Respiratory Medicine Case Reports 19 (2016) 1–4

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Association of influenza with severe pneumonia/empyema in the community, hospital, and healthcare-associated setting

Masafumi Seki [a, *], Ryota Fuke [a], Nozomi Oikawa [a, b], Maya Hariu [a, b], Yuji Watanabe [a, b]

[a] Division of Infectious Diseases and Infection Control, Tohoku Medical and Pharmaceutical University Hospital, Sendai City, Miyagi, Japan
[b] Laboratory for Clinical Microbiology, Tohoku Medical and Pharmaceutical University Hospital, Sendai City, Miyagi, Japan

ARTICLE INFO

Article history:
Received 21 April 2016
Received in revised form
21 May 2016
Accepted 23 May 2016

Keywords:
Influenza
Non-typeable *Haemophilus influenzae*
Beta-lactamase negative *Haemophilus influenzae*
Vaccine

ABSTRACT

We presented three cases of influenza-related severe pneumonia/empyema that occurred in one season. *Case 1:* A 76-year-old diabetic man, developed empyema as a result of severe community-acquired pneumonia (CAP) secondary to *Haemophilus influenzae*, as confirmed on sputum culture. Nasal swab was positive for influenza A antigen. After drainage of empyema, intravenous peramivir and piperacillin/tazobactam were administered for 3 days and 2 weeks, respectively, followed by oral levofloxacin for 2 weeks. Eventually, he recovered. In this case, the isolated *H. influenzae* was non-typeable and negative for beta-lactamase.
Case 2: A 55-year-old man with suspected cerebral infarction and diabetes mellitus (DM) developed severe pneumonia/empyema as result of hospital-acquired pneumonia (HAP). Although influenza A antigen was detected, no bacterium was isolated from the sputum, blood, or pleural effusion. He showed severe hypoxia, but recovered after administration of peramivir and levofloxacin with prednisolone for 5 days and 2 weeks, respectively.
Case 3: A 76-year-old woman with heart failure and DM was followed-up on an outpatient basis and was under nursing home care for four months. Subsequently, she developed pneumonia and was admitted to our hospital; influenza antigen was isolated from nasal swab. Healthcare-associated pneumonia (HCAP)/empyema were diagnosed and were effectively treated with peramivir and levofloxacin for 4 days and 1 week, respectively.
In diabetic patients, influenza virus may possibly accelerate pneumonia/empyema due to bacterial co-infection. Although non-typeable *H. influenzae* is a rare causative pathogen of empyema, it can be expected as a result of "pathogen shift" due to the increased use of the *H. influenzae* type b vaccine in Japan.

1. Introduction

Influenza virus infection is a major respiratory infectious disease that generally induces bronchitis [1,2]. It causes an acute febrile illness with malaise and respiratory failure and is sometimes lethal in the elderly if the bronchitis develops into pneumonia [3–5].

Influenza pneumonia has been classified into primary influenza virus pneumonia and bacterial infection-related pneumonia. The latter type is more frequent and the symptoms, including cough and sputum production, are similar to those of bacterial pneumonia; in addition, infiltrative shadows usually appear on chest radiographs [2,5,6]. Synergic effects between influenza virus and bacteria have been suggested. However, empyema that is related with influenza virus infection is rare [2,7–9], Here, we describe three patients who were suspected to have developed pneumonia in association with influenza virus infection during the 2015–2016 season. These were severe cases of community-acquired pneumonia (CAP)/empyema co-infected with *Haemophilus influenzae,* hospital-acquired pneumonia (HAP)/empyema, and healthcare-associated pneumonia (HCAP)/empyema.

2. Case report

2.1. Case 1

A 76-year-old man presented at the emergency room in February 2016 with acute pain around the left shoulder and high

* Corresponding author. Division of Infectious Diseases and Infection Control, Tohoku Medical and Pharmaceutical University Hospital, 1-12-1 Fukumuro, Miyagino-ku, Sendai City, Miyagi 983-8612, Japan.
E-mail address: seki@hosp.tohoku-mpu.ac.jp (M. Seki).

