

Novel H1N1 Influenza A Viral Infection Complicated by Alveolar Hemorrhage

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We report a complication of the novel H1N1 influenza A viral infection not yet described during this 2007–2009 pandemic. Pulmonary hemorrhage is a known complication of influenza pneumonia, including well documented reports from previous pandemics. A 57-year-old African American female presented with fevers, progressive shortness of breath, and cough. After being admitted with an initial diagnosis of myocardial infarction, hemoptysis developed. Nasopharyngeal swabs rapid testing was negative for influenza A and B antigen, but a polymerase chain reaction test for influenza A type H1N1 was positive. A fiberoptic bronchoscopy for ongoing hemoptysis demonstrated diffuse erythema and bleeding, and bronchoalveolar lavage was consistent with alveolar hemorrhage. Progressive hypoxemic respiratory failure ensued, eventually leading to her demise. Our case highlights one of the more feared complications that may have been more common in prior outbreaks, such as the 1918 “Spanish Flu.” Autopsy studies from the 1918 influenza pandemic found severe tracheobronchitis (oftentimes hemorrhagic), septal edema, necrotizing bronchiolitis, alveolitis, and extensive hemorrhage, as opposed to the more benign laryngitis and tracheobronchitis that is commonplace in other influenza infections. Similar pathology appearances, including pulmonary hemorrhage, have also been described in H5N1 outbreaks in China and Thailand. It is crucial for pandemic preparedness planning that additional careful and complete autopsy study of this present pandemic influenza infection be performed and reported to answer questions regarding the natural history, pathology, and pathogenesis of this novel H1N1 influenza. Key words: influenza; H1N1; pandemic; pulmonary hemorrhage; pneumonia; hemoptysis; alveolar hemorrhage; hypoxemic respiratory failure; pulmonary hemorrhage. [Respir Care 2010;55(5):623–625. © 2010 Daedalus Enterprises]

Introduction

We report a complication of the novel H1N1 influenza, a viral infection not yet described during this 2007–2009 pandemic. Pulmonary hemorrhage is a known complication of influenza pneumonia, including well documented reports from previous pandemics. Some accounts during the 1918 “Spanish Flu” include reports of patients “choking to death by evening, their lungs swamped with blood, foam, and pus,”¹ and blood that “pours out of the nostrils

so as to stain a large part of the white sheets in which the bodies are wrapped.”² Per the World Health Organization, as of November 2009, more than 206 countries and overseas territories have reported laboratory-confirmed cases of pandemic influenza H1N1, including over 6,250 deaths. We suspect that severe cases of viral influenza pneumonia have a higher incidence of alveolar hemorrhage than has been documented.

Case Report

A 57-year-old African American female presented to an outside hospital complaining of fevers to 40°C, shortness of breath, and cough for 24 hours prior to presentation. Her medical history was notable for hypertension and mild chronic obstructive pulmonary disease that did not affect her activity level: she could climb a flight of steps without dyspnea. Her only medication was hydrochlorothiazide. She was noted to have a troponin of 1.4 ng/mL and admitted with a diagnosis of non-ST-elevation myocardial

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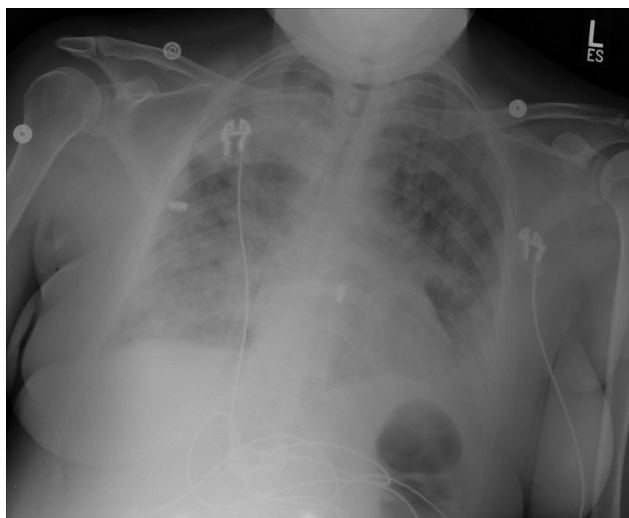


Fig. 1. Chest radiograph after admission to the outside hospital shows bilateral alveolar infiltrates.

infarction. She was started on metoprolol, aspirin, and heparin. Eight hours after a heparin infusion began, she developed hemoptysis, and heparin was discontinued. Repeat chest radiograph (Fig. 1) revealed bilateral alveolar infiltrates, unchanged from admission. She remained hypoxic and febrile, at which point ceftriaxone and azithromycin were initiated. She required mechanical ventilation 4 days after initial presentation, secondary to hypoxemic respiratory failure.

Upon arrival to our hospital she was sedated and placed on volume-control ventilation, using the Acute Respiratory Distress Syndrome Network protocol. Physical examination revealed an overweight (BMI 27 kg/m²) female with bloody secretions throughout the ventilator circuit, which increased as she coughed or was suctioned. She was febrile and hemodynamically stable. Lung examination was notable for diffuse rhonchi and decreased breath sounds at the bases. The remainder of her examination was within normal limits. Laboratory studies included a white-blood-cell count of 12,500/mL, hematocrit of 33.2%, platelet count of 143,000/mL, creatinine of 1.4 mg/dL, normal urinalysis, B-type natriuretic peptide of 85 pg/mL, and a trending-downward troponin at 0.17 ng/mL. The coagulation study revealed a mildly elevated prothrombin time (17.8 s) and partial thromboplastin time (37 s). Rheumatologic workup, including antinuclear antibody, anti-double stranded antibody, antineutrophil cytoplasmic antibodies, and anti-glomerular basement membrane antibody, were negative. Arterial blood gas values while breathing 80% oxygen were pH 7.37, P_{CO}₂ 47 mm Hg, and P_O₂ 141 mm Hg. Prior to transfer she had empirically been placed on vancomycin, piperillin/tazobactam, and oseltamivir. Computed tomogram (Fig. 2) revealed diffuse air-space disease, without evidence of substantial effusions, lymphadenopathy, masses, or abscess.

