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ORIGINAL ARTICLE

Pneumonia induced by swine-origin influenza A (H1N1) infection: chest computed tomography findings in children

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Abstract
Purpose. The purpose of this study was to determine the features of chest computed tomography (CT) in children with swine-origin influenza A (H1N1) virus (S-OIV).
Materials and methods. The study population consisted of 16 children with laboratory-confirmed S-OIV infection (12 boys, 4 girls), with an age range of 5–10 years (mean 6.3 years). Pneumonia was suspected in these patients based on clinical features or confirmed by radiography. All subjects underwent CT for close evaluation of pneumonia, including characteristics, distribution, extent, and other findings such as pleural effusion, pneumothorax, and pneumomediastinum.
Results. The predominant CT finding was consolidation plus ground-grass opacity (GGO) (11/16, 69%). The consolidation-dominant pattern was found in 10 of 16 (66%) patients, and 1 (6%) was GGO-dominant. One (6%) had only GGO. In all, 7 of the 16 patients had segmental or lobar consolidation. Abnormal opacities were primarily distributed in the central lung zone (8/16, 50%) and were multifocal (15/16, 94%). Four showed atelectasis (4/16, 25%). Pneumomediastinum was observed in 4 of 16 (25%). One patient had negative radiographic findings but was positive on CT.
Conclusion. Multifocal consolidation with central distribution is a common CT finding in children with S-OIV, but there are few GGO-dominant cases. Widespread consolidation (segmental or lobar) is also common.

Key words H1N1 · CT · Children · Swine-origin influenza A · Pneumonia

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Introduction

The novel swine-origin influenza A (H1N1) virus (S-OIV), first reported as a human infectious disease in April 2009, is now found worldwide.[1] Although most patients with S-OIV infection show mild symptoms with self-limited or no complications, a percentage of patients have severe symptoms, particularly pneumonia or respiratory failure.[1–3] The high pathogenicity of S-OIV in the lung, similar to that of the severe acute respiratory syndrome (SARS) virus, was reported in July 2009.[4] Severe respiratory symptoms with S-OIV infection were suspected to be related to the high pathogenicity of the virus.

Although a considerable number of cases of severe pneumonia have been reported, there are relatively few chest computed tomography (CT) studies in patients with S-OIV infection.[5–12] Despite evidence that children are at high risk for developing S-OIV, and large numbers of children have contracted the disease,[2,13] only one consecutive-patients study on chest radiography in children and two consecutive-patients studies on chest CT findings in children have been published.[11,12,14] The the purpose of this study was to determine the features of chest CT in children with S-OIV infection.

Materials and methods

Subjects

Approval for this study was obtained from the institutional clinical research ethics board. Because the present study was retrospective, informed consent was waived. A total of 28 children (≤ 15 years old) were admitted to our facility for fever and hypoxia (pulse oxygen saturation <93% in room air) between September 16, 2009, and November 30, 2009. All 28 patients were suspected of having S-OIV infection and had already been diagnosed as having pneumonia based on initial radiography or clinical symptoms. We performed CT examinations in all 28 patients for two reasons: First, the first patient who was admitted in our facility as having S-OIV pneumonia presented with severe respiratory failure and needed mechanical ventilation. Therefore, we performed chest CT in all patients for close evaluation of pneumonia and to detect pneumonia at an early stage, which is difficult to detect by radiography. Second, because the common clinical courses of S-OIV in children and the factors of aggravation were unknown in the autumn of 2009, an unknown clinical course for this patient cohort became a concern.

Of the 28 patients, 26 were confirmed to have S-OIV infection based on the results of real-time reverse transcriptase polymerase chain reaction (RT-PCR) of nasopharyngeal swabs; the other 2 patients were confirmed as negative for S-OIV and were excluded from the study population. Of the 26 patients with S-OIV, we targeted those who underwent CT examination within 24 h from admission and did not receive antiviral drugs before admission. Finally, 10 patients were excluded, and 16 patients were enrolled as the study population. We retrospectively reviewed the chest CT scans of these 16 children with S-OIV.

The study population consisted of 12 boys and 4 girls with a mean age of 6.3 years (range 5–10 years). Patient characteristics are summarized in Table 1. Seven patients had asthma as an underlying medical condition.