http://dx.doi.org/10.1016/j.rmcr.2016.05.005

fever accompanied by extreme fatigue that had persisted for a week. He had a medical history of hypertension and diabetes mellitus (DM), but had never smoked. Physical examination indicated the following: temperature of 39.5 °C, blood pressure of 97/50 mmHg, respiratory rate of 23 breaths/min, and consciousness level of E3V4M1 on the Glasgow Coma Scale. There were crackles (rhonchi) on the lower left lung field and chest radiography indicated infiltrative shadows and pleural effusion on the left (Fig. 1A and B). His initial white blood cell (WBC) count was 28,600/L and C-reactive protein (CRP) was 25.0 mg/dL A 6 French pigtail tube was inserted subcutaneously under ultrasound guidance. Turbid yellow fluid was drained and results of the analysis are as follows: pH 7.4, Total protein 5.2 g/L, Lactate dehydrogenase 4491 U/L, Glucose 66 mmol/L, Cytology neutrophils dominant, and gram negative bacilli were found. *H. influenzae* was identified in respiratory specimens and was found as a non-typeable and beta-lactamase negative type; minimum inhibitory concentration (MIC) test according to the Clinical and Laboratory Standards Institute criteria revealed susceptibility to levofloxacin, piperacillin, ciprofloxacin, and gentamicin, but not to ampicillin (ABPC) and ampicillin/sulbactam (ABPC/SBT). Rapid antigen test for influenza A was positive. Thus, we diagnosed that he was influenza virus-related secondary bacterial empyema due to *H. influenzae.*

After drainage of pleural effusion, intravenous peramivir 300 mg daily for 3 days and piperacillin/tazobactam 4.5 g every 8 hours for 14 days improved the chest radiograph findings and the inflammatory markers, such as WBC (7600/L) and CRP (4.46 mg/dL). He was discharged from the hospital after completing the course of treatment and continued oral levofloxacin administration for more two weeks.

2.2. Case 2

A 55-year-old man with a history of DM and suspected cerebral infarction developed pneumonia 1 month after admission for loss of consciousness in February 2016. Physical examination revealed temperature of 38.1 °C, blood pressure of 89/60 mmHg, respiratory rate of 30 breaths/min, dehydration, and crackles (rhonchi) on both

