Jpn J Radiol (2011) 29:301–306
DOI 10.1007/s11604-010-0558-2

ORIGINAL ARTICLE

Various computed tomography findings of 2009 H1N1 influenza in 17 patients with relatively mild illness

Su Young Kim · Jeung Sook Kim · Chan Sup Park

Received: October 15, 2010 / Accepted: December 27, 2010

Abstract
Purpose. We retrospectively analyzed the computed tomography (CT) findings of H1N1 virus infection in 17 patients with relatively mild illness.
Materials and methods. From September 2009 to January 2010, a total of 17 patients with confirmed H1N1 infection were included in the study (mean age 30.7 years). All patients were managed as outpatients or required short hospitalization without ventilation assistance. The CT scans were assessed for the presence of nodules, ground glass opacity (GGO), consolidation, bronchial wall thickening, reticulation, effusion, and lymph node enlargement. Location and distribution were evaluated.
Results. The most frequent manifestation was a mixture of nodules, consolidation, and GGO (5/17, 29.4%). In one case there was a focal area of bronchiolitis (centrilobular nodules with tree-in-bud appearance), and 10 of 17 cases (58.8%) showed bronchial wall thickening (findings of bronchitis/peribronchitis) and/or other abnormalities. In 16 of the 17 cases (94.1%) there were CT abnormalities with bilateral and random distribution without zonal predominance. Pleural effusions were seen in eight cases (47.1%).
Conclusion. In contrast to several reports so far, CT findings of H1N1 virus infection in patients with mild illness are variable, including suggestive findings of inflammation involving large and/or small airways. This study showed various CT findings overlapping with other viral, atypical, or bacterial pneumonia and even cryptogenic organizing pneumonia.

Key words Chest CT · H1N1 virus · Swine-origin influenza A · Infectious disease

S.Y. Kim
Department of Radiology, Inje University Ilsan Paik Hospital, Kyunggi-Do, Korea

J.S. Kim (✉)
Department of Radiology, Dongguk University Ilsan Hospital, 814 Siksa-Dong, Ilsandong-Gu, Goyang-Si, Gyeonggi-Do 410-773, Korea
Tel. +82-31-961-7823; Fax +82-31-961-8281
e-mail: jeungkim@dumc.or.kr; swimminkim@hanmail.net

C.S. Park
Department of Radiology, Kwandong University Myongji Hospital, Kyunggi-Do, Korea

Introduction

In the spring of 2009, an outbreak of novel swine-origin influenza A (H1N1 virus) was first reported in Mexico, after which it rapidly spread worldwide. This pandemic influenza A (H1N1) caused increased morbidity and mortality in a young population who were not generally at risk for severe illness with the usual seasonal influenza.[1,2] To date, many reports have described the clinical and epidemiological characteristics of this 2009 H1N1 infection in many countries.[1–5]

There have been only a few reports reviewing the radiological features of 2009 H1N1 infection[6–9]; and in those studies, most computed tomography (CT) examinations were in patients who had a severe clinical course. So far, frequently reported radiographic and CT findings of H1N1 infection were focal or multifocal patchy consolidations and ground-glass opacities, resembling organizing pneumonia. In severe cases, those abnormalities progressed to extensive airspace disease, and the radio-

graphic findings somewhat resembled those of severe acute respiratory syndrome (SARS).

During the peak season of this pandemic influenza A in Korea (Fall and Winter 2009), many patients were confirmed by reverse transcriptase polymerase chain reaction assay (RT-PCR), but most patients had relatively mild illness. We defined the term "relatively mild illness" as a condition that has no requirement of intensive care unit (ICU) admission or advanced mechanical ventilation therapy and can be managed by conservative treatment in an outpatient setting or brief hospitalization.

In some patients with mild illness, CT examinations were requested for several reasons: depiction of viral pneumonia itself or differentiation from another infectious disease, such as primary pulmonary tuberculosis or exclusion of other possibilities if there was chest pain or hemoptysis. Therefore, we focused on the CT features of H1N1 infection in those patients as it was thought that their CT features might indicate a relatively early stage of the disease. To have adequate knowledge about various CT features of H1N1 infection is important for radiologists in the differential diagnosis. In this article we reviewed the CT findings of H1N1 infection in 17 patients who had relatively mild illness.

