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Case Report

Influenza A Virus Infection and Pulmonary Microthromboembolism

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Ohrui, T., Takahashi, H., Ebihara, S., Matsui, T., Nakayama, K. and Sasaki, H. *Influenza A Virus Infection and Pulmonary Microthromboembolism.* Tohoku J. Exp. Med., 2000, **192** (1), 81-86 —— This report presents the cases of two patients with rapidly progressive hypoxemia associated with influenza A(H3N2) virus infection, who were diagnosed with influenza related acute pulmonary microthromboembolism by serum D-dimer, lung perfusion and ventilation scans and computed-tomography scan of the chest, and were successfully treated by anti-coagulant therapy. The present cases suggest that acute onset pulmonary microthromboembolism should be considered in some patients with sudden, unexplained dyspnea during an outbreak of influenza infection and prompt diagnosis is essential to save the patient from acute death associated with influenza. ——
influenza; hypoxemia; D-dimer; pulmonary perfusion scan; anti-coagulant therapy © 2000 Tohoku University Medical Press

Influenza has been a significant and highly contagious disease of global importance for a long time. Influenza is an acute febrile illness caused by infection with influenza type A or B virus that occurs in outbreaks of varying severity almost every winter (Francis and Maassab 1965). In addition to the enormous morbidity that accompanies epidemic or pandemic influenza, substantial mortality is also associated with such outbreaks (Francis and Maassab 1965). Among several complications of influenza related to the high mortality, pulmonary complications are grave, especially in the elderly (Fry 1959).

According to the Ministry of Health and Welfare, nearly 1300 people died of influenza virus infection during the 1998-1999 outbreak in Japan, of whom 90% were senior citizens. Some of these patients were reported to have died suddenly, due to acute respiratory failure without overt pneumonia.

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We report two patients with rapidly progressive hypoxemia associated with influenza A(H3N2) virus infection, who were diagnosed with influenza related acute pulmonary microthromboembolism by serum D-dimer, lung perfusion and ventilation scans and a computed-tomography (CT) scan of the chest, and were successfully treated by anti-coagulant therapy.

Case Report

Patient 1, an 86-year-old woman was admitted to hospital with rapidly progressive dyspnea in January, 1999. She had been well until 2 days before presentation with high grade fever (39.6°C), dry cough and myalgia. Her past history was important only for mild, well-controlled hypertension. On examination, she was breathless, her respiratory rate was 28/minute, and her pulse rate was 108 beats/minute. Analysis of blood gas revealed severe hypoxemia (PaO_2 33 mmHg), hypocarbia ($PaCO_2$ 28 mmHg), and pH 7.55 under air breathing. A chest radiograph showed dilated pulmonary arteries, but no infiltration in the lung fields (Fig. 1). A CT scan of the chest showed dilatation of the bilateral pulmonary arteries, but no infiltration in the lung fields (Fig. 2). Sputum and blood cultures were negative. Lung function tests showed a normal vital capacity of 78% predicted and a normal forced expiratory volume in one second % (86%). The blood test showed leukopenia (2400/mm^3), thrombocytopenia (10×10^4/mm^3), and a normal red blood cell count (391×10^4/mm^3). Blood coagulation tests were normal. However, a serum level of D-dimer increased to 415 ng/ml (normal range $<$ 150 ng/ml), strongly suggesting the existence of venous thrombi

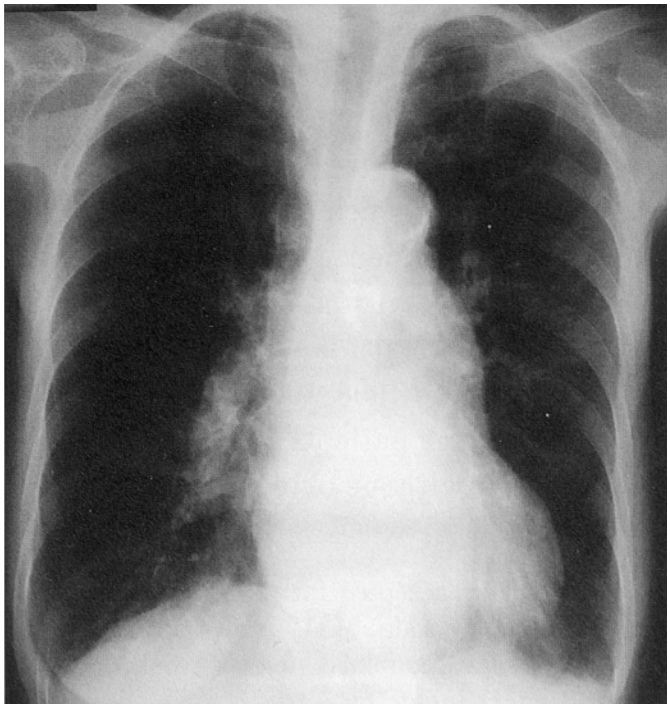

Fig. 1. Chest radiograph showing dilated pulmonary arteries, but no infiltration in the lung fields.

