2009 H1N1 Influenza Infection: Spectrum Of Chest CT Findings, With Radiologic-Pathologic Correlation
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Citation

Abstract
The novel influenza A H1N1 virus resulted in the recent influenza pandemic of 2009. In this article, we describe the spectrum of thoracic computed tomography (CT) findings in 8 patients with laboratory-confirmed H1N1 infection. Peribronchovascular and subpleural groundglass opacities and consolidations, pulmonary embolism, and pleural effusions are recently reported findings. Volume loss, bronchial wall thickening, bronchiectasis, mosaic attenuation, and lymphadenopathy are not commonly reported findings. Cryptogenic organizing pneumonia developed as a complication in one of our H1N1 cases, which has not been previously reported. We also describe radiologic-pathologic correlation in an additional case, where autopsy demonstrated diffuse alveolar damage.

INTRODUCTION
In the spring of 2009, the novel influenza A H1N1 virus, now referred to as 2009 H1N1, marked the first major influenza pandemic in over 40 years.1 The Centers for Disease Control and Prevention (CDC) estimated there were 57 million cases of H1N1 influenza infection, 257,000 hospitalizations, and 11,690 virus related deaths between April 2009 and January 16, 2010.2 As of 21 February 2010, the World Health Organization reported more than 213 countries and overseas territories or communities worldwide with reported laboratory confirmed cases of pandemic 2009 H1N1 influenza, including at least 16,226 deaths.3 Following a 1-7 day incubation period, the majority of patients present with flu-like symptoms including cough, fever, sore throat, rhinorrhea, and dyspnea. A confirmed H1N1 case is determined when a patient demonstrates influenza-like illness and positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) or positive viral culture.4 Most cases have been self-limited, but patients with comorbidities, including immunosuppression, diabetes, and chronic cardiopulmonary disease are more likely to require hospitalization.5 Antiviral treatment is recommended for all patients requiring hospitalization, regardless of when symptoms began.1

The aim of this article is to describe the spectrum of thoracic computed tomography (CT) findings in 8 patients admitted to the hospital and confirmed to have H1N1 by RT-PCR. We further discuss pathology findings at autopsy of another confirmed case to help better understand the radiologic-pathologic correlation.

CHEST RADIOGRAPHY
Chest radiographs obtained within 24 hours of presentation to the hospital displayed a range of findings from a normal radiograph to patchy consolidations and groundglass opacities (Fig. 1).

Figure 1
Figure 1: 43-year-old otherwise healthy male who presented to the emergency room (ER) with 7 day history of fever, dyspnea, cough, weight loss. He was hypoxic and H1N1 infection was confirmed. Chest radiograph performed at presentation revealed patchy bilateral groundglass opacities (arrows) (A) that rapidly progressed to patchy bilateral consolidations (B). Trace pleural effusions were occasionally identified. The first published report on the 2009 H1N1 virus demonstrated bilateral patchy opacities affecting 3 or 4 lung quadrants in 61% of inpatients.5 A recent study describes an abnormal
initial chest radiograph in 42% of all H1N1 patients, and in 100% of patients admitted to the intensive care unit (ICU).\textsuperscript{6}

COMPUTED TOMOGRAPHY
The majority of our 8 patients obtained initial chest CT studies within one day of admission. However one patient obtained a chest CT study 27 days after admission.

PULMONARY FINDINGS
The pulmonary findings described below are consistent with the Fleischner Society glossary.\textsuperscript{7} Groundglass opacity, consolidation, and pulmonary embolism are all recently reported CT findings in H1N1 patients. Groundglass opacity on CT is defined as hazy increased opacity of lung, with preservation of underlying bronchial and vascular margins, and may be caused by subtotal displacement of air in the alveoli.\textsuperscript{7} Consolidation on CT is defined as increased opacity of lung, with obscuration of underlying bronchial and vascular margins, caused by total replacement of alveolar air.\textsuperscript{7} Three of our patients demonstrated isolated groundglass opacities without any consolidations, including 1 patient with lobular groundglass opacities (Fig. 2).

Figure 2
Figure 2: Chest CT performed at presentation in same patient as in Figure 1. (A,B) demonstrates lobular groundglass opacities in a peribronchovascular (short arrow) and subpleural (long arrow) distribution.

Five patients demonstrated mixed groundglass opacities and consolidations (Fig. 3).

A recent study of CT findings demonstrated isolated groundglass opacities in 60%, mixed groundglass opacities and consolidation in 30% and isolated consolidations in 10% of H1N1 patients.\textsuperscript{8} Patients with consolidations may have a more severe clinical course.\textsuperscript{8,9} The distribution of opacities in our patients was interesting in that 6 of 8 patients demonstrated a peribronchovascular and subpleural pattern. This is consistent with the pattern described for influenza virus in general\textsuperscript{10}, and H1N1 specifically.\textsuperscript{11,12,13} Pulmonary embolism was seen in 1 of our patients (Fig. 4).

