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Influenza vaccine-induced interstitial lung disease

To the Editor:

Influenza is a serious disease that can spread around the world in seasonal epidemics, resulting in the deaths of an estimated 250,000 to 500,000 people every year [1]. Vaccination is the most effective method for preventing secondary complications and the risk of influenza-related hospitalisation and death. The influenza vaccine is safe in general, and the most common side-effects, such as injection-site reaction, pain, fever, myalgia and headache, are not important clinically [2]. However, a few case reports of interstitial lung disease (ILD) caused by influenza vaccine have been published. We report a case of influenza vaccine-induced ILD with a review of the literature.

A 75-yr-old female was referred to our hospital (Komatsu Municipal Hospital, Komatsu, Japan) for evaluation of fever and chest radiograph abnormalities in November 2011. 2 weeks previously she had received the influenza vaccine (trivalent inactivated vaccine: A/California/7/2009 [H1N1]-like, A/Victoria/210/2009 [H3N2]-like, and B/Brisbane/60/2008-like antigens). She had developed a fever 1 week before admission, and a chest radiograph revealed patchy airspace infiltrates in both lungs (fig. 1a). She received garenoxacin without any improvement and was then referred to our hospital for further evaluation. She had a medical history of hypertension, anaemia and chronic renal failure due to diabetes, and had started regular haemodialysis at the age of 74 yrs. She had no past history of pulmonary disease and her chest radiograph the previous month was normal. Her medications included valsartan, furosemide, isosorbide dinitrate and cilnidipine, which had remained unchanged for 2 yrs. She also had an insulin injection every day. She was a nonsmoker and had no allergies to foods or drugs.

On examination her blood pressure was 154/47 mmHg, heart rate was 98 beats·min^{-1}, oxygen saturation was 96% on room air and her temperature was 37.7°C. Physical examination revealed no abnormalities. Chest computed tomography (CT) revealed bilateral ground-glass opacities and patchy infiltration in a predominantly peribronchial and subpleural distribution (fig. 1b). Laboratory findings revealed C-reactive protein of 5.5 mg·L^{-1} and lactate dehydrogenase level of 539 IU·L^{-1}. Serology tests for several autoimmune markers and tumour markers were negative. The serum levels of Krebs von den Lungen-6 (KL-6), surfactant protein-D (SP-D) and surfactant protein-A (SP-A) were increased to 1,720 U·mL^{-1} (normal range <500 U·mL^{-1}), 924 ng·mL^{-1} (normal range <110 ng·mL^{-1}) and 115 ng·mL^{-1} (normal range <43.8 ng·mL^{-1}), respectively. Pulmonary function tests were: forced vital capacity (FVC) 1.46 L (normal range 68.2% predicted); forced expiratory volume in 1 s (FEV_1) 1.31 L (normal range 95.6% pred); FEV_1/FVC ratio 89.7%; and diffusing capacity of the lung for carbon monoxide 5.52 mL·min^{-1}·mmHg^{-1} (normal range 28.2% pred). There were no abnormalities seen on echocardiography. The findings of the bronchoalveolar lavage (BAL) fluid revealed 45.0% macrophages, 52.7% lymphocytes, 0.3% neutrophils and 2.0% eosinophils. The CD4+/CD8+ ratio of lymphocytes was 1.18. BAL fluid cultures for bacteria, fungi and mycobacteria were negative, and cytology was unremarkable. Transbronchial lung biopsy (TBLB) specimens revealed interstitial inflammation with lymphocytes, mild interstitial fibrosis, and reactive hyperplastic type II pneumocytes. There were no findings of infection, granuloma or malignancy. These findings were consistent with a diagnosis of ILD.

Based on the clinical course, a possible cause was influenza vaccination. The temporal relationship between influenza vaccination and clinical symptoms argued strongly for a causative role of this agent. Several evaluations support the assessment that the ILD could not be explained by other causes, including infections, collagen vascular disease, granulomatous or pulmonary oedema. A drug lymphocyte stimulation test (DLST) on her peripheral lymphocytes gave a positive reaction to the influenza vaccine with a stimulation index of 296% (normal range <180%).

She was started on oral prednisolone at 30 mg daily. Her symptoms and laboratory data were remarkably improved (C-reactive protein 0.1 mg·L^{-1}, lactate dehydrogenase 207 IU·L^{-1}, KL-6 175 U·mL^{-1}, SP-D 17.2 ng·mL^{-1}, SP-A 60.9 ng·mL^{-1}), and the repeated chest radiograph and CT demonstrated almost complete resolution of the bilateral opacities (fig. 1c and d). Prednisolone was then subsequently tapered and was withdrawn at 2 months. She has been observed without recurrence.