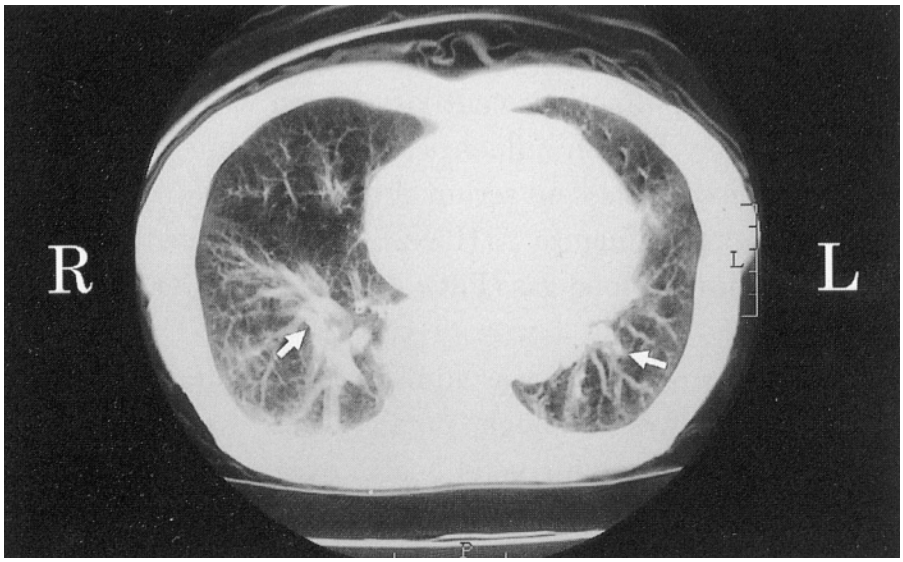

Fig. 2. Computed-tomography (CT) scan of the lower chest performed shortly after admission showed dilatation of the bilateral lower pulmonary arteries (arrows).

(Perrier et al. 1999). A pulmonary perfusion scan showed multiple small defects in bilateral lung fields (Fig. 3). By contrast, a pulmonary ventilation scan was normal. An ultrasound examination of the heart revealed substantial enlargement of the right ventricle, without overt valvular disorders. Lower-limb ultrasonography did not detect the existence of deep vein thrombosis. Permission for a pulmonary angiography was not obtained.

A possible diagnosis of pulmonary microthromboembolism associated with influenza virus infection was made and she was intensively treated with oxygen, 5000 IU/day of heparin and 60 000 IU/day of urokinase for 5 days. On day 3 after admission, her condition improved. On day 7 after admission, the

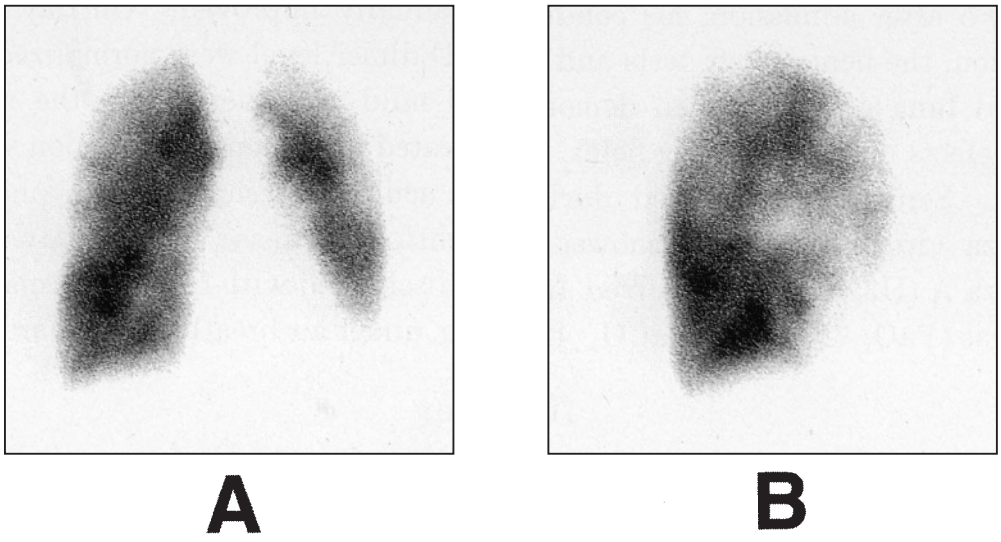

Fig. 3. Pulmonary perfusion scan performed on day 2 after admission. A: Antero-posterior view. B: Right lateral view.

hematology tests and D-dimer level were normalized, and a repeated lung perfusion scan demonstrated slight improvement in the multiple small defects in both lung fields. A repeated pulmonary ventilation scan was normal. Sera obtained on the third hospital day had an influenza A complement-fixing antibody titer of less than 1 : 32 and the convalescent serum obtained three weeks thereafter showed a titer of 1 : 2048 against influenza A(H3N2). She survived and was discharged with mild abnormalities in blood gas (PaO_2 69 mmHg, $PaCO_2$ 36 mmHg, under air breathing) in February 1999.

