

Chest Radiographic and CT Findings in Novel Swine-Origin Influenza A (H1N1) Virus (S-OIV) Infection

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OBJECTIVE. This article reviews the chest radiographic and CT findings in patients with presumed/laboratory-confirmed novel swine-origin influenza A (H1N1) virus (S-OIV) infection.

MATERIALS AND METHODS. Of 222 patients with novel S-OIV (H1N1) infection seen from May 2009 to July 2009, 66 patients (30%) who underwent chest radiographs formed the study population. Group 1 patients ($n = 14$) required ICU admission and advanced mechanical ventilation, and group 2 ($n = 52$) did not. The initial radiographs were evaluated for the pattern (consolidation, ground-glass, nodules, and reticulation), distribution, and extent of abnormality. Chest CT scans ($n = 15$) were reviewed for the same findings and for pulmonary embolism (PE) when performed using IV contrast medium.

RESULTS. Group 1 patients were predominantly male with a higher mean age (43.5 years versus 22.1 years in group 2; $p < 0.001$). The initial radiograph was abnormal in 28 of 66 (42%) subjects. The predominant radiographic finding was patchy consolidation (14/28; 50%) most commonly in the lower (20/28; 71%) and central lung zones (20/28; 71%). All group 1 patients had abnormal initial radiographs; extensive disease involving ≥ 3 lung zones was seen in 93% (13/14) versus 9.6% (5/52) in group 2 ($p < 0.001$). No group 2 patients had $> 20\%$ overall lung involvement on initial radiographs compared with 93% of group 1 patients (13/14). PEs were seen on CT in 5/14 (36%) of group 1 patients.

CONCLUSION. Chest radiographs are normal in more than half of patients with S-OIV (H1N1) and progress to bilateral extensive air-space disease in severely ill patients, who are at a high risk for PE.

Novel swine-origin influenza A (H1N1) virus (S-OIV), more commonly known as swine flu, was first reported in Mexico in April 2009 [1]. Since then it has rapidly spread to many countries around the world. In June 2009, the World Health Organization (WHO) declared the emergence of a global pandemic, raising the alert level to phase 6 (pandemic phase), on the basis of documented human-to-human spread of infection in at least three countries of two WHO regions [1, 2]. As of July 6, 2009, 122 countries have reported a cumulative total of 94,512 cases, with 429 fatalities, for a case fatality rate (CFR) of 0.45% [3]. The overwhelming majority of cases have been reported from the United States, which alone accounts for more than one third of reported cases. A total of 33,902 cases have been reported from the United States, with 170 fatalities or a CFR of 0.5% [3].

The clinical manifestations are varied and include flulike symptoms such as fever, cough, sore throat, body aches, headache, chills, and fatigue. In addition, nausea, vomiting, and/or diarrhea have been reported [4]. There is ongoing S-OIV (H1N1) activity. With the upcoming annual influenza season in the United States, knowledge of the radiologic features of S-OIV is important, as well as the virus's potential complications. In this article we review the chest radiographic and CT findings in patients with presumed or confirmed S-OIV (H1N1) infection treated at a tertiary-care hospital in Michigan.

Materials and Methods

This study was approved by our institutional review board with a waiver of informed consent. The study population included all patients presenting to the University of Michigan Health System between May 1, 2009 to July 18, 2009 with flulike symptoms who were positive for influenza A by either a direct

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fluorescent antigen-antibody test or a viral culture screen, and who underwent thoracic imaging. A total of 222 patients were identified; 31 of these patients had further testing of respiratory specimens with real-time reverse transcription polymerase chain reaction (RT-PCR) at the Michigan Department of Community Health (MDCH) and Centers for Disease Control and Prevention (CDC), and were confirmed to have S-OIV (H1N1). The others were presumed to have S-OIV (H1N1) based on the fact that no other viruses were circulating in the community at any frequency.

