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Short Article

Lower respiratory tract hemorrhage associated with 2009 pandemic influenza A (H1N1) virus infection

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Background Influenza-associated lower respiratory tract hemorrhage (LRTH) has been reported in previous pandemics and is a rare complication of seasonal influenza virus infection. We describe patients with LRTH associated with 2009 pandemic influenza A (H1N1) (pH1N1) virus infection identified from April 2009 to April 2010 in the United States.

Methods We ascertained patients with pH1N1-associated LRTH through state and local surveillance, the Emerging Infections Program, and CDC s Infectious Diseases Pathology Branch. All patients had influenza A, evidence of pneumonia, and evidence of LRTH.

Results We identified 44 cases; the median number of days from illness onset to clinical signs of LRTH was one. Hemoptysis or respiratory tract bleeding was documented in 40% of pH1N1-associated LRTH cases, often present early during the course of illness. Twenty-one (48%) patients with LRTH had no other hemorrhagic diatheses. Seven (23%) patients with LRTH received antiviral treatment within two days of illness onset.

Conclusions During influenza season, clinicians should consider influenza infection in the differential diagnosis for patients presenting with hemoptysis or other signs or symptoms of LRTH. While the impact of timing of antiviral therapy on this complication has not been studied, the rapid progression of LRTH may support use of early empiric therapy. Continued investigation is necessary to betterdefine the clinical spectrum of both seasonal influenza- and pH1N1-associated LRTH.

Keywords Hemorrhage, influenza, pH1N1, viral pneumonia.

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Introduction

Lower respiratory tract hemorrhage (LRTH) has been described in influenza-associated fatalities from previous pandemics and is a rarely reported complication of seasonal influenza infection whose epidemiology is poorly described.[1] Autopsy findings from fatal cases of 2009 pandemic influenza A (pH1N1) have identified airway inflammation, edema, diffuse alveolar damage, microscopic intra-alveolar hemorrhage, and varying degrees of pulmonary hemorrhage.[2–4] We describe the clinical and epidemiologic characteristics of patients with pH1N1-associated LRTH identified from April 2009 to April 2010 in the United States.

Materials and methods

We ascertained pH1N1-associated LRTH cases in three ways. First, we asked state and local health departments to identify cases via established surveillance systems. Second, we reviewed medical records reported by the Emerging Infections Program (EIP) for patients with the ICD-9-CM diagnosis code for hemoptysis. EIP surveillance has been described previously.[5] Third, we reviewed forms accompanying tissue specimens from pH1N1-associated fatalities submitted to CDC's Infectious Diseases Pathology Branch for evidence of LRTH.[4] We defined LRTH cases as patients with laboratory-confirmed influenza A infection,[1]

radiographic evidence of or diagnosis of pneumonia in the medical record, respiratory bleeding documented in the medical record or autopsy report and documentation of blood during bronchoscopy or of gross lung tissue hemorrhage on autopsy, or documentation of copious amounts of hemoptysis or frank blood from the respiratory tract. We used SAS 9.2 for all data analysis (SAS Institute, Cary, NC, USA).

Clinical and demographic information was abstracted from patient medical records. Illness onset was defined as the date of fever or respiratory symptom onset. Obesity was documented in the medical record or identified using calculated body mass index (BMI) as previously described.[6] We excluded patients receiving maintenance anticoagulation therapy, intravenous heparin or antithrombin III therapy during hospitalization, and those diagnosed with cirrhosis of the liver or other hemorrhagic diatheses.

This investigation was part of the public health response to the pH1N1 pandemic and was not considered to be research in accordance with the federal human subjects protection regulations and CDC's Guidelines for Defining Public Health Research and Public Health Non-Research.

Results

Reported cases

We identified 44 patients meeting our case definition for LRTH. Forty-two (95%) of the 44 patients were confirmed to have pH1N1 by RT-PCR, and two were confirmed to have influenza A whose subtype was not determined.

Patient characteristics

The median age of LRTH patients was 25 years (range: 1–73 years); 14 (32%) were younger than 18 years of age (Table 1). Fourteen (32%) LRTH patients had no significant past medical history. Among LRTH patients with a report of past medical history, pulmonary co-morbidities were most commonly reported. Of the 41 LRTH patients for whom BMI was calculated, 18 (44%) were obese.

