Severe Pneumonia Caused by a Novel Influenza A (H1N1) Virus in an Asymptomatic Emphysematous Smoker

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Abstract

A 49-year-old female presented with diarrhea and a high fever followed by progressive dyspnea. Until this presentation, she had been healthy except for chronic dyspepsia and diarrhea. She had a smoking habit of 15 pack-years. Laboratory tests revealed lymphopenia, hypoalbuminemia and hypogammaglobulinemia. A rapid influenza test in combination with an RT-PCR assay revealed the presence of the novel influenza A (H1N1) virus. Chest computed tomography revealed centrilobular emphysema. This report suggests that regular smoking may become a risk for severe pneumonia in patients presenting with the novel influenza A (H1N1) virus, when accompanying asymptomatic emphysema is combined with other problems such as hypoalbuminemia and hypogammaglobulinemia.

Key words: novel influenza A (H1N1), viral pneumonia, centrilobular emphysema, smoking habits, hypoalbuminemia, hypogammaglobulinemia

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Introduction

An outbreak of a respiratory illness caused by the novel influenza A (H1N1) virus occurred worldwide spread since it was first identified in Mexico in late March 2009 (1, 2). Most confirmed cases of the novel influenza A (H1N1) virus infection were characterized by self-limited, uncomplicated febrile respiratory illness and symptoms similar to seasonal influenza (cough, sore throat, rhinorrhea, headache and myalgia), but approximately 20-30% of all such cases have also involved vomiting or diarrhea, neither of which is typical of seasonal influenza (3-5). From 2 to 7% of the patients confirmed to have the novel influenza A (H1N1) virus infection require hospitalization (6). A number of severe cases with confirmed novel influenza A (H1N1) virus infection including some instances of death have been reported in Japan since August 2009 (3).

The WHO guidelines report that the risk populations are infants and children aged under 5 years of age, the elderly over 65 years of age, nursing home residents, pregnant women, patients with chronic co-morbid conditions such as cardiovascular, respiratory (such as bronchial asthma) or liver diseases, and diabetes (6). It is important to identify the risk factors in individual patients in order to properly manage the disease. However, the novel influenza A (H1N1) virus also causes severe pneumonia infrequently in patients who are not normally considered to be included in the at-risk population. This report describes such a patient but with asymptomatic pulmonary emphysema and chronic dietary symptoms associated with a smoking habit. This case suggests the possibility that regular smoking with accompanying asymptomatic emphysema and chronic diarrhea may together be an important risk factor for severe pneumonia in a novel influenza A (H1N1) virus infection, while also discussing additional conditions which may promote the progression of respiratory diseases.

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A 49-year-old Japanese female visited a nearby clinic because of fever (38°C) and watery diarrhea. She had been healthy except for chronic dietary symptoms such as dyspepsia and diarrhea. She was a regular smoker with a history of 15 pack-years. A rapid influenza test against influenza A virus using a nasopharyngeal-swab specimen was negative. With treatment by antibiotics (Cefcapene pivoxil hydrochloride hydrate) for 4 days, high fever over 39°C and diarrhea sustained. In addition, she complained of dyspnea, and thus was referred to a local hospital. Her body temperature was 39.1°C, the heart rate was regular at 115 beats/min and the blood pressure was 103/38 mmHg. The oxygen saturation by pulse oximetry (SpO₂) was slow and thus was referred to a local hospital. Her body temperature was 39.1°C, the heart rate was regular at 115 beats/min and the blood pressure was 103/38 mmHg.

The laboratory findings showed leucopenia (3,440/µL), lymphopenia (310/µL), thrombocytopenia (13.5×10³/µL), and elevated levels of serum aspartate aminotransferase (AST, 56 U/L), lactate dehydrogenase (LD, 772 U/L), glucose (201 mg/dL), HbA1C 4.7% and CRP (17.47 mg/dL). Coagulation tests were normal. Hypogammaglobulinemia was observed (0.7 g/dL); the serum level of IgG, IgA and IgM was 578 (reference value: 870-1,700), 79 (110-350) and 37 (110-350) mg/dL, respectively. Antinuclear antibody was negative. HIV antibody, HBs antigen and HCV antibody were negative. The data of blood gas (FiO₂ 1.0) showed pH 7.455, PaO₂ 84.1 Torr, PaCO₂ 29.9 Torr and HCO₃⁻ 20.7 mEq/L. SpO₂ was 94%. A rapid influenza test against influenza A virus using a nasopharyngeal-swab specimen was positive and an RT-PCR assay demonstrated the novel influenza A (H1N1) virus. Bacterial cultures of expectoration, urine and blood (2 sets) were negative. Ziehl-Neelsen stain of sputum, and Legionella and Pneumococcus capsular antigens in the urine were negative.

