CASE REPORT

Influenza Vaccination-associated Acute Thrombocytopenia and Diffuse Alveolar Hemorrhage: A Case Report

Yuji Yamamoto 1, Yuko Ohara 1,2, Ami Iwai 1, Reina Hara 1, Takanori Matsuki 1, Kiyoharu Fukushima 1, Yohei Oshitani 1, Hiroyuki Kagawa 1, Kazuyuki Tsujino 1, Kenji Yoshimura 1, Mari Miki 1, Keisuke Miki 1, Masahide Mori 1 and Hiroshi Kida 1

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, hematomata, and bloody stool. In addition, a very low platelet count (<5×10³/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 181×10³/μL. He received an influenza vaccine (A/Singapore/GP1908/2015(H1N1) pdm09, 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...
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°C, 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, 2×10^9/μL; erythrocyte count, 4.78×10^12/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, 8.0 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 of an acute left paratonsillar abscess.

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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 4.78×10^12/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 2×10^12/μL| HBs antigen negative                      |
| Coagulation         | HBV-DNA negative                           |
| PT-INR 1.13         | Anti-HCV core antibody negative            |
| APTT 29.3 sec.      | 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-mesales virus IgM negative            |
| ALT 27 U/L          | Anti-mesales virus IgG positive            |
| 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      | PaCO₂ 34.0 mmHg                            |
| Creatinine 0.92 mg/dL | PaO₂ 41.7 mmHg                           |
| Uric acid 6.7 mg/dL | HCO₃ 21.7 mmol/L                          |
| Sodium 137 mEq/L    | BE -1.5 mmol/L                            |
| Potassium 4.9 mEq/L | SaO₂ 72.2 %                                |
| Chloride 99.9 mEq/L |                                            |
| Glucose 216 mg/dL   |                                            |
| HbA1c (NGSP) 7.7 %  |                                            |
| C-reactive 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: hepatitis 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.
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 11x10^3/μL and the methylprednisolone dose was tapered to 125 mg daily on day 4. The platelet count fell to 2x10^3/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 103x10^3/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.

Exubation 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 latency time between vaccination and the onset of thrombocytopenia, the patient’s thrombocytopenia was probably secondary to influenza vaccination.
The clinic also carries out intravenous immunoglobulin (IVIG) treatment. The intravenous immunoglobulin therapy was given to the patient because of severe 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 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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