Of the 222 patients, the 66 patients (30%) who underwent chest radiographic imaging (some also with CT) formed the study population. Of these patients, 25 were confirmed to have S-OIV (H1N1). The study population consisted of 36 men and 30 women with a mean age of 26.7 years (range, 9 months to 60 years). The 66 patients were divided into two groups. Group 1 consisted of 14 patients who required advanced mechanical ventilation, defined as either high-frequency oscillatory or bilevel ventilation; all of these patients were confirmed to have S-OIV (H1N1), and of this group, there were five deaths. Group 2 consisted of the remaining 52 patients who were either managed as outpatients or required brief hospitalization without advanced mechanical ventilation; all of these patients fully recovered. Given the different clinical course of the two groups, the radiologic findings for each group are described separately. Group 1 patients were older (mean, 43.5 years versus 22.1 years, $p = 0.000002$; independent samples t test) compared with group 2 and had a higher proportion of men (the male:female ratio for group 1 was 11:3 vs 25:27 for group 2).

Radiologic Assessment

Portable radiographic examinations were performed with digital radiography equipment (Mobile DaRt, Shimadzu) using a standardized technique (90 kV, 5 mAs, 72-inch film-focus distance for the anteroposterior view, broad tube focus). The posteroanterior and lateral projection radiographs were performed with digital radiography equipment (GE Definium 8000, GE Healthcare) using 120 kVp, 2 mAs for a posteroanterior radiograph, 9 mAs for a lateral radiograph, and a 72-inch film-focus distance. The images were reviewed on a PACS viewer with a 2,560 × 2,048 pixel monitor (Magicview, version VF50, Siemens Healthcare).

Fifty patients had posteroanterior and lateral projection radiographic images, and 16 patients had only anteroposterior portable bedside radiographs. Twenty-four patients had follow-up chest radiographs (14 in group 1 and 10 in group 2) within 1 week of the initial chest radiographic images.

Chest CT examinations were performed in 15 patients (10 in group 1 and five in group 2), of which

12 had a previous chest radiographic study available for analysis. Three patients transferred from another hospital had no prior radiographs available for review and the CT was the first available imaging study. Of the 12 patients who had previous radiographs, 11 were abnormal and one had a normal initial radiograph (CT in this patient was ordered for suspected pulmonary embolism [PE]). Three of the initial CT scans were obtained using a variety of CT scanners and protocols at referring hospitals before the patients were transferred to our institution.

Iodinated contrast material was administered for 12 CT examinations, 11 of which were performed specifically for evaluation of PE (8 at our institution and 3 at referring hospitals). Our CT PE protocol uses 1.25 mm collimation reconstructed at 0.625 mm intervals and 125 mL of IV contrast material (Isovue-300, Bracco Diagnostics) administered at 4 mL/s. The three noncontrast CTs were performed with 2.5 mm collimation. The scans at our institution were performed on 64-MDCT (LightSpeed VCT, GE Healthcare).

Two fellowship-trained radiologists with thoracic imaging experience of 6 years and 17 years reviewed all the chest radiographic images and CT examinations in consensus. On the initial chest radiographic images, the lung parenchyma was classified as normal or abnormal. The abnormalities were further characterized as consolidation (opacification obscuring the underlying vessels), ground-glass opacity (GGO; increased attenuation without obscuring the underlying vessels), nodules, and reticulation. Any additional lung findings were recorded. The anatomic distribution was characterized as unilateral or bilateral, and as predominantly central, peripheral, or diffuse. Each lung was divided into upper, middle, and lower lung zones (each comprising a third of the craniocaudal extent of the lungs on frontal radiograph) and zonal involvement was assessed. The extent of abnormality was subjectively graded as the percentage of each zone involved and an average calculated for each radiologic study. The presence of lymph node enlargement and pleural effusions were recorded. Similar findings were evaluated on the chest CTs. In addition to the chest radiographic evaluation, the presence of PE also was recorded for CT examinations performed with IV contrast.