Materials and methods

This retrospective study was approved by the institutional review boards of three centers participating in the study.

Patients

A total of 27 consecutive patients were included in this study who were positive for influenza A (H1N1) virus by RT-PCR and who underwent chest CT from September 2009 to January 2010 in the three university hospitals in Goyang, Korea. Of the 27 patients, 8 were excluded because of the presence of co-infection with other pathogens that had been detected in sputum and/or blood cultures. Another two patients (only one underwent CT examination) who required intubation and mechanical ventilation within a few days after admission and had extensive airspace consolidation and GGO on their chest radiographs and CT scan were also excluded. In all, 17 patients who were managed as outpatients or required hospitalization of less than 20 days without need of intubation or mechanical ventilation were included in this study.

We reviewed the medical records of all patients. The clinical symptoms are summarized in Table 1. Our study population consisted of 10 males and 7 females with an average age of 30.7 years (range 9–79 years). Altogether, 4 of the 17 patients had one or more underlying disease, including bronchiectasis ($n = 2$), diabetes ($n = 2$), chronic renal failure ($n = 1$), and angina ($n = 1$). They received both oseltamivir and antibiotics and fully recovered clinically.

CT scanning protocol

Thin-section multidetector (MD)CT ($n = 3$) or volumetric CT of the thorax with ($n = 15$) or without ($n = 7$)

Table 1. Overall clinical assessment of 25 patients with confirmed H1N1 virus infection

Patient no.	Sex/age (years)	Symptoms (duration before CT)/underlying disease	Concomitant pulmonary complication
1	F/9	Cough, fever (4D)	
2	M/9	Cough, sputum, fever (2D)	Pneumomediastinum
3	M/17	Cough, fever, dyspnea (2D)	Pneumomediastinum, PIE
4	M/17	Cough, sputum, fever (4D)	
5	F/9	Cough, fever, abdominal pain (3D)	
6	M/16	Cough, sore throat, fever (2D)	
7	M/28	Cough, sputum, fever, dyspnea (7D)	
8	F/48	Cough, sputum, fever (3D)	
9	M/19	Cough, sore throat, fever (3D)/bronchiectasis	
10	F/37	Cough, sputum, sore throat, fever (5D)	
11	M/37	Cough, sputum, sore throat, fever (7D)	
12	F/23	Cough, sore throat, fever, hemoptysis (4D)	
13	M/25	Cough, fever (3D)	
14	F/32	Cough, sputum, fever, chest pain (6D)	
15	M/79	Cough, sputum, fever (4D)/bronchiectasis	
16	F/64	Cough, sputum, fever, dyspnea (5D)/DM, CRF, angina	
17	M/53	Cough, sputum, fever (6D)/DM	

CT, computed tomography; D, days of symptom duration before CT; DM, diabetes mellitus; CRF, chronic renal failure; PIE, pulmonary interstitial emphysema

contrast enhancement were performed using a variety of CT scanners (one was 16-row MDCT and two were 64-row MDCT) with 1.0-mm collimation at 6- or 10-mm intervals for thin-section CT and 2.0- to 5.0-mm reformation, 120- to 140-kV tube potential, and 150–210 mAs for conventional CT. All images were viewed at window settings optimized for lung (width 1500 HU, level −700 HU) and mediastinum (width 350 × 450 HU, level 40 × 45 HU).

Image review

All images were reviewed retrospectively by two thoracic radiologists with more than 10 years' experience using a viewing workstation and until they reached a consensus. The pattern of the abnormalities was assessed for the presence of consolidation (increased lung attenuation with obscuration of underlying pulmonary vessels), ground-glass opacity (GGO: opacification without obscuring the underlying vessels), nodules, bronchial wall thickening (BWT), and reticulation (irregular linear opacities). The nodular patterns were subdivided into centrilobular, ill-defined airspace nodules (termed acinar nodules, usually 6–10 mm diameter), and large nodules (≥1 cm diameter). In addition to these particular abnormalities, other specific findings were recorded. The anatomical distribution was classified as unilateral or bilateral, as predominantly peripheral if the lesion was in the outer one-third of the lung, as peribronchovascular if there was a predominance of abnormalities along the bronchovascular bundles, or as random. Location was assessed in each lung as upper, middle, and lower lobes. The presence of pleural effusion and lymph node enlargement and concomitant complications such as pneumothorax or pneumomediastinum were also recorded. We summarized the results separately in pediatric and adult patients by age 18 years (<18 years versus ≥18 years). The results are given as the mean.

