Pulmonary imaging of pandemic influenza H1N1 infection: relationship between clinical presentation and disease burden on chest radiography and CT

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ABSTRACT. The potential for pulmonary involvement among patients presenting with novel swine-origin influenza A (H1N1) is high. To investigate the utility of chest imaging in this setting, we correlated clinical presentation with chest radiographic and CT findings in patients with proven H1N1 cases. Subjects included all patients presenting with laboratory-confirmed H1N1 between 1 May and 10 September 2009 to one of three urban hospitals. Clinical information was gathered retrospectively, including symptoms, possible risk factors, treatment and hospital survival. Imaging studies were re-read for study purposes, and CXR findings compared with CT scans when available. During the study period, 157 patients presented with subsequently proven H1N1 infection. Hospital admission was necessary for 94 (60%) patients, 16 (10%) were admitted to intensive care and 6 (4%) died. An initial CXR, carried out for 123 (78%) patients, was abnormal in only 40 (33%) cases. Factors associated with increased likelihood for radiographic lung abnormalities were dyspnoea ($p < 0.001$), hypoxaemia ($p < 0.001$) and diabetes mellitus ($p = 0.023$). Chest CT was performed in 21 patients, and 19 (90%) showed consolidation, ground-glass opacity, nodules or a combination of these findings. 4 of 21 patients had negative CXR and positive CT. Compared with CT, plain CXR was less sensitive in detecting H1N1 pulmonary disease among immunocompromised hosts than in other patients ($p = 0.0072$). A normal CXR is common among patients presenting to the hospital for H1N1-related symptoms without evidence of respiratory difficulties. The CXR may significantly underestimate lung involvement in the setting of immunosuppression.

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In late March 2009, an outbreak of respiratory illness caused by novel swine-origin influenza A virus (H1N1) was identified in Mexico [1]. In June that year, the World Health Organization (WHO) declared a global pandemic [2]. Since then the virus has spread worldwide and by 8 November 2009 more than 206 countries had reported laboratory-confirmed cases of H1N1 to the WHO, with more than 6250 related deaths [2, 3].

Risk factors and clinical manifestations associated with H1N1 have been previously reported [4–9]. Significantly less attention has been given to the imaging findings of H1N1 that may serve as early indicators of the presence and impending severity of disease. Early recognition of radiological patterns may have an impact in timely management of critically ill patients with H1N1. We examined the chest X-ray (CXR) and CT findings in

newly diagnosed cases of H1N1, and evaluated the relationship between risk factors, symptoms and extent of disease on the CXR compared with CT.

Methods and materials

A retrospective electronic chart review was performed from 1 May to 10 September 2009 at Jackson Health Systems (JHS): Jackson Memorial Hospital (an academic 1500-bed tertiary care centre), Jackson North Hospital (382 beds) and Jackson South Hospital (199 beds) acute care centres. The Institutional Review Board for JHS and the University of Miami waived the requirement for informed consent.

Cases were defined as all patients who presented with symptoms of an influenza-like illness in whom infection was subsequently confirmed by a rapid influenza test (RIT) (BinaxNOW® influenza A&B test, Inverness Medical International, Princeton, NJ), a viral culture or a nasopharyngeal washing with real-time reverse transcription polymerase chain reaction (RT-PCR)

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(Florida Department of Health and Focus Diagnostics, Cypress, CA).

A retrospective review of consecutive cases was performed using electronic medical records. Data obtained included date of visit or hospitalisation, demographics, symptoms, hospital and intensive care unit (ICU) admission and discharge dates, requirement for mechanical ventilation and vital status at discharge. Comorbidities collected included obesity, pregnancy, haematological or solid malignancies, transplant recipient, human immunodeficiency virus (HIV) serostatus and whether acquired immune deficiency syndrome (AIDS) criteria were met: neutropenia (absolute neutrophil count (ANC) <1000), diabetes mellitus, chronic obstructive pulmonary disease (COPD), chronic kidney disease, chronic liver disease, cardiomyopathy and peripheral vascular disease [10]. Patients were considered immunosuppressed if they had lymphoma or leukaemia, were receiving corticosteroids or other immunosuppressive medications, were neutropenic, had received a bone marrow or solid organ transplant or had AIDS.