The extent of chest radiographic abnormality in the two groups was analyzed by using the chi-square test. Analysis was performed by using computer software (SAS, version 7.0; SPSS). A p value of less than 0.05 was considered to indicate statistical significance.

Results

The initial chest radiographic images available for review were obtained an average of

4 days (range, 1–20 days) after the onset of clinical symptoms, at the time of either a clinic visit or hospital admission. A subset of patients ($n = 13$, all from group 1) were referred to the surgical ICU (SICU) for advanced mechanical ventilation and possible extracorporeal life support (ECLS). For these patients, whenever available, the oldest available imaging study from the referring hospital performed for the current acute influenza illness was used for review and was considered the initial study ($n = 5/13$). Of the eight patients for whom the outside radiographs were not available, the first chest radiograph obtained at the time of admission to the SICU was considered the initial study ($n = 8/13$) and was obtained an average of 4 days (range, 1–10 days) after hospitalization at the outside institution.

The imaging findings are summarized in Table 1. The first available radiograph was normal in 38/66 (58%) patients. None of the patients in group 1 had a normal initial radiograph, compared with 38/52 or 73% of patients in group 2. The first available chest radiographs were abnormal in all 14 or 100% of patients in group 1 and 14/52 or 27% of patients in group 2 (overall, 42% of patients or 28/66 had an abnormal radiograph). When abnormal, the lung abnormalities were bilateral in 71% or 20/28 patients (14/14 in group 1, and 6/14 in group 2), and unilateral in the remaining eight patients (all from group 2). All 14 patients in group 1 who required advanced mechanical ventilation had abnormal initial radiographic images with bilateral lung involvement.

The predominant chest radiographic finding was patchy consolidation (14/28 or 50%), including 7/14 in group 1 and 7/14 in group 2. GGO alone or a mixture of GGO and consolidation were each the second most common predominant findings, found in 7/28 or 25% of patients. One patient with patchy consolidation also showed ill-defined nodular opacities on chest radiographic images, confirmed on subsequent CT.

The lung abnormalities were most commonly found in the lower lung zones (20/28 or 71%) (Fig. 1) or were diffuse (7/28 or 25%). In one patient, the findings were most extensive in the middle lung zone perihilar region. The air-space disease was more commonly seen in the central lung zones (20/28 or 71%) (Fig. 1); 8/28 had no central versus peripheral preponderance on the initial radiograph.

The extent of disease was greater in group 1 patients requiring advanced mechanical ventilation, with involvement of three or more lung zones in 13/14 (93%) group 1 patients,

Chest Radiographic and CT Findings in H1N1

TABLE 1: Summary of Radiographic and CT Findings in Patients With Clinically Presumed or Laboratory-Confirmed H1N1 S-OIV Infection

Patients With Presumed or Confirmed H1N1 S-OIV	Group 1 ^a n = 14	Group 2 ^b n = 52	All n = 66
Normal initial chest radiograph	0	38 ^c (73%)	38 (58%)
Abnormal initial chest radiograph	14 (100%)	14 (27%)	28 (42%)
Distribution (when initial chest radiograph was abnormal)			
a. Unilateral involvement on chest radiograph	0	8 ^d (8/14; 57%)	8 (8/28; 29%)
b. Bilateral involvement on chest radiograph	14 (100%)	6 (6/14; 43%)	20 (20/28 or 71%)
Pattern of radiographic abnormality			
a. Consolidation	7 (7/14; 50%)	7 (7/14; 50%)	14 (14/28; 50%)
b. Ground-glass opacity (GGO)	2 (2/14; 14%)	5 (5/14; 36%)	7 (7/28; 25%)
c. GGO+ consolidation	5 (5/14; 36%)	2 (2/14; 14%)	7 (7/28; 25%)
Predominance			
a. Lower zone	8 (8/14; 57%)	12 (12/14; 86%)	20 (20/28; 71%)
b. Central zone	7 (7/14; 50%)	13 (13/14; 93%)	20 (20/28; 71%)
Extent on initial radiograph			
a. > 20%	13 (13/14; 93%)	0	13 (13/66; 20%)
b. < 20%	1 (1/14; 7%)	52 (52/52; 100%)	53 (53/66; 80%)
c. 3 or more involved zones	13 (13/14; 93%)	5 (5/52; 10%)	18 (18/66; 27%)
Pulmonary embolism	5 (5/14; 36%)	0	5 (5/66; 8%)
Final outcome: death	5 (5/14; 36%)	0	5 (5/66; 8%)