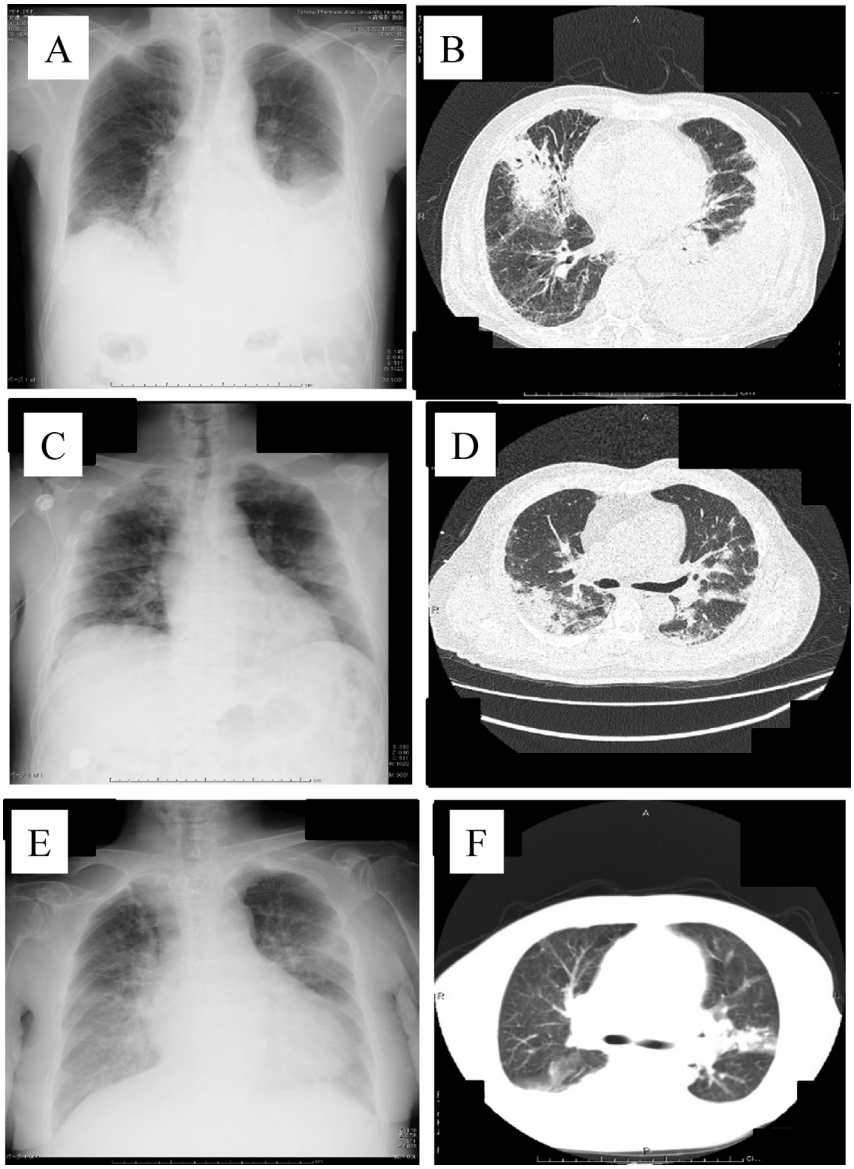

Fig. 1. Chest radiography and computed tomography images of Case 1 (A and B), Case 2 (C and D), and Case 3 (E and F). All images showed infiltration shadows and pleural effusions, suggested severe pneumonia/empyema.

lung fields. Chest radiography indicated infiltrative shadows on both lung fields with right-sided pleural effusion (Fig. 1C and D). Oxygen saturation was 88% at an O_2 support of 15 L/min by face mask. His initial WBC count was 9400/L and CRP was 11.4 mg/dL. We unfortunately could not perform pleural puncture because his respiratory status was poor. No bacterium was determined in blood cultures and respiratory specimens, but influenza A antigen from nasal swab was positive. He was diagnosed as influenza-related HAP/empyema.

The patient was placed on non-invasive positive pressure ventilation and oxygenation was improved. Intravenous peramivir 300 mg once daily for 5 days, followed by levofloxacin 500 mg once daily with prednisolone 125 mg once daily for 14 days improved the chest radiograph findings and the pneumonia.

2.3. Case 3

A 76-year-old woman with heart failure and DM was admitted to the emergency room in February 2016 due to dyspnea and disturbed consciousness. She was followed-up as an outpatient and had been under nursing care in a geriatric facility for four months. Physical examination indicated a temperature of 38.5 °C, respiratory rate of 22 breaths/min, and blood pressure of 108/66 mmHg. There were crackles (rhonchi) on the left lung field and oxygen saturation was 92% at an O_2 support of 10 L/min by mask. Chest radiography indicated pleural effusion with infiltrative shadows mainly on the left lower lung field (Fig. 1E and F). Her initial WBC count was 5700/L and CRP was 2.13 mg/dL. We could not perform pleural puncture, and no bacterium was detected in blood cultures and pleural fluid specimens. However, influenza A antigen from nasal swab was positive. Thus, we suspected that she was also influenza virus-related secondary bacterial pneumonia.

Intravenous peramivir 300 mg once daily for 4 days and levofloxacin 500 mg once daily for 1 week were administered. She eventually recovered and returned to the nursing home one month later after admission.

3. Discussion

Despite major efforts in prevention and treatment, influenza A virus infection accounts for significant morbidity and mortality [4,5], which have been attributed to the development of respiratory complications, including pneumonia.

In this report, we described and compared three influenza-related severe pneumonia/empyema cases (Table 1). These cases were found in one season and hospitalized same period although each case occur sporadically. Influenza is usually spread in the community. However, hospital-acquired and healthcare-associated influenza-related complications have recently increased and have become problems in Japan due to the rising population of the aging society [10]. Similar cases of HAP and HCAP might be common in our country recently, but these types were frequently severe because they usually showed hypoxia that needed O_2 support due to old age and other comorbidities, including heart failure [10,11].

In contrast to HAP and HCAP, CAP is thought to be more common; for influenza-related cases, *H. influenzae* and *Streptococcus pneumoniae* were the major pathogens indicated [1,12]. *H. influenzae*, especially the non-typeable strains due to the presence of different or undetectable capsular polysaccharides, has been known as a causative pathogen of mild mucosal infections, such as bronchopneumonia or otitis media in elderly persons and children [13]. However, as demonstrated in our cases, *H. influenzae* can also be a cause of influenza virus-related severe pneumonia/empyema.

Previously, we reported a case of invasive fatal pneumonia with sepsis due to a non-typeable *H. influenzae* strain and suggested an increasing incidence of invasive and severe infections, including pneumonia, bacteremia, and meningitis due to *H. influenzae* type b (Hib) [14]. The incidence of Hib has decreased markedly, probably due to the widespread use of Hib conjugate vaccines in Japan and other countries. However, the incidence of invasive infections caused by non-typeable *H. influenzae* has increased [15,16]. This phenomenon has recently become known as “pathogen shift”, as exemplified by one of our cases.

