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Original Article

Clinical characteristics of influenza virus-induced lower respiratory infection during the 2015 to 2016 season

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ABSTRACT

Background: Influenza A(H1N1)pdm09 virus infections often manifest severe respiratory symptoms, particularly in patients with a past history of allergic disease. Most of these findings were reported during the 2009 pandemic. The purpose of this study was to detail the clinical characteristics of influenza virus-induced lower respiratory infection (LRI) during the A(H1N1)pdm09-predominant 2015–2016 season.

Methods: We retrospectively reviewed the clinical characteristics of influenza-induced LRI cases in children admitted to a tertiary children's hospital. Molecular diagnostic evaluation was performed on samples obtained from the most severe cases.

Results: We identified 66 patients with influenza-associated hospitalization and included 21 patients with influenza virus-induced LRI for analyses. Twelve patients (57%) were admitted to the pediatric intensive care unit, seven (33%) required mechanical ventilation, and three (14%) required extracorporeal membrane oxygenation. Plastic bronchitis (PB) was identified in six patients (29%), among whom a past medical history of asthma or food allergy were noted in all six patients. A past history of allergic disease was more common among patients with, than among those without, PB ($p = 0.009$). A(H1N1)pdm09 was detected from all the PB cases, and phylogenetic analyses of the hemagglutinin and neuraminidase genes demonstrated that this virus belonged to subclades 6B.1 and 6B.2. In the six PB cases, we found one patient with H275Y mutation in neuraminidase.

Conclusion: Allergic disease was a risk factor for developing PB due to influenza A(H1N1)pdm09 infection during the 2015–16 season.

1. Introduction

An influenza A(H1N1)pdm09 (H1N1pdm09) pandemic occurred in 2009, resulting in numerous deaths and cases of severe respiratory failure requiring intensive care, including mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [1,2]. Severe respiratory failure associated with plastic bronchitis (PB), a condition characterized by rigid branching mucus casts that obstruct the airway, was also reported in 2009 season [3–5]. Chronic lung disease, immunosuppressive status, cardiac disease, pregnancy, diabetes mellitus, obesity in adults, and asthmatic status in children were identified as risk factors for developing severe respiratory failure due to H1N1pdm09 infection during the 2009 season [6,7].

Seasonal influenza due to H1N1pdm09 occurred during the 2010–2011, 2013–2014, and 2015–2016 seasons worldwide [8–10]. National surveillance in Japan during the 2015–2016

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season reported that H1N1pdm09 accounted for 86% of cases of influenza A virus infection [9]. Although the clinical features of pediatric patients with H1N1pdm09 in the 2009 season have been documented, clinical information regarding H1N1pdm09 infections in other seasons is relatively scarce. In general, we hypothesize that influenza pandemics tend to be more severe than seasonal outbreaks due to the lack of host immunity. However, risk factors for developing severe complications during a pandemic might differ from those in seasonal outbreaks due to differences in host immunity or genetic changes in the circulating strain. These questions require further research to be answered.

We therefore performed a retrospective study to identify the clinical characteristics of lower respiratory infection (LRI) due to influenza in the 2015–2016 season, in which H1N1pdm09 was the predominant strain.

2. Materials and methods

This study was conducted at the National Center for Child Health and Development, a pediatric tertiary care hospital in Tokyo, Japan. We performed a retrospective chart review of all the patients in whom influenza was diagnosed. We included patients under the age of 18 years who were hospitalized for influenza-related LRI between December 2015 and April 2016. Patients hospitalized for acute encephalopathy, febrile seizure, febrile delirium or croup were excluded.

Clinical information including age, gender, underlying disease, past medical history, immunization history, clinical course, and prognosis was collected from patients' medical records. Underlying diseases were classified as allergic (asthma or food allergy), neurological, cardiac, renal, hepatic, or immunological. Patients with primary immunodeficiency and those receiving immunosuppressive agents were included. Each condition was counted separately in patients with multiple conditions.

2.1. Clinical definition of lower respiratory infection

LRI included pneumonia and bronchitis and was defined by cough as the principal respiratory symptom, accompanied by respiratory distress or desaturation. PB was diagnosed in patients in whom the disease showed rapid progression leading to severe respiratory failure and large consolidation on the chest radiograph, but whose respiratory status improved dramatically after suctioning of the mucous plug [5].