Results

The CT findings of all 17 patients are summarized in Table 2. The frequencies of the abnormalities were as follows, in order of frequency: nodule (15/17, 88.2%), BWT (10/17, 58.8%), GGO (9/17, 52.9%), consolidation (9/17, 52.9%), interlobular septal thickening (2/17, 11.8%), and reticulation (1/17, 5.9%). The patterns of nodules were ill- defined airspace nodules in most cases (14/15), and one case had centrilobular nodules with a tree-in-bud appearance (1/15) (Fig. 1). Most cases showed a mixture of these abnormalities in varying degree in both pediatric and adult patients. Only one case manifested as isolated bronchial wall thickening in both lungs. The most frequent manifestation was a mixture of nodules, consolidation, and GGO (5/17, 29.4%) (Fig. 2), followed by a mixture of nodules, consolidation, GGO, and BWT (3/17, 17.6%), a mixture of nodules and BWT (3/17, 17.6%), a mixture of nodules, GGO, and BWT (2/17, 11.8%) (Fig. 3), a mixture of nodules and consolidation (2/17, 11.8%), a mixture of nodules, consolidation, and BWT (1/17, 5.9%), and

Table 2. CT findings of 25 patients with confirmed H1N1 virus infection

Finding	<18 years (n = 6)	≥18 years (n = 11)	Total (n = 17)
Abnormalities			
Nodule	6/6 (100%)	9/11 (81.8%)	15/17 (88.2%)
GGO	5/6 (83.3%)	4/11 (36.4%)	9/17 (52.9%)
Consolidation	4/6 (66.7%)	5/11 (45.5%)	9/17 (52.9%)
BWT	4/6 (66.7%)	6/11 (54.5%)	10/17 (58.8%)
Interlobular septal thickening	1/6 (16.7%)	1/11 (9.1%)	2/17 (11.8%)
Reticulation	0	1/11 (9.1%)	1/17 (5.9%)
Manifestation of CT abnormality			
Nodule + Consol + GGO	2/6 (33.3%)	3/11 (27.3%)	5/17 (29.4%)
Nodule + Consol + GGO + BWT	2/6 (33.3%)	1/11 (9.1%)	3/17 (17.6%)
Nodule + BWT	1/6 (16.7%)	2/11 (18.2%)	3/17 (17.6%)
Nodule + GGO + BWT	1/6 (16.7%)	1/11 (9.1%)	2/17 (11.8%)
Nodule + Consol + BWT	0	1/11 (9.1%)	1/17 (5.9%)
Nodule + Consol	0	2/11 (18.2%)	2/17 (11.8%)
BWT	0	1/11 (9.1%)	1/17 (5.9%)
Distribution			
Bilateral	6/6 (100%)	10/11 (90.9%)	16/17 (94.1%)
Unilateral	0	1/11 (9.1%)	1/17 (5.9%)
Random	6/6 (100%)	10/11 (90.9%)	16/17 (94.1%)
Pleural effusions	3/6 (50%)	5/11 (45.5%)	8/17 (47.1%)

GGO, ground-glass opacity; BWT, bronchial wall thickening; Consol, consolidation

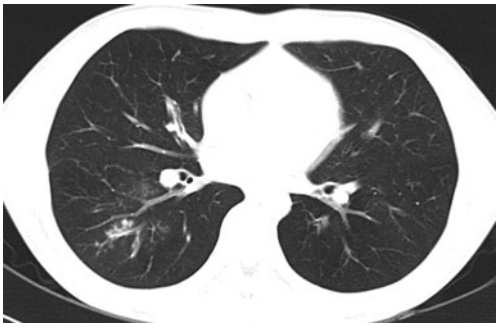

Fig. 1. Case 6, a 16-year-old boy. Conventional chest computed tomography (CT) image with lung window shows a focal area of centrilobular nodules with a tree-in-bud appearance in the right lower lobe and mild bronchial wall thickening involving medial segmental bronchus in the right middle lobe