Chest radiographs

For each patient who had CXR studies of the thorax, the CXR at presentation was re-read by two board-certified radiologists who reviewed the imaging studies together and reported consensus findings. The radiologists were aware of the patients' diagnosis of H1N1, but were unaware of clinical signs, symptoms or other medical history.

Each lung was divided into nine zones on the anterior projection. The top of the aortic arch and the caudal margin of the right hilum defined the transition between the upper, middle and lower three zones of each lung. The medial, middle and lateral three zones of each lung were equally spaced. The presence of any of the following findings in each zone was recorded, as defined in the Fleischner Society glossary [11]: consolidation, ground-glass opacity (GGO), nodule (0.5–3 cm), interstitial opacity, pleural effusion and lymphadenopathy (mediastinal and/or hilar). If a previous CXR from 1 month or more before the selected radiograph was available, then only new findings were recorded in order to reduce the likelihood of attributing subacute or chronic diseases to H1N1. After recording all findings, a single "predominant" finding (or negative result) was designated for each CXR. From the 18 lung zones (9 per lung), the distribution of disease was characterised as unilateral, bilateral, medial, lateral, upper, mid, lower or no lung zone predominance.

Chest CT scans

The presence or absence of disease in each pulmonary segment was recorded. In addition to the findings described for chest radiographs, the distribution of GGO was assessed. Lobular distribution was defined as the demarcation of involved secondary pulmonary lobules along their interlobular septal boundaries. If the sum of the segments with a lobular GGO distribution was greater than the sum of the segments without, the

patient was designated as having a lobular distribution of disease. An additional finding recorded from CT scans was the presence or absence of centrilobular or "tree-in-bud" nodules, as distinguished from discrete focal nodules as previously described. The distribution of disease was characterised as unilateral, bilateral, central, peripheral, upper, middle or lower lobe predominant, or not. Patients who had a chest CT also had the temporally closest CXR analysed for zones with parenchymal abnormalities for comparison with the CT findings.

Statistical analysis

Categorical variables were compared using Fisher's exact test and the χ^2 test as appropriate. Continuous variables were compared across groups using *t*-tests or the Mann-Whitney test as appropriate for the data distribution.

Linear regression, comparing involved segments on CT scan with involved zones on CXR, was used to generate an equation predicting the number of involved

Table 1. Chest radiographic and CT findings in H1N1 infection

Finding	CXR (n=123)	CT (n=21)
Main finding		
Consolidation	28 (23)	9 (43)
Ground glass	5 (4)	8 (38)
Interstitial disease	4 (3)	0 (0)
Nodule	1 (1)	1 (5)
Tree in bud	N/A	1 (5)
Adenopathy	1 (1)	0 (0)
Effusion	1 (1)	1 (5)
No disease	83 (67)	1 (5)
Consolidation	32 (26)	13 (62)
Air bronchogram(s)	3 (2)	5 (24)
Ground glass opacity (GGO)	9 (7)	14 (67)
GGO lobular distribution	N/A	12 (57)
Nodule	2 (2)	3 (14)
Tree in bud	N/A	4 (19)
Lungs involved		
None	84 (68)	2 (10)
Unilateral	16 (13)	4 (19)
Bilateral	23 (19)	15 (71)
Predominant lung disease area ^a		
Upper	1/39 (3)	4/19 (21)
Mid	4/39 (10)	0/19 (0)
Lower	21/39 (54)	8/19 (42)
Medial (CXR)/central (CT)	6/39 (15)	2/19 (11)
Lateral (CXR)/peripheral (CT)	1/39 (3)	7/19 (37)
Pleural effusion		
Unilateral	3 (2)	5 (24)
Bilateral	0 (0)	3 (14)
Adenopathy		
Hilar	3 (2)	5 (24)
Mediastinal	1 (1)	3 (14)

CXR, chest radiograph.

Numbers in parentheses represent percentages.

^aPercentages are calculated from those studies with parenchymal findings.

zones based on the number of involved segments. The ratio of actual to predicted zones of involvement was interpreted as a measure of CXR sensitivity for each case. Patients with no predicted CXR involvement were excluded from analyses comparing patients' characteristics with CXR sensitivity.