Clinical characteristics

Twenty-two of 44 (50%) LRTH patients had at least one healthcare encounter prior to hospitalization; the median duration from illness onset to first healthcare encounter was 2 days (range: 0–9; Table 2). Overall, 36 (82%) patients were hospitalized; the median duration from illness onset to hospitalization was 3 days. Of the eight patients who were not hospitalized, all were fatalities. Thirty-five (97%) of the 36 hospitalized patients were admitted to the intensive care unit (ICU). Hospitalized patients frequently had life-threatening complications, including acute respiratory distress syndrome (ARDS) (84%) and renal failure (58%). Thirty-two of 44 (73%) patients had hemoptysis (22%), pulmonary hemorrhage (34%), or both (44%); 18 patients had hemoptysis prior to or on the first day of hospitalization. The median number of days from reported illness onset to clinical signs of LRTH was one (Figure 1).

Table 1. Characteristics of patients with pH1N1-associated lower respiratory tract hemorrhage (LRTH)

Characteristic	LRTH cases (n = 44)
Male: *n* (%)	21 (49)
Age in years: median (range)	25 (1–73)
Age category in years: *n* (%)	
<5	1 (2)
5–9	2 (5)
10–17	11 (25)
8–29	11 (25)
30–49	10 (23)
50–64	8 (18)
>64	1 (2)
Race and ethnicity: *n* (%)	
White	14 (32)
Black	7 (16)
Hispanic	7 (16)
Other	2 (5)
Unknown	14 (32)
Medical history: *n* (%)	
None reported	14 (32)
Pulmonary disorders	10 (23)
Asthma	8 (18)
COPD	2 (5)
Other*	2 (5)
Cardiovascular disease	4 (9)
Kidney disease**	3 (7)
Diabetes mellitus	6 (14)
Immunosuppressive conditions†	2 (5)
Neurologic/Neuromuscular conditions††	1 (2)
Pregnancy	2 (5)
Hypertension	8 (18)
Obstructive sleep apnea	1 (3)
Other medical conditions	4 (9)
BMI††††: median (range)	31 (14–81)
Obesity††††: *n/N* (%)	18/41 (44)
pH1N1 monovalent influenza vaccine‡: *n/N* (%)	2/29 (7)
Seasonal trivalent influenza vaccine‡: *n/N* (%)	2/18 (11)
Deceased: *n* (%)	42 (95)

*Other pulmonary disorders: restrictive lung disease, hypersensitivity pneumonitis, chronic bronchitis, emphysema, and permanent tracheostomy.

**Kidney disease: end stage renal disease, chronic renal disease, renal artery stenosis, polycystic kidney disease.

†Immunosuppressive conditions: lymphoma within the last 12 months, immunosuppressive medication, and pancytopenia.

††Neurologic/neuromuscular conditions were Angelman's syndrome, cerebral palsy, hydrocephalus, microcephaly, seizure disorder, myasthenia gravis, quadriplegia, developmental delay, and lead toxicity.

†††Pregnant women and children <2 years of age were excluded from analysis of BMI and obesity.

‡Received at least 2 weeks prior to onset of illness.

Table 2. Clinical characteristics of patients with pH1N1-associated lower respiratory tract hemorrhage

Characteristic	*n*/*N* (%)
Number of healthcare encounters: median (range); *n* = 44	2 (0–3)
Days from illness onset to first encounter: median (range); *n* = 40	2 (0–9)
>1 healthcare encounter	22/44 (50)
Hospitalization	36/44 (82)
Days from illness onset to admission: median (range); *n* = 36	3 (0–13)
Hospital days of stay: median (range); *n* = 36	8 (0–36)
ICU admission	35/44 (80)
ICU days of stay: median (range); *n* = 27	8 (0–35)
Days from hospitalization to ICU admission: median (range); *n* = 31	0 (0–4)
Days from illness onset to death: median (range); *n* = 40	10 (1–38)
Complications of illness during hospitalization	
Acute respiratory distress syndrome	31/37 (84)
Liver failure	2/20 (10)
Renal failure	14/24 (58)
Pulmonary embolism	6/35 (17)
Disseminated intravascular coagulation	8/32 (25)
Co-infection with another pathogen	17/44 (39)
Invasive pulmonary infection	13/44 (30)
Treatment and medical care	
Blood pressure maintenance medication	31/39 (79)
Antiviral treatment	32/40 (80)
Days from illness onset to treatment: median (range); *n* = 31	4 (0–14)
Received within 2 days of illness onset	7/31 (23)
Antimicrobial therapy	34/44 (77)
Anticoagulation therapy	21/44 (48)
Mechanical ventilation	38/44 (89)
Intubation	32/38 (82)
ECMO	6/38 (16)
Days ventilated: median (range); *n* = 38	6 (0–36)

Seventeen (39%) patients had evidence of co-infection with another pathogen. Methicillin-resistant *Staphylococcus aureus* (MRSA) infection was identified in 6 (36%) patients. Other co-infections included *Streptococcus pyogenes*, herpes simplex, parainfluenza virus type 1, *Pseudomonas* species, *Acinetobacter baumannii*, and unspecific fungal infection. Four reports of co-infection did not identify a pathogen.

