (-), chest telangiectasias (+), no yellow skin, no skin ecchymosis or hyperpigmentation, no sclera jaundice, no bulbar conjunctiva edema, no pale eyelid conjunctiva, normal heart and lungs, smooth abdomen, no visible abdominal veins, normal umbilicus, soft abdominal muscles, tenderness (-), rebound tenderness (-), no palpable mass, Murphy’s sign (-), liver not palpable below the right costal arch, spleen not palpable below the left costal arch, percussion tenderness over the liver area (-), shifting dullness (-), normal bowel sounds, no pitting edema in the lower limbs, and flapping tremor (-). Laboratory tests showed WBC $2.25 \times 10^9/L$, hemoglobin 114 g/L, platelets $55 \times 10^9/L$, total bilirubin 36.7 $\mu\text{mol/L}$, albumin 32.9 g/L, alanine aminotransferase 37 U/L, aspartate aminotransferase 71 U/L, PT 13.8 s, glycosylated hemoglobin 5.2%, creatinine 64 $\mu\text{mol/L}$, hepatitis B surface antigen (HBsAg) (-), hepatitis B surface antibody (anti-HBs) (+), hepatitis B e antigen (HBeAg)

(-), hepatitis B e antibody (anti-HBe) (+), and hepatitis B core antibody (anti-HBc) (+). After admission, the patient received symptomatic and supportive care, including liver-supporting therapy, albumin infusion, cough-reducing medicine and expectorant, and hypotensive drugs. The cause of liver cirrhosis was unknown, and bile duct disease was considered. Therefore, the patient was scheduled to undergo upper abdomen MRI and magnetic resonance cholangiopancreatography (MRCP) to rule out bile duct conditions. On the afternoon of May 27, 2019, the patient went to the Department of Radiology for plain and enhanced upper abdomen MRI and MRCP. Before the MRI, the patient took oral gadobenate dimeglumine solution (3 mL diluted in 500 mL of normal saline) and received an intramuscular injection of anisodamine (10 mg). The MRI started at 7:00 pm. At 7:35 pm, 5.8 mL of gadobenate dimeglumine solution (Multihance, lot: 1810005B, Shanghai Bracco Sine Pharmaceutical Co., Ltd., China) and 20 mL of sodium chloride solution were bolus injected (iv) via a high-pressure injector. A few minutes later, the patient felt unwell during the two-phase dynamic enhanced scan. The physician immediately entered the exam room to communicate with the patient. The patient complained of nausea and was uncooperative. The scan was terminated. With the assistance of staff, the patient walked to the entrance of the scan room and then suddenly lost consciousness and was unresponsive. Gadobenate dimeglumine-induced anaphylactic shock was diagnosed based on the temporal relationship between the onset of symptoms and the injection. The medical staff immediately established vein access for rehydration and volume expansion and administered oxygen therapy. In addition, cardiopulmonary resuscitation was promptly performed due to the loss of major arterial pulse and respiration, and drugs including epinephrine 1 mg, dexamethasone 5 mg, and methylprednisolone 80 mg were intravenously injected. At 7:48 pm, the patient’s blood pressure was 105/41 mmHg, and his pulse was 125 bpm. The emergency department was contacted for help. Upon arrival, the emergency physician found the patient lying supine on the floor, with a blue or purple complexion, no responsiveness, and no carotid arterial pulse. Chest compression and balloon-assisted ventilation continued. The patient’s heart sounds resumed, and he was transferred to the emergency room for further treatment. Cardiac arrest recurred during transfer, and rescue therapy, including chest compressions and balloon-assisted ventilation, was readministered. In the emergency room, the patient continued to receive chest compressions

