Exacerbation of connective tissue disease-associated interstitial lung disease due to influenza vaccination

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ARTICLE INFO

Keywords:
Influenza vaccine
Connective tissue disease-associated interstitial lung disease
CTD-ILD
Interstitial pneumonia

ABSTRACT

Vaccinations against influenza viruses are widely used all over the world. There are reports, however, of some associated adverse events, and there are some case reports of interstitial lung disease occurring after influenza vaccination. We experienced the case of exacerbation of connective tissue disease-associated interstitial lung disease (CTD-ILD) after influenza vaccination, and this is the first reported case, as far as we know. The patient responded quite well to corticosteroids administration. Influenza vaccination for patients with chronic lung disease including CTD-ILD is strongly recommended, but we should be aware of possible adverse events.

1. Introduction

Influenza is one of the most prevalent contagious diseases in the world and spreads every year. Influenza symptoms are mostly mild, although occasionally can be fatal, especially for the elderly and those with underlying diseases. Influenza vaccinations reduce the number of hospitalizations and deaths [1,2]. The European League Against Rheumatism (EULAR) strongly recommends that influenza vaccination should be considered for patients with autoimmune inflammatory rheumatic disease (AIIRD) [3]. However, there are some case reports that indicate a relationship between influenza vaccination and interstitial lung disease. We hereby report a case where influenza vaccination seems to have caused exacerbation of connective tissue disease-associated interstitial lung disease (CTD-ILD).

1.1. Case presentation

A 71-year-old woman was referred to our hospital for evaluation of fever, exertional dyspnea and fatigue in November 2020. She had received the influenza vaccine (A/Guangdong-Maonan/SWL/2019 [H1N1], A/HongKong/2671/2019 [H3N2], B/Phuket/3073/2013, and B/Victoria/705/2018) nine days before her visit. She was in good shape for 30 and quit at 60.

On examination her temperature was 38.7 °C, blood pressure was 120/70 mmHg, heart rate was 100/min, respiratory rate was 20/min and SpO2 was 94% (room air). She felt difficulty in breathing even when walking on level ground. A physical examination revealed fine crackles in both lung bases. Complete blood count revealed white blood cells at 10.0 * 10^9/L (with neutrophils comprising 77.9%, lymphocytes 12.3%, eosinophils 2.8%, and basophils 0.2%), mild anemia with hemoglobin of 10.1 g/dL, and a platelet count of 122,000 /μL. Biochemistry assays showed C-reactive protein (CRP) to be 15.07 mg/dL, lactate dehydrogenase (LDH) 310 U/L, soluble interleukin-2 receptor (sIL-2R) 1448 U/mL, and Krebs von den Lungen-6 (KL-6) 355 U/mL. Serology tests for anti-cyclic citrullinated peptide antibody (ACPA) were positive (21.8 U/mL), but was negative for any autoimmune markers.
and for infectious diseases including an influenza antigen test and SARS-CoV-2 PCR test. Chest radiograph and computed tomography revealed ground-glass opacities and infiltrates in both lungs and no enlarged lymph nodes to indicate the recurrence of lymphoma (Fig. 1A).

Based on the clinical course, influenza vaccination may have triggered the exacerbation of underlying interstitial lung disease and the progression of acute respiratory failure. Her fever came down to normal immediately after intravenous methylprednisolone administration at 1000 mg for 3 days. Thus, oral prednisolone administration at 40 mg was started and gradually tapered. KL-6 slightly rose to 566 U/mL, but other laboratory data improved (CRP 0.09 mg/dL, LDH 235 U/L, sIL-2R 476 U/mL). Her complaint of fatigue and exertional dyspnea gradually decreased day by day and chest radiograph showed improvement of bilateral ground-glass opacities. Hence, she left our hospital at the 15th hospital day (Fig. 2). The computed tomography performed 10 days after her discharge demonstrated almost complete vanishment of bilateral ground-glass opacities and infiltrates (Fig. 1B). No recurrence of interstitial pneumonia was observed. Oral prednisolone was withdrawn at four months.

2. Discussion

Influenza vaccine is one of the most prevalent inactivated vaccines and is administered all over the world. Based on the national law in Japan every elderly person over 65 years old and the persons over 60 years old with underlying diseases are designated to receive a vaccination annually. Consequently, over 50 million Japanese people get vaccinated every year. Its efficacy in decreasing hospitalization and the mortality rate of influenza has been reported by several researchers [1, 2]. It is said to be a relatively safe vaccination, but some adverse events including interstitial pneumonia are reported every year. According to the Ministry of Health, Labor and Welfare of Japan, 278 cases (0.00049%) were reported as adverse events due to influenza vaccination in the 2019 season, and three were suspected of vaccination-related interstitial pneumonia [4].

A systematic search of PubMed found nine case reports including 11 cases of interstitial lung disease associated with the influenza vaccine (Table) [5-13]. Nine patients of them survived due to early detection and corticosteroids administration, but the others died despite all efforts. Four patients had a medical history of chronic pulmonary disease (1 lung cancer, 1 extrinsic allergic alveolitis to parakeets, 2 idiopathic pulmonary fibrosis), but none had suffered from connective tissue disease-associated interstitial lung disease (CTD-ILD). As far as we know, this is the first reported case of CTD-ILD exacerbation caused by
Therefore, we prioritized treatment over diagnosis because the acute respiratory failure of this patient progressed rapidly. In addition, it was risky to perform the bronchoscopy, and methylprednisolone treatment is that we assumed it could be severe and not to perform unnecessary bronchoscopy exams during the COVID-19 pandemic [15]. In addition, it was risky to perform the bronchoscopy, and corticosteroid administration might have been unnecessary as the patient's condition is ameliorated. In retrospect, however, high-dose methylprednisolone treatment could prevent pneumonia from worsening. Thus, it is very important to tell patients to see doctor as soon as possible when there is something wrong after vaccination.

### 3. Conclusion

We experienced the case of the exacerbation of CTD-ILD due to influenza vaccination and early corticosteroids treatment achieved a favorable outcome. It is strongly recommended that the elderly and patients with chronic pulmonary disease including CTD-ILD should have influenza vaccination for the overall benefit, but physicians should also know that influenza vaccination can cause and exacerbate underlying interstitial lung disease. Early detection and corticosteroids administration could prevent pneumonia from worsening. Thus, it is very important to tell patients to see doctor as soon as possible when there is something wrong after vaccination.

### Declaration of competing interest

The authors state that they have no conflict of interest (COI) about this case report.

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