Original Article

The (H1N1) 2009 Pandemic Influenza Pneumonia among Adult Patients in Japan

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SUMMARY: The recent H1N1 influenza pandemic involved several cases of influenza pneumonia. Although influenza pneumonia may have occurred more frequently in fatal cases, the clinical characteristics of influenza pneumonia in Japan remain unclear. We conducted a retrospective cohort study of adult patients with influenza pneumonia, for which questionnaires were sent to respiratory physicians working in 2,491 hospitals across Japan. Questionnaires were returned by 994 physicians (39.9%), providing data on 346 influenza pneumonia cases. The case-fatality ratio was 8.2% (27 cases). Pure influenza viral pneumonia was observed in 94 cases, which were most frequently young adults with chief complaints of non-productive cough and dyspnea. Radiological imaging showed diffuse ground-glass opacity. Corticosteroid therapy and mechanical ventilation were more frequently used for pure influenza viral pneumonia, but these modalities were not correlated with poor treatment outcomes. Anti-influenza antiviral drugs were prescribed in 335 cases (96.8%). In the recent pandemic in Japan, several pure influenza viral pneumonia cases were observed, but we found no variances in mortality between the different types of pneumonia. Almost all cases were treated with anti-influenza antiviral drugs, which may have contributed to its relatively low mortality rate.

INTRODUCTION

Endemic influenza shows increased morbidity and mortality every year. While most cases appear to be self-limiting and uncomplicated, they present with sudden onset of fever, myalgia, headache, and cough that resolve spontaneously within a week, and some patients develop respiratory complications that can lead to influenza-related death. Influenza-related lower respiratory tract complication of pneumonia, referred to as influenza pneumonia, has been observed more frequently during pandemics. Indeed, many fatal cases of influenza pneumonia were reported worldwide during the Spanish influenza pandemic (1,2). Similarly, the other two pandemics of the 20th century showed higher rates of severe influenza pneumonia (3,4).

On June 11, 2009, the World Health Organization announced a swine-oriented influenza virus pandemic, now known as the (H1N1) 2009 pandemic, which rapidly spread worldwide (5) and caused many cases of influenza pneumonia (5–8). Epidemiological data indicated that 15.7–66% hospitalized patients showed chest X-ray abnormalities compatible with pneumonia (9–12). Among those with severe disease, pure influenza viral pneumonia frequently resulted in acute respiratory distress syndrome (13).

In Japan, national surveillance data up to March 23, 2010 revealed that almost 20.6 million people were affected by influenza and 17,640 were hospitalized (14). Furthermore, these data showed that the mortality rate among patients aged 40–60 years was higher for seasonal influenza (14), similar to that reported overseas (9,15), and the incidence of influenza pneumonia was more frequent in fatal cases. In Japan, 198 deaths occurred during one pandemic period, although the incidence of pneumonia and its clinical characteristics remain unclear.

In this study, to evaluate the characteristics of the (H1N1) 2009 pandemic influenza pneumonia among adult patients in Japan, we conducted surveillance of influenza pneumonia in patients admitted to the respiratory wards of 2,491 hospitals across Japan. Here we report the findings.

MATERIALS AND METHODS

Study design and data collection: In a retrospective cohort study of adult patients with influenza pneumonia, questionnaires were sent to respiratory physicians working in 2,491 hospitals (over 200 beds) across Japan. Data were collected by mail. This study conformed to the principles of the Declaration of Helsinki and was approved by the institutional review board (approval no. 778).

Study definition: The influenza pandemic period was from April 1, 2009 to April 30, 2010. Patients with H1N1 infections were confirmed by rapid immunofluorescence influenza diagnostic kits and/or reverse transcription-PCR. Because the epidemiological
data showed that almost all influenza A infections were A(H1N1)pdm09 without H3N2 during the 2009/2010 pandemic period, it is generally accepted that the rapid diagnostic kit that diagnosed influenza A infection referred to H1N1pdm infection during this pandemic period (16).