Patient 2, an 81-year-old man was admitted to hospital for acute shortness of breath following three days of cough, myalgia and malaise in February 1999. The patient had been in relatively good health except for benign prostate hypertrophy. Initial examination showed the pulse rate to be 102 beats per minute; respirations, 26 per minute; and temperature, 40.1°C. Results of chest examination were entirely normal. Arterial blood gases were PaO_2 45.9 mmHg, $PaCO_2$ 41.3 mmHg and pH 7.402 under air breathing. Laboratory studies showed a hematocrit value of 39%, a white blood cell count of 5000/mm^3, and a platelet count of 17×10^4/mm^3. A serum level of D-dimer increased to 550 ng/ml. Other coagulation studies disclosed no abnormalities. Blood and sputum cultures were negative. Lung function tests showed a normal vital capacity of 88% predicted and a normal forced expiratory volume in one second% (82%). A chest x-ray film and a CT scan of the chest were almost normal, except for dilatation of the bilateral pulmonary arteries. A pulmonary perfusion scan showed multiple small defects in both lung fields with a normal ventilation scan. A pulmonary angiography could not be performed because of sustained high grade fever. An ultrasound examination of the heart revealed substantial enlargement of the right ventricle, without overt valvular disorders. Lower-limb ultrasonography did not detect the existence of deep vein thrombosis. He was intensively treated with oxygen, 5000 IU/day of heparin and 60 000 IU/day of urokinase for five days. On day 5 after admission, his condition gradually improved. On day 10 after admission, the hematology tests and serum D-dimer level were normalized, and a repeated lung perfusion scan demonstrated mild improvement in the multiple small defects in bilateral lung fields. A repeated pulmonary ventilation scan was normal. Serum was obtained during the acute and convalescent phases for influenza virus studies and showed an eightfold increase in antibody titer to influenza A (H3N2). He survived and was discharged with mild abnormalities in blood gas (PaO_2 72 mmHg, $PaCO_2$ 42 mmHg, under air breathing) in March, 1999.

Discussion

So far, there have been no reports describing the direct relevance of influenza infection to the occurrence of acute pulmonary microthromboembolism. Four cases of young women with influenza A infection, who had an initial diagnosis of pulmonary embolism that was finally disproved by the clinical course and by

repeated pulmonary perfusion scan or a pulmonary angiogram were reported (Lynn et al. 1977). In their study, pulmonary ventilation scans were not performed coincident with perfusion scans, and serum levels of D-dimer or fibrin degradation product, a direct evidence of intravascular coagulation, were not measured. Furthermore, two patients had overt pneumonia and the other two had histories of the use of contraceptives and pulmonary embolism.

In the present study, although we could not perform pulmonary angiography, two patients had clinical and laboratory findings strongly suggestive of pulmonary microthromboembolism. We diagnosed pulmonary microthromboembolism based on the clinical course, increased levels of serum D-dimer without findings of disseminated intravascular coagulation (DIC) and prolonged perfusion abnormalities with normal ventilation scans. The clinical symptoms and the abnormal lung perfusion scan can be usually attributed to influenza associated pneumonitis, which causes inflammatory exudate and hemorrage in the lower airways and alveoli (Lynn et al. 1977; Oda et al. 1989). To our knowledge, the present cases are the first patient with influenza A infection suffering from acute pulmonary microthromboembolism without overt pneumonitis. We could not detect any other risk factors for venous thrombosis than influenza viral infection in these patients. Both patients were successfully treated by anti-coagulant therapy and could survive with mild abnormalities in blood gas.

Previous studies have shown that certain viral infections can induce intravascular coagulation (McKay and Margaretten 1967). Possible mechanisms by which viruses can trigger the blood coagulation system include the hemagglutinating capacity of the virus itself (Francis and Maassab 1965), agglutination and lysis of platelets with release of coagulation factors into the circulation (Terada et al. 1966), the formation of procoagulant immune complexes from the combination of virus with circulating antibodies (McKay and Margaretten 1967), and the generation of oxygen free radicals (Oda et al. 1989). Oxygen free radicals are known to induce thrombosis in microvessels via activation of platelet aggregation (Jourdan et al. 1995). Influenza has been described as a cause of DIC which could account for coagulation abnormalities (Davison et al. 1973; Shenouda and Hatch 1976). In our two patients, the results of laboratory studies for DIC were negative and there were no symptoms suggestive of DIC.

During the past 15 years in the USA, the circulation of influenza A (H3N2) viruses has often been associated with more severe disease and with excess pneumonia and influenza mortality (Cox and Subbarao 1999). No virus specific factors have yet been identified to account for this trend. Influenza A (H3N2) seems to be more harmful than other serological types of influenza viruses in that it causes a high rate of complications, including pulmonary microthromboembolism.

The present cases suggest that acute onset pulmonary microthromboembolism should be considered in some patients with sudden, unexplained dyspnea during

an outbreak of influenza infection and prompt diagnosis is essential to save the patient from acute death associated with influenza.

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