In our Case 1, the isolated non-typeable strain was beta-lactamase negative and ABPC-resistant *H. influenzae* (BLNAR). This type has also increased and reached nearly 50% of all *H. influenzae* strains isolated in Japan [17]. Carbapenems and fluoroquinolones were known as the effective antibiotics for BLNAR. However, we underscore rational use of these antibiotics to prevent emergence of resistant strains of *H. influenzae* and other bacteria, including *Pseudomonas aeruginosa* [18]. For these reasons, piperacillin may be an appropriate first choice to treat CAP during influenza season [19].

All three patients reported here had relatively poor control of DM (Table 1). An inhibited and weak immune response predisposes DM as one of the most important comorbidities in pneumonia and empyema [1,11,20]. Anaerobes, which are difficult to culture, are known as the causative pathogens in empyema and have been frequently isolated from DM patients [21]. Unfortunately, the causative bacteria were not detected in Case 2 and Case 3; nevertheless, anaerobic bacterial etiology was suspected to have worsened the influenza-related HAP and HCAP in these diabetic patients.

In conclusion, we encountered three severe influenza-related pneumonia/empyema cases in one season and hospitalized same period although they occurred sporadically. All patients had poorly-controlled DM and were suggested to have weak immune status. Although influenza-related CAP may be common, influenza-related HAP and HCAP may be emerging important diseases in Japan. Due to the widespread availability of the Hib vaccine, it is important to be aware that non-typeable *H. influenzae* could be a possible pathogen in influenza-related severe pneumonia/empyema in elderly persons.

Table 1
Comparison of the three types of influenza-related empyema.

	Patient 1	Patient 2	Patient 3
Category	CAP	HAP	HCAP
Age/Sex	76/Male	55/Male	76/Female
Comorbidity	Hypertension	Cerebral infarction	Heart failure
Diabetes	Yes	Yes	Yes
(HbA1c)	(8.4)	(6.6)	(7.4)
Severity			
CURB65	Severe	Severe	Severe
Chest X-ray	Middle range	Middle range	>2/3
Shock	No	Yes	No
Respirator	No	Yes	No
WBC (cells/L)	28,600	9400	5700
CRP (mg/dL)	25.0	11.1	2.13
Influenza type	A	A	A
Bacteria	*H influenzae*[a]	None	None
30-day Survival	Survived	Survived	Survived

[a] Nontyeable ane Beta-lactamase non-producing type, CAP: Community-acquired pneumonia, HAP; Hospital-acquired pneumonia, and HCAP: healthcare-associated pneumonia, respectively.

Conflict of interest

None.

Acknowledgements

This work was supported by Japanese Society for the Promotion of Science Grant-in-Aid for Scientific Research 26461158 (to M.S.).

References

[1] L.A. Mandell, R.G. Wunderink, A. Anzueto, J.G. Bartlett, G.D. Campbell, N.C. Dean, et al., Infectious diseases society of america; american thoracic society., infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults, Clin. Infect. Dis. 44 (2007) S27–S72.

[2] D.B. Louria, H.L. Blumenfeld, J.T. Ellis, E.D. Kilbourne, D.E. Rogers, Studies on influenza in the pandemic of 1957-1958. II. Pulmonary complications of influenza, J. Clin. Investig. 21 (1959) 213–265.

[3] W.P. Glezen, S. Greenberg, R.L. Atmar, P.A. Piedra, R.B. Couch, Impact of respiratory virus infections on persons with chronic underlying conditions, JAMA 283 (2000) 499–505.

[4] T. Mauad, L. Hajjar, G.D. Callegari, L.F. da Silva, D. Schout, F.R. Galas, et al., Lung pathology in fatal novel human influenza A (H1N1) infection, Am. J. Respir. Crit. Care Med. 181 (2010) 72–79.

[5] M. Seki, Yanagihara K. KosaiK., Y. Higashiyama, S. Kurihara, K. Izumikawa, et al., Disease severity in patients with simultaneous influenza and bacterial pneumonia, Intern Med. 46 (2007) 953–958.

