Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9399-17
Intern Med 57: 707-711, 2018
http://internmed.jp

【 CASE REPORT 】

Seasonal Influenza Vaccine-induced Pneumonitis Presenting with Multiple Pulmonary Nodules

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Abstract:
A 39-year-old woman received a seasonal influenza vaccine in November 2015 and subsequently experienced malaise, low-grade fever, and chest discomfort. A chest X-ray performed 2 weeks after vaccination showed multiple nodular shadows in both lungs and ground-glass shadows in both lower lung fields. Her bronchoalveolar lavage fluid contained an unusually high number of lymphocytes, and a drug-induced lymphocyte stimulation test for seasonal influenza vaccine was positive. Transbronchial lung biopsy revealed the presence of granulomatous inflammation. Thereafter her abnormal chest shadow spontaneously improved. Based on these findings, the patient was diagnosed with drug-induced pneumonitis due to an influenza vaccine.

Key words: drug-induced pneumonitis, seasonal influenza vaccine, multiple nodules, granuloma, drug-induced lymphocyte stimulation test

(Intern Med 57: 707-711, 2018)
(DOI: 10.2169/internalmedicine.9399-17)

Introduction

Annual seasonal influenza vaccination is recommended for elderly people in Japan to prevent them from contracting influenza or serious related conditions. Its common side effects include reddening, swelling, and pain at the vaccination site. Other side effects, such as low-grade fever, headache, and malaise, may sometimes occur but usually improve within a few days. We herein report the case of a patient who experienced persistent low-grade fever and malaise after seasonal influenza vaccination. A chest X-ray obtained 2 weeks after vaccination showed rare imaging characteristics that were consistent with drug-induced pneumonitis.

Case Report

A 39-year-old woman received a seasonal influenza vaccine in November 2015. Approximately 6 hours later, she developed a low-grade fever and experienced malaise and chest discomfort. Four days later, she presented to our hospital's Department of Internal Medicine, where she was prescribed clarithromycin and acetaminophen. Although her symptoms showed some improvement, they did not disappear completely. She was reexamined 2 weeks after the vaccination, at which time a chest X-ray revealed multiple nodular shadows in both lungs and ground-glass shadows in both lower lung fields (Fig. 1). She was admitted to hospital for further investigation and treatment.

The patient's previous medical history included bronchial asthma, lumbar disk herniation, mammary adenoma, ureteral stones, and sensitivity to sunlight, which was treated with olopatadine. She did not smoke and had not previously suffered an allergic reaction to clarithromycin, acetaminophen, or seasonal influenza vaccines. In addition, abnormal shadows were not pointed out in chest X-ray that had been taken at a medical examination six months previously.

On admission, the patient's temperature was 37.8℃ and her arterial blood oxygen saturation (SpO_2) level was 96%. The only noteworthy physical finding was mild fine crackles in both lower lung fields. Computed tomography (CT) revealed multiple nodular shadows in both lungs, ground-glass shadows that were predominantly located in the lower lobes, a small amount of pleural effusion, and mild mediastinal

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Received: April 25, 2017; Accepted: June 12, 2017; Advance Publication by J-STAGE: November 1, 2017
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lymph node enlargement. The nodular shadows were randomly distributed and somewhat ill-defined (Fig. 2A).

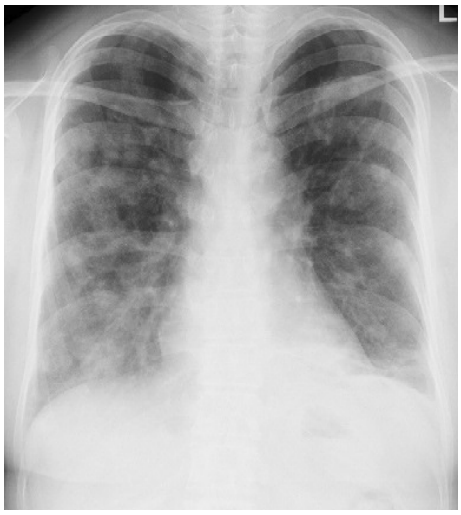

Figure 1. A chest X-ray obtained on admission shows multiple nodular shadows in both lungs and ground-glass shadows in both lower lung fields.

The laboratory test results are shown in Table. Other than an elevated C-reactive protein level, there were no signs suggesting mycosis, connective tissue disease, or vasculitis, and tests for tumor markers were negative. On bronchoscopy, bronchoalveolar lavage (BAL) was performed from the right middle lobe bronchus (right B^4), and a transbronchial lung biopsy (TBLB) specimen was obtained from the right lower lobe bronchus (right B^8). The BAL fluid contained 3.36×10^5/mL cells: 58% lymphocytes, 12% neutrophils, 7% eosinophils, and 23% alveolar macrophages; the proportion of lymphocytes was unusually high. The CD4/CD8 ratio was 1.94. Bacterial cultures were negative, and polymerase chain reactions to detect *Mycobacterium tuberculosis* and *Mycobacterium avium complex* were negative.