^aGroup 1: Patients who required advanced mechanical ventilation, defined as either high-frequency oscillatory or bilevel ventilation.

^bGroup 2: Patients who were either managed as outpatients or required brief hospitalization without advanced mechanical ventilation.

^cFour patients with normal initial radiographs developed air-space disease on follow-up (three on follow-up radiographs and one on CT performed within a week).

^dOne patient with unilateral involvement on initial chest radiograph had bilateral GGO on follow-up CT (3 days later).

and only 5/52 or 9.6% of group 2 patients ($p < 0.001$, chi-square test). Also, overall extent of lung involvement was > 20% in 13/14 group 1 patients, versus < 20% in all group 2 patients. The one patient in group 1 who had less extensive disease involving only two zones on the first day of the onset of clinical symptoms markedly worsened in the following 6 days with extensive bilateral lung disease involving all lung zones. Most patients in group 2 had < 10% involvement (9/14) and 5/14 had 10–15% involvement.

Significant lymph node enlargement was not identified on any chest radiographic images. Pleural effusions were seen on radiographs in five patients (two from group 1 and three from group 2).

Thoracic CT Scans

Thoracic CT scans ($n = 15$) were performed at a variable time after the chest radiographs in 12 subjects; CT was the first available imaging technique in three patients (all from group 1).

In group 1, 10 patients underwent a CT study. For three of these patients the CT was

performed before the initial radiographs, and for the remaining seven patients the CT examinations were performed between 0 and 30 days after the chest radiographs. The CT examinations showed a combination of GGO and consolidation in nine subjects, and predominantly GGO in one patient. The distribution of parenchymal abnormality was diffuse without zonal predominance in seven patients (70%), and with lower lung predominant in three. The abnormality was central predominant in five patients (50%), diffuse in four patients (40%), and peripheral predominant in one patient. A CT examination of one patient from the referring hospital showed peripheral and lower-lung-predominant focal ground-glass opacities (Fig. 2), which were also seen on the CT scout topogram, and which became progressively worse and diffuse in distribution on the first available radiograph that was performed 5 days after the CT examination.

In group 2, five patients underwent a thoracic CT scan within 0–5 days after their initial chest radiograph. In three patients, the chest CT findings correlated with the ra-

diographic findings. One patient with a normal initial radiograph (Fig. 3A) underwent a CT examination for suspected PE 3 days later that showed no embolism, and mild nodular right upper lobe ground-glass opacity that was occult on the chest radiographic images (Fig. 3B). Additionally, another patient (group 2) with unilateral involvement on chest radiographic images had multifocal bilateral GGOs on a CT examination performed 5 days later, with some areas showing new or progressive air-space disease and other areas improved.

Looking at all of the CT examinations in the group 1 and 2 patients together, nodular opacities were seen on CT in six patients (Fig. 4), but only appreciated on the corresponding radiographs in one patient. Similarly, septal thickening was seen on CT in two patients, and occult on chest radiographic images.