Influenza vaccine-induced ILD is rare, and very few studies have focused on the disease. According to the vaccine adverse event reporting system established by the Centers for Disease Control and Prevention and the Food and Drug Administration

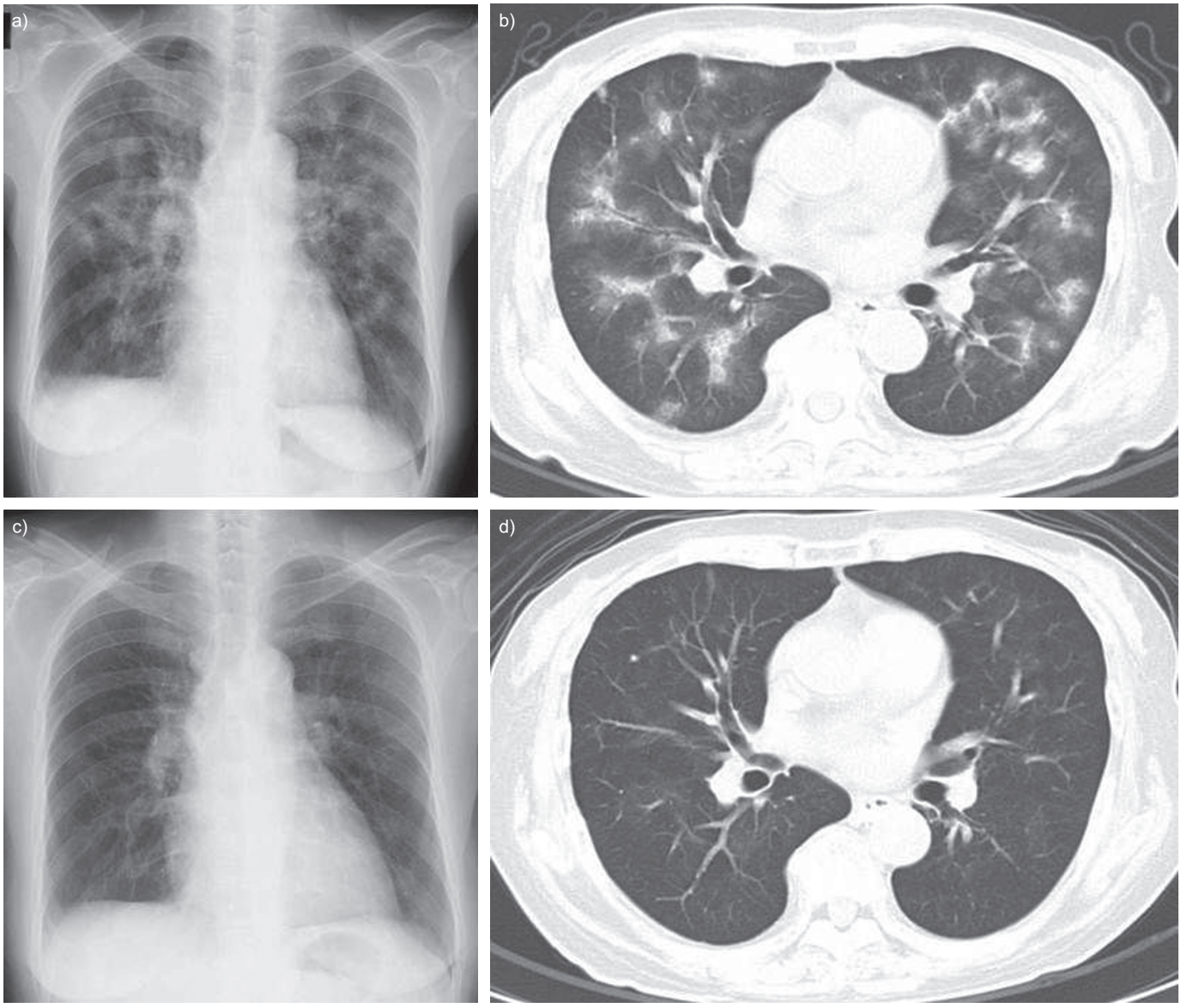

FIGURE 1. a) Chest radiograph showing patchy airspace infiltrates in both lungs. b) Chest computed tomography (CT) image showing bilateral ground-glass opacities and patchy infiltration in predominantly peribronchial and subpleural distribution. c) Chest radiograph and d) CT after 4 weeks of follow-up showing almost complete resolution of the bilateral opacities.

between 1990 and 2011, only three cases of ILD after influenza vaccination have been reported [3]. However, details of the cases were not listed.

A review of the literature found a total of six cases of influenza vaccine-induced interstitial lung disease (table 1) [4–9]. Including the present case, the median age was 59 yrs and four patients were male. The time of onset was 1–2 days after vaccination in four patients and 6–10 days in three patients. Four patients had pre-existing lung diseases, including lungs in the post-operative state. The common clinical symptoms included fever (n=6) and dyspnoea (n=5). The findings of chest CT scans were bilateral ground-glass opacities and/or patchy infiltration. All patients recovered after treatment with corticosteroids and survived. However, the ILD of cases 4 and 5 became severe, and aggressive treatments, including mechanical ventilation, were required.

The mechanism of drug-induced ILD is not well understood. However, two mechanisms have been proposed: cytotoxic lung injury and immune-mediated lung injury [10]. In our patient, immune-mediated reaction of the lung to the vaccine was suspected, based on the lymphocytic alveolitis in the BAL fluid and TBLB, efficacy of corticosteroid, and a positive DLST. These findings are consistent with other cases. TBLB performed in two cases (cases 3 and 6) revealed interstitial lymphocyte infiltration. All cases were improved by corticosteroids. DLST was performed in two cases (cases 3 and 6) and both were positive. DLST measures the proliferation of T-cells to a drug *in vitro* [11]. Although data as to the sensitivity and specificity of the DLST is lacking and it is not always helpful for the diagnosis of drug hypersensitivity, in this case there was immune-mediated reaction of T-cells to the vaccine.

TABLE 1 Summary of the seven reviewed cases

Case	First author [ref.]	Vaccine	Sex	Age yrs	Onset of ILD day	Previous illness	Symptoms	Chest CT	Treatment	Outcome
1	JOHNSTON [4]	NA	M	58	10	Pneumothoraces (after lobectomy), arthritis, AMI, nephrolithiasis	Fever, dyspnoea, weight loss	NA	Corticosteroids	Survival
2	HEINRICHS [5]	2009, seasonal	F	59	6	Extrinsic allergic alveolitis to parakeets	Fever, dyspnoea, joint pain	Bilateral GGO, patchy infiltration	Corticosteroids	Survival
3	KANEMITSU [6]	2009, seasonal	M	74	1	GERD	Fever, dry cough	Bilateral patchy infiltration	Corticosteroids	Survival
4	BHURAYANONTACHAI [7]	2009, H1N1	F	38	1	None	Dyspnoea, myalgia	Bilateral lung infiltration	NA (aggressive treatment)	Survival
5	UMEDA [8]	2009, H1N1	M	57	2	Idiopathic pulmonary fibrosis	Fever, dyspnoea	Bilateral GGO	Corticosteroids, CPA, CyA, sivelestat, PMX-DHP	Survival
6	KUMAMOTO [9]	2009, H1N1	M	61	2	Lung cancer (after lobectomy and chemotherapy)	Fever, dyspnoea, dry cough	Bilateral GGO	Corticosteroids	Survival
7	Present study	2011, seasonal	F	75	7	Blood pressure, diabetes, dialysis	Fever	Bilateral patchy infiltration	Corticosteroids	Survival

ILD: interstitial lung disease; CT: computed tomography; AMI: acute myocardial infarction; GERD: gastro-oesophageal reflux disease; GGO: ground-glass opacities; NA: not available; CPA: cyclophosphamide; CyA: cyclosporine A; PMX-DHP: polymyxin-B direct hemoperfusion.

From the literature review, we hypothesise about some risk factors for ILD. First, pre-existing lung disease, including lungs in the post-operative state, may be a risk factor. Four patients had pre-existing lung disease and especially case 5 developed an acute exacerbation of idiopathic pulmonary fibrosis. Secondly, pandemic influenza A (H1N1) vaccine may be associated with the occurrence of ILD. Three patients (case 4, 5 and 6) were given monovalent H1N1 vaccine, and our patient was given a vaccine which contains H1N1-like antigen. Finally, genetic background may be a risk factor, because most of the cases are reported from Asia. However, the limitations of this review include the small number of cases reporting bias and incomplete information in several sources of data. To evaluate the association between influenza vaccine-related ILD and these factors, further clinical or observational studies in more patients are needed.

In conclusion, influenza vaccination is the most effective and safe method for preventing influenza-related serious events. Clinicians should be aware of the risk for ILD induced by influenza vaccine. It may become serious without treatment, but early detection and treatment lead to complete remission. Careful clinical history and examination are needed in any vaccinated patients with unexplained fever and/or dyspnoea.

Satoshi Watanabe*, Yuko Waseda*, Hazuki Takato*, Kanako Inuzuka*, Nobuyuki Katayama*, Kazuo Kasahara* and Masaki Fujimura#

*Dept of Respiratory Medicine, Cellular Transplantation Biology, Kanazawa University Graduate School of Medicine, Kanazawa, and #Dept of Respiratory Medicine, National Hospital Organization, Nanao Hospital, Nanao, Japan.

Correspondence: S. Watanabe, Dept of Respiratory Medicine, Cellular Transplantation Biology, Kanazawa University Graduate School of Medicine, 13-1, Takara-machi, Kanazawa 920-8641, Japan. E-mail: swatanabe@staff.kanazawa-u.ac.jp

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Bronchial endoscopic ultrasound elastography: preliminary feasibility data

To the Editor:

Medical elastography consists of biomechanically characterising a zone of tissue on the basis of its response to the application of mechanical stress. This stress can be quasistatic (local compression) or vibratory (propagation of shear waves). In the various medical applications of elastography, the response to the stress is described by mapping the tensile modulus, or Young's modulus. Young's modulus corresponds to the slope of the stress–strain relationship measured during a series of tensile tests [1]. The elasticity of a tissue depends on its nature, its state (fat infiltration or fibrosis) and its homogeneity. A tumour situated in a zone of healthy tissue can, therefore, be detected by its decreased elasticity. The tumour can also be described in space, based on the principle that within anisotropic materials (typically represented by heterogeneous tissues), the value of Young's modulus varies as a function of the direction of the force applied to the material tested. Simple colour coding of the tensile response provides mapping of the elasticity of the zone examined. Very hard tissues are generally coded as blue, while soft tissues are coded as red and intermediate tissues are coded as green.

Elastography is now used in various fields of medicine, often in combination with ultrasound (ultrasound elastography, sometimes called computer-assisted palpation). It has been applied to the diagnosis of breast [2], thyroid [3] and prostate tumours [4], in vascular disease [5], and in hepatology [6]. Elastography has also been combined with gastrointestinal endoscopic ultrasound to investigate pancreatic masses [7] and nodal invasion by rectal cancer [8]. A recent meta-analysis of the performances of gastrointestinal endoscopic ultrasound elastography to distinguish between benign and malignant lymph nodes concluded to a sensitivity of 88%, a specificity of 85% and an area under the receiver operating characteristics curve of 0.9456 [9]. These performances are superior to those of endoscopic ultrasound alone [10].

To our knowledge, elastography in combination with bronchial endoscopic ultrasound has not yet been evaluated. We report preliminary feasibility data and the first evaluation of this technique. This study was approved by the local ethics committee (Comité de Protection des Personnes Ile-de-France 6 Pitié-Salpêtrière, Paris, France).

All patients referred to our centre for assessment of mediastinal lymphadenopathy between February and May 2012 were studied by bronchial endoscopic ultrasound elastography under light general anaesthesia (10 patients, 13 lymph node areas measuring 10–30 mm). Real-time elastographic mapping was performed using an ultrasound elastography module incorporated into a ultrasound machine (Hi-vision Avius®; Hitachi Medical Systems, Kashiwa, Japan) coupled with a bronchial endoscopic ultrasound probe (EB1970 video bronchoscope; Pentax, Tokyo, Japan). Elasticity colour mapping was performed for each lymph node studied by superimposing the colour coding of tensile responses with the endoscopic B-mode ultrasound image and by defining the frequency histogram of the responses in the zone studied. Transbronchial needle aspiration (TBNA) was performed in each case using a 22-gauge needle (sono Tip® EBUS; MediGlobe, Rosenheim, Germany) by targeting, as far as possible, the zone identified as being the least elastic.

Colour mapping of the tissue studied and the corresponding elasticity histogram were obtained in every case (fig. 1). The elastography module proved easy to use and prolonged the examination time by only a few minutes. The five lymph nodes demonstrated to be malignant on histological examination of the TBNA material were characterised by decreased elasticity (dominant blue colour, elasticity ranging from 10 to 49 on the histogram and >80% of the tissue considered to be ''hard'' in the target zone) (table 1). No malignant cell was identified in the other eight lymph nodes (elasticity ranging from 55 to 167 and 6–71% hard zones) regardless of the final diagnosis. Although discussing specificity and sensitivity is not reasonably possible with such a small sample, these preliminary results are consistent with the results published for gastrointestinal endoscopic ultrasound [9, 10]. Notably, mediastinoscopy was not performed in those of our patients where TBNA did not provide diagnostic proof because a therapeutic decision was taken based on other factors (table 1). In future