The histopathological examination of the TBLB specimen revealed granulomatous inflammation with alveolar macrophage aggregations (Fig. 3). The regions of mild inflammation surrounding the aggregations were primarily populated by lymphocytes; multinucleated giant cells were also present, but no necrosis was evident. Periodic acid-Schiff, Grocott, and Ziehl-Neelsen staining were all negative, and Elastica van Gieson staining showed no apparent vasculitis.

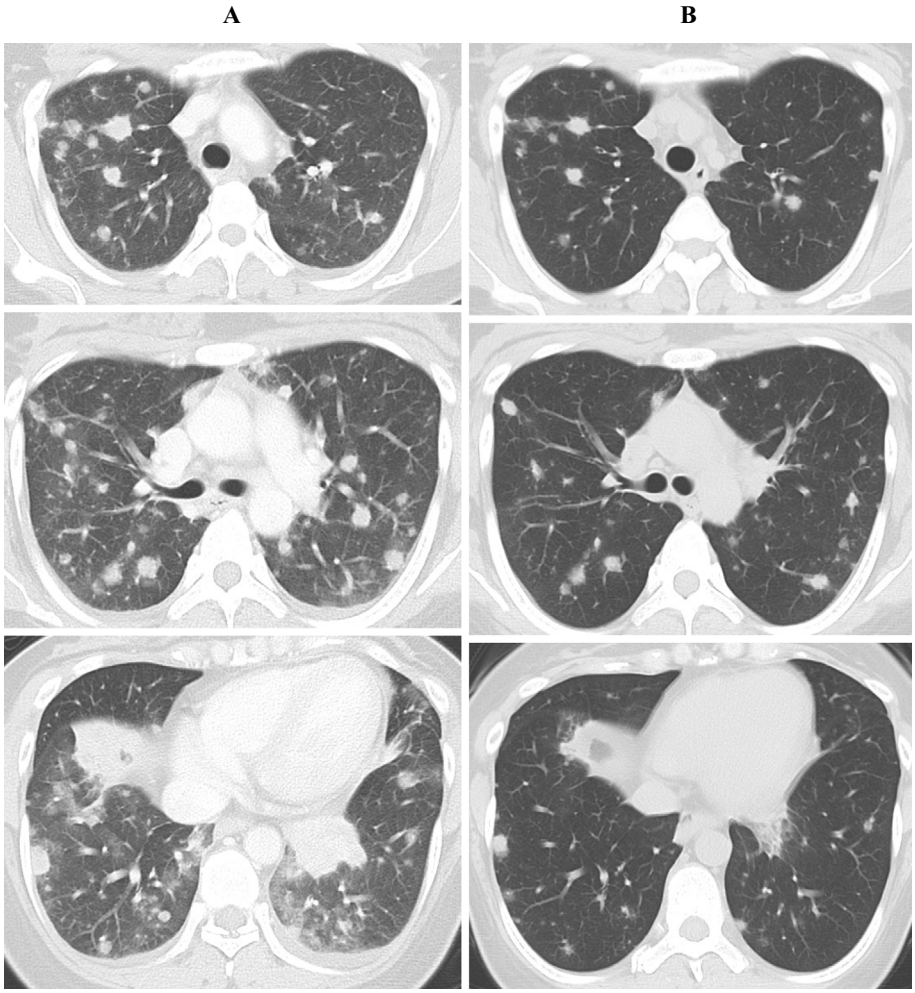

Figure 2. (A) A CT scan on admission. Bilateral multiple nodular shadows are seen in both lung fields. (B) One month after admission, the multiple nodular shadows were found to have decreased in size.

Table. **Laboratory Data on Admission.**

Complete blood counts		Serological studies	
WBC	7,100 /μL	CRP	4.65 mg/dL
Neutrophils	64.5 %	PCT	0.04 ng/mL
Lymphocytes	24.2 %	β-D-glucan	<5.0 pg/mL
Monocytes	7.3 %	Cryptococcus Ag	(-)
Eosinophils	3.9 %	Aspergilllus Ag	(-)
Hb	12.6 g/dL	KL-6	326 U/mL (<500)
Plt	334×10^3 /μL	ANA	<×40
Blood chemistry		PR3-ANCA	<1.0 U/mL
TP	6.3 g/dL	MPO-ANCA	<1.0 U/mL
Alb	3.2 g/dL	ACE	10.0 IU/L (8.3-21.4)
AST	17 IU/L	CEA	0.9 ng/mL (<5.0)
ALT	11 IU/L	CA19-9	11.8 U/mL (<37)
LDH	253 IU/L	CYFRA	0.9 ng/mL (<3.5)
T-Bil	0.2 mg/dL	Pro-GRP	35.4 pg/mL (<65)
BUN	7.5 mg/dL	NCC-ST-439	2.6 U/mL (<7.0)
Cre	0.44 mg/dL	Arterial blood gases (Room air)	
Na	137 mEq/L	pH	7.422
K	4.2 mEq/L	$PaCO_2$	44.2 torr
BS	133 mg/dL	PaO_2	74.1 torr
		HCO_3^-	28.2 mmol/L

TP: total protein, Alb: albumin, BS: blood sugar, CRP: C-reactive protein, PCT: procalcitonin, KL-6: Krebs von den Lungen-6, ANA: anti-nuclear antibody, PR3-ANCA: proteinase-3 anti-neutrophil cytoplasmic antibody, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, ACE: angiotensin converting enzyme, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, CYFRA: cytokeratin-19 fragment, Pro-GRP: pro-gastrin releasing peptide, NCC-ST-439: nation cancer center-stomach-439

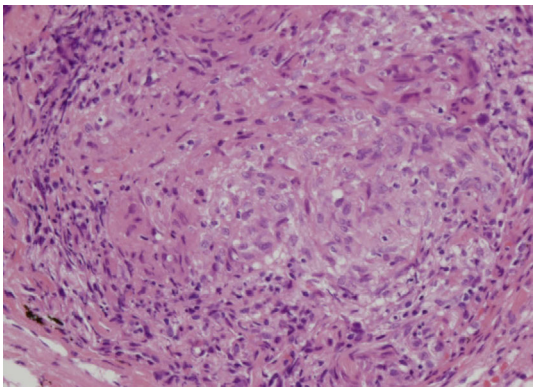

Figure 3. **The histological examination of the TBLB specimen revealed granulomatous inflammation with the aggregation of histiocytes (Hematoxylin and Eosin staining, ×100). TBLB: trans bronchial lung biopsy**

In a drug-induced lymphocyte stimulation test (DLST) for the seasonal influenza vaccine, the stimulation index was positive in both the peripheral blood (3.90) and the BAL fluid (3.53). After admission, the multiple nodular shadows decreased in size without treatment, and the ground-glass shadows and pleural effusion essentially disappeared (Fig. 2B). Based on the clinical course and the test results, drug-induced pneumonitis due to the seasonal influenza vaccine was diagnosed. At the time of writing, six months after her admission, the patient remains under observation (including imaging), and the nodular shadows have gradually continued to fade.

Discussion

An unusual feature of this case was the appearance of multiple nodules on chest X-rays and the presence of granulomas in pathological specimens. A previous case of drug-induced pneumonitis due to seasonal influenza vaccine involved ground-grass opacities with some interlobular septal thickening on images and organizing pneumonia on pathology (1). Drug-induced pneumonitis has a wide range of pathological manifestations, which are distinguishable by imaging (2, 3). The typical manifestation is diffuse infiltration or ground-glass shadows in both lungs, whereas the presence of multiple nodules is considered rare. Several cases of multiple nodules due to bleomycin were reported in the 1980s (4-9), and scattered cases of multiple nodules due to ticlopidine (10), minocycline (11), fludarabine (12), amiodarone (13), and salazosulfapyridine (14) were reported thereafter; however, the pathological presentations in all of these cases included interstitial fibrosis and intraluminal organizations, with lymphocytic or eosinophilic infiltration. There are no reported cases of the granuloma type that was seen in our patient. Although granulomas have been observed in the cases of drug-induced pneumonitis associated with methotrexate (15), everolimus (16), and the Bacillus Calmette-Guérin (BCG) vaccine (17), the CT findings in those cases did not resemble the findings in our patient.

Camus et al. categorized nodule opacity on CT scans as micronodular or macronodular (2). These investigators associated BCG and methotrexate with micronodular opacities that present pathologically as granulomas, and amiodarone and bleomycin with macronodular opacities that present pathologically as organizing pneumonia. The CT pattern in our patient was considered to be macronodular. However, because the pathological diagnosis in this case was based on tiny samples obtained by TBLB, it is possible that the nodules may not represent granulomas. On the other hand, some patients exhibit more than one pathological pattern, and several different patterns may be simultaneously present on CT scans (18, 19).

The diagnostic criteria for drug-induced pneumonitis that were established by Camus et al. do not include a positive DLST result (2). In a previous study, 66.9% of 175 patients with this disorder showed a positive DLST result (20). Many studies have used the DLST to diagnose drug-induced pneumonitis in response to vaccines other than the influenza vaccine, especially in Japan; however, the false negative results in a previous report (21) have hampered universal recognition of its effectiveness. Our study showed positive DLST results in both the blood and BAL fluid. This was in agreement with another study in which the BAL fluid of a patient with drug-induced pneumonitis due to seasonal influenza vaccine showed DLST positivity (1). We considered the DLST to be a useful tool for diagnosing drug-induced pneumonitis; however, we relied on our overall assessment.

It is extremely interesting that the patient in our report developed the side effects described in the present case, as she had not previously experienced an allergic reaction to a seasonal influenza vaccine. After April 2015, the influenza vaccine was changed to include four viral strains rather than three; however, according to the manufacturer's Interview Form, this did not entail any alterations in the processing or excipients of the vaccine (22). On the Pharmaceutical and Medical Devices Agency website, the number of cases of drug-induced pneumonitis due to seasonal influenza vaccines was the same as in previous years (23), despite the increase in the number of strains. The antigenicity of the influenza virus frequently shows slight changes from year to year, and vaccines typically include the most prevalent strains. Such changes may account for the side effects reported in the present case. We instructed the patient to forego influenza vaccinations in the future.

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

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