Pulmonary emboli were identified on CT in 5/14 patients or 36% of patients admitted to the SICU. These included a large saddle embolus straddling the bifurcation of the main pulmonary artery in one patient (Fig. 5), lobar emboli in one patient, segmental

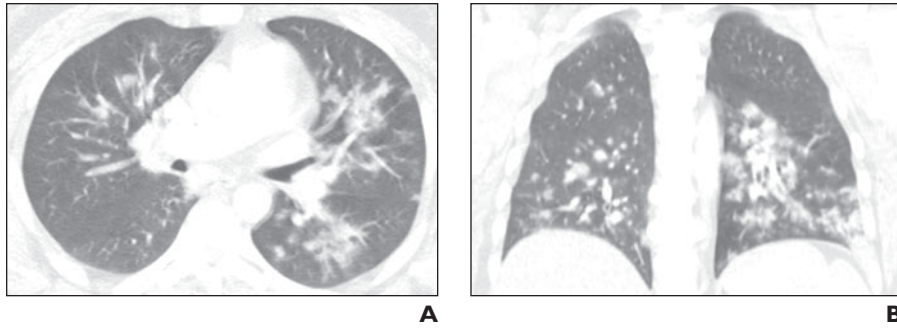


Fig. 1—33-year-old woman with laboratory-confirmed S-OIV (H1N1) requiring extracorporeal life support.

A and B, Axial and coronal reformatted images from contrast-enhanced CT examination performed to evaluate for pulmonary embolism shows perihilar and lower-lung-predominant patchy ground-glass opacities. Though no pulmonary emboli were seen on this examination, follow-up CT examination 12 days later showed new segmental and subsegmental pulmonary emboli, most likely related to patient's hypercoagulable state.

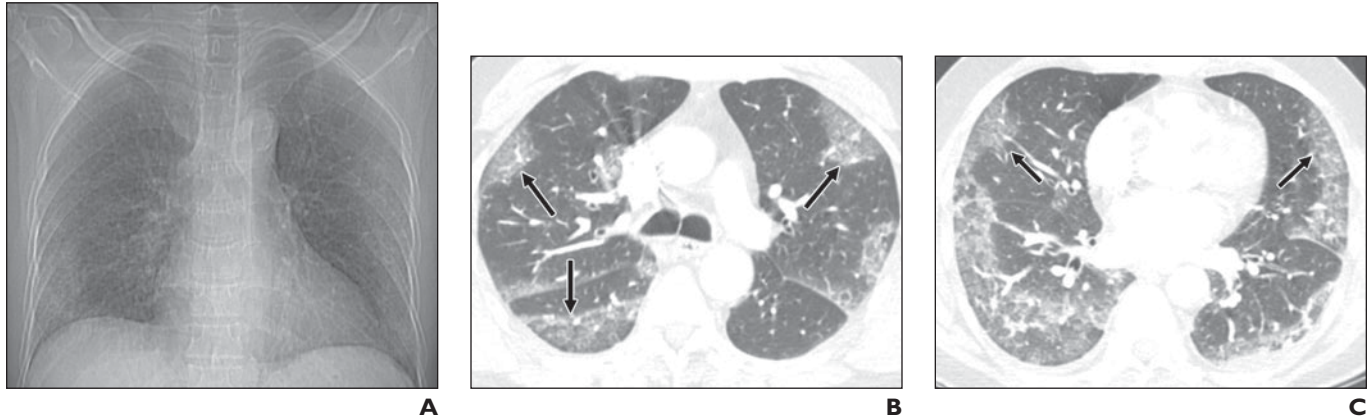


Fig. 2—57-year-old man with laboratory-confirmed S-OIV (H1N1) requiring advanced mechanical ventilation with adverse outcome.

A–C, Scout image (**A**) from chest CT examination shows peripheral and lower-lung-predominant ground-glass opacities (arrows) similar to organizing pneumonia pattern, confirmed on axial CT images (**B** and **C**).

emboli in two patients, and subsegmental emboli only in one patient. Two additional patients had deep venous thrombosis in the leg veins on indirect CT venography, confirmed on ultrasound.

Of the five patients with pleural effusions on chest radiography, CT studies were available in four, which confirmed the same. Tiny pleural effusion on CT in one patient from group 2 was not appreciable on radiographs. Lymph node enlargement was only seen on CT in one patient, related to known preexisting sarcoidosis.

