Case Report

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A Delayed, Unusual Non-Cardiogenic Pulmonary Edema after Intravascular Administration of Non-Ionic, Low Osmolar Radiocontrast Media for Coronary Angiography

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Non-cardiogenic pulmonary edema (NCPE) is a rare adverse reaction to iodinated radiocontrast media (RCM), in which all previous cases were immediate reactions. A 56-year-old male was given iopamidol, a non-ionic, low osmolar RCM, during coronary artery angiography. He developed pulmonary edema and fever a day after the procedure. Despite diuretic therapy, the patient's pulmonary edema worsened and his high fever persisted. The patient's pulmonary edema was eventually resolved with intravenous steroid treatment. We interpreted the patient's condition as NCPE manifesting as a delayed reaction to RCM. To our knowledge, our case is the first to show NCPE as a delayed hypersensitivity reaction. **(Korean Circ J 2013;43:500-503)**

KEY WORDS: Pulmonary edema; Hypersensitivity; Contrast media.

Introduction

General adverse reactions to iodinated radiocontrast media (RCM) are divided into immediate (occurring within 1 hour of administration) and delayed reactions (occurring from 1 hour to 1 week after administration).[1-4] Immediate hypersensitivity reactions are usually anaphylactoid reactions that range from rashes and a sensation of flushing to life-threatening severe reactions,[1-4] while delayed reactions are predominantly exanthematous skin reactions that are self-limiting.[1)3)5)6)] Non-cardiogenic pulmonary edema (NCPE) following intravascular injection of RCM is rare. Furthermore, all reported cases of NCPE associated with non-ionic RCM were immediate reactions.

Herein, we report a rare case of NCPE presenting as a delayed-type manifestation with a review of the literature.

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Case

A 56-year-old male was admitted to the outpatient clinic with a 6-day history of chest pain on exertion lasting for over 10 minutes per episode. The patient has been treated for hypertension and diabetes mellitus at our hospital since 2009. He had no history of allergies. On admission, his blood pressure and pulse rate were 95/55 mm Hg and 70 bpm, respectively. The electrocardiogram showed ST-segment elevation with Q-wave formation in II, III, and aVF, and reciprocal ST-segment depression in I, aVL, and V 4-6 (Fig. 1). His troponin-T level was elevated to 3.03 ng/mL (reference range: 0-0.100 ng/mL), while creatine kinase-MB was within the normal limit. His initial chest radiography showed no pulmonary edema and no cardiomegaly (Fig. 3A). Echocardiography showed hypokinesia from the base to the mid-inferior wall with preserved left ventricle (LV) systolic function (Ejection fraction=56% by Biplane modified Simpson's formula). He was diagnosed with recent myocardial infarction. Coronary angiography demonstrated a critical stenosis in the mid right coronary artery (RCA) with thrombolysis in myocardial infarction grade I flow (Fig. 2A) and an insignificant stenosis in the left coronary artery. He underwent stent placement (a 4.0×18 mm Everolimus-eluting stent) in the mid RCA (Fig. 2B). The patient was given 200 mL of iopamidol (Isovue-300, Dongkook pharmaceuticals, Seoul, Korea), a non-ionic, low osmolar (616 mOsm/kg water) RCM. About 3 hours after the procedure, he developed a fever of above 38°C. However, the patient was not experiencing a rash, itching, an-