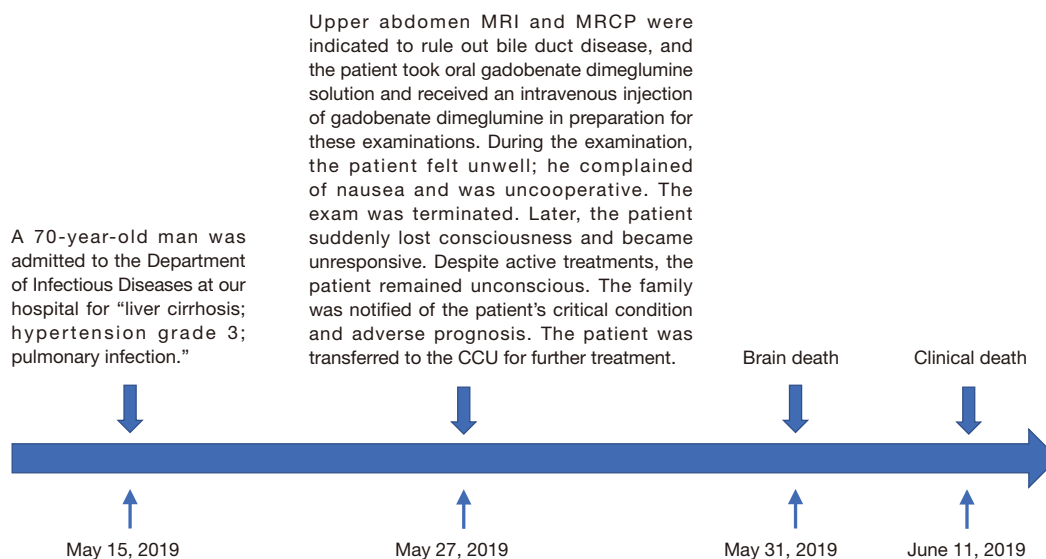


Figure 1 Timeline.

and balloon-assisted ventilation in addition to rehydration and volume expansion [compound ammonium chloride injection (500 mL, iv), 5% glucose injection (500 mL, iv)] and vasoactive drugs [norepinephrine (18 mg, bolus) + dopamine (180 mg, bolus)] to maintain blood pressure. An anesthesiologist was consulted and performed emergency endotracheal intubation, and the patient was connected on a ventilator. Additionally, a cardiologist was consulted and performed emergency placement of a temporary pacemaker. Despite active treatments, the patient remained unconscious. Norepinephrine (18 mg, iv) and dopamine (180 mg, iv) were administered to maintain blood pressure. Physical examination showed blood pressure 90/45 mmHg and heart rate 103 bpm. Blood oxygen saturation (SpO₂) was 100% with ventilator-assisted ventilation. The pupils were round and of equal size (approximately 6 mm), with no light reflex. The carotid arterial pulse was palpable. The family was notified of the patient's critical condition and adverse prognosis. The patient was transferred to the critical care unit (CCU) for further treatment. Unfortunately, he underwent brain death on May 31 and clinical death on June 11 due to his rapidly progressing and uncontrolled conditions. The timeline is shown in *Figure 1*.

Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images. The content involved here was following the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013).

Discussion

The causes of liver cirrhosis are various, which can be roughly divided into infectious, chemical damage, autoimmune, cholestasis, metabolic and genetic, vascular. Cholestasis includes congenital biliary atresia, allagile syndrome, progressive familial cholestasis and so on. Clinically, there are many examination methods for bile duct diseases, including contrast-enhanced ultrasound, two-dimensional ultrasound, computed tomography, magnetic resonance imaging, magnetic resonance cholangiopancreatography, probe confocal laser micro endoscopy and so on. The cause of liver cirrhosis was unknown, and bile duct disease was considered. Therefore, the patient was scheduled to undergo upper abdomen MRI and magnetic resonance cholangiopancreatography (MRCP) to rule out bile duct conditions.

Gadobenate dimeglumine is a paramagnetic contrast used during diagnostic MRI. It has hepatobiliary specificity (6,7) with very good imaging performance. A small amount is absorbed by normal liver cells after intravenous injection and excreted via the bile ducts while maintaining the chemical structure of gadobenate dimeglumine. It allows the visualization of local angiogenesis and perfusion, which reflect the hepatic blood supply and recent liver function, thereby providing a reference for clinical diagnosis (2). Gadobenate dimeglumine-enhanced dynamic MRI effectively improves the diagnostic accuracy for focal liver

lesions (8). Studies (9,10) have shown that during MRI, gadobenate dimeglumine enhancement of the hepatobiliary phase effectively helps identify focal nodular hyperplasia, atypical nodular hyperplasia cirrhosis, and liver cancer. The recommended dose of gadobenate dimeglumine is 0.1 mmol/kg body weight in adults (0.2 mL/kg for 0.5 M solution). There is no need to adjust the dose in patients with liver function damage. Therefore, the dose used for this patient was within the recommended range.

Contrast-related allergic reactions vary greatly in severity, and they can be divided into acute, late, or ultra-late adverse reactions based on onset time. Gadolinium-containing contrast agents are widely used during MRI and have fewer but possibly more severe adverse reactions than iodine-based contrast agents. As with other gadolinium contrast agents, gadobenate dimeglumine-induced allergies/allergic/hypersensitivity reactions have been reported (11). Their severity varies, and they may be serious or life-threatening and can lead to anaphylactic shock (12) or even death. Adverse reactions may involve one or more organs and systems, including respiratory, cardiovascular, and/or skin and mucosal tissues (13), especially in patients with a history of asthma or other allergic diseases. Studies have shown that the overall incidence of gadobenate dimeglumine-induced adverse reactions is only 0.76% (14), which is lower than that of other MRI contrast agents. In a prospective observational safety study, more than 130,000 patients were followed up over 7.5 years for gadobenate dimeglumine-induced adverse events. The results showed that the incidence of acute adverse reactions was 0.18% (15), indicating that gadobenate dimeglumine has a good safety profile.

Patient's sex, age, site, and specific MRI procedure are related to acute adverse reactions (16). Anaphylactic shock is a known serious adverse reaction of gadobenate dimeglumine injection. In this patient, anaphylactic shock was probably related to gadobenate dimeglumine injection given the temporal relationship and known drug safety information. The Patient had known risk factors (age >60 years, grade 3 hypertension, and diabetes) for contrast agents. Further research is needed to investigate whether these factors contribute to anaphylactic shock.

Gadobenate dimeglumine cannot be mixed with other drugs for injection. Before gadobenate dimeglumine injection, the patient in the present study took oral gadobenate dimeglumine solution (diluted) and intramuscular anisodamine injection 10 mg. The purpose of oral gadobenate dimeglumine solution (diluted) is to suppress surrounding intestinal fluid signals and ensure good

duodenum filling and quality images. Anisodamine is an M receptor blocker. It can block the binding of acetylcholine and M receptor, relax the smooth muscle of biliary tract, slow down peristalsis, reduce the artifacts caused by the movement of biliary tract, and maintain the clarity of scanning image, which is conducive to diagnosis. The main adverse reactions of anisodamine were accelerated heart rate, dysuria, dry mouth, blush and so on. No allergic reaction was reported. Anisodamine also has not been reported to increase the incidence of gadolinium meglumine allergic reactions (17). He was the only patient who experienced gadobenate dimeglumine-induced adverse reactions on the day of his examination. A review of 5-year data showed that the incidence of gadobenate dimeglumine-induced serious adverse reactions at our hospital is less than 0.01%. Before using gadolinium meglumine, the patients were treated with liver protection, albumin supplement, cough and expectorant, and hypotension, and the basic condition was good. According to the correlation between the shock signs and the injection time, the patient was diagnosed as one case of anaphylactic shock caused by gadolinium meglumine, which involved multiple organ systems (respiratory, cardiovascular and liver). After treatment, the patient failed and eventually died. The patient's family has consented to the publication of this case report.

Diagnostic contrast agents (such as gadobenate dimeglumine) should be used in hospitals with emergency rescue equipment, such as cardiopulmonary resuscitation equipment, and trained medical staff. Before gadobenate dimeglumine injection, it is important to ask the patient's allergy history carefully and inform the patient of possible adverse reactions. The trained physicians control the injection pressure and speed of contrast agent and confirm that emergency rescue drugs are available to treat any adverse reactions (such as anaphylactic shock) that occur during the exam. After injection, the patient should be closely monitored for 15 minutes to ask whether they feel uncomfortable and make preparations for first aid. Because most of the serious adverse reactions occurred in this period of time. Moreover, the patient should be observed at the hospital for one hour after injection. At the end of the examination, patients need to be told to drink more water to promote drug excretion from the kidney. Once the patients have adverse reactions after medication, they must be treated symptomatically in time.

Clinicians should carefully weigh the clinical benefits and risks of gadobenate dimeglumine. The manufacturer's instructions for use and the China Food and Drug

Administration (CFDA) approved package insert should be updated in a timely manner to reflect new safety information and reported risks in order to provide the best drug information to clinicians.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/apm-21-1076>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-21-1076>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and the Declaration of Helsinki (as revised in 2013).

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