Fig. 2. Case 7, a 28 year-old man. Coronal reformatted multidetector CT (MDCT) shows the mixture of nodules, consolidation, and ground-glass opacity (GGO) with interlobular septal thickening in the right upper lobe

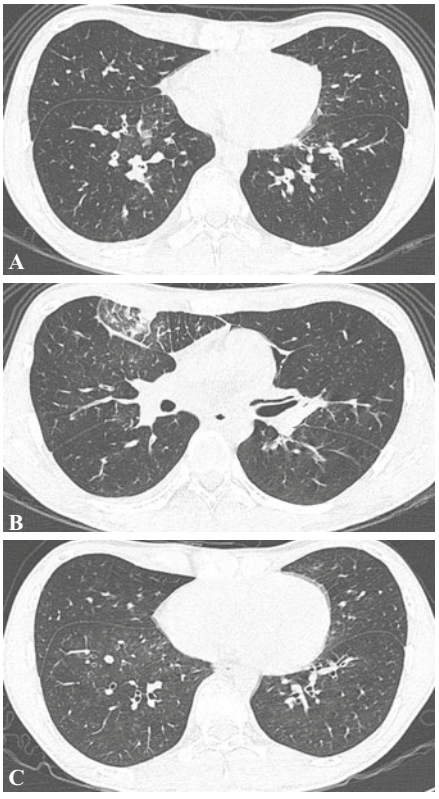

Fig. 3. Case 3, a 17-year-old boy. **a** Initial thin-section CT scan shows multifocal bronchial wall thickening with subtle GGO in the peribronchial area in both lower lobes. **b** Axial image at the level of the bronchus intermedius reveals pneumomediastinum and interstitial emphysema along the left upper lobe bronchus as a concomitant complication. Bronchial wall thickening is seen in both lower lobe superior segments, and focal consolidation and interlobular septal thickening are noted in the right upper lobe. **c** Follow-up thin-section CT scan obtained 7 days after that in **a** shows significant resolution of bronchial wall thickening in both lower lobes. Poorly defined nodules or subtle GGO remain in the right lower lobe

isolated BWT (1/17, 5.9%). One case showed multifocal patchy opacities with central GGO and peripheral consolidation, appearing with a reversed halo sign, which has been described as one of the CT findings of cryptogenic organizing pneumonia (1/17, 5.9%) (Fig. 4). The CT findings of six patients <18 years of age in our study were also nonspecific and overlapped with findings in adults. The anatomical distributions of these abnormalities were bilateral and random without zonal predominance in 16 of 17 cases (94.1%) (Fig. 4). One patient had unilateral diffuse parenchymal involvement (1/17, 5.9%) (Fig. 5). Two patients (cases 2, 3) had pneumomediastinum and pulmonary interstitial emphysema as complications of pulmonary infection (Fig. 3b). Pleural effusions were seen in 8 of 17 cases (47.1%, unilateral in 5 and bilateral in 3 patients) although the amount was small in all cases. There was no significant lymph node enlargement in any of the patients.

Discussion

To date, radiographic and CT findings of H1N1 infection have been sporadically reported with limited cases in the radiological literature.[6–9] The most frequent and common findings were bilateral GGO and consolidations with an alveolar disease pattern. Progression to extensive airspace disease developed in severe cases.[6–8]

The similarity of radiological findings in H1N1 infection and SARS has been raised.[10] A few published articles showed imaging appearances somewhat similar to those of SARS and revealed the absence of small airway

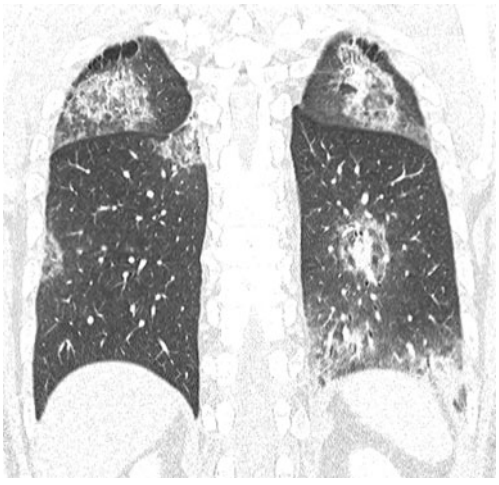

Fig. 4. Case 17, a 53-year-old-man with diabetes. Coronal reformatted MDCT image (2.0 mm reformation) shows multifocal patchy mixed densities of GGO and consolidation with random distribution. Some lesions appear with reversed halo signs (central GGO and surrounding consolidation of ring shapes). Differential diagnosis includes cryptogenic organizing pneumonia or atypical or unusual bronchopneumonia