Statistical analyses were performed using NCSS 2004 (Kaysville, UT).

Results

The Infection Control Log included 170 patients with laboratory-confirmed H1N1 infection during the study period. Of these, 13 were thought to have likely or possible hospital acquisition of disease and were excluded from further analysis. Among the 157 remaining patients who presented with symptoms attributable to H1N1 infection, RT-PCR was positive in 112/112 (100%) cases, viral culture in 26/26 (100%) cases and RIT in 87/153 (57%) cases.

Analysing the RIT results, we identified 40/87 (46%) of RIT-positive patients compared with 52/66 (79%) RIT negative who were hospitalised ($p<0.001$); 9/87 RIT

positive compared with 6/66 RIT negative who were admitted to an intensive care unit (ICU) ($p=0.99$). There was no statistically significant difference in hospital or ICU lengths of stay or risk of death based on these RIT results.

Chest radiography

Of 157 patients who presented with H1N1-related symptoms, 123 (78%) had at least one chest radiograph (84 inpatients and 39 outpatients). The initial CXR was carried out on the day of presentation in 109 (89%) cases. The initial CXRs were normal in 83 (67%) cases. Consolidation was the most common abnormality observed in CXRs (Table 1), present in 26% of patients and the predominant finding in 23%. When present, consolidation involved four (median) (2–9 interquartile range) lung zones. Nine (7%) patients presented with GGOs, and this was the predominant finding in five patients (4%).

Among the 39 patients found to have parenchymal abnormalities on initial CXR, findings were bilateral in 23 (59%) patients and unilateral in 16 (41%). Lower zone findings were predominant in 21 (54%) CXRs, 4 (10%)

Table 2. Association of risk factors with having an abnormal chest radiograph

Risk factor	Factor absent (positive CXR/total)	Factor present (positive CXR/total)	p-Value
Male	22/59 (37)	16/64 (25)	0.17
Race			0.13
White	10/18 (56)		
Black	17/69 (25)		
Hispanic	9/27 (33)		
Asian	0/1 (0)		
Other or unknown	2/8 (25)		
Cough	8/18 (44)	28/102 (28)	0.17
Dyspnoea	15/76 (20)	23/45 (51)	<0.001*
Fever	10/33 (30)	27/89 (30)	0.99
Malaise	23/60 (38)	15/62 (24)	0.12
Diarrhoea	35/110 (32)	1/10 (10)	0.28
Hypoxaemia	18/96 (19)	20/26 (77)	<0.001*
Pregnant	36/116 (31)	2/7 (29)	0.99
Obese	25/90 (28)	7/20 (35)	0.59
Morbidly obese	30/107 (28)	3/4 (75)	0.078
Transplant	36/113 (32)	2/7 (29)	0.99
Neutropenic	38/121 (31)	0/1 (0)	0.99
Steroids	34/111 (31)	4/11 (36)	0.74
HIV	36/110 (33)	2/12 (17)	0.34
AIDS	36/113 (32)	2/9 (22)	0.72
CVA	37/120 (31)	1/2 (50)	0.53
COPD	27/99 (27)	11/23 (52)	0.079
CHF	37/117 (32)	1/5 (20)	0.68
Connective tissue disease	37/121 (31)	1/1 (100)	0.31
Dementia	38/119 (32)	0/3 (0)	0.55
Hemiplegia	38/122 (31)	0/0	
Lymphoma	38/121 (31)	0/1 (0)	0.99
Myocardial infarction	38/120 (32)	0/2 (0)	0.57
Peripheral vascular disease	37/118 (31)	1/4 (25)	0.99
Diabetes mellitus	30/109 (28)	8/13 (62)	0.023*
Liver disease	37/118 (31)	1/4 (25)	0.99
Chronic kidney disease	35/116 (30)	3/6 (50)	0.37
Malignancy	38/121 (31)	0/1 (0)	0.99
Immunosuppressed	30/98 (31)	8/22 (36)	0.62

AIDS, acquired immune deficiency syndrome; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; HIV, human immunodeficiency virus.

Numbers in parentheses represent percentages.

* $p<0.05$.

had mid-lung zone predominance and one had upper lung zone predominance. Neither medial nor lateral predominance was present in 32 (82%) cases.

Lung parