

## Sudden Death of an Inpatient Due to Anaphylactoid Reaction: The Importance of Determining Correct Cause of Death at Autopsy

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### Abstract

Under the revised Medical Service Law, in-depth investigations of unpredictable deaths in health facilities must be undertaken. To illustrate our suggested procedure for investigating the sudden death of inpatients, and to emphasize the importance of postmortem examinations, we discuss an unusual forensic autopsy case. An 82-year-old Japanese woman with a 17-year history of type 2 diabetes and angina pectoris suddenly died after the injection of a water-soluble, nonionic contrast medium called iso-hexol (Omnipaque). The forensic autopsy and postmortem blood examination revealed an elevated serum level of tryptase (242 µg/L), a normal serum level of IgE (64 IU/mL) and 5076 µg/mL of iso-hexol, but no morphological evidence suggesting injury or disease. Therefore, the cause of death was confirmed as a fatal anaphylactoid reaction caused by the injected contrast medium. Although severely adverse reactions from nonionic contrast media are rare, patients should be observed carefully after administration of such compounds. This case also illustrates the importance of determining the correct cause of sudden death by performing an autopsy and subsequent analytical examinations. The possibility of anaphylactic/anaphylactoid reaction should be considered in all cases of sudden unexpected deaths in hospitals or clinics.

**Keywords:** Sudden death; Anaphylactoid reaction; Contrast medium; Autopsy; Medical service law

### Introduction

Sudden death can occur even in hospitals or clinics. It is important to accurately determine whether the death should be attributed to medical malpractice or unpredictable circumstances. Determining the cause of death also contributes to the improvement of medical safety measures which then prevent unfavorable outcomes for patients in the future. From October 2015, directors of all hospitals or clinics in Japan are obliged to report unexpected deaths to the Center of Medical Safety Promotion under the revised Medical Service Law. Furthermore, they have to establish a Domestic Investigating Committee to investigate the cause and circumstances of the death of the patient as well as the relationship between the death and medical intervention. Therefore, for the physicians, standardized and acceptable procedures for handling the sudden death of inpatients need to be implemented.

We present a sudden death case of an inpatient. We emphasize the importance of postmortem examination by autopsy to determine the correct cause of death and discuss further preventive measures relating to such situations.

### Case Circumstances

An 82-year-old Japanese woman with a 17-year history of type 2 diabetes and angina pectoris was transferred to the hospital by ambulance after she began feeling drowsy. On arrival, her systolic blood pressure was 80 mmHg, but could still respond to the doctor's questions. Her general condition improved after an infusion of sugar and electrolyte solution, and her systolic blood pressure remained above 100 mmHg two days later. She had no history of allergies or

anaphylactic episodes. She had undergone examination requiring a contrast medium 14 years earlier without complications, but further details of this treatment were unknown. This time, on the twelfth day post-admission, enhanced computed tomography (CT) examination was performed using a water-soluble, nonionic contrast medium known as iso-hexol (Omnipaque). First, 20 ml of iso-hexol was injected intravenously for 30 seconds, at which time the patient indicated no discomfort. Ten minutes after the injection of the remaining 90 ml of iso-hexol, the patient complained of nausea and then lost consciousness. The patient suffered a cardiopulmonary arrest. Despite extensive resuscitation attempts, the patient was pronounced dead one and a half hours after the injection of iso-hexol. To determine the actual cause of death, a forensic autopsy was performed next day.

At autopsy, no injury or evidence of disease was found as a cause of death. No findings indicated anaphylactic reactions, lingual edema, or glottal edema. Histologic examination revealed atherosclerosis of the large blood vessels and mild hypertrophy of the left ventricle. Examination of the postmortem blood revealed a hemoglobin level of 12.2 g/dl; total leucocyte count of 23800/mm<sup>3</sup>; eosinophils of 970/mm<sup>3</sup>; and a platelet count of 306000/mm<sup>3</sup>. In the biochemical examination of the postmortem blood, results included a total protein level of 6.6 g/dl, albumin of 2.4 g/dl, an elevated serum level (242 µg/L) of tryptase (normal range: <9.0 µg/L), and a normal serum level of IgE (64 IU/mL). Additionally, 5076 µg/mL of iso-hexol was detected using high performance liquid chromatography. Therefore, the cause of death was determined to be an anaphylactoid reaction following the iso-hexol injection.

### Discussion

Acute allergic reactions are uncommon but well recognized as a possible cause of sudden death [1]. Allergic reactions can occur

immediately after the administration of certain drugs, and subsequently symptoms such as cardiac arrhythmia, collapse or hypotension manifest. Ebbsen et al. examined 732 patients who had died in a hospital and concluded that 18.2% of the deaths were classified as adverse drug events, either directly or indirectly [2]. When the agent directly causes the degranulation of mast cells without IgE involvement, this type of hypersensitivity reaction is described as an anaphylactoid reaction. Anaphylactic reactions are caused by the degranulation of mast cells via IgE mediation. Measuring pharmacologically active substances released from mast cells during their degranulation in the patient's blood is valuable for the diagnosis of an anaphylactoid reaction. Serum mast cell tryptase has also become a useful and reliable indicator of systemic mast cell activation in the clinical assessment of an allergic condition [3]. Tryptase, a mediator stored in the secretory granules of mast cells, is a useful indicator of the anaphylactic/anaphylactoid reaction owing to its relatively long half-life in the blood [4,5].

For the diagnosis of sudden deaths, measuring these parameters from victims' blood is important. According to an autopsy study for 56 anaphylactic deaths, no specific macroscopic and microscopic findings were present in most cases, but tests for specific IgE and mast cell tryptase helped to determine whether anaphylactic reaction was the cause of the deaths [2]. Even in the postmortem examination, elevated tryptase level confirmed the diagnosis of anaphylactic/anaphylactoid reaction [6,7].

Improving medical safety practice by investigating the cause of sudden death within medical facilities (including both medical

malpractice and non-medical malpractice) is very important. The results of this analysis may prove useful for the prevention of any similar recurrences. As shown in this case, the possibility of anaphylactic/anaphylactoid reactions should be considered in all cases of sudden unexpected deaths in hospitals or clinics.

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