gioedema, rales or wheezing in the lung field. The patient did not complain of any other symptoms, such as dyspnea, and his vital signs were stable. We decided to observe him; we took his bacterial and viral cultures. The next day, high fever persisted and the patient started to complain of mild dyspnea. Chest radiography showed diffuse bilateral alveolar infiltrates (Fig. 3B). Arterial blood gas analysis revealed a pH of 7.436, a PCO_2 of 30.2 mm Hg, a PO_2 of 75.9 mm Hg, and an oxygen saturation of 95.7%, while receiving nasal cannula oxygen at a flow rate of 5 L/min. The patient's white blood cell count was 9400/mm^3, but eosinophil levels were not raised. Follow-up echocardiography revealed preserved LV systolic function without interval change, in comparison with the initial study. The elevated troponin-T level was on the decline from baseline. We did not perform invasive hemodynamic monitoring of Swan-Ganz catheterization or central line insertion. At first, we dealt the patient's condition as cardiogenic pulmonary edema due to fluid or osmolar overload. The patient received intravenous furosemide and antibiotics. However, he was still febrile (up to 40°C) and pulmonary edema became progressively worse despite negative volume balance (Fig. 3C). Subsequently, the patient was diagnosed with NCPE manifesting as a delayed reaction to RCM despite some limitations, such as the absence of eosinophilia and pulmonary wedge pressure monitoring. The patient was promptly given intravenous hydrocortisone and antihistamine. We cut his dosage of diuretics and discontinued antibiotic treatment after 48 hours when all of his cultures were negative. The patient's fever stopped and the pulmonary edema started to improve one day after the initiation of steroid injection (Fig. 3D). The patient was discharged from the hospital 7 days after the index procedure with complete recovery from pulmonary edema (Fig. 3E).

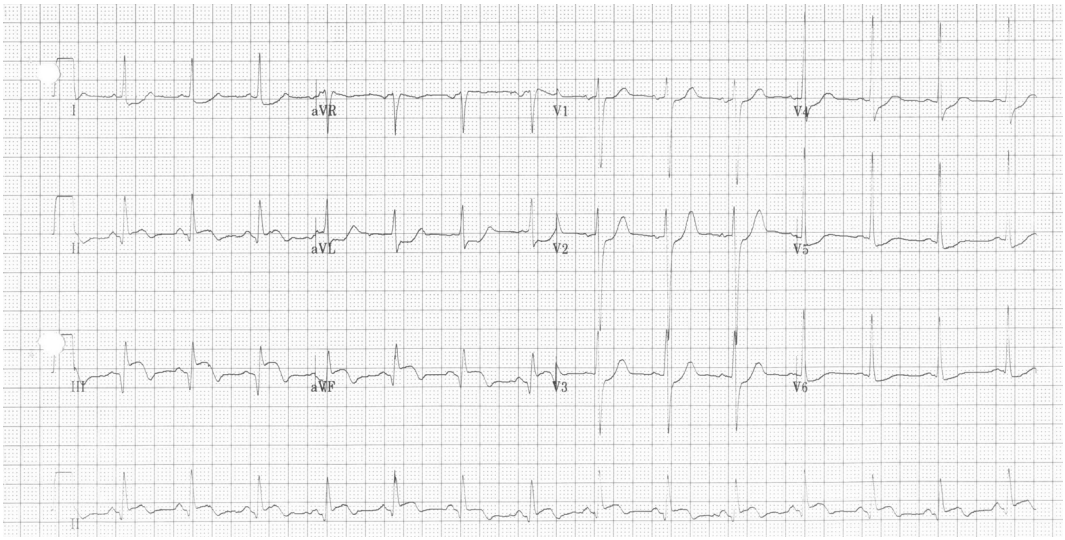

Fig. 1. The electrocardiogram shows ST-segment elevation with Q-wave formation in II, III, and aVF, and reciprocal ST-segment depression in I, aVL, and V 4-6.