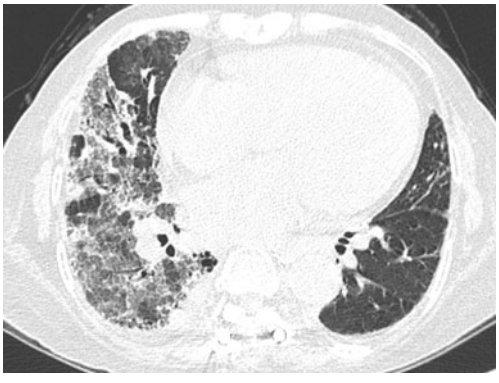

Fig. 5. Case 16, a 64-year-old woman with underlying diabetes, chronic renal failure, and angina. Conventional CT image with lung window shows diffuse unilateral involvement of GGO with bronchial dilatation in the right lung. Mild reticulation and focal subpleural consolidation are also seen

disease.[6–8] It is difficult to explain the lack of findings of small airway disease—such as centrilobular nodules, tree-in-bud opacities, mosaic attenuation—in SARS and H1N1 infection. Two explanations are possible: Small airway disease develops early in the course of H1N1 infection and then either diminishes or progresses to a different pattern of abnormality; and CT is usually performed in more severely affected patients.[3,11]

Agarwal et al.[6] reported a high risk for pulmonary embolism (36%) in patients with severe illness. Although all 17 CT collections in our study were not performed with embolism protocol, pulmonary embolism in larger arteries was not detected in 15 cases with contrast-enhanced CT scans performed on a 64- or 16-MDCT scanner.

Lessler et al.[4] reported an outbreak of 2009 ///H1N1 influenza at a high school in New York. Most of the students and employees confirmed or suspected of having 2009 H1N1 influenza had self-limited febrile respiratory illness, although spread of the disease was rapid and extensive. In one early surveillance of the 2009 H1N1 influenza in China that included 426 patients (mean age 23.4 years), most of the patients had mild illness.[5] The population included in our study had relatively mild illness, and patients who required ICU admission and advanced mechanical ventilation were excluded from the study.

One case in our study showed diffuse bronchial wall thickening and focal centrilobular nodular infiltrates with tree-in-bud appearance, suggesting combined large and small airway disease (Fig. 1). The most common CT abnormalities in our study were nodules (ill-defined airspace nodules in most cases) and BWT. This result can be explained by the fact that the CT scans were performed in the patient with relatively mild illness during an early course of the disease.

One case in our study had multifocal patchy opacities with a reversed halo sign. This appearance has been described as one of the CT findings of cryptogenic organizing pneumonia,[12] but it can be seen in various diseases such as other bacterial or fungal infections, pulmonary infarct, Wegener's granulomatosis, and lipoid pneumonia.

In the study by Libster et al.,[1] the radiographic findings in 76 of 251 children were briefly described. The most frequent radiological diagnosis was focal (33%) or multifocal (45%) pneumonia; in 29% the pneumonia was bilateral. The CT findings of 6 patients under the age of 18 years in our study were also nonspecific and overlapped with findings in adults. BWT was frequently seen in both pediatric and adult patients. Viral infections of the lower respiratory tract generally are infections of the bronchial epithelium and peribronchial interstitial tissue, and they result in thickening of the bronchial wall, mucosa, and peribronchial tissue (termed bronchitis/peribronchitis).[13–15]

Two patients in our study had interlobular septal thickening. We presume that it is the result of the spread of inflammation from the peribronchial axial interstitium to the peripheral interstitium. CT of a fatal case of H1N1 infection by Mollura et al.[8] showed the pattern of peribronchial airspace disease (peripheral GGO), suggestive of less airway inflammation.

