

CASE REPORT

Autopsy case of delayed anaphylactic shock due to contrast medium

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ABSTRACT

We report an autopsy case of delayed anaphylactic shock due to contrast medium. A 17-year-old Japanese man underwent angiography using non-ionic contrast medium under the suspected diagnosis of Buerger's disease. Initial symptoms appeared 6 h after the administration of the contrast medium, and death was confirmed 11 h later. Considering the clinical course and the results of the autopsy, we concluded that the direct cause of the patient's death was severe acute circulatory failure due to a delayed allergic reaction to the contrast medium. The reported incidence of serious delayed reactions or biphasic reactions to non-ionic contrast medium is extremely low; however, we should be aware of such rare adverse reactions.

Key words: allergy, autopsy, biphasic reaction, contrast medium, delayed anaphylactic shock, fatal.

INTRODUCTION

Iodinated X-ray contrast media are among the most frequently used pharmaceuticals for intravascular administration. Although the newer low osmolality, non-ionic contrast media are generally well tolerated, it is widely recognized that they give rise to immediate or delayed adverse reactions in susceptible individuals. Most serious adverse reactions, such as anaphylactic shock, are of the immediate type. Delayed reactions including biphasic reactions have recently gained attention, possibly due to a significant decrease in immediate type reactions with the increased use of non-ionic contrast medium. We herein report a fatal case of delayed anaphylactic shock due to contrast medium.

CASE REPORT

A 17-year-old Japanese man was referred to our department on 12 January 2009 because of repeated Raynaud's phenomenon in his fingers for 2 months. He had a medical history of bronchial asthma, which had been quiescent without regular medication. In 2008, he was diagnosed as having primary sclerosing cholangitis and ulcerative colitis, for which he had been given a corticosteroid equivalent to 12.5 mg prednisolone daily. In his family history, his elder brother died of osteosarcoma. As no clinical signs of collagen diseases were observed, the patient was admitted for angiography

on 12 February 2009 under the suspected diagnosis of Buerger's disease.

Angiography using Omnipark (Dai-ichi Sankyo, Tokyo, Japan) containing iohexol was carried out at 14.00 hours on 12 January. Welts appeared on his chest, which were alleviated by the administration of Saxizon (Kowa, Tokyo, Japan), hydrocortisone sodium succinate, 500 mg i.v. Thereafter, his general condition was stable. At 18.00 hours the patient complained of a mild headache. He again complained of a headache at 21.30 hours and vomited at 22.40 hours. He was diagnosed with respiratory alkalosis caused by hyperventilation, and emergency treatment using the paper bag method was applied. However, at 23.35 hours he became unconscious and his condition suddenly deteriorated. Resuscitation was performed; however, he died at 01.14 hours on 13 February.

Post-mortem computed tomography imaging showed no signs of intracranial hemorrhage. Abnormal findings included cerebral edema, left maxillary sinusitis, pneumonia or alveolar hemorrhage predominantly in the left lung, pleural effusion and pericardial effusion.

Pulmonary embolism caused by a thrombus was temporarily suspected as the direct cause of death, and an autopsy was performed. However, no thrombus was demonstrated. Macroscopic autopsy findings revealed cerebral swelling and pulmonary congestion and hemorrhage in a wide area of the lower lobe of the left lung (Fig. 1). The lymph nodes were enlarged throughout the body. The

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Figure 1. In the macroscopic findings, lung conjunction and edema were observed. No lung infarction was noted.

aortic diameter was somewhat narrow, but no arterial or venous thrombi were present.

Macroscopic examination revealed congestive findings and hemorrhages in multiple organs, indicating circulatory impairment. However, no lesions that might explain sudden death, such as organ embolism or infarction, were observed. Edema, hemorrhage and inflammatory cell infiltration were noted in the heart, lungs and elsewhere (Figs 2,3). Infiltration of mast cells in multiple organs was histologically prominent, indicating that these mast cells contributed to increased vascular permeability. There was no conspicuous activity of ulcerative colitis or primary sclerosing cholangitis. Considering the clinical course and autopsy findings, the cause of death was established as acute circulatory failure resulting from vascular hyperpermeability due to delayed anaphylactic drug allergy to the contrast medium. Serum tryptase levels measured after his death were within normal limits.

DISCUSSION

Delayed allergy to contrast media develops more than 1 h after the administration of a contrast medium, and symptoms may appear after several hours to several days. The most common reactions are skin rash, headache, itching, nausea and dizziness. Skin rash is the most common allergic reaction and a review of the spontaneous reports documented erythema, urticaria, angioedema or exanthema.¹ Most contrast medium-induced delayed skin reactions appear to be mild to moderate.² In two large Japanese studies,^{3,4} no respiratory symptoms and only one case of hypotension 5 days after contrast medium administration were reported. Similar results were reported by Pedersen *et al.*⁵ in their survey of 2656 contrast medium-treated patients.