Rapid antigen tests were performed for all patients at the referring hospital and/or at our facility. Results of the rapid antigen tests were positive in 12 of the 16 patients and negative in the remaining 4. However, as all patients in this study were ultimately found to be positive for S-OIV infection on the basis of RT-PCR findings, the four negative rapid antigen tests were determined to be falsely negative. Five patients had received antibiotics (azithromycin, ceftriaxone, amoxicillin, cefozopran, or clarithromycin) before admission.

Blood cultures were performed for all patients, and none of the results were positive. Sputum culture was performed for one patient, and it provided no evidence of bacterial pneumonia.

Table 1. Patient characteristics and medical backgrounds of children with S-OIV infection

Characteristic	Data
Age (years)	6.3 (5–10)
Sex: M/F (no.)	12/4
Laboratory-confirmed S-OIV infection	16 (100%)
Duration from onset to CT (days)	1.8 (0–4)
Influenza encephalopathy (no.)	0
Duration of hospitalization (days)	6.4 (4–9)
Peak CRP level during hospitalization (mg/l)	31 (7–68)
CRP level on admission (mg/l)	28 (3–68)
Peak WBC count during hospitalization, (/μl)	10 500 (4500–27 200)
WBC count on admission (/μl)	10 500 (4500–27 200)
Patients with asthma (no.)	7 (44%)
Administration of antibiotics before admission (no.)	5 (31%)
Rapid antigen test performed (no.), positive/negative	16 (100%), 12/4

Data are given as the median (range) unless otherwise stated
S-OIV, swine-origin influenza virus; CT, computed tomography; CRP, C-reactive protein; WBC, white blood cell

Imaging techniques

The CT examinations were performed on all patients in the present study using 64-multidetector CT (MDCT) (Aquilion 64, Toshiba, Tokyo, Japan). None of the patients underwent repeat MDCT studies. The MDCT instrument had a gantry speed of 0.5 s, tube voltage of 120 kVp, and collimation of 0.5 mm. The tube current was regulated automatically by the volume exposure control (EC) technique. CT images were reconstructed as 1-mm sections with no overlap. All CT examinations were performed without the use of contrast material.

Imaging analysis

Two radiologists (4 years and >20 years of experience in chest imaging, respectively) reviewed the chest CT images independently, and final interpretations were made by consensus. All images were reviewed on a picture archiving and communication system (PACS) workstation. Abnormal parenchymal opacities were classified as consolidation (defined as opacity obscuring the underlying vessels), ground glass opacity (GGO) (defined as increased attenuation without obscuring the underlying vessels), nodules or centrilobular nodules, or mixed. Because the study population consisted of children, several patients were not able to adequately hold their breath during the CT examination. Therefore,

motion artifacts occurred on the CT, and bronchovascular bundle thickening (BVBT) could be interpreted in only 12 of 16 cases, with interpretation being difficult in the remaining 4 cases. The distribution of abnormal opacities was classified as peripheral dominant, central dominant, or no tendency in the distribution. The number of lobes affected by abnormal opacity was counted. The extent of opacities was classified as focal, multifocal, or diffuse. Other findings, such as pleural effusion, pneumomediastinum, and pneumothorax, were also recorded. Mediastinal lymphadenopathy was excluded from the evaluation because contrast was insufficient without a contrast material being used, and motion artifact frequently occurred.

Results

Laboratory confirmation of S-OIV infection was obtained for all patients. Chest CT examinations were performed an average of 1.8 days (range 0–4 days) after the onset of clinical symptoms. None of the 16 patients required intubation or mechanical ventilation. After admission, oseltamivir was administered to all patients, and antibiotics (ampicillin/sulbactam plus azithromycin or panipenem plus azithromycin) were administered empirically to prevent complications of bacterial pneumonia. Several patients received corticosteroids for asthmatic symptoms. The average hospitalization time was 6.4 days (range 4–9 days), and all patients recuperated from S-OIV infection without sequela. One patient presented with status epilepticus on admission, but none of the patients showed evidence of influenza encephalopathy.