Considering the results of our study and recently published radiological reports,[6–9] we presume that the H1N1

virus infection can manifest as airspace disease dominantly, airway inflammation dominantly, or both depending on the severity and underlying conditions of a patient.

We acknowledge some limitations of our study. It was retrospective and included a small sample size. There were no cases with histopathological proof by lung biopsy. The CT scan of the case that showed infiltrates with a centrilobular nodular pattern (Fig. 1) was not obtained with a high-resolution CT protocol, so the use of the term "centrilobular" may be inappropriate. Finally, the underlying diseases such as bronchiectasis or chronic renal failure in three patients might have affected the imaging appearances.

Conclusions

The CT findings of 2009 H1N1 infection are various, manifesting as a mixture of nodules, consolidations, GGO, and BWT in varying degrees with a predominantly bilateral and random distribution. We think that during the early period of the disease and in mildly affected patients, the H1N1 virus can manifest as small-airway or large-airway diseases such as other viral pneumonia (e.g., adenovirus, respiratory syncytial virus, other types of influenza virus). Moreover, CT findings sometimes overlap with atypical or bacterial pneumonia and even cryptogenic organizing pneumonia.

Acknowledgment. This article was assisted by a 2007 scientific research grant from Inje University.

References

1. Libster R, Bugna J, Coviello S, Hijano DR, Dunaiewsky M, Reynoso N, et al. Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. N Engl J Med 2010;362:45–55.
2. Chowell G, Bertozzi SM, Colchero MA, Lopez-Gatell H, Alpuche-Aranda C, Hernandez M, et al. Severe respiratory disease concurrent with the circulation of H1N1 influenza. N Engl J Med 2009;361:674–9.
3. Perez-Padilla R, Rosa-Zamboni D, Ponce de leon S, Hernandez M, Quinones-Falconi F, Bautista E, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 2009;361:680–9.
4. Lessler J, Nicholas G, Reich BA, Derek ATC, New York City Department of Health and Mental Hygiene Swine Influenza Investigation Team. Outbreak of 2009 pandemic influenza A (H1N1) at a New York City school. N Engl J Med 2009; 361:2628–36.
5. Cao B, LI XW, Mao Y, Wang J, Lu HZ, Chen YS, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. N Engl J Med 2009;361: 2507–17.
6. Agarwal PP, Cinti S, Kazerooni EA. Chest radiographic and CT findings in novel swine-origin influenza A (H1N1) virus (S-OIV) infection. AJR Am J Roentgenol 2009;193:1488–93.
7. Ajlan AM, Quiney B, Nicolaou S, Muller NL. Swine-origin influenza A (H1N1) viral infection; radiographic and CT findings. AJR Am J Roentgenol 2009;193:1494–9.
8. Mollura DJ, Asnis DS, Crupi RS, Conetta R, Feigin DS, Bray M, et al. Imaging findings in a fatal case of pandemic swine-origin influenza A (H1N1). AJR Am J Roentgenol 2009;193: 1500–3.
9. Lee CW, Seo JB, Song JW, Lee JS, Kim MY, Chae EJ, et al. Pulmonary complication of novel influenza A (H1N1) infection: imaging features in two patients. Korean J Radiol 2009;10:531–4.
10. Abekka HA. X-rays and CT offer predictive power for swine flu diagnosis. Available at: www.diagnosticimaging.com/news/display/article/113619/1425699#. Published June 30, 2009. Accessed September 9, 2009.
11. Ketai LH. Conventional wisdom: unconventional virus. AJR Am J Roentgenol 2009;193:1486–7.
12. Kim SJ, Lee KS, Ryu YH, Yoon YC, Choe KO, Kim TS, et al. Reversed halo sign on high-resolution CT of cryptogenic organizing pneumonia: diagnostic implications. AJR Am J Roentgenol 2003;180:1251–4.
13. Conte P, Heitzman ER, Markarian B. Viral pneumonia, roentgen pathological correlations. Radiology 1970;95:267–72.
14. Osborne D. Radiologic appearance of viral disease of the lower respiratory tract in infants and children. AJR Am J Roentgenol 1978;13:29–33.
15. Han BK, Son JA, Yoon HK, Lee SI. Epidemic adenoviral lower respiratory tract infection in pediatric patients: radiographic and clinical characteristics. AJR Am J Roentgenol 1998;170:1077–80.