Of the patients admitted to the SICU, three patients developed bacterial pneumonia, with one case of *Pseudomonas* infection in a patient who developed pneumatoceles on CT

(Fig. 6), and one case each of *Escherichia coli* and *Citrobacter* infection. All infections were diagnosed with bronchoalveolar lavage.

Follow-Up Radiographs

Follow-up radiographs were available for all 14 patients in group 1 (done on a daily basis) and for 10/52 patients in group 2. The daily radiographs showed a waxing and waning course in group 1. In group 2, there was disease progression in 4/10 (three with normal initial radiographs), waxing and waning pattern with simultaneous areas of improvement and worsening of air-space disease in one patient, and unchanged normal appearance in five patients. If the most abnormal ra-

diograph in the course of illness was considered for comparison between the two groups, the disease extent was > 20% in 14/14 patients of group 1 and 1/52 patients in group 2 and involvement of three or more lung zones was seen in 14/14 patients of group 1 versus 6/52 patients in group 2.

Discussion

Seasonal influenza is an acute respiratory illness that occurs particularly during the winter months. Influenza virus belongs to the orthomyxovirus family of RNA viruses and human disease is predominantly caused by types A and B [5]. Type A virus is the most virulent and can easily mutate; many sub-

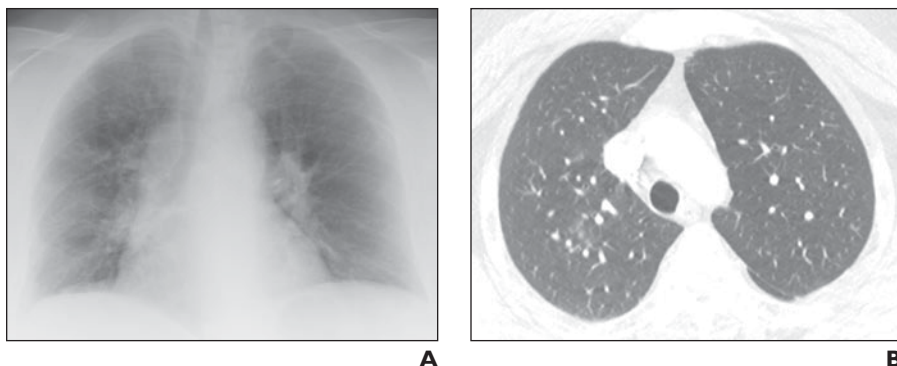


Fig. 3—53-year-old woman with influenza A and presumed S-OIV (H1N1). Patient required brief period of hospitalization and recovered uneventfully without need for ICU admission.

A, Chest radiograph obtained at time of presentation to emergency department, 3 days after onset of clinical symptoms, is normal.

B, Contrast-enhanced axial CT done for evaluation of suspected pulmonary embolism shows mild nodular ground-glass opacity in right upper lobe.

Chest Radiographic and CT Findings in H1N1

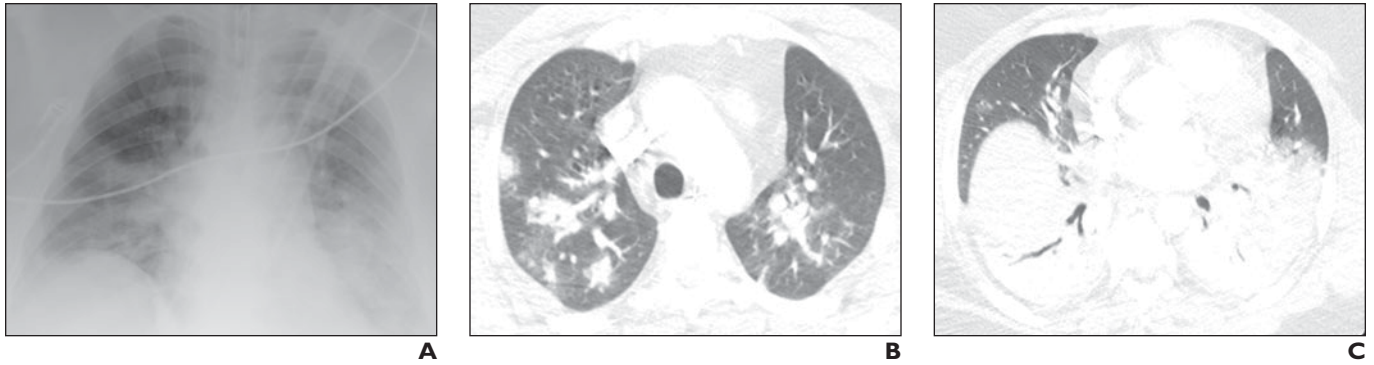


Fig. 4—43-year-old man with laboratory-confirmed S-OIV (H1N1) referred to surgical ICU service for extracorporeal life support evaluation. **A**, Portable chest radiograph obtained 4 days after onset of clinical symptoms shows widespread air-space disease, with central and lower lung predominance. **B** and **C**, Axial contrast-enhanced chest CT performed on same day to evaluate for pulmonary embolism shows nodular upper lobe opacities (**B**), not appreciated on chest radiograph, and extensive bilateral lower lobe consolidation (**C**). Acute pulmonary embolism was also found (not shown).

types of type A have been identified on the basis of the occurrence of surface glycoproteins, hemagglutinin (H), and neuraminidase (N). The novel H1N1 virus has features of North American and Eurasian swine, avian, and human influenza viruses [1, 6].

Perez-Padilla et al. [1] reported the clinical and epidemiologic features of the first 18 patients with laboratory-confirmed S-OIV from Mexico. The authors concluded that S-OIV infection can cause severe illness (12/18 required mechanical ventilation) and death (7/18 patients). Also, in contrast to seasonal influenza, in which people at extremes of age (i.e., the elderly and young children) are at a higher risk, the novel influenza virus commonly affects young to middle-aged patients (more than half the patients were 13–47 years and 90% of patients were < 52 years of age). Most patients in this series had received antibiotics and bacterial infection was not found to be a major factor contributing to severity of illness. All 18 patients had an abnormal chest radiograph, with bilateral patchy air-space disease affecting the basal segments and involving three to four lung segments in 11/18 patients.

The clinical findings of 10 patients from our institution with confirmed S-OIV admitted for advanced mechanical ventilation have been previously described in a *Morbidity and Mortality Weekly Report* [7]. Some striking facts were brought out by this report. There was a high prevalence of obesity: 90% of patients (9/10) had a body mass index (BMI) ≥ 30 , while 70% (7/10) were extremely obese with a BMI ≥ 40 . All 10 patients were reported to have abnormal chest radiographs with bilateral abnormality, five patients had PE, and one patient had isolated deep venous thrombosis. These 10 patients are included

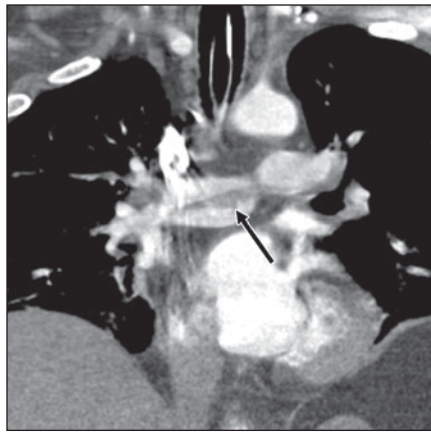


Fig. 5—28-year-old man with laboratory-confirmed S-OIV (H1N1) requiring advanced mechanical ventilation with adverse outcome. Coronal reformatted image from contrast-enhanced chest CT examination shows saddle embolus (arrow) straddling bifurcation of main pulmonary artery.

in our review of the 14 patients who required advanced mechanical ventilation.

In our study we have tried to evaluate not only the imaging appearance of the severe form of illness (in patients needing SICU admission and advanced mechanical ventilation), but also the radiographic appearance of mild disease. Chest radiographs were obtained in 30% or 66 of 222 patients with presumed or confirmed S-OIV (H1N1) infection, potentially important to know when imaging plans are made for pandemic planning. Our findings indicate that the initial chest radiographic images are normal in more than half of patients with S-OIV infection, most of whom were outpatients. The most frequent pattern of abnormality is alveolar disease that is bilateral, with lower and central lung preponderance. In hospitalized patients, the abnormalities progressed to severe air-space disease. Also, we

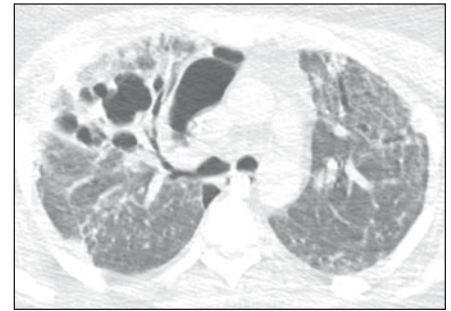


Fig. 6—33-year-old woman with laboratory-confirmed S-OIV (H1N1) requiring extracorporeal life support. *Pseudomonas* infection was confirmed on subsequent bronchoalveolar lavage. Follow-up CT 41 days after onset of clinical symptoms shows new pneumatoceles in right upper lobe and small medially loculated right pneumothorax. Patient had two prior chest CTs done on day 5 and day 21 (from onset of illness), which showed perihilar and lower predominant ground-glass opacities, consolidation, and nodularity. Also, segmental and subsegmental pulmonary emboli in lower lobes were noted on second CT (on day 21).

found several patients with severe disease who developed acute PE during their hospital stay. In one of the patients, a large saddle embolus required an interventional procedure for mechanical fragmentation of the embolus. Although sepsis and acute respiratory distress syndrome are known to represent hypercoagulable states, acute PE is not a common complication of influenza infection [7, 8]. Van Wissen et al. [9] conducted a study evaluating the frequency of influenza in a cohort of patients with a clinical suspicion of PE and found that influenza A infection was less common (1%) among patients with proven PE, than those

without PE (4.3%). The authors concluded that influenza infection is not an important risk factor for PE. However, a limitation of the study is the fact that the authors used a control group of patients with symptoms of chest pain and/or dyspnea, and not randomly selected individuals. There is a report of two patients with influenza A (H3N2) who developed acute PE diagnosed on CT [10]. The study of laboratory-confirmed S-OIV (H1N1) from Mexico did not report a high incidence of PE [1]. Knowledge of this complication, which presumably is secondary to a hypercoagulable state in these patients, is important not only for the clinicians taking care of the patient but also for the radiologist so as to avoid missing emboli on contrast-enhanced CTs performed for other reasons.

Our study has some limitations. It is retrospective in nature. We do not have laboratory evidence of confirmed S-OIV infection in a subset of patients (particularly in the group that had mild disease and a favorable outcome). These patients were presumed to have S-OIV based on the positive influenza A test and the fact that very little seasonal influenza A was circulating during the study period. The initial radiographs obtained at the time of first clinic visit for some patients, particularly those transferred from other hospitals, for advanced me-

chanical support were not available. Hence, our results may be biased toward finding greater disease burden on the initial radiograph in this group and it is conceivable that some of these patients may have had a normal/mildly abnormal radiograph at their first clinical presentation but deteriorated rapidly and developed extensive disease at the time of SICU admission. Lastly, we do not know what the clinical features were that led to performing outpatient chest radiographic images, and how these patients may differ from patients who did not undergo radiographic imaging, as 70% of infected individuals did not have thoracic imaging.

We conclude that the radiographs are normal in more than half of patients with S-OIV (H1N1) infection, but manifest as extensive bilateral air-space disease in hospitalized patients requiring advanced mechanical ventilation. These patients are also at risk for developing PE, which should be carefully sought for on contrast-enhanced CT scans.

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