Influenza pneumonia is classified into three categories according to the definition by Louria et al. (17): (i) pure influenza viral pneumonia (i.e., primary influenza virus pneumonia, where pneumonia is caused only by the influenza virus and no bacterial pathogens are detected); (ii) secondary bacterial pneumonia (i.e., influenza complicated by secondary bacterial pneumonia, where once the influenza symptoms have resolved, bacterial pneumonia develops); and (iii) mixed viral and bacterial pneumonia (i.e., influenza virus and bacterial pneumonia that occur simultaneously). The severity of pneumonia was evaluated using the Pneumonia Severity Index (PSI) (18).

**Questionnaire:** The questionnaire items inquired about age (in 10-year intervals), sex, and comorbidities, such as chronic respiratory disease, chronic heart disease, chronic renal disease, chronic hepatic disease, cerebrovascular disease, hematological disorders, diabetes mellitus, collagen vascular disease, malignancy, HIV/AIDS, current smoking, pregnancy, and obesity.

All cases of pneumonia were classified into four types: pure influenza viral pneumonia, secondary bacterial pneumonia, mixed viral and bacterial pneumonia, and miscellaneous, according to the diagnosis by the attending physician.

Data were collected on the type and use of anti-influenza antiviral agents, corticosteroids, oxygen, and mechanical ventilation. Treatment outcome and length of hospital stay (categorized by number of weeks) were also recorded.

**Statistical analysis:** Frequency analysis (as percentages) was used for descriptive statistical analysis of non-parametric data. Patient baseline characteristics, clinical presentation and laboratory findings, pneumonia severity, treatment, and outcome were compared using the Pearson chi-square test. A $P$-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS statistical software (version 21.0.0.0; IBM, Armonk, N.Y., USA).

**RESULTS**

**Patient characteristics and types of pneumonia:** Questionnaires were returned by 994 physicians (response rate, 39.9%), which provided data on 346 cases of influenza pneumonia. Data on age were available for 343 cases that were subjected to analysis. A diagnosis of the type of pneumonia was established by the

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td>No underlying medical conditions</td>
<td>161 (47)</td>
</tr>
<tr>
<td>Chronic respiratory diseases</td>
<td>102 (29)</td>
</tr>
<tr>
<td>Chronic heart diseases</td>
<td>37 (11)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34 (10)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>31 (9)</td>
</tr>
<tr>
<td>Obesity</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>23 (7)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Collagen vascular diseases</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Chronic renal diseases</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Chronic liver diseases</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Hematological disease</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 1. Underlying medical condition in influenza pneumonia

Fig. 1. Patient age (in 10-year intervals) and type of pneumonia.
attending physician on the basis of physical findings, laboratory test results, and chest X-ray findings. Moreover, either computed tomography (CT) or microbiological analysis was performed in 316 cases (91.3%).

Sixteen of the 346 cases did not state the type of pneumonia, and of the remaining 330 cases, pure influenza viral pneumonia accounted for 96 cases (29%), mixed viral and bacterial pneumonia for 135 cases (41%), secondary bacterial pneumonia for 55 cases (17%), and miscellaneous for 44 cases (13%). Details of the age categories and types of pneumonia are shown in Fig. 1. Underlying medical conditions were reported in 185 cases (Table 1).

**Microbiology:** Microbiological testing was performed in 198 cases (57.2%), and *Streptococcus pneumoniae* was the major agent detected in 67 cases (34.2%). Other detected pathogens included *Haemophilus influenzae* (*n* = 4, 2.0%), *Mycoplasma pneumoniae* (*n* = 4, 2.0%), *Pseudomonas aeruginosa* (*n* = 4, 2.0%), *Klebsiella pneumoniae* (*n* = 3, 1.5%), *Streptococcus viridans* (*n* = 2, 1.0%), *Enterobacter cloacae* (*n* = 1, 0.5%), *Enterococcus faecalis* (*n* = 1, 0.5%), and *Leuconostoc* spp. (*n* = 1, 0.5%).