Figure 3
Figure 3: 58-year old HIV positive male with diabetes and coronary artery disease presented to the ER with 6 day history of dyspnea and productive cough. He tested positive for H1N1 and developed rapidly progressive acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. Chest CT performed within 1 day of presentation revealed confluent perihilar consolidations (short arrow) and ground glass opacities (long arrow) and small bilateral pleural effusions.

Figure 4
Figure 4: 26-year old otherwise healthy male who presented to the ER with fever, shortness of breath, cough and respiratory distress, tested positive for H1N1 and ultimately developed respiratory failure requiring 6 days of mechanical ventilation. Chest CT performed within 1 day of presentation (A) demonstrated mixed peribronchovascular and subpleural groundglass opacities and consolidations. Chest CT performed 7 days later (B) demonstrated a subsegmental pulmonary embolus (arrow) in the right lower lobe.
Pulmonary embolism has been reported as a complication of H1N1 infection in 36% of patients admitted to the ICU.\(^6\)

The following CT findings have either been reported infrequently or not at all for H1N1 patients. However, these findings have been observed in other viral infections. Volume loss was seen in 2 patients (Fig. 5), which has not been reported previously.

**Figure 5**

Figure 5: Otherwise healthy 40-year male who presented to the ER with a 7 day history of cough, fevers and shortness of breath, was found to be H1N1 positive and hypoxic. Chest CT performed within 3 days of presentation demonstrated volume loss indicated by elevation of the minor fissure (long arrow). There were also peribronchovascular consolidation (short arrow) and subpleural groundglass opacities.

Bronchial wall thickening and bronchiectasis were seen in 2 patients (Figs. 6, 7).

**Figure 6**

Figure 6: 51-year old hypertensive male presented to the ER with a 2 week history of cough and was found to be hypoxic. He tested positive for H1N1, and chest CT performed within 1 day of presentation revealed bronchial wall thickening and bronchiectasis (arrow), subtle ground glass opacity in the right lung, and small bilateral effusions.

Bronchial wall thickening and bronchiectasis were reported in 100% and 50% of immunocompromised patients respectively.\(^13\) Mosaic attenuation was present in 1 of our patients (Fig. 7), which has not been reported previously.
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**Figure 7**

39-year obese male with hypertension presented with a 4 day history of fever, cough, dyspnea on exertion. Patient was found to be H1N1 positive and hypoxic, eventually requiring positive pressure ventilation. Chest CT performed at presentation revealed mosaic attenuation demonstrated by alternating low-attenuation (short arrow) and normal attenuation (long arrow) of the lung, as well as bibasilar areas of bronchiectasis and bronchial wall thickening.

Centrilobular nodules were present in 1 of our patients (Fig. 8).

**Figure 8**

Same patient as in Figure 7. Chest CT demonstrates scattered centrilobular nodules (thin arrows) and patchy ground glass opacities.

Small groundglass nodules have been previously reported in 1 of 15 ICU patients.6 Centrilobular nodules have been reported in 3 of 8 immunocompromised patients.13 A large pneumonia involving a single lobe was seen in 1 of our patients, whose sputum, bronchoalveolar lavage, and blood cultures were all negative, except for H1N1 (Fig 9).

**Figure 9**

63-year old hypertensive female presented to the ER with a 4 day history of fever, chills and cough. Patient was H1N1 positive, but all other sputum, bronchoalveolar lavage and blood cultures were negative. Patient was admitted to the ICU, developed ARDS and has remained hospitalized for over 2 months. Chest radiograph (A) and CT (B) performed within 2 days of presentation demonstrates large left upper lobe mixed consolidation and groundglass opacity and small left pleural effusion.

This pattern has been reported in 1 of 8 immunocompromised patients.13 Eight weeks after presentation, this patient of ours developed peribronchovascular and subpleural consolidations and bronchiectasis, representing organizing pneumonia (Fig 10), also referred to as cryptogenic organizing pneumonia (COP).

**Figure 10**

Same patient as in Figure 9. Chest radiograph (A) and CT (B) performed 8 weeks after presentation demonstrate bilateral peribronchovascular (short arrow) and subpleural (long arrows) consolidations, as well as bronchiectasis.

COP is an interstitial lung disease that can occur following a respiratory tract infection, and is manifested by patchy consolidations that reflect intraalveolar fibroblast proliferation (Fig 11).14
To our knowledge, this is the first reported occurrence of organizing pneumonia as a complication of H1N1 viral infection. In a study of influenza A viral infection in general, COP was reported as a finding in 1 of 12 patients.\textsuperscript{15}

Lower respiratory tract infections with influenza virus in general may be categorized as pneumonia and bronchitis/bronchiolitis. All of our H1N1 patients demonstrated pneumonia represented by groundglass opacities and/or consolidations. Two of our H1N1 patients demonstrated bronchitis/bronchiolitis represented by bronchial wall thickening, bronchiectasis, centrilobular nodules and mosaic attenuation. In a study of the predominant CT finding in inpatients with influenza, multifocal consolidations (14\%) and groundglass opacities (19\%) were findings that represented pneumonia, while bronchial wall thickening (14\%) and tree-in-bud opacities (14\%) represented bronchitis/bronchiolitis.\textsuperscript{16}

**MEDIASTINAL AND PLEURAL FINDINGS**

Mild mediastinal lymphadenopathy was seen in 2 of our patients, with no other predisposing conditions to explain the lymph node enlargement (Fig. 12).

Lymphadenopathy has been reported once in 2 prior studies, however this was related to known preexisting disease in 1 study.\textsuperscript{6,13} Small pleural effusions were seen in 3 of our patients (Fig. 13).

**Pleural effusions have been reported in 7\% of ICU patients\textsuperscript{8}, as well as 25\% of inpatients\textsuperscript{5}.

**PATHOLOGIC CORRELATION**

We report an additional case of a fatality due to H1N1 infection in a young patient with preexisting interstitial
fibrosis (Fig 14).

**Figure 14**

Figure 14: 22-year old female with history of fibrotic nonspecific interstitial pneumonitis (NSIP) presented to the ER with worsening shortness of breath, and was found to be hypoxic and H1N1 positive. She required emergent mechanical ventilation for acute respiratory failure, and expired 7 days later. Baseline chest CT (A) and radiograph (B) performed 3 months prior to presentation demonstrated chronic groundglass opacities/ consolidations and traction bronchiectasis (arrow), predominantly in the right lung.

The antemortem chest radiograph in this patient demonstrated bilateral patchy groundglass opacities and consolidations (Fig 15).

**Figure 15**

Figure 15: (A) Chest radiograph at presentation in same patient as in Figure 14, demonstrated new bilateral patchy airspace opacities (arrow). (B) Gross specimen of the lungs at autopsy demonstrated congested, boggy and consolidated lung.

The autopsy of this patient revealed diffuse alveolar damage (Fig 16).

**Figure 16**

Figure 16: Same patient as in Figures 14 and 15. Photomicrographs of hematoxylin-eosin–stained tissue sections at autopsy (original magnification x10). (A) Inflammatory cells and detached pneumocytes within alveoli (long arrow) indicated an active process. (original magnification x 40), hyaline membrane outlining the alveoli (short arrow) indicated exudative diffuse alveolar damage (DAD). (B) Extensive intra-alveolar hemorrhage (arrow). (C) Fibroblastic proliferation (arrow) indicated a background of chronic interstitial fibrosis (arrow).

Influenza A viruses (including the H1N1 strain) bind to specific receptors in the columnar epithelial cells of the respiratory tract, interfere with host cell protein synthesis, and lead to apoptosis. This leads to edema, necrotizing bronchitis, and alveolar hemorrhage. The patchy peribronchial pattern of opacities (Fig. 2) in influenza, and H1N1 in particular, may be explained by the pathologic finding of hyaline membrane formation in the alveolar parenchyma immediately surrounding the bronchioles, known as diffuse alveolar damage (DAD). Although DAD has not been established upon lung biopsy of a living H1N1 patient, Mauad et al. found DAD in 20 (95%) of 21 autopsies in H1N1 patients; 71% of these H1N1 fatalities had the clinical diagnosis of acute respiratory distress syndrome (ARDS), which also manifests as DAD. Gill et al. demonstrated DAD in 25 (74%) of 34 autopsies in H1N1 fatalities, and categorized the DAD findings into early exudative (acute) phase (64%), concomitant exudative (acute) and subacute proliferative (organizing) phases (28%), and concomitant proliferative (organizing) and late fibrotic phases (8%). Chest CT obtained in 2 of their H1N1 cases that were uncomplicated by pneumonia, demonstrated subpleural and peribronchovascular groundglass opacities,
with or without consolidations.18 Ichikado et al. found that groundglass opacities and consolidation correspond with exudative or early proliferative phase, while traction bronchiectasis or bronchoclelasis represents late proliferative or fibrotic phase of DAD and carry a worse prognosis.20

CONCLUSION

Chest CT findings in H1N1 include a wide spectrum of abnormalities that have been detailed above, and are also seen with other viral infections. The interesting distribution of peribronchovascular and subpleural groundglass opacities and consolidations likely represents the sequelae of diffuse alveolar damage in the immediate peribronchiolar regions. Organizing pneumonia may occur as a complication of H1N1 infection and should be considered in the event of a prolonged hospital course, as the patient’s management may change with this diagnosis.

References

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