Imaging findings are summarized in Table 2. Eleven cases (69%) showed consolidation plus GGO (Fig. 1); of these, 10 cases (63%) were consolidation-dominant and only one case (6%) was GGO-dominant. Consolidation only was found in 3 of 16 cases (19%). In addition to these findings, segmental or lobar consolidation was found in seven patients (44%). Of these seven patients, five (31%) had widespread consolidation with volume loss (as evidenced by atelectasis) (Fig. 2), and two (13%) had widespread consolidation without volume loss (Fig. 3). Abnormal opacities were predominantly found in the central zone of the lung (8/16, 50%), especially in the peribronchovascular area; fewer patients had abnormalities in the peripheral zone (3/16, 19%). The remaining patients (5/16, 31%) had no tendency in distribution. Lung abnormalities were unilateral in 6 of the 16 patients (38%) and bilateral in 10 patients (63%). With respect to the extent of opacities, abnormal findings were multifocal in 15 of the 16 patients (94%) and focal in 1 patient

Table 2. Chest CT findings in children with S-OIV infection and clinically presumed or confirmed pneumonia

Chest CT findings	No. of patients ($n = 16$)
Characteristics of abnormal opacities	
Consolidation only	3 (19%)
Consolidation with GGO	11 (69%)
Consolidation dominant	10 (63%)
GGO dominant	1 (6%)
GGO only	1 (6%)
Centrilobular nodules with GGO	1 (6%)
Distribution of abnormal opacities	
Central dominant	8 (50%)
Peripheral dominant	3 (19%)
No tendency	5 (31%)
Unilateral or bilateral abnormal opacities	
Unilateral	6 (38%)
Bilateral	10 (63%)
Extent of abnormal opacities	
Focal	1 (6%)
Multifocal	15 (94%)
BVBTin whom interpretation was possible	9/12 (75%)

GGO, ground-glass opacity; BVBT, bronchovascular bundle thickening

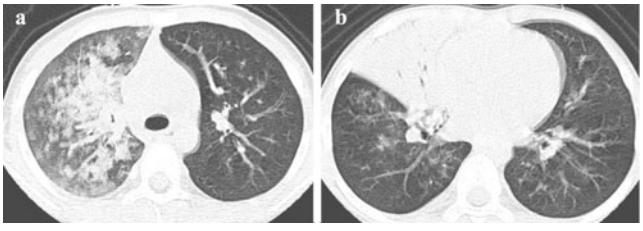

Fig. 1. A 5-year-old boy with laboratory-confirmed swine-origin influenza A (H1N1) virus (S-OIV) infection complained of fever, diarrhea, and shortness of breath. **a**, **b** Axial images from unenhanced computed tomography (CT) shows multifocal consolidation and ground-grass opacities (GGO) in the right upper lobe. Lobar consolidation of the right middle lobe with volume loss was observed (partial atelectasis). Abnormal opacities were observed only in the right lung; the left lung was intact apart from bronchial wall thickening. Motion artifacts are present on CT

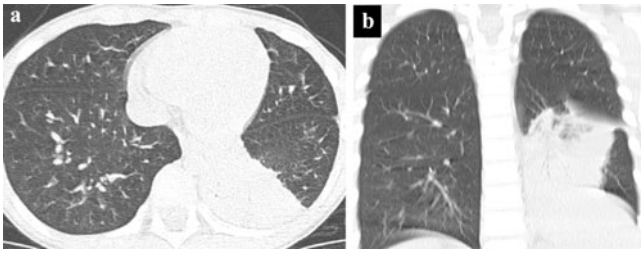

Fig. 2. A 5-year-old boy with laboratory-confirmed S-OIV infection presented to the emergency department with fever, shortness of breath, and cough. **a**, **b** Axial and coronal images from unenhanced CT show consolidation with volume loss in the lateral basal and posterior basal segments of the left lower lobe and elevation of the left diaphragm. The consolidation with volume loss was interpreted as atelectasis