The chest X-ray findings demonstrated bilateral diffuse reticulonodular densities and patchy consolidations (Fig. 1). There were no apparent findings suggestive of typical emphysema including obvious bullae, paucity of parenchymal markings, and hyperlucency. The chest CT showed either peribronchovascular or lobular consolidation, multifocal ground-glass attenuation with interstitial and interlobular septal thickening and pleural effusions. In addition, airbronchogram signs, a reticular pattern and upper lung predominant centrilobular air cysts were noted (Fig. 2-A, B). The finding of small centrilobular air cysts suggested the existence of centrilobular emphysema. An electrocardiogram revealed left axis deviation and low voltage of the limb lead.

Treatment with oxygenation under a respirator, together with the administration of oseltamivir and antibiotics (ceftriaxone and ciprofloxacin) was started. On Day 3, both the body temperature (36.8°C) and SpO₂ (97-98%; FiO₂ 0.6) improved. On Day 5, the laboratory data revealed normal counts for leukocytes (WBC 4,500/µL), lymphocytes (310/µL), thrombocytes (13.5×10³/µL), and elevated levels of serum aspartate aminotransferase (AST, 56 U/L), lactate dehydrogenase (LD, 772 U/L) and C-reactive protein (CRP, 18.56 mg/dL). A rapid influenza test against influenza A virus using a nasopharyngeal-swab specimen was negative. With a diagnosis of interstitial pneumonia, she was admitted to the local hospital. She was treated with oxygenation (O₂ 10 L/min), and a combination of antibiotic (cefozopran, 1 g) and corticosteroid (methylprednisolone, 500 mg).

While these treatments were administered for several hours, the dyspnea progressed and the SpO₂ was not sufficiently improved (88%), thus she was immediately transported to Tokai University Hospital (Day 1). A physical examination upon admission revealed emaciation (height 147 cm, body weight 37 kg, and a Body Mass Index 17.1). Her body temperature was 37.4°C, the respiratory rate was 27/min and the heart rate was regular at 93 beats/min. The blood pressure was 92/32 mmHg. The breath sounds were attenuated in the right lung and small coarse crackles were heard in bilateral lungs.

The laboratory findings included leucopenia (2,100/µL) with severe lymphopenia (84/µL), thrombocytopenia (12.3×10³/µL), hypoalbuminemia (2.2 g/dL), and elevated levels of serum AST (65 U/L), LD (772 U/L), glucose (201 mg/dL), HbA1C 4.7% and CRP (17.47 mg/dL). Coagulation tests were normal. Hypogammaglobulinemia was observed (0.7 g/dL); the serum level of IgG, IgA and IgM was 578 (reference value: 870-1,700), 79 (110-350) and 37 (110-350) mg/dL, respectively. Antinuclear antibody was negative. HIV antibody, HBs antigen and HCV antibody were negative. The data of blood gas (FiO₂ 1.0) showed pH 7.455, PaO₂ 84.1 Torr, PaCO₂ 29.9 Torr and HCO₃⁻ 20.7 mEq/L. SpO₂ was 94%. A rapid influenza test against influenza A virus using a nasopharyngeal-swab specimen was positive and an RT-PCR assay demonstrated the novel influenza A (H1N1) virus. Bacterial cultures of expectoration, urine and blood (2 sets) were negative. Ziehl-Neelsen stain of sputum, and Legionella and Pneumococcus capsular antigens in the urine were negative.

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Six months after discharge, blood examination showed normal CBC counts with 51% of neutrophils and 40% of lymphocytes. The serum level of albumin was normal (4.2 g/dL) and those of IgG, IgA and IgM were low at 578 (reference value: 870-1,700), 79 (110-350) and 37 (110-350) mg/dL, respectively. The pulmonary function test showed normal FEV₁/FVC (90.4%), and slightly abnormal V50/V25 (3.14; normal range ≤3.0) which suggested a mild abnormality of the small airway.
Figure 2. Chest CT on Day 1, which had been provided by the previous hospital. A. Chest CT showed either peribronchovascular or lobular consolidations, multifocal ground-glass attenuation with interstitial and interlobular septal thickening, and pleural effusion. In addition, a reticular pattern and upper lung predominant centrilobular air cysts (arrows) were noted. B. Air-bronchogram signs (arrowheads) were observed.

Figure 3. Chest X-rays on Day 7. Chest X-ray on Day 7 showed further improvement in the bilateral lungs.

Figure 4. Chest CT on Day 11. Upper lung predominant centrilobular air cysts were clearly seen (arrows).

Discussion

From 2-7% of the patients with confirmed novel influenza A (H1N1) virus infection require hospitalization, mainly due to severe pneumonia and encephalopathy (6). The novel influenza A (H1N1) virus infrequently causes severe pneumonia in patients who are not normally considered to belong to the high risk population. This report described a patient, who had a smoking habit accompanying asymptomatic centrilobular emphysema in CT, a mild abnormality of the small airway on pulmonary function test, and gastrointestinal symptoms such as lack of appetite and occasional diarrhea.

The chest CT findings revealed the typical characteristics of novel influenza A (H1N1) pneumonia including bilateral patchy alveolar opacities, linear reticular, or nodular shadows (interstitial opacities) (2, 7). These findings are thus considered to reflect the histological features of pneumonia in influenza, such as bronchiolitis and interstitial edema and inflammation accompanied by diffuse alveolar damage. In addition to that, centrilobular air cysts were observed, thus suggesting underlying centrilobular emphysema. Centrilobular emphysema is commonly seen in the elderly and habitual smokers (8, 9). An abnormality of the small airway function is also seen in smokers (10, 11). WHO reports that risk factors of respiratory diseases include bronchial asthma and obstructive pulmonary diseases (4). However, an asymptomatic and mild pulmonary emphysematous change with a mild abnormality of the small airway such as in smokers has not yet been clearly defined as a high risk population. A substantial number of previously healthy patients have been reported to complain of dyspnea sensations or to have pneumonia (2, 3). The novel influenza A (H1N1) virus has an affinity to airway epithelial cells, thus it could cause bronchitis and bronchiolitis (12, 13). Pulmonary emphysema in smokers includes such a large portion in the general population that this alone could not account for the frequency of the non-obvious risk population among those who require hospitalization. It is therefore reasonable to presume that additional factors are necessary for respiratory disease to develop from bronchitis and bronchiolitis to diffuse alveolar damage (13, 14).
The current patient had an immunodeficiency status as demonstrated by lymphopenia, hypogammaglobulinemia and hypoalbuminemia, which could be suggested as additional risks. Lymphopenia is a common finding of novel influenza A (H1N1) virus infection, and hypogammaglobulinemia and hypoalbuminemia are associated with the initial manifestation in an acute infection such as the novel influenza A (H1N1) virus. Severe immunosuppression such as bone marrow transplantation and human immunodeficiency virus infection is a known risk factor in novel influenza A (H1N1) virus infection (2), and hypoalbuminemia is generally known to be a poor prognostic factor in bacterial and viral infections. However, asymptomatic immunosuppression such as mild hypogammaglobulinemia, which was seen in smokers like the current case (15, 16), has not yet been identified as a risk. A low body weight and gastrointestinal disorders are common in smokers (17-19), as was also observed in the current case. Dietary problems are a major contributing factor, including anorexia, dyspeptic symptoms and diarrhea. These problems would affect the catabolism of the serum plasma, even leading to hypoalbuminemia and hypogammaglobulinemia. The findings in the present case suggest that patients in the no apparent risk population may have asymptomatic or unrecognized backgrounds, which can become a complex risk when combined.

A chest X-ray is not sufficiently sensitive for the detection of the early stages of emphysema. Chest CT is the current definitive test for establishing the presence or absence of emphysema. A chest CT should thus be performed when a patient demonstrates chronic respiratory diseases because of a history of tobacco smoking and/or cardio-pulmonary symptom such as shortness of breath. Other risk factors, which may worsen the respiratory disease, should be checked in the laboratory data such as lymphopenia, hypoalbuminemia and hypogammaglobulinemia, as well as liver and kidney functions. Moreover, whenever the novel influenza A (H1N1) virus infection is considered in a patient, the treatment with oseltamivir should be started as early as possible in order to prevent the progression of the severe pneumonia and to promote early recovery.

In summary, in the present case with the novel influenza A (H1N1) virus infection, a long history of tobacco smoking resulting in asymptomatic pulmonary emphysema and/or an abnormality of the small airway with chronic gastrointestinal symptoms and asymptomatic immunodeficiency was suggested as a risk for severe pneumonia. Smoking habits could be considered as one of the important risk factors for severe pneumonia with the novel influenza A (H1N1) virus infection in otherwise healthy patients, particularly when other unrecognizable backgrounds, such as asymptomatic immunodeficiency, are added. Further studies with more cases and elucidation of the risk factors associated with the novel influenza A (H1N1) virus infection in otherwise healthy populations are warranted.

References