2.2. Diagnosis of influenza

All patients were diagnosed using a rapid antigen test for influenza (Espline Influenza A & B-N (FUJIREBIO, Tokyo, Japan)). The sensitivity and specificity of the test are reportedly 96.8% and 97.6% for influenza A, and 88.1% and 97.6% for influenza B, respectively when measured against a standard diagnosis by cell culture or nested reverse transcription polymerase chain reaction results [11]. Total nucleic acids were extracted from specimens, which were additionally taken from endotracheal tube aspirates, from all patients who had PB using the QIAamp DNA Mini kit (QIAGEN) and analyzed by real-time quantitative polymerase chain reaction (qPCR) using the Fast-track Diagnostics respiratory pathogens 21 (FTDRP21) multiplex assay kit (Fast-track Diagnostics, Luxembourg). The panel shows 21 respiratory pathogens including: influenza A, influenza A (H1N1) swl, influenza B, rhinovirus, coronavirus NL63, 229E, OC43, and HKU1, parainfluenza 1, 2, 3, and 4, human metapneumovirus A/B, bocavirus, respiratory syncytial virus A/B, adenovirus, enterovirus, parechovirus, mycoplasma pneumonia, and an internal control [12]. Genome sequencing for the hemagglutinin (HA) and neuraminidase (NA) genes was performed using specific primers (Supplemental table: Table S1). The determined sequences are available from DDBJ/EMBL/GenBank database under the accession numbers LC270874 to LC270885. The phylogenetic trees were constructed by the neighbor-joining method using MEGA 6 software [13]. The other sequences analyzed for phylogenetic trees were obtained from the EpiFlu database of the Global Initiative on Sharing All Influenza Data [14].

2.3. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics ver.22 (IBM, Tokyo, Japan). Fisher's exact test for categorical

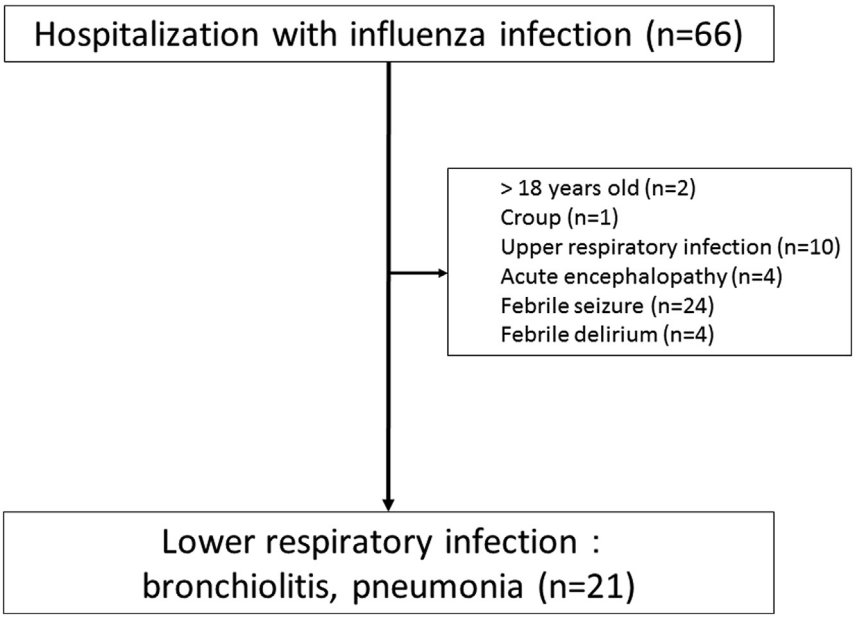

Fig. 1. Flow diagram for study inclusion. Sixty-six patients were hospitalized with the diagnosis of influenza. Lower respiratory infection was diagnosed in 21 patients after excluding patients >18 years old, and those with acute encephalopathy, febrile seizure, febrile delirium, croup, or upper respiratory infection.

variables and Mann-Whitney *U* test for continuous variables were used for the analyses. $P < 0.05$ (two-sided) was considered significant. This study was approved by the institutional review board at National Center for Child Health and Development (IRB-1278).

3. Results

We identified 66 patients with influenza-associated hospitalization, and included 21 patients with influenza virus-induced LRI for analysis (Fig. 1).

Table 1 shows the demographic and clinical characteristics of the patients at the time of admission. Males predominated (n = 15, 71%), and the median age was 7 years. Nine (42%) patients had a history of asthma and all patients with a neurologic disease (n = 4, 19%) had cerebral palsy, two of whom had had a tracheostomy. Only four (19%) patients received the influenza vaccine during this season. Patients who were admitted to the intensive care unit, required mechanical ventilation, and required ECMO comprised 57%, 33%, and 14% of the study pool, respectively. Six patients received the diagnosis of PB and required mechanical ventilation, while among these three also required ECMO for pulmonary support. Table 2 shows the details of these cases. Major underlying conditions in the cases with PB were asthma (n = 5, 83%) and food allergy (n = 3, 50%). Among the patients with asthma, two had moderate persistent asthma and were using inhaled corticosteroid as a controller, and three patients had intermittent asthma which did not require a controller. The median of white blood cell count on admission was 15790/μl (range 9730/μl–19050/μl), which were neutrophil predominant (median: 91%, range: 72%–96%) with eosinophils accounting for less than 2% (median: 0.6%, range 0.1%–1.9%).

Eighteen (86%) cases were due to influenza type A infection, and three were due to type B infection. Specimens from the six patients with PB were analyzed by real-time qPCR and identified as H1N1pdm09 infections. Other pathogens were not detected by the FTDRP21 multiplex PCR assay. The results of the phylogenetic analysis of the HA and NA genes are shown in Figs. 2 and 3. The genes from all of these cases belonged to subclades 6B1 and 6B.2, which were predominant in the 2015–2016 season. We also performed full genome sequencing for two specimens obtained from the patient 2 and 5 who required ECMO. The sequence data for the NA gene revealed that patient 2 was infected with the oseltamivir-resistant H275Y mutant virus from the specimen taken before the treatment of neuraminidase inhibitor. Although patient 2 was treated with peramivir, the duration of intubation and hospitalization was similar to that in patients infected by the non-resistant strain. No other known relevant mutations were identified in the analysis in patient 2 and 5.

We divided patients with influenza A into two groups, those with or without PB and compared their demographics to identify the risk factors for developing PB, which might be considered a more severe form of influenza-related LRI (Table 3). Among the covariates, the presence of allergic diseases was more commonly observed in patients with PB [6/6 (100%) vs 3/12 (25%): $p = 0.009$].

Table 1
Patients characteristics.

Patients (n = 21)	Cases (%)
Demographics	
Sex (male)	15 (71)
Age (year): median (IQR)	7 (3.6–8.5)
Underlying disease	16 (76)
Allergic disease	11 (52)
Asthma	9 (43)
Food allergy	4 (19)
Neurologic disease	4 (19)
Kidney disease	2 (10)
Liver disease	1 (5)
Other[a]	1 (5)
Immunocompromised status[b]	3 (14)
Influenza vaccination	4 (19)
Characteristics of Influenza infection	
Type of virus	
Influenza A	18 (86)
Influenza B	3 (14)
Time from onset to admission (days): median (IQR)	2 (1–2)
Admission within 48 h from onset[c]	16 (76)
Plastic bronchitis	6 (29)
Intensive care unit	12 (57)
Mechanical ventilation	7 (33)
ECMO	3 (14)
Hospitalization days: median (IQR)	8 (6–10)
Prognosis (death)	0 (0)

Abbreviations: ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.
[a] One case of congenital arthrogryposis.
[b] Nephrotic syndrome with cyclosporine, post liver transplantation for biliary atresia.
[c] The onset of illness was defined as the first day of fever.

4. Discussion

We retrospectively reviewed cases of influenza-related LRI from the 2015–2016 season, which suggested that the presence of allergic disease, including asthma and food allergy, when compounded with an influenza virus infection, was a risk factor for developing PB.

Asthma has been identified as a risk factor for developing PB [15,16]. Severe respiratory failure due to PB caused by H1N1pdm09 infection in children was reported during the 2009 season [3,4,7]. Similarly, in our study, development of the severest form of respiratory failure, PB, due to H1N1pdm09, was associated with an underlying allergic disease such as asthma. Interestingly, the severity of asthma ranged from intermittent to moderate persistent, suggesting that the risk of PB development may not depend on the severity of asthma. This lack of association between the severity of the underlying asthma and the severity of LRI due to

Table 2
Demographic data and clinical course in six cases of plastic bronchitis.

Patient	Age (years)	Sex	Asthma	Current treatment for asthma	Food allergy	Virus type	Vaccination	Duration from onset to antiviral drugs (days)	Mechanical ventilation	ECMO
1[a]	3	Female	+	ICS	+	A	−	1	+	−
2[b]	5	Male	−	−	+	A	−	1	+	+
3	7	Male	+	None	+	A	−	1	+	−
4	7	Male	+	None	−	A	−	1	+	+
5	7	Male	+	ICS	−	A	+	2	+	+
6	11	Female	+	None	−	A	−	1	+	−

Abbreviations: ICS, inhaled corticosteroid therapy; ECMO, extracorporeal membrane oxygenation.
[a] Epilepsy and post-tracheostomy.
[b] Nephrotic syndrome controlled with cyclosporine.

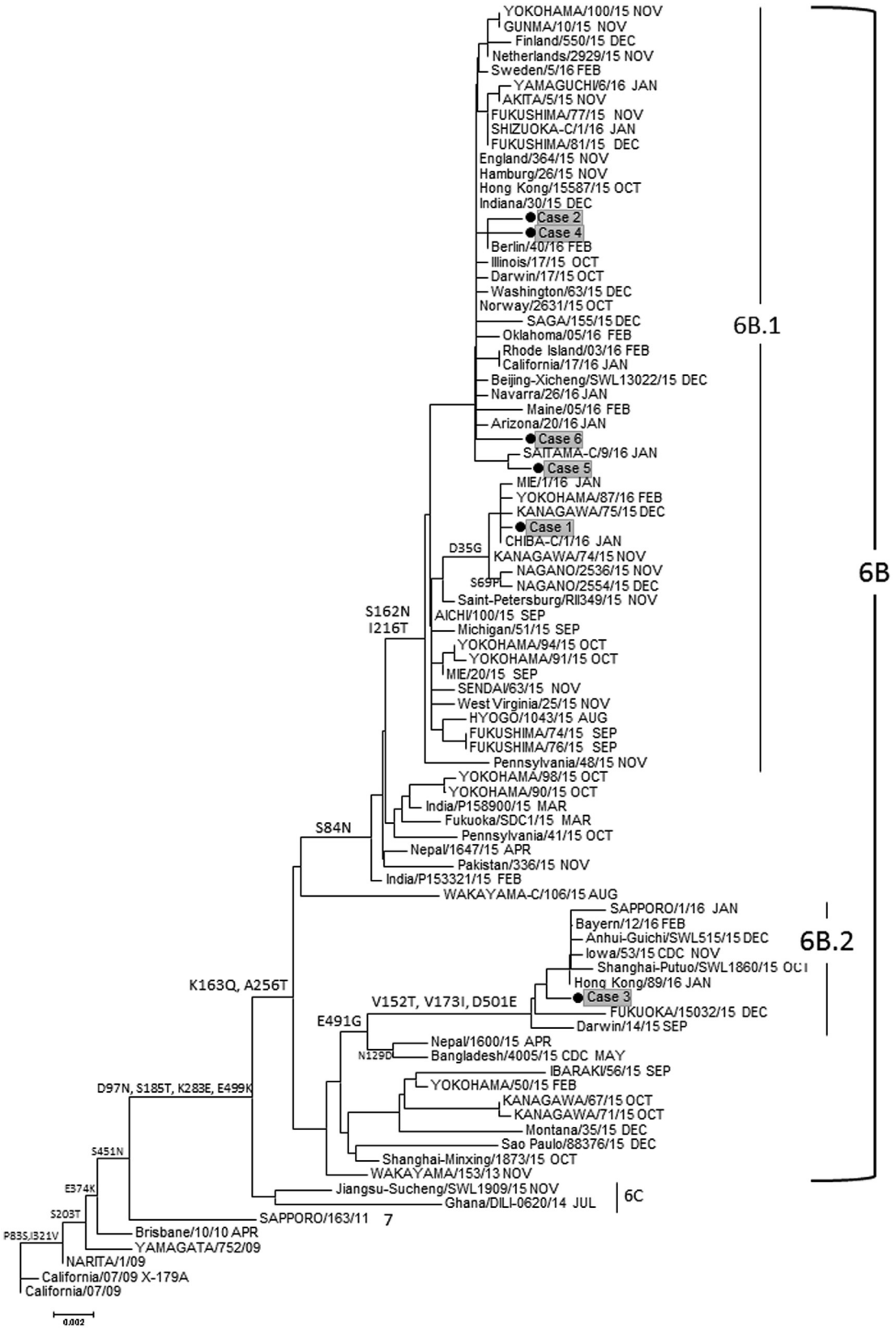

Fig. 2. Phylogenic analysis of the HA gene in six influenza A(H1N1)pdm09 cases. The name of each strain in the tree was shortened; e.g., A/YOKOHAMA/100/2015 was written YOKOHAMA/100/15. All cases but one (case 3) belonged to genetic subclade 6B.1. Case 3 belonged to subclade 6B.2.