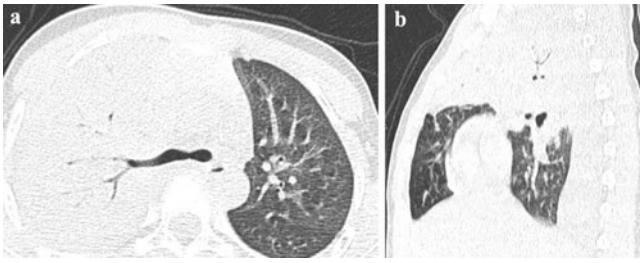

Fig. 3. A 6-year-old boy with laboratory-confirmed S-OIV infection was taken to the emergency department with fever, shortness of breath, cough, and confusion. **a** Unenhanced CT performed on admission shows right upper lobe (whole lobe) consolidation without volume loss but with an air bronchogram. This opacity had almost disappeared on a chest radiograph acquired the fifth day after admission (not shown). **b** Sagittal reconstruction image shows prominent consolidation on the right upper whole lobe and the apical segment of the right lower lobe with pleural effusion. The right middle lobe is relatively clear

Table 3. Number of lobes affected by abnormal parenchymal opacities

Lung region	No. (n = 16)
Right side	
RUL	10 (63%)
RML	6 (38%)
RLL	10 (63%)
RUL + RML + RLL	26 lobes/16 patients
Left side	
LUL	2 (13%)
Lingula	6 (38%)
LLL	8 (50%)
LUL + lingula + LLL	16 lobes/16 patients
Mean lobes involved	2.6 lobes/patient

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe

(6%); none of the patients had diffuse opacities. Pleural effusion was observed in only one patient (6%), and pneumomediastinum was observed in 4 of the 16 patients (25%). Pneumothorax was not observed in any patients. BVBT was observed in 9 of the 12 patients (75%) in whom interpretation was possible.

The number of lobes affected by abnormal parenchymal opacities is shown in Table 3. The mean number of affected lobes was 2.6 (range 1–4). Right lobes were predominantly affected (26 right lobes vs. 16 left lobes). One patient had negative chest radiography but positive CT findings.

Discussion

In the present study, the predominant pattern of abnormality was multifocal consolidation regardless of the presence of GGO. These abnormal opacities were primarily distributed in the central lung zone. Although to the best of our knowledge eight studies on CT findings in S-OIV infection have been published, there are only two consecutive-patients studies on CT findings in children with S-OIV.[5–12] In particular, Mori et al.[11] and Zhao et al.[12] provided the first two reports about CT findings of children with S-OIV. Although the results of Mori et al. had some similarity with our results, there is no unifying trend linking the previous eight studies about CT findings with the present study.

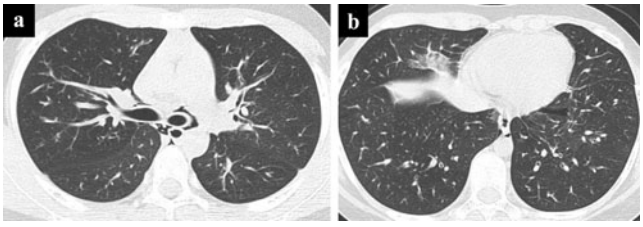

Fig. 4. A 10-year-old boy with laboratory-confirmed S-OIV (H1N1) presented to the emergency department with fever, cough, shortness of breath, and nausea. **a**, **b** Unenhanced CT shows a pneumomediastinum and patchy GGO in the medial segment of the right medial lobe

Influenza viruses are divided into three types (A, B, C), based on internal-membrane and nucleoprotein antigens. Of the three, types A and B influenza viruses can cause viral pneumonia.[15,16] The CT features of pneumonia caused by seasonal influenza include centrilobular nodules, representing alveolar hemorrhage, and GGO or consolidation with lobular distribution predominantly in the central lung zone.[15,17] There were few cases of centrilobular nodules in either of the previous studies on S-OIV infection or in the present study. GGO is frequently observed with viral pneumonia caused by seasonal influenza, whereas there were few GGO-dominant cases in the present study.[17] Additionally, widespread consolidations (segmental or lobar) were observed in 7 of 16 cases in the present study. These findings are uncommon in seasonal influenza; rather, they resemble the radiological features of avian H5N1 influenza infection in which segmental consolidation in chest CT was reported by Qureshi et al.[18] In addition, it was reported that S-OIV shows increased ex vivo replication in human bronchial epithelium and lung tissues as well as increased replication and pathological changes in the lung of non-human primates.[3,19] Therefore, we suggest that widespread consolidations are related to the high pathogenicity of S-OIV, although the possibility of bacterial superinfection cannot be ruled out.