**Clinical presentation and laboratory findings:** Clinical data of 286 cases were analyzed for each type of pneumonia. Patient complaints included non-productive cough (41.7%) and dyspnea (59.4%), and physical examinations revealed tachypnea (22.9%) more frequently in cases of pure influenza viral pneumonia compared with other types. Radiological studies were performed by chest CT in 279 cases (80.6%) in addition to chest X-ray. Chest CT showed diffuse (34.5%) and ground-glass opacity (76.2%) in pure influenza viral pneumonia, while single lobar consolidation was found in pneumonia associated with bacterial superinfection (Fig. 2). Pneumonia severity as determined by the PSI, was available in 276 cases (Table 2).

**Treatment and outcome:** Almost all cases (96.8%) were treated with anti-influenza antiviral drugs, namely oseltamivir (89%), zanamivir (10%), and peramivir (1%). Supplemental treatments are listed in Fig. 3. Overall mortality from influenza pneumonia was 8.2% (27 cases), no differences were found between each type of pneumonia (*P* = 0.677). Length of hospital stay was under 14 days in 64.7% cases, and no differences were apparent between the types of pneumonia (data not shown).

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**Table 2. Pneumonia severity and mortality as determined by the Pneumonia Severity Index**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Pure influenza viral pneumonia</th>
<th>Secondary bacterial pneumonia</th>
<th>Mixed viral and bacterial pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (% ) Fatal no. (%)</td>
<td>No. (% ) Fatal no. (%)</td>
<td>No. (% ) Fatal no. (%)</td>
</tr>
<tr>
<td>I</td>
<td>36 (38.3) 0</td>
<td>20 (37.0) 0</td>
<td>31 (24.2) 1 (3.2)</td>
</tr>
<tr>
<td>II</td>
<td>27 (28.7) 3 (11.1)</td>
<td>11 (20.4) 0</td>
<td>32 (25.0) 0</td>
</tr>
<tr>
<td>III</td>
<td>14 (14.9) 1 (7.1)</td>
<td>8 (14.8) 1 (12.5)</td>
<td>24 (18.2) 1 (4.2)</td>
</tr>
<tr>
<td>IV</td>
<td>16 (17.0) 5 (31.3)</td>
<td>13 (24.1) 2 (15.4)</td>
<td>32 (25.0) 4 (12.5)</td>
</tr>
<tr>
<td>V</td>
<td>1 (1.1) 0</td>
<td>2 (3.7) 0</td>
<td>9 (0.7) 6 (66.7)</td>
</tr>
</tbody>
</table>

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**Fig. 2. Symptoms and physical, laboratory, and radiological findings in influenza pneumonia.**
Fig. 3. Supplemental treatments for influenza pneumonia.

DISCUSSION

During recent influenza pandemics, pneumonia has been frequently observed as a lower respiratory complication (5–8). In Japanese national surveillance data up to March 23, 2010, 198 fatal cases were reported, 157 of which involved adults (14). In the present study, data from 346 pneumonia cases, of which 27 were fatal, were gathered and analyzed.

In the Asian influenza pandemic of 1957, Louria et al. reported that 6 of 33 cases (18.2%) were pure influenza viral pneumonia (17), and Hers et al. found pure influenza viral pneumonia in 20% of all influenza pneumonia cases (19). Although pure influenza viral pneumonia is thought to be rare in interpandemic periods, it is frequently observed during pandemics. Indeed, in the recent 2009 pandemic, there were many reports of primary viral pneumonia (5,12,20). Our study revealed that pure influenza viral pneumonia occurred more frequently among young adults, while bacterial pneumonia was frequently observed in older patients. Severe pure influenza viral pneumonia tends to be rare during outbreaks of seasonal influenza, but more than a few cases of primary viral pneumonia were observed in the recent pandemic.