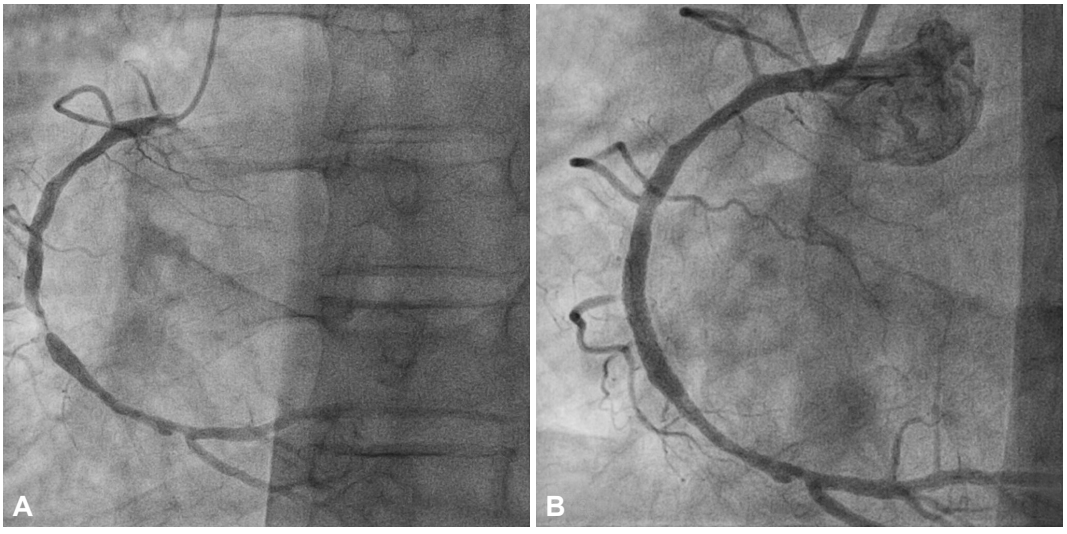

Fig. 2. Coronary angiography reveals a critical stenosis in the mid right coronary artery (A). A drug-eluting stent was deployed (B).

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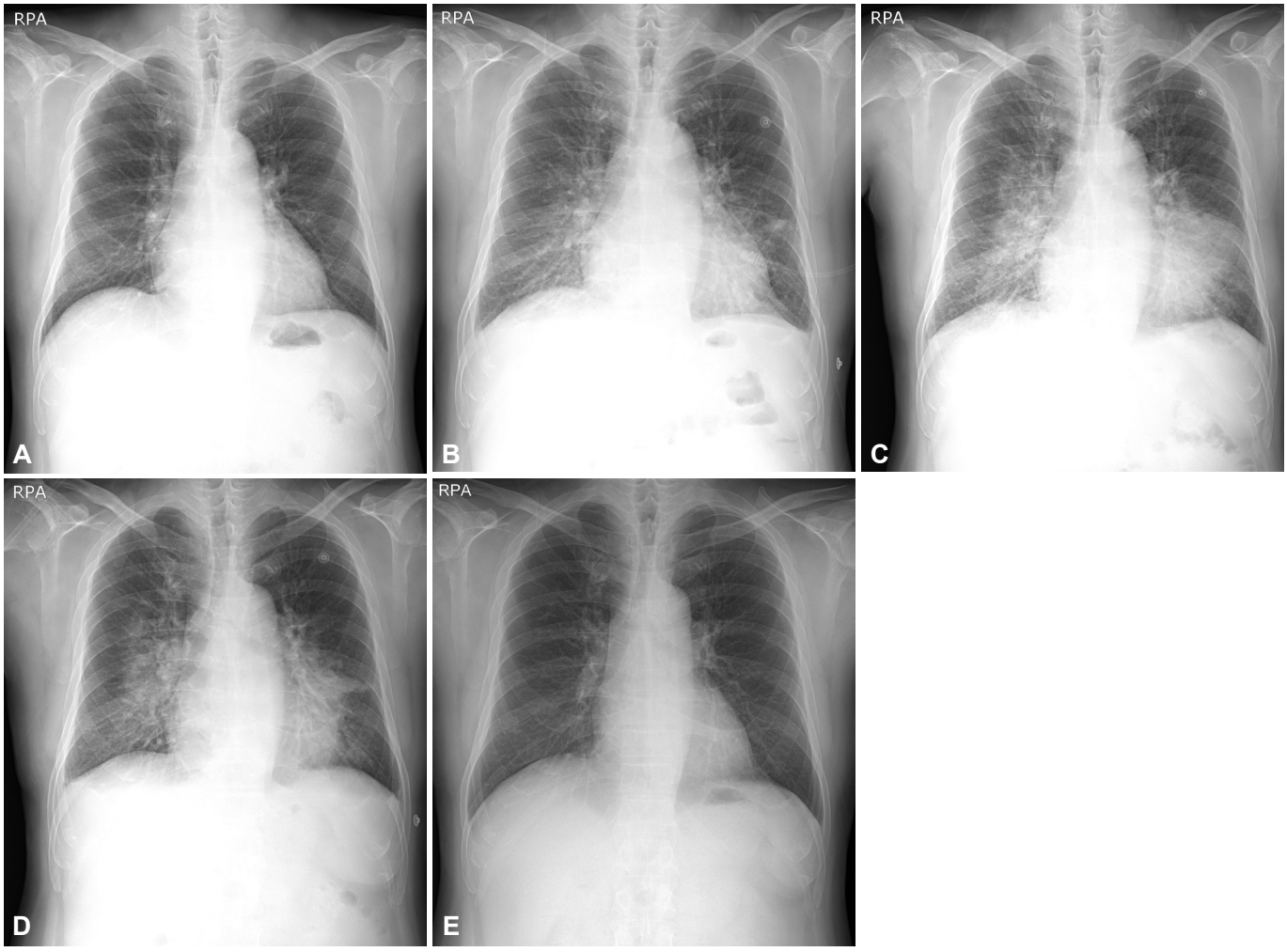