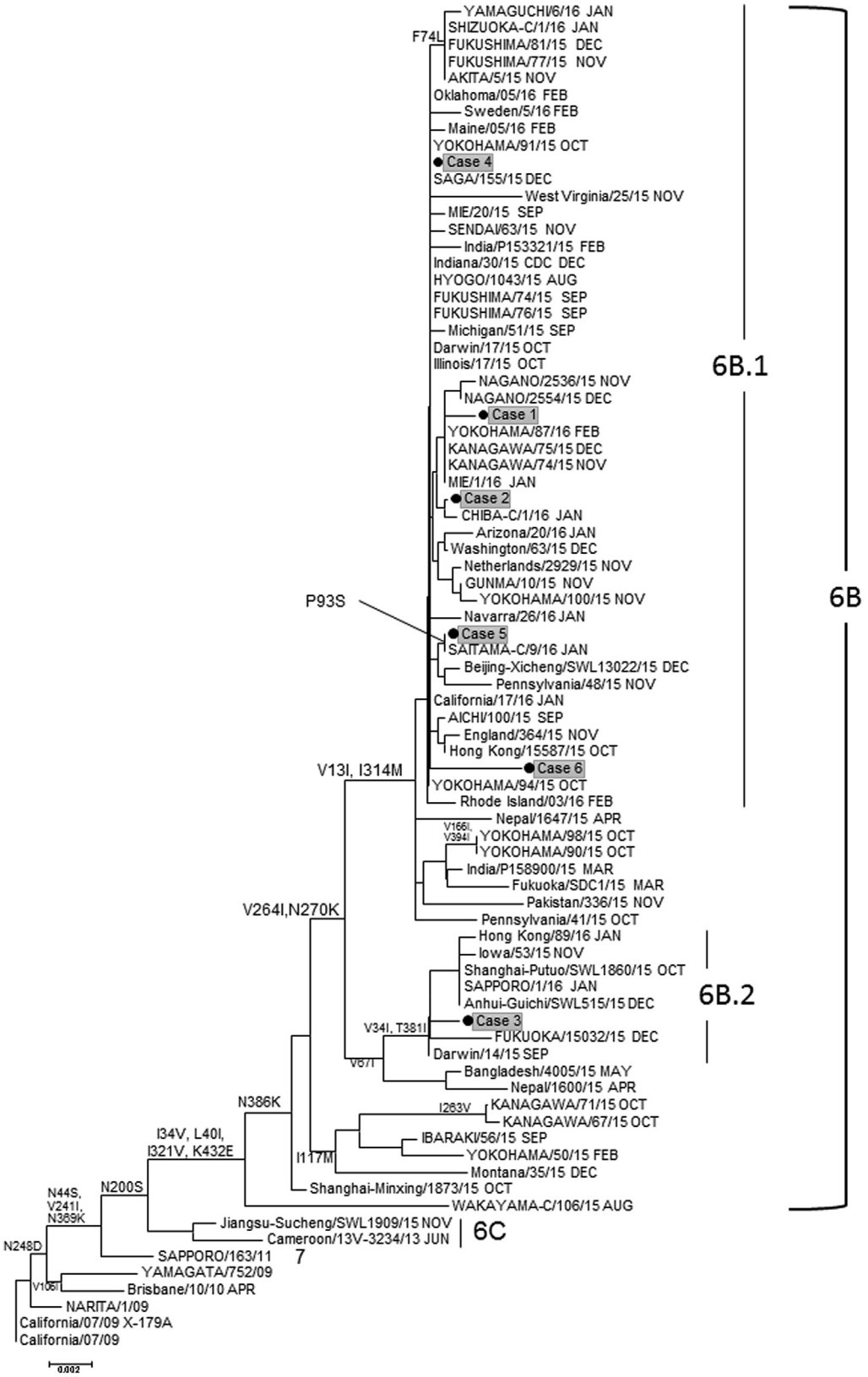

Fig. 3. Phylogenic analysis of the NA gene in six influenza A(H1N1)pdm09 cases. The name of each strain is shown in Fig. 2. All cases but one (case 3) belonged to subclade 6B.1. Case 3 belonged to subclade 6B.2.

Table 3
Comparison of background in plastic bronchitis cases and non-plastic bronchitis cases in influenza A virus lower respiratory infection.