[6] M. Seki, Hashiguchi K. SuyamaN, A. Hara, K. Kosai, S. Kurihara, et al., A patient with fulminant influenza-related bacterial pneumonia due to Streptococcus pneumoniae followed by Mycobacterium tuberculosis infection, Intern Med. 47 (2008) 2043–2047.

[7] J.A. McCullers, J.E. Rehg, Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor, J. Infect. Dis. 186 (2002) 341–350.

[8] M. Seki, Tomono K. HigashiyamaY., K. Yanagihara, H. Ohno, Y. Kaneko, et al., Acute infection with influenza virus enhances susceptibility to fatal pneumonia following Streptococcus pneumoniae infection in mice with chronic pulmonary colonization with Pseudomonas aeruginosa, Clin. Exp. Immunol. 137 (2004) 35–40.

[9] M. Seki, K. Yanagihara, Y. Higashiyama, Y. Fukuda, Y. Kaneko, H. Ohno, et al., Immunokinetics in severe pneumonia due to influenza virus and bacteria coinfection in mice, Eur. Respir. J. 24 (2004) 143–149.

[10] S. Kohno, Y. Imamura, Y. Shindo, M. Seki, T. Ishida, S. Teramoto, et al., Clinical practice guidelines for nursing- and healthcare-associated pneumonia (NHCAP), Respir. Investig. 51 (2013) 103–126.

[11] M. Seki, K. Hashiguchi, A. Tanaka, K. Kosai, T. Kakugawa, Y. Awaya, et al., Characteristics and disease severity of healthcare-associated pneumonia among patients in a hospital in Kitakyushu, Jpn. J. Infect. Chemother. 17 (2011) 363–369.

[12] The committee of the the Japanese Respiratory Society guidelines for the management of pneumonia the Japanese Respiratory Society guidelines for the management of community-acquired pneumonia in adults, Respirology 11 (2006) S1–S133.

[13] J.S. Kroll, R. Booy, Haemophilus influenzae: capsule vaccine and capsulation genetics, Mol. Med. Today. 2 (1996) 160–165.

[14] S. Hamaguchi, M. Seki, N. Yamamoto, T. Hirose, N. Matsumoto, T. Irisawa, et al., Case of invasive nontypable Haemophilus influenzae respiratory tract infection with a large quantity of neutrophil extracellular traps in sputum, J. Inflamm. Res. 5 (2012) 137–140.

[15] T. Kastrin, M. Paragi, J. Kolman, M. Cizman, A. Kraigher, M. Gubina, Slovenian meningitidis study group characterisation of invasive Haemophilus influenzae isolates in Slovenia, 1993-2008, Eur. J. Clin. Microbiol. Infect. Dis. 29 (2010) 661–668.

[16] F. Resman, M. Ristovski, J. Ahl, A. Forsgren, J.R. Gilsdorf, A. Jasir, et al., Invasive disease caused by Haemophilus influenzae in Sweden 1997-2009;evidence of increasing incidence and clinical burden of non-type b strains, Clin. Microbiol. Infect. 17 (2011) 1638–1645.

[17] S. Nakamura, K. Yanagihara, M. Seki, K. Izumikawa, Y. Higashiyama, Y. Miyazaki, et al., Clinical characteristics of pneumonia caused by beta-lactamase negative ampicillin resistant Haemophilus influenzae (BLNAR), Scand. J. Infect. Dis. 39 (2007) 521–524.

[18] A. Fujii, M. Seki, M. Higashiguchi, I. Tachibana, A. Kumanogoh, K. Tomono, Community-acquired, hospital-acquired, and healthcare-associated pneumonia caused by Pseudomonas aeruginosa, Respir. Med. Case Rep. 12 (2014) 30–33.

[19] M. Seki, Y. Higashiyama, Y. Imamura, S. Nakamura, S. Kurihara, K. Izumikawa, et al., A clinical comparative study of piperacillin and sulbactam/ampicillin in patients with community-acquired bacterial pneumonia, Intern Med. 48 (2009) 49–55.

[20] C. Hotta-Iwamura, K.V. Tarbell, Type 1 diabetes genetic susceptibility and dendritic cell function: potential targets for treatment, J. Leukoc. Biol. 20 (2016) 1115–1150.

[21] K.Y. Chen, P. Hseuh, Y.S. Liaw, P.C. Yang, K.T. Luh, A 10-year experience with bacteriology of acute thoracic empyema: emphasis on Klebsiella pneumoniae in patients with diabetes mellitus, Chest 117 (2000) 1685–1689.