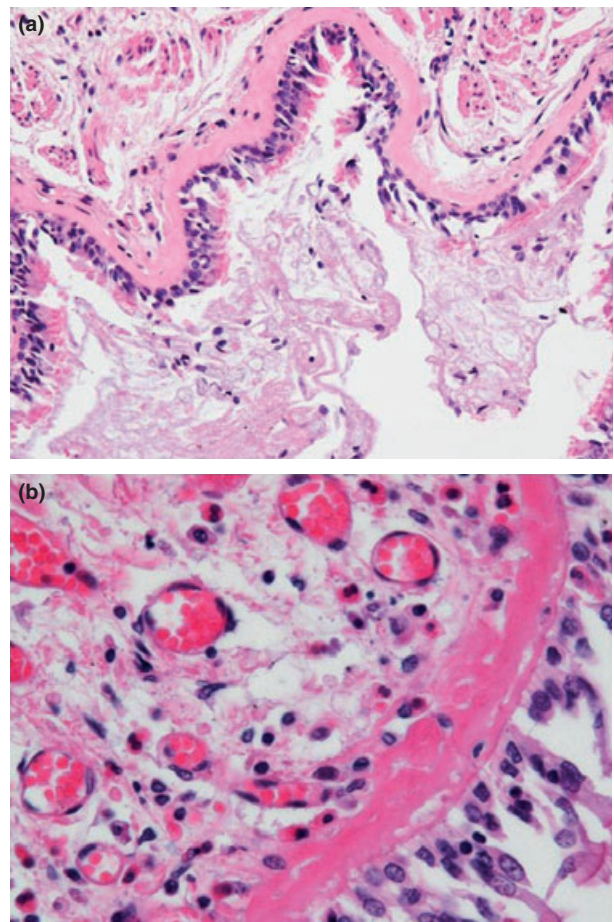


Figure 2. (a) Histopathological findings of bronchi. Massive mucous secretion in the bronchial lumen was noted. Hematoxylin-eosin (HE), original magnification $\times 100$. (b) Thickened basement membrane of the bronchi, edema and congestion of the bronchial wall, infiltration of leukocytes and mast cells were prominent (HE, $\times 400$).

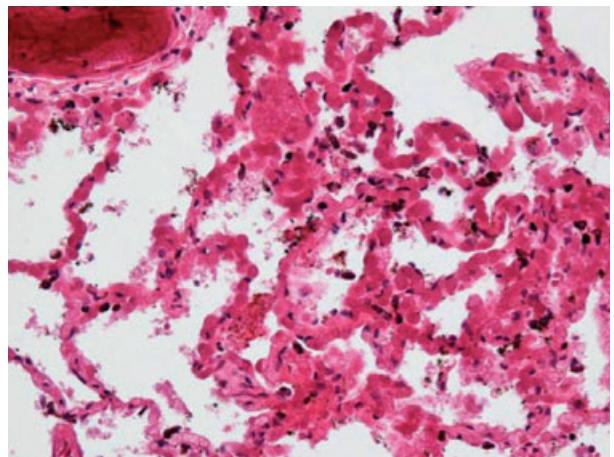


Figure 3. Edema, hemorrhage, congestion and inflammatory cell infiltration were observed in the lungs (HE, $\times 200$).

The reported incidence of more serious delayed reactions to non-ionic contrast media is extremely low. One patient suffered from a severe life-threatening reaction with hoarseness as well as facial and throat swelling and shortness of breath which occurred 24 h after the administration of iohexol.⁶ Severe cutaneous vasculitis was also reported to develop after urography with non-ionic contrast medium and one of these patients died.^{7,8} Stevens-Johnson syndrome has been reported in a patient with active systemic lupus erythematosus, which developed 8 h after administration of iopamidol and the patient died 6 weeks later.⁹

A past history of adverse reactions to contrast media seems to be one of the most important risk factors for both immediate and delayed allergy-like reactions. Previous reports pointed out that patients with a history of allergy to contrast media have a twofold increase in risk for delayed allergy-like reactions to non-ionic contrast media and women are more prone to both immediate and delayed allergy-like reactions, with a twofold higher risk of such reactions than men.^{2,4} Furthermore, the prevalence of reactions seems to be higher in patients with cardiac disease^{4,10} as well as in patients with diabetes mellitus and liver and kidney disease.² Furthermore, a previous report pointed out that the incidence of delayed skin reactions was higher in Japan than in other countries.¹¹ It could be due to ethnic differences, differences in the type of medication used or simply due to a longer observation period after administration in Japan.

Anaphylactic reaction is a clinically indistinguishable syndrome involving similar mediators but not mediated by immunoglobulin E antibody and not requiring previous sensitization. Clinically, the level of serum tryptase level has been shown to be a useful marker of anaphylactic reactions, though elevation was not noted in our case. The elevated serum tryptase level after the onset of symptoms strongly suggests that continued mast cell degranulation can occur during protracted anaphylaxis.¹² Tryptase is a neutral protease stored in the secretory granules of all mast cells. Mast cell activation is thought to be the principle determination of clinical severity in this model of systemic anaphylaxis.¹²

Anaphylaxis can take a biphasic course. Recognition of, and interest in the biphasic reactions has been increasing, as evidenced by a recent comprehensive review.¹³⁻¹⁶ The incidence of biphasic anaphylactic event varies from 1–20%, and the onset of relapsed symptoms ranges 1–78 h, usually 8 h, after resolution of the initial event. The relapsed symptoms may be less severe or more severe than the initial one and can be anaphylactic and fatal.¹⁵ The converse of the finding that a longer time to resolution predicted an increased risk of biphasic reactivity would be that a shorter time to resolution may predict an absent second phase response.¹⁴ In many cases of anaphylaxis, the severity of second-phase reactions is underrecognized and undertreated with potentially life-threatening consequences.

Our patient had a history of asthma and other diseases, suggesting that he had a predisposition to allergy that may explain a background factor for delayed side-effects of the contrast medium.

Considering the clinical course and the autopsy findings, we concluded that the direct cause of the patient's death was severe acute circulatory failure caused by delayed allergy to non-ionic contrast medium. Compared with an immediate type allergy, a delayed type allergy could be overlooked and little is known about its incidence and severity. Specific management and preventative strategies by allergen are discussed, and skin testing could be useful in implicating delayed hypersensitivity reaction to contrast media.⁷ However, sufficient evidence is required as skin testing has not been performed recently in clinical practice. Careful pretest diagnostic interviews, circumspect post-test monitoring, appropriate treatment to resolve immediate and a supportive system for sudden changes are mandatory.

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