Pneumomediastinum was observed in four patients (25%) (Fig. 4), although it is a relatively rare complica-

tion of asthma or lower airway tract infection in children.[20,21] Pneumomediastinum is associated with rupture of alveoli induced by hyperinflation of the lung or laceration of the bronchus or trachea caused by strong coughing.[21,22] Hyperinflation of the lung is a known major finding of chest radiography in children with S-OIV.[14] In addition, two studies reported on pneumomediastinum with S-OIV infection in children.[12,22] Pneumomediastinum subsequent to influenza infection is relatively rare, and the report by Hasegawa et al. suggested that a high prevalence of pneumomediastinum may be a characteristic pathological finding of S-OIV infection.[22] The present study concurs with this suggestion. The existence of pneumomediastinum may be considered indirect evidence of hyperinflation, suggesting severe inflammation of the small airways or bronchioles.

Bronchovascular bundle thickening was observed in three-fourths of patients in whom interpretation was possible. This finding is compatible with the study by Lee et al., who reported prominent peribronchial markings as important findings on chest radiography of children with S-OIV.[14] Although the interpretation of BVBT was difficult in four cases because of motion artifacts, BVBT was one of the common findings in the present study.

Zhao et al.,[12] Deng et al.,[23] and Terano et al.[24] reported that plastic bronchitis occurred in patients with S-OIV. Our institution had a CT examination of one patient with plastic bronchitis that was proven by bronchoscopy. However, this patient was excluded from the imaging interpretation because the CT examination was performed on the seventh day after admission. Several other patients with lobar or segmental atelectasis were clinically suspected to have minor plastic bronchitis, but bronchoscopic evaluation was not performed and the patients improved without bronchoscopy.

In the present study, the most common underlying medical condition was asthma (7/16 cases, 44%). Other reports have also documented asthma as the most common underlying medical condition that increases the risk of severe influenza or influenza complications in children; this finding is compatible with the results in the present study.[2,11,25–27] Although obesity was also reported as a major underlying medical condition, none of the patients in the present study was obese.[2]

One patient in our study had negative chest radiography but a positive CT examination. Abbo et al. also reported several patients who was negative for radiograph but positive for CT.[8] Therefore, if a patient with S-OIV presents with hypoxia but has negative radiography, a chest CT examination would be deemed useful to detect pneumonia at an early stage.

Widespread consolidation with central dominant and pneumomediastinum may be characteristics of S-OIV and might help distinguish S-OIV from seasonal influenza and other viral infections. However, it could be difficult to rule out bacterial pneumonia by these characteristics. There are few published CT findings in children with S-OIV, and more are needed to establish the characteristics of S-OIV in children.

The present study has several limitations. First, the study is retrospective and used data from a single institution. Therefore, a selection bias may exist. Because our institution does not have a neonatal or a pediatric intensive care unit, treatment of severely ill patients, such as those needing percutaneous cardiopulmonary support, is difficult. Second, there was the possibility of bacterial co-infection. Another study demonstrated bacterial co-infection by bronchoalveolar lavage.[5] However, because the current study population comprised children, an invasive examination was avoided. According to reports by Flood et al.[28] and Ruuskanen et al.,[29] bacterial pneumonia is suggested when the C-reactive protein (CRP) level is >40 mg/l[28] or >60 mg/l[29] or the white blood cell count (WBC) is >15 000/ml,[29] respectively. In the present study, the peak CRP level was 31 mg/l, and the WBC was 10 500/ml. That is why we thought that pneumonia in our patients might be induced by the S-OIV alone. Nevertheless, because antibiotics were administered empirically to all patients, the possibility of bacterial co-infection cannot completely be excluded. Third, because the study population consisted of children, several patients could not hold their breath and were moving during the CT examinations. Therefore, motion artifacts made it difficult to evaluate minute findings such as BVBT and mediastinal lymphadenopathy. Finally, no information on the relation between CT and histopathology could be obtained because none of the patients underwent lung biopsy or autopsy.

Conclusion

The most common CT finding in children with S-OIV infection is multifocal consolidation regardless of the presence of GGO, with primary distribution in the peribronchovascular area of the central lung zone. Segmental or lobar consolidation was observed in almost half of the patients. Few GGO-dominant cases were observed.

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