In our study, 185 cases of pneumonia (53.5%) had underlying medical conditions with chronic respiratory diseases being the most frequently observed. Underlying conditions or factors associated with complications or poor outcome during pandemic influenza have been reported and particularly include chronic lung disorders, such as asthma or chronic obstructive pulmonary disease, chronic cardiovascular disease, diabetes, pregnancy, and severe obesity (8,11,15,21); these are major comorbidities, and our study supported these results, with the exception of pregnancy.

On microbiological testing, S. pneumoniae was the most common pathogen found in cases of pneumonia associated with bacterial superinfection, which was compatible with previous reports (2,9,20,21). The next most common pathogen was H. influenzae, which may have been due to underlying chronic lung disorders. As with other reports (2,9,13,22), S. aureus, which was predominated less frequently in community-acquired pneumonia, was also detected in the culture results from this pandemic influenza pneumonia.

The characteristics of pure influenza viral pneumonia, as diagnosed by respiratory physicians, included non-productive cough, dyspnea, low leukocyte count (<4,000 cells/μL), and respiratory failure. Radiological findings in our study included ground-glass opacity in the bilateral lung fields, indicating diffuse alveolar damage. These radiological findings of pure influenza viral pneumonia are compatible with those of other reports (23), and the clinical characteristics of this patient cohort suggested difference from pneumonia with bacterial superinfection.

Pneumonia severity, as evaluated by the PSI, showed that over 70% pure influenza viral pneumonia cases were diagnosed as low risk (classes I–III). Although it is generally accepted that pure influenza viral pneumonia has a more severe clinical course, it may account for a greater number of mild cases than previously believed. On the other hand, PSI is largely dependent on age and underlying diseases. Patients with pure influenza viral pneumonia are usually young with no underlying conditions; therefore, these cases tended to be less severe compared with real severity. A previous report also indicated that community-acquired pneumonia due to pandemic influenza should not be based on current pneumonia severity scores because they underestimate mortality rates (24). Therefore, the PSI may not be suit-
able to evaluate the severity of influenza pneumonia. Additional reports and studies are needed to evaluate precise pneumonia severity rates.

In cases of pure influenza viral pneumonia, antibiotics are used less frequently than other types of pneumonia, while corticosteroids are used more frequently. Although we found no correlation with mortality, mechanical ventilation was performed more often, indicating that pneumonia itself was more severe. It is widely accepted that pure influenza viral pneumonia is a severe disease with a relatively high mortality rate; however, we found no difference from patterns of other types of pneumonia in Japan. In cases of influenza pneumonia, almost all patients were treated with anti-influenza antiviral drugs, which may have contributed to the decreasing mortality rate.

Several limitations to this study should be addressed. First, the questionnaire was retrospective and voluntary, and a diagnosis of pneumonia depended on the attending physician; therefore, the true proportion of influenza pneumonia was not necessarily reflected in the collected data. However, a diagnosis of pneumonia was based on multiple modalities, including CT and microbiological analysis. Indeed, there were different patterns of influenza pneumonia among the reported cases, which suggested that the data appeared to include more than a few cases of primary viral pneumonia. Second, the response rate of this questionnaire was limited (approximately 40%) and only 27 of 157 (17.2%) deaths in adults were reported; therefore, recall bias was likely a factor in this study. However, as the study targeted almost 2,500 respiratory departments of hospitals nationwide, the response seemed reasonable and should accurately reflect trends in pneumonia during the most recent pandemic. Finally, some variables in the collected data were categorical and not provided as detailed numerical data, in line with the guidelines of the institutional review board. Therefore, more exact statistical analysis was impossible, although the categorical data made it easier to answer the questionnaire, and thus, may have improved the response rate.

In summary, the findings of our study have several implications. In the recent pandemic in Japan, several pure influenza viral pneumonia cases were observed, which occurred more frequently in young adult patients. Our study indicated that current pneumonia severity scores do not always accurately reflect mortality, and we found no differences in mortality rates between the different types of pneumonia. Almost all cases were treated with anti-influenza antiviral drugs, which may have contributed to the relatively low mortality rate of influenza pneumonia.

Conflict of interest None to declare.

REFERENCES