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【 CASE REPORT 】

Influenza Vaccination-associated Acute Thrombocytopenia and Diffuse Alveolar Hemorrhage

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Abstract:
Influenza vaccination can trigger various adverse reactions, and thrombocytopenia is also rarely reported. Although patients with mild thrombocytopenia are sometimes asymptomatic, severe thrombocytopenia can cause severe bleeding. We herein report a rare case of severe thrombocytopenia that occurred within one day of influenza vaccination and diffuse alveolar hemorrhage (DAH) leading to acute respiratory failure. The patient was treated with glucocorticoid pulse therapy, intravenous immunoglobulin, and temporary mechanical ventilation, and eventually he made a full recovery. Vaccine-related thrombocytopenia and DAH should be considered adverse reactions, even if they develop very soon after vaccination.

Key words: vaccine, acute respiratory failure, adverse reaction

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Introduction

Influenza vaccination can trigger various adverse reactions. Previous studies have reported a number of severe adverse reactions of influenza vaccination, including Guillain-Barré syndrome, convulsion, Bell's palsy, and thrombocytopenia (1-3). The pathogenesis of vaccine-related thrombocytopenia is unclear due to its rarity, and some cases of vaccine-related thrombocytopenia are induced by secondary immune thrombocytopenic purpura (ITP) (3, 4). Although patients with mild thrombocytopenia are asymptomatic, severe thrombocytopenia can cause bleeding, such as skin petechiae, hematoma, and bloody stool. In addition, a very low platelet count ($<5\times10^3$/μL) often induces fatal complications, including subarachnoid or intracerebral bleeding (4); however, diffuse alveolar hemorrhage (DAH) is rarely reported. DAH can show radiographic alveolar shadows and hemoptysis, which sometimes leads to acute respiratory failure.

We herein report a rare case of severe thrombocytopenia and DAH after influenza vaccination, which rapidly triggered acute respiratory failure.

Case Report

A 78-year-old Japanese man was admitted to our hospital with acute dyspnea and malaise. The patient had no acute infection in the preceding weeks. His platelet count 3 months before admission was 181×10^3/μL. He received an influenza vaccine [A/Singapore/GP1908/2015(H1N1) pdm 09, A/Hong Kong/4801/2014(H3N2), B/Phuket/3073/2013, and B/Texas/2/2013] 1 day before admission, and he had malaise after vaccination. His medical history included chronic obstructive pulmonary disease with 4-7 L/min of home oxygen therapy via nasal cannula, type 2 diabetes mellitus, and hypertension. He had previously received influenza vaccinations without any remarkable symptoms. *Pseudomonas aeruginosa* had been detected as colonized bacteria from his previous sputum cultures. He used inhaled budesonide, formoterol, and tiotropium. In addition, he had been prescribed amlodipine, alogliptin, and repaglinide. He

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Table. Blood Examination Findings on Admission.

Hematology		Serology	
Leukocytes	17,200 /μL	Anti-nuclear antibody	40 times
Neutrophils	96.0 %	Anti-CCP antibody	0.6 U/mL
Lymphocytes	2.0 %	Anti-SS-A antibody	1.0 IU/mL
Monocytes	2.0 %	Anti-PR3 ANCA	1.0 IU/mL
Erythrocytes	4.78 $\times 10^6$/μL	Anti-MPO ANCA	1.0 IU/mL
Hemoglobin	16 g/dL	PAIgG	2,930 ng/10^7 cells
Hematocrit	45.3 %	Anti-*H.pylori* IgG	8.0 U/mL
Platelets	2 $\times 10^3$/μL	HBs antigen	negative
Coagulation		HBV-DNA	negative
PT-INR	1.13	Anti-HCV core antibody	negative
APTT	29.3 s	HIV antigen	negative
Fibrinogen	390 mg/dL	Anti-HIV antibody	negative
D-dimer	0.99 μg/mL	Anti-HTLV-1 antibody	negative
Antithrombin III	76.6 %	EA-DR IgG	negative
Biochemistry		Anti-EBNA-antibody	40 times
Total protein	6.5 g/dL	Anti-rubella virus IgM	negative
Albumin	4.2 g/dL	Anti-rubella virus IgG	positive
AST	22 U/L	Anti-measles virus IgM	negative
ALT	27 U/L	Anti-measles virus IgG	positve
LDH	263 U/L	Arterial blood gas tests	
Total bilirubin	1.16 mg/dL	(on room air)	
Creatine kinase	171 U/L	pH	7.421
BUN	18.4 mg/dL	$PaCO_2$	34.0 mmHg
Creatinine	0.92 mg/dL	PaO_2	41.7 mmHg
Uric acid	6.7 mg/dL	HCO_3^-	21.7 mmol/L
Sodium	137 mEq/L	BE	-1.5 mmol/L
Potassium	4.9 mEq/L	SaO_2	72.2 %
Cloride	99.9 mEq/L		
Glucose	216 mg/dL		
HbA1c (NGSP)	7.7 %		
C-reative protein	4.48 mg/dL		
KL-6	526.1 U/mL		
β-D-glucan	negative pg/mL		

PT-INR: international normalized ratio for prothrombin time, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, HbA1c (NGSP): hemoglobin A1c (National Glycohemoglobin Standardization Program), KL-6: sialylated carbohydrate antigen KL-6, Anti-CCP antibody: anti-cyclic citrullinated peptide antibody, Anti-PR3 ANCA: anti-proteinase 3 anti-neutrophil cytoplasmic antibodies, Anti-MPO ANCA: anti-myeloperoxidase anti-neutrophil cytoplasmic antibodies, PAIgG: platelet-associated IgG, *H. pylori*: *Helicobacter pylori*, HBs antigen: hepatitis B surface antigen, HBV: hepatitis B virus, HCV: hepatis C virus, HIV: human immunodeficiency virus, HTLV-1: human T-cell leukemia virus type 1, EA-DR IgG: Epstein-Barr virus-early antigen, diffuse type and restricted type IgG, EBNA: Epstein-Barr virus nuclear antigen

was not taking any antithrombotics and had not been prescribed any new drugs for a half year. He was an ex-smoker and had a smoking history of 61 pack-years. He had no history of allergy.

On admission, his body temperature was 36.9℃, his heart rate was 97 beats/min, his blood pressure was 132/70 mmHg, and his respiratory rate was 33 breaths/min. His oxygen saturation was 67% on room air and 89% with a 90% non-rebreather mask. In addition, he developed mucosal bleeding and hematoma in his mouth, and he had skin petechiae on his whole body.

The results of blood analyses on admission were as follows: total leukocyte count, 17,200/μL; platelet count, 2× 10^3/μL; erythrocyte count, 4.78×10^6/μL with eumorphism; hemoglobin, 16.0 g/dL; hematocrit, 45.3%, C-reactive protein (CRP), 4.48 mg/dL; anti-nuclear antibody (ANA), 40 times; anti-*Helicobacter pylori* (*H. pylori*) IgG, 8 U/mL. The patient was negative for hepatitis B virus DNA, anti-hepatitis C virus core antibody, human immunodeficiency virus (HIV) antigen, and anti-HIV antibody. With the exception of the patient's ANA titer, his blood coagulation test findings and immunological workup were normal. The sputum and blood cultures were negative for bacteria and fungi. Rapid testing for influenza viruses A and B were negative. The results of other laboratory tests are shown in Table.

Chest computed tomography (CT) suggested the presence

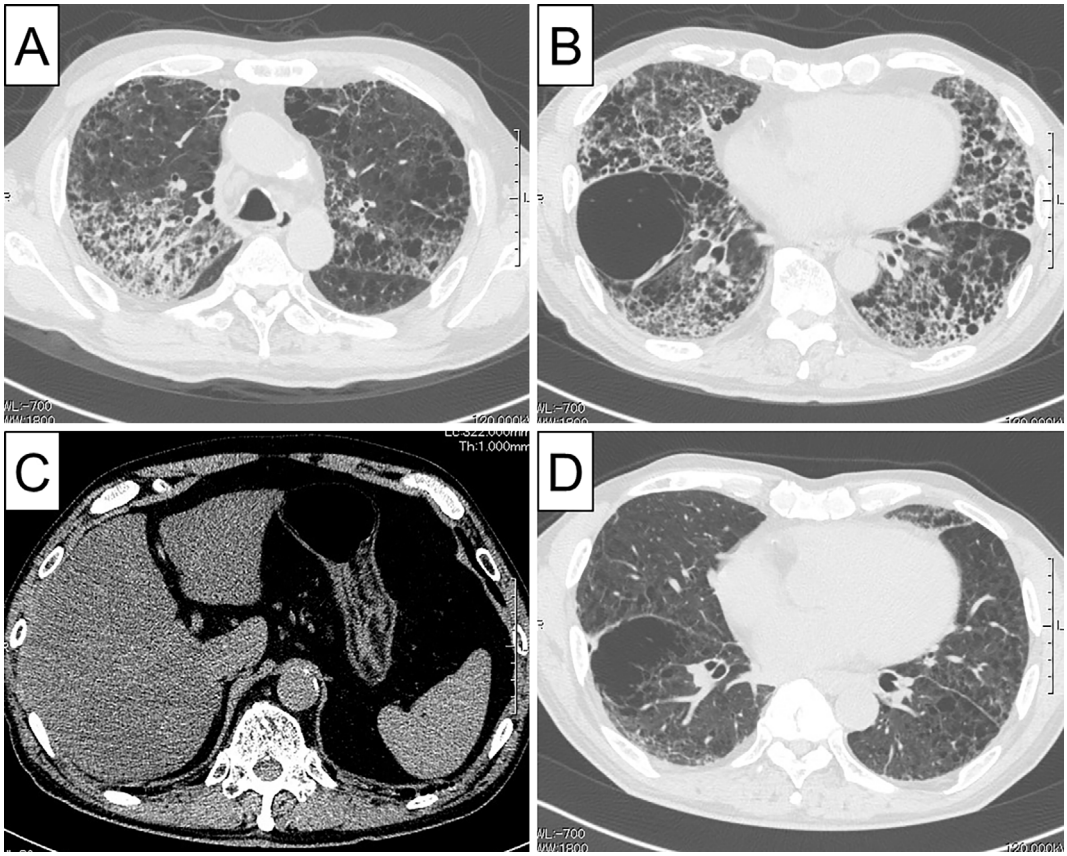

Figure 1. **Computed tomography (CT) on admission (A-C) and four years before admission (D). Chest CT reveals pulmonary infiltration in the bilateral lung field, diffuse emphysema, and a bulla in the right lower lobe on admission (A, B). Liver cirrhosis and splenomegaly were not detected on abdominal CT (C). The comparison of the CT images on admission (B) with those obtained four years prior to the patient's admission (D) revealed that the emphysema and bulla were stable.**

of infiltrative shadows in the bilateral lung fields. Liver cirrhosis and splenomegaly were not detected. In addition, diffuse low-attenuation areas and a bulla on the right lower lobe had been stable for four years (Fig. 1). A bone marrow biopsy was not performed due to severe thrombocytopenia and acute respiratory failure. An endoscopic *H. pylori* urease test and urea breath test were limited by concurrent lansoprazole therapy and mucosal bleeding in his mouth. Malignant cells were not detected in the peripheral blood.

The patient was diagnosed with thrombocytopenia that was probably secondary to influenza vaccination based on the latency time between vaccination and the onset of thrombocytopenia. Our examinations did not detect any other cause of thrombocytopenia.

Accordingly, the patient was treated with glucocorticoid pulse therapy with intravenous methylprednisolone (1,000 mg per day for 3 days), intravenous immunoglobulin (IVIG; 20 g, daily), and platelet transfusion (20 units per day). On day 2, hemoptysis induced by DAH caused the patient's respiratory failure to deteriorate, and mechanical ventilation was initiated. After 3 days of glucocorticoid pulse therapy and IVIG, the patient's platelet count increased to 11×10^3/μL and the methylprednisolone dose was tapered to 125 mg daily on day 4. The platelet count fell to 2×10^3/μL again after the dose reduction; glucocorticoid pulse therapy and IVIG were therefore resumed from days 10 to 12. Despite reducing the methylprednisolone dose to 60 mg on day 13, his platelet count increased to 103×10^3/μL, and the mucosal bleeding improved. Tracheostomy was performed on day 15 because the patient needed long-term mechanical ventilation. The methylprednisolone dose was gradually reduced without a relapse of thrombocytopenia or a worsening of the respiratory condition.

Extubation was performed on day 50, and he was treated with oral prednisolone (20 mg, daily). Prednisolone was ceased without recurrence on day 87. After recovering and undergoing rehabilitation, he was discharged on day 123 (Fig. 2).

Discussion

The present case suggests that rapid and severe thrombocytopenia can develop secondarily to influenza vaccination even in a very short latency time and that influenza vaccination potentially cause DAH. In the present case, it was difficult to differentiate alternative causes of thrombocytopenia including ITP, as the performable examinations were limited by the patient's severe condition. Given the very short la-

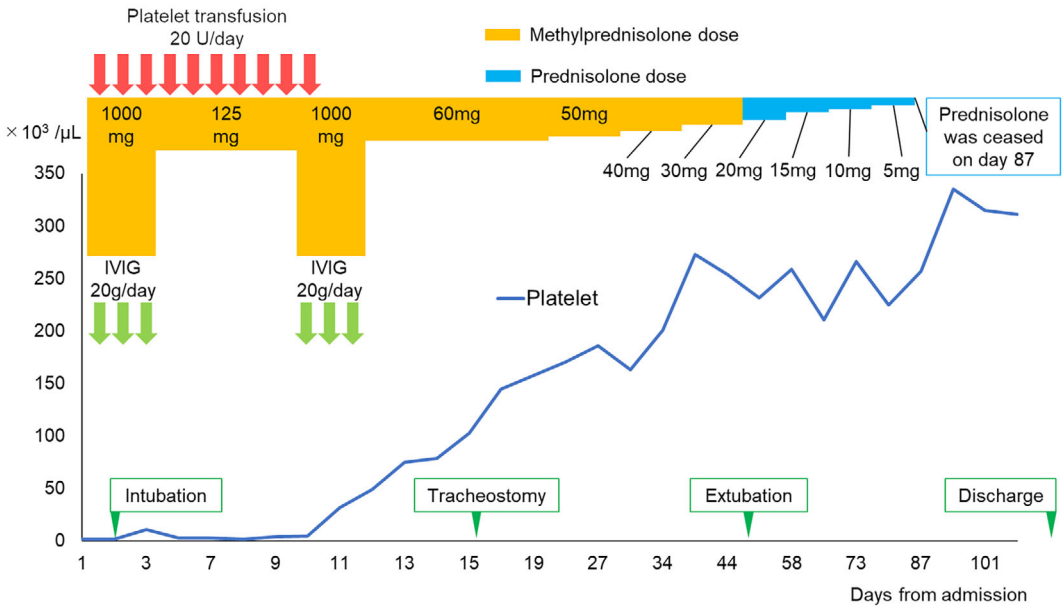

Figure 2. **The clinical courses during hospitalization. IVIG: intravenous immunoglobulin**

tency time and the success of stopping treatment, the patient might not have had primary ITP but rather vaccine-related thrombocytopenia.

The pathogenesis of vaccine-related thrombocytopenia has not been completely elucidated, but influenza vaccination can trigger secondary ITP (3, 5-7). The onset of vaccine-related ITP has a strict time relationship, developing within 4-35 days after influenza vaccination (4, 7). Treatment with glucocorticoids can be stopped in most reported cases of vaccine-related ITP (6-9). By contrast, 80% of patients with primary ITP develop chronic ITP (persistent for more than 1 year), necessitating additional therapies (10).

In the present case, glucocorticoid pulse therapy and IVIG were performed based on the severe conditions complicated by thrombocytopenia and DAH. Although no definite glucocorticoid dose has been reported in patients with severe thrombocytopenia and DAH, Uchiyama et al. reported that the combination of glucocorticoid pulse therapy, IVIG, and 2 mg/kg/day of methylprednisolone was effective (11). Thus, the present case was initially treated according to that report. The platelet count increased consequently, regardless of the patient's response to glucocorticoids; therefore, given the clinical course, primary ITP was considered unlikely. Although he had potentially been sensitized by the previous vaccination, vaccine-related ITP may also have been incompatible given the too-short latency time. Other pathogeneses of thrombocytopenia might therefore have been involved; however, the pathogenesis of vaccine-related thrombocytopenia remains unknown. Adjuvants contained in anti-influenza vaccines are unlikely to trigger thrombocytopenia (12); the major components of anti-influenza vaccines might therefore trigger thrombocytopenia.

In addition, a very low platelet count (<5×10^3/μL) often induces fatal complications, including subarachnoid or intracerebral bleeding and mucosal bleeding, but DAH is rarely reported (4, 11, 13-15). DAH is sometimes secondary to various immune reactions, such as autoimmune diseases and inflammation due to pulmonary infections (11, 15). However, no preceding infections or immune disorders were detected in this case. Given the patient's malaise and the inflammation before the onset of DAH, the influenza vaccine itself might have increased the vascular permeability and triggered DAH, although the mechanism remains unknown.

In conclusion, we encountered a case of vaccine-related thrombocytopenia and DAH that led to severe respiratory failure, from which a full recovery was achieved. The pathological role of influenza vaccination in thrombocytopenia and DAH remains unclear, and further investigations are required.

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

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References

1. Dieleman J, Romio S, Johansen K, et al. Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. BMJ **343**: d3908, 2011.
2. Martín Arias LH, Sanz R, Sáinz M, Treceño C, Carvajal A. Guillain-Barré syndrome and influenza vaccines: a meta-analysis. Vaccine **33**: 3773-3778, 2015.
3. Huang WT, Huang WI, Huang YW, Hsu CW, Chuang JH. The reporting completeness of a passive safety surveillance system for pandemic (H1N1) 2009 vaccines: a capture-recapture analysis. Vaccine **30**: 2168-2172, 2012.
4. Perricone C, Ceccarelli F, Nesher G, et al. Immune thrombocytopenic purpura (ITP) associated with vaccinations: a review of reported cases. Immunol Res **60**: 226-235, 2014.
5. Grimaldi-Bensouda L, Michel M, Aubrun E, et al. A case-control study to assess the risk of immune thrombocytopenia associated

with vaccines. Blood **120**: 4938-4944, 2012.

6. Ikegame K, Kaida K, Fujioka T, et al. Idiopathic thrombocytopenic purpura after influenza vaccination in a bone marrow transplantation recipient. Bone Marrow Transplant **38**: 323-324, 2006.

7. Nagasaki J, Manabe M, Ido K, et al. Postinfluenza vaccination idiopathic thrombocytopenic purpura in three elderly patients. Case Rep Hematol **2016**: 7913092, 2016.

8. Kelton JG. Vaccination-associated relapse of immune thrombocytopenia. JAMA **245**: 369-370, 1981.

9. Satoh E, Nei T, Kuzu S, et al. Acute lung injury accompanying alveolar hemorrhage associated with flu vaccination in the elderly. Intern Med **54**: 3193-3196, 2015.

10. Nazi I, Kelton JG, Larché M, et al. The effect of rituximab on vaccine responses in patients with immune thrombocytopenia. Blood **122**: 1946-1953, 2013.

11. Uchiyama M, Hattori A, Tanaka T, et al. Acute idiopathic thrombocytopenic purpura complicated with diffuse alveolar hemorrhage in an elderly patient. Intern Med **48**: 1449-1452, 2009.

12. Isai A, Durand J, Le Meur S, Hidalgo-Simon A, Kurz X. Autoimmune disorders after immunisation with Influenza A/H1N1 vaccines with and without adjuvant: EudraVigilance data and literature review. Vaccine **30**: 7123-7129, 2012.

13. Hashmi HRT, Venkatram S, Diaz-Fuentes G. A case report of an elderly woman with thrombocytopenia and bilateral lung infiltrates. Medicine (Baltimore) **94**: e2235, 2015.

14. Das S, Cherian S, Hamarneh W, et al. Diffuse alveolar hemorrhage secondary to idiopathic thrombocytopenic purpura; an extremely rare presentation. Chest **142**: 469A, 2012.

15. Kobayashi T, Tsuyuguchi K, Kasai T, Suzuki K. Pulmonary tuberculosis complicated with severe thrombocytopenia with diffuse alveolar hemorrhaging during anti-tuberculosis chemotherapy: an autopsy report. Intern Med **57**: 3285-3288, 2018.