CASE REPORT

Acute Lung Injury Accompanying Alveolar Hemorrhage Associated with Flu Vaccination in the Elderly

Etsuko Satoh 1,2, Takahito Nei 2,3, Shinichi Kuzu 1,4, Kumi Chubachi 1, Daisuke Nojima 1, Namiko Taniuchi 1, Yoshimitsu Yamano 1 and Akihiko Gemma 2

Abstract

Flu vaccinations are administered worldwide every winter for prevention. We herein describe a case of acute lung injury resulting from a pathologically confirmed alveolar hemorrhage, which may have been closely related to a preceding vaccination for pandemic influenza A of 2009/10. The present patient had been hospitalized with an acute lung injury after flu vaccination one year prior to the present hospitalization, however, he received another flu vaccination. We should consider a vaccine-related adverse reaction as a potential cause of pulmonary disease if patients present with this illness during the winter season.

Key words: acute lung injury, alveolar hemorrhage, flu vaccination

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Introduction

Vaccination is the primary form of prophylaxis against infectious diseases, however, severe adverse drug responses (ADR), which are reactions other than the desired immune response, do occur at a very low frequency. The environment surrounding influenza has markedly changed after the influenza A (H1N1) pandemic of 2009/10 (H1N1 pdm). Sporadic ADR cases have been reported since the H1N1 pdm vaccine was introduced in 2010 (1-10). We herein report a case in which we pathologically diagnosed a typical pulmonary alveolar hemorrhage attributable to the H1N1 pdm flu vaccine.

Case Report

An 82-year-old man with hypertension, angina pectoris, and paroxysmal atrial fibrillation was referred to our hospital for an evaluation of a fever, bloody sputum, and dyspnea several days after receiving antimicrobial agents for pneumonia. He had been hospitalized with an acute lung injury (ALI) one year previously (Fig. 1A-C), however, the cause of his ALI had not been identified despite diagnostic tests being performed. He was treated for five months, starting at the disease onset, with systemic corticosteroids. His familial and medical histories were unremarkable. He neither smoked nor drank alcohol regularly. He had no history of caring for animals. Moreover, he had no history of allergies to drugs, foods, or inhaled substances.

Chest roentgenography showed an infiltration shadow in the lower right lung field (Fig. 1D), and computed tomography (CT) revealed ground-glass opacities with diffuse expansion not only in the right lung but also in the left lung (Fig. 1E, F). Radiological findings suggested ALI, and the patient was emergently hospitalized with a diagnosis of recurrent acute respiratory failure.

On admission, there were no remarkable blood examination findings. Biochemistry and serology analyses, including tests for myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA), were negative (Table).

After this admission, the bronchoalveolar lavage (BAL) fluid was collected using optical bronchoscopy to investigate the possible causes of ALI. The BAL fluid was bloody and hemosiderin-laden macrophages were seen on microscopic reflected images. Lung tissue obtained by a transbronchial lung biopsy also revealed the presence of hemosiderin-laden

1Department of Respiratory Medicine, Ebina General Hospital, Japan, 2Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Japan, 3Department of Infection Control and Prevention, Nippon Medical School Hospital, Japan and 4Department of Pulmonary Medicine/Medical Oncology, Tama-Nagayama Hospital, Japan

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Correspondence to Dr. Takahito Nei, takahitonei@gmail.com
macrophages in alveolar areas (Fig. 2), however, evidence of vasculitis was minimal. He was administered steroids and his condition gradually improved. Steroid therapy was continued for approximately five months, with gradual tapering.

A review of the patient’s medical problems revealed that he had been regularly given medications for cardiac disease (amlodipine, aspirin, losartan, bepridil, and cilostazol) and an antimicrobial agent (sulbactam-ampicillin). Interestingly, he had received an influenza vaccination before each hospitalization. He had been given an influenza vaccination 10 days prior to the ALI diagnosis at the first admission one year previously. At the first admission, we had not suspected ADR developing after vaccination against H1N1\textsubscript{pdm}. The next year, he had also been vaccinated for the second time by chance; two weeks later, he began to suffer from bloody sputum. This strongly supported our assumption that ALI with alveolar hemorrhage in this case was associated with influenza vaccination.

We therefore diagnosed the patient with ALI due to influenza vaccination and administered steroid (methylprednisolone) treatment. We were able to control the disease activity and steroid therapy was continued for approximately six months, with gradual tapering of the dosage.

**Discussion**

The 2009 H1N1 influenza virus was first detected in the United States (US) in April 2009 (H1N1\textsubscript{pdm}) (11-14), and the outbreak occurred not only in the US and Mexico, but also Europe and Japan. As soon as the pandemic was recognized, the vaccine for H1N1\textsubscript{pdm} was developed and used in many countries worldwide. In the US, reports documented by the Vaccine Adverse Event Reporting System (VAERS, https://vaers.hhs.gov/index) of ADR with flu vaccination totaled 10,085 cases, 7.2% of which were severe. There were 48 fatalities, of which two were caused by respiratory ADRs, however, the details of the causative factors of drug-related pulmonary disorders were not reported (1, 2). On the other hand, there were 7 reports of severe cases in Spain, 4 of which had respiratory ADRs (3). These included respiratory distress syndrome in a 6-year-old boy and pneumonia in a 94-year-old man. In Korea, 178 vaccine-related severe ADR cases including Guillain-Barré syndrome, neurologic abnormalities such as acute disseminated encephalomyelitis and anaphylactic disorders were reported. However, none of the Korean cases had respiratory ADRs (4). In Italy, a case-control study was conducted to show the effectiveness and safety of H1N1\textsubscript{pdm} vaccination for children, and only one case of vasculitis was reported (5). Thus, there are very few
descriptions of vaccine-related vasculitis or pulmonary injury.

In Japan, the Ministry of Health, Labour and Welfare reported ADRs to the H1N1^{1st} vaccine (from October 2009 to March 2010) and the seasonal flu vaccine (from April 2007 to March 2010) (6). ADRs to the former vaccine included five interstitial pneumonia cases, four which experienced exacerbation and one with allergic purpura. The latter vaccine resulted in two cases of interstitial pneumonia (one case with exacerbation), nine with thrombocytopenia purpura, and five with allergic purpura (6). In addition, several Japanese reports have described flu vaccine-related interstitial pneumonia (15-17). Moreover, there are reports of cases with systemic vasculitis (18-20), two of which had positive MPO-ANCA results (18, 19). These vasculitis cases raise the possibility of an association with flu vaccine (21). However, vaccine-related interstitial pneumonia or systemic vasculitis appears to be rare.

Watanabe et al. reported a 7-year-old girl who developed H1N1^{1st} vaccination-related Henoch-Schönlein purpura (HSP), despite having previously received an inoculation against the seasonal influenza annually (22). There are additives in the H1N1^{1st} vaccine, but not in the seasonal flu vacci-
cine. Certain additives have, in fact, been suggested to be associated with the onset of HSP. However, the causative associations between HSP onset and these additives were unclear (23).

Generally, additives are included in vaccine preparations. For instance, squalene, a naturally occurring substance found in plants, animals, and humans, is added to vaccines as an adjuvant, and thimerosal, a well-established antiseptic and antifungal agent, is also included in most vaccine formulations (24). Mild erythema, muscular pain, fatigue, and severe lassitude are the reported side effects of these additives, however, there have been no reports of serious ADRs (25).

To the best of our knowledge, this is the first reported case of ALI with pathologically confirmed pulmonary alveolar hemorrhage developing after vaccination against H1N1^{1st}. Furthermore, the history of the previous H1N1^{1st} vaccinations, despite several seasonal flu vaccinations before the pulmonary events, is clinically significant.

In conclusion, we herein experienced a case of pathologically confirmed pulmonary alveolar hemorrhage associated with H1N1^{1st} flu vaccination. Our present case strongly suggests that physicians should be aware of the potential of this serious ADR developing after vaccination against H1N1^{1st} but not seasonal flu. Therefore, pulmonary injury or alveolar hemorrhage in the influenza season should always prompt physicians to consider the possibility of flu vaccination-related ADR.

The authors state that they have no Conflict of Interest (COI).

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References


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