Twenty-three (52%) patients were diagnosed with complications known to cause hemorrhage, including disseminated intravascular coagulation (DIC), pulmonary embolism (PE), and MRSA co-infection. The remaining 21 (48%) patients had no known hemorrhagic diatheses reported during their course of illness.

Treatment

Most (80%) LRTH patients were treated with antiviral medications during the course of their illness; 7 (23%) received treatment within 2 days of illness onset. Anticoagulation therapy was used in 21 (48%) LRTH patients. Thirty-nine (89%) patients and all hospitalized patients required mechanical ventilation (Table 2).

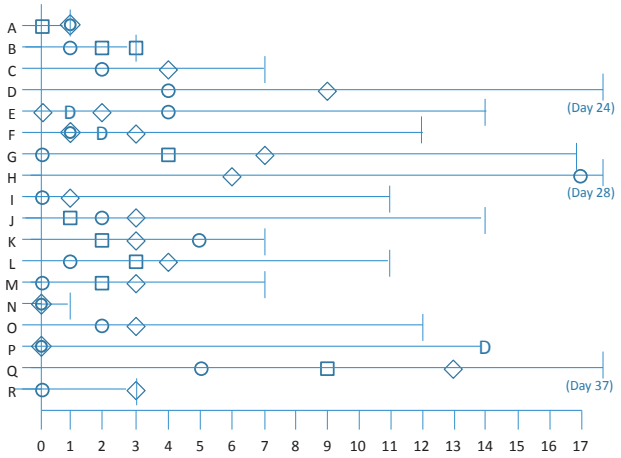

Figure 1. Time course of hemorrhage, healthcare encounter history, and death for 18 patients with pH1N1-associated lower respiratory tract hemorrhage and hemoptysis or pulmonary hemorrhage reported. *x*-axis: time from illness onset. *y*-axis: case. ○ = hemorrhage onset, □ = healthcare encounter, ◇ = hospital admission, D = hospital discharge, | = death.

Outcome

Forty-two (95%) patients died; 8 (19%) deaths occurred at home or in the emergency department. The median duration from illness onset to death was 10 days (range: 1–38). Of the 36 hospitalized patients with LRTH, 7 (19%) died within 1 day of hospitalization. Overall, 33 (79%) LRTH fatal cases had autopsy evidence of LRTH.

Discussion

We describe 44 patients with LRTH associated with pH1N1 virus infection; half of the patients had no identifiable cause for hemorrhage other than primary viral pneumonia. Although the majority of patients had chronic medical conditions, a third were otherwise healthy. Most patients were young, consistent with other reports of severe illness in pH1N1 patients.[6–8] Clinical decline after illness onset was abrupt and resulted in death for most patients. Clinical evidence of LRTH (e.g., hemoptysis or respiratory tract bleeding) was documented for 40% of patients, and these signs were often present early during the course of illness.

One-half of the patients in this series had at least one healthcare encounter prior to hospitalization, and five presented with hemoptysis. Most patients had conditions that placed them at increased risk for complications of influenza, and initiation of antiviral therapy during an outpatient encounter may have improved their outcome.[9]

In one-half of hospitalized patients, hemoptysis began prior to or on the day of hospital admission. Hemoptysis has been identified as a symptom of progressive disease suggesting oxygen impairment or cardiopulmonary insufficiency and may have been an early clinical indicator of severe illness requiring urgent patient management.[10]

Other studies have reported pulmonary hemorrhage in pH1N1-associated fatalities. Mauad *et al.* suggested that pulmonary hemorrhage was associated with underlying medical conditions. We identified LRTH in 14 otherwise healthy patients, suggesting that LRTH can occur in otherwise healthy adults.

This study has several limitations. First, our patients may not accurately represent the spectrum of outcomes due to pH1N1-associated LRTH. Because case ascertainment relied partially on autopsy evidence and many state and local health departments limited pH1N1 surveillance to severe cases, our findings likely overestimate mortality associated with LRTH and pH1N1 infection. Second, we were unable to determine the etiology of pH1N1-associated LRTH in many of our patients. In more than half of our cases, LRTH could have been due to concomitant PE, DIC, liver failure, or invasive pulmonary co-infection, instead of a direct result of primary viral pneumonia. However, we identified 21 patients whose LRTH was most likely due to primary viral pneumonia. These data suggest that pH1N1-associated LRTH can be caused by either primary viral pneumonia or other complications associated with pH1N1 infection. Third, when calculating the number of days between illness onset and notable events in a patient's course of illness (e.g., receipt of antiviral therapy, hospital admission, and death), we used the date reported in the medical record as the date of illness onset, which may be subject to patient recall bias. Thus, we may under- or overestimate the number of days between illness onset and events in a patient's course of illness. Finally, we were unable to establish the prevalence of pH1N1-associated LRTH from the 44 cases we identified. Thus, it is impossible to determine whether pH1N1-associated LRTH occurred with greater or less frequency relative to previous pandemic or seasonal influenza infections. However, among patients with laboratory-confirmed influenza infection identified by EIP surveillance, 71 (1·1%) of 6572 patients were identified from April 15, 2009, to April 30, 2010, with the ICD-9-CM code for hemoptysis, while only 37 (0·5%) of 7293 patients were identified with the ICD-9-CM code for hemoptysis during the 2005–2006 to 2008–2009 influenza seasons, when the pH1N1 virus was not circulating (CDC unpublished data). Thus, LRTH might occur more often in the setting of a novel influenza virus infection compared with seasonal influenza infections. Further studies are necessary to determine the prevalence of LRTH associated with influenza infections.

Clinicians should consider influenza infection in the differential diagnosis for patients presenting with hemoptysis or other signs or symptoms of LRTH in the presence of fever or other influenza symptoms when influenza viruses are known to be circulating. Early empiric antiviral therapy, ideally within 48 hours of symptom onset, based on a clinical suspicion of influenza infection should supersede diagnostic test results, especially when patients present with symptoms associated with possible severe illness such as hemoptysis. Clinicians should also consider bacterial co-infection in these instances. Continued investigation is necessary to better define the clinical spectrum of both seasonal influenza and pH1N1-associated LRTH and its risk factors.

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Author contribution

EDK, MR, JN, AF, MK, DMB, W-JS, SRZ, KW, LK, LF, and MAJ have made substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data; EDK, MR, AF, LF, and MAJ have drafted the submitted article or revised it critically for important intellectual content; EDK, MR, JN, AF, MK, DMB, W-JS, SRZ, KW, LK, LF, and MAJ have provided final approval of the version to be published; and EDK is guarantor of the study.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Appendix 1

2009 Pandemic H1N1 Influenza-Associated Lower Respiratory Tract Hemorrhage Working Group members: Candece Adkins, Jannifer G. Anderson, Roger Anderson, Katie Avery, Christine Barr, Steven Baty, Ruth Belflower, Matt Bolinger, John Boss, Carol Browning, Lesley Bullion, Gayle Butler, Hector Contreras, Molly Crockett, Connie Cronley, Virginia Dato, Ann DeLaCruz, Phyllis Dudley, Lynne Fenner, Pamela Firetti, Laura Fleege, Donna Fravey, Karen Gieseker, Elisa Gutierrez, Emily Hallberg, Julie Hand, Thomas Haupt, Vivian Hawkins, Sandi Henley, Danali Herley, Kathleen Hill, Joy Holbrook, Nina Huynh, Sherif Ibrahim, Barbara Jones, Tona L'Estrange, Johnathan Ledbetter, Pamela G. Lewis-O'Connor, Yi-Chun Lo, Janice Louie, Sherry Lyles, Matthew McLane, Lori Maron, Peggy Oakes, Shannon Page, Nicole Patterson, Susan Peters, Ranjani Rajan, Ariene Reeves, Carol Roberts, Alicia Rodriquez, Kara San Joaquin, Ruta Sharangpani, Emily Sickbert-Bennett, Nancy Spina, Lori Swope, Deb Thompson, Diana Thurston, Jennifer Tripp, Elisabeth Vaeth, Meredith Vandermeer, Althea Venida, Nathan Wang, Robin Williams, and Robert Willis.