	PB (+)	PB (−)	p-value
	n = 6 (%)	n = 12 (%)	
Sex (male)	4 (67)	9 (75)	1.00
Age (year): median (IQR)	7.5 (5.0–8.6)	6.3 (2.1–9.8)	0.55
Underlying disease	6 (100)	7 (58)	0.11
Allergic disease	6 (100)	3 (25)	0.009
Asthma	5 (83)	3 (25)	
Food allergy	3 (50)	0 (0)	
Neurologic disease	1 (8)	2 (17)	1.00
Immunocompromised status	1 (17)	1 (8)	1.00
Kidney disease	1 (8)	1 (8)	1.00
Liver disease	0 (0)	0 (0)	1.00
Influenza vaccination	1 (17)	3 (25)	1.00

Abbreviations: PB, plastic bronchitis; IQR, interquartile range.

H1N1pdm09 infection was also observed in the 2009 season [17]. Thus the recognition of asthma as a risk factor for severe H1N1pdm09 infection appears to apply to the 2015–2016 season.

In line with our own findings, PB reportedly developed as a result of the rapid infiltration of casts composed of fibrin and eosinophilic inflammatory infiltrates suggesting involvement of an allergic process [15]. A previous report on PB associated with influenza among patients with asthma demonstrated eosinophils in bronchial casts, whereas peripheral white blood cells were neutrophil dominant [18]. Although pathology of bronchial casts were not performed in our patients, peripheral white blood cells were neutrophil predominant supporting the previous findings. Animal models of asthma have also shown eosinophilic inflammation in influenza-induced airway inflammation [19,20].

All cases of PB in our study were caused by H1N1pdm09 infection. The high affinity of H1N1pdm09 to the lower respiratory tract has been reported in animal models and suggests the existence of specific virulence factors accountable for host-pathogen interactions [21]. The phylogenetic analysis of the HA and NA genes from all cases of PB observed in this study showed that these genes belonged to subclades 6B.1 and 6B.2, which were the commonest circulating strains during the 2015-16 season [9]. We also performed full genome sequencing for two specimens obtained from the patient 2 and 5 who required ECMO, without finding any variations known to be associated with virulence. Although limited, these data suggested that the patients' host factors, rather than a viral factor peculiar to these severe cases, were more important for developing severe respiratory failure.

Antiviral drugs may improve the outcome of severe respiratory failure due to influenza. A previous report suggested that a delay in administering antiviral drugs might be associated with increased severity [22]. However, PB in most of our patients progressed rapidly within one day of onset, making early antiviral therapy difficult. The median time from onset of fever to admission was two days, the time-frame within which 76% of the patients were admitted. Therefore, our findings may support the importance of immunization in the prevention of severe influenza. Although our study was not designed to demonstrate the effectiveness of the influenza vaccine, previous reports have shown a vaccine efficacy rate of 61%–63% against A(H1N1)pdm09 and prevention of hospitalization in 76% of cases [8,23]. The rate of immunization was four in 21 (19%) in the admitted patients and one in six (17%) in PB, which was lower than the general immunization rate of 50% in Japan [24]. Thus, our findings support the current recommendations to vaccinate children.

A mutation known to cause oseltamivir resistance was found in one case. However, there was no difference in the clinical course or duration of intubation and admission, when compared with the five other cases. Resistance to oseltamivir is reportedly not associated with duration of fever in the patients with H1N1pdm09 infection [25]; however, evidence regarding the association with respiratory distress is lacking.

There are two limitations to this study. First, real-time qPCR for strain typing was performed for only six cases of PB; unfortunately, the remaining 12 cases of influenza A could not be analyzed due to the retrospective study. However, because national surveillance in Japan revealed that 86% of influenza A infections in the 2015–2016 season were due to H1N1pdm09, we assumed that the majority of our patients in whom influenza A infection was diagnosed might also have an H1N1pdm09 infection. This would compromised the comparison of the PB and non-PB groups. Second, the number of cases was small to perform a statistical analysis, possibly leading as a result to an underestimation of the effects of other potential risk factors. Further studies enrolling more patients are needed to assess more accurately the impact of these underlying diseases on the development of severe respiratory infection.

In conclusion, severe respiratory failure including PB due to H1N1 pdm09 influenza was observed during the 2015–2016 season. Allergic conditions were considered to be a risk factor for developing PB.

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Authorship statement

All authors meet all of the following ICMJE authorship criteria 1) conceptualizing and designing the study, acquisition of data, or analysis and interpretation of data, 2) drafted the article or revising it critically for important intellectual content 3) final approval of the version to be submitted.

Conflict of interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jiac.2018.01.002.

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