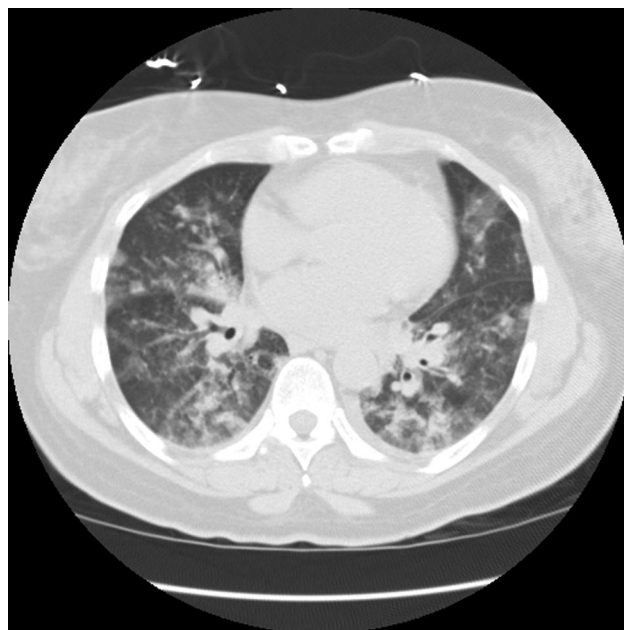


Fig. 2. Representative computed tomogram slice taken at our institution shows diffuse air-space disease.



Fig. 3. Bronchoalveolar lavage fluid immediately after the retrieval from the bronchi shows progressive bloody return: the fluid in the first syringe (right) was clear, that in the second syringe (middle) was slightly blood-tinged, and that in the third syringe (left) is obviously bloody.

Fiberoptic bronchoscopy revealed diffuse airway erythema and bleeding, but no endobronchial lesions or localized bleeding. Bronchoalveolar lavage of the right lower lobe showed progressively bloody return, consistent with alveolar hemorrhage (Fig. 3). Microbiologic and cytologic examination revealed no evidence of infection or malignancy. Nasopharyngeal swabs rapid testing was negative for influenza A and B antigen, but a polymerase chain reaction test for influenza A type H1N1 returned positive.

Progressive hypoxemic respiratory failure occurred over the next 6 days, with continued profuse bloody secretions, despite attempts at replacing coagulation factors. Family members declined an autopsy.

Discussion

To our knowledge this is the first reported case of clinically evident alveolar hemorrhage and massive hemoptysis related to the novel H1N1 "swine" influenza virus. One case report noted "limited hemoptysis" without evidence of alveolar hemorrhage.³ A retrospective review from the initial Mexican outbreak noted "blood in sputum" in 6 of 18 patients, but that report provided no bronchoscopy data or further explanation.⁴ Our case highlights one of the more feared complications that may have been common in prior outbreaks, such as the 1918 "Spanish Flu." Autopsy studies from that pandemic noted severe tracheobronchitis (oftentimes hemorrhagic), as opposed to the more benign laryngitis and tracheobronchitis that is commonplace in other influenza infections. Large autopsy studies of the 1918 pandemic noted diffusely swollen and inflamed bronchial surfaces with evidence of hemorrhagic bronchitis and tracheobronchitis in 50% of the cases, and oftentimes luminal filling with frothy blood-stained material thought to be fibrin and erythrocytes.⁵

Previous pathology studies of influenza have noted changes within the upper and lower respiratory tract, including edema, hemorrhage, and necrosis. Histologic evaluation of lung tissue in previous autopsy studies found septal edema, necrotizing bronchiolitis, alveolitis, and extensive hemorrhage.^{2,6,7} Two recent autopsy reports from patients affected by the 2009 H1N1 "swine" influenza have been published. A report of 5 patients in Mexico noted one death associated with cerebral and pulmonary hemorrhage.⁶ Another report from Brazil noted 20 of 21 patients with various degrees of alveolar hemorrhage at autopsy.⁸ Some experts believe massive cytokine release in H1N1 influenza may contribute to the rapid-onset pulmonary disease and death.^{7,9} Some of these same studies identify the 1918 H1N1 strain of influenza as 100 times more lethal than traditional influenza.⁹ Similar pathologic appearances, including pulmonary hemorrhage, have been described in H5N1 outbreaks in China and Thailand.¹⁰

As our patient appeared to develop hemoptysis after minimal time on anticoagulation, and had persistent hemoptysis after discontinuation, anticoagulation should be carefully considered in these patients, secondary to the known incidence of hemorrhage in autopsy series. However, in a recent report from Australia in which anticoagulation was used for extracorporeal membrane oxygenation support, the incidence of hemorrhagic respiratory complications in patients with H1N1 was only 10%.¹¹ No further data were provided regarding the severity of hem-

orrhage, its clinical implications, or its relationship to mortality.

The spectrum of observed pathologic changes related to influenza infection appears to differ little from pandemic to pandemic, but some authors believe that bacterial co-infections have led to differences in mortality in each pandemic.¹² Bacterial secondary infection does not appear to be a large contributor to mortality in the current H1N1 pandemic, per reports from Mexico,⁴ Argentina,¹³ and California.^{14,15} It is crucial for pandemic preparedness planning that additional careful and complete autopsy study of this present pandemic influenza infection be performed and reported to answer important questions about the natural history, pathology, and pathogenesis of the novel H1N1 influenza.

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