Fig. 3. Serial chest radiographs. A: no pulmonary edema at the initial presentation. B: newly appeared bilateral alveolar infiltrates a day after the procedure. C: rather aggravated pulmonary edema despite intravenous furosemide therapy. D: slightly improving the pulmonary edema after initiation of intravenous steroid. E: complete resolution of pulmonary edema at discharge.

Discussion

Today, non-ionic, low osmolar RCM such as non-ionic monomer: Iohexol (Omnipaque), iopamidol (Isovue), Ioversol (Optiray) and non-ionic dimer: Iodixanol (Visipaque, iso-osmolar to plasma, 290 mosm/kg water) are widely used, while ionic RCM are hardly available in clinical practice. Non-ionic RCM significantly lowers the risk of mild to moderate adverse reactions compared to ionic RCM. Mild to moderate immediate reactions have been reported in 3.8% to 12.7% of patients receiving ionic monomeric RCM and in 0.7% to 3.1% of patients receiving non-ionic RCM.[1)3)4)] Severe immediate reactions, such as anaphylaxis and severe hemodynamic compromise, have been reported in 0.16% and 0.03% of patients with ionic and non-ionic RCM, respectively.[1)3)4)] In general, more severe hypersensitivity reactions to RCM manifest as immediate anaphylactic reactions.[2)4)] The onset of immediate reactions is very rapid, with about 70% occurring within 5 minutes after injection and 96% of severe or fatal reactions such as anaphylactic shock, severe angioedema, pulmonary edema, and cardiac arrest occurring within 20 minutes after injection.[1)] There are commonly recommended pretreatment protocols for immediate severe allergic reactions to RCM.[4)] It is also common to use an iso-osmolar agent, iodixanol, for purported safety, especially in the cardiac catheterization laboratory, even though a higher incidence of delayed skin reactions have been reported compared to low osmolar monomers.[3)4)] On the other hand, the most representative delayed adverse reaction is exanthematous skin eruption. Such exanthemas have been reported to affect 1% to 3% of RCM-exposed patients and are usually mild to moderate in severity and self-limiting within 7 days, showing recovery in up to 75% of those affected within 3 days.[1)5-8)] Prophylaxis is generally not recommended.[1)5-7)]

Non-cardiogenic pulmonary edema caused by non-ionic RCM is rare. Only a few reports on NCPE caused by both ionic and non-ionic RCM have been published. Moreover, they all were immediate reac-

tions.[9-13] Although systemic symptoms with more immediate-type manifestations such as hypotension, dyspnea, abdominal pain and fever have been occasionally reported,[1)8)14)] a late-onset NCPE, such as our case has not yet been reported.

The pathogenesis of contrast-induced NCPE remains controversial. Such pulmonary edema could be caused by mediator release and complement activation resulting in endothelial damage or by a direct irritant effect of the drug on the lungs.[12)] The primary emergency treatment is oxygen with continuous positive airway pressure, or invasive ventilation with positive end expiratory pressure.[15)] Treatment of anaphylaxis was not beneficial and diuretics should be given with caution.[12)] Corticosteroids can be given to prevent or decrease the severity of the reaction, but should not be expected to be of immediate benefit.[4)]

In conclusion, we experienced a rare case of NCPE of a delayed-type hypersensitivity reaction following non-ionic RCM exposure. It is important for clinicians to be aware of this entity, as manifestation can be quite unusual and life-threatening, and to distinguish the condition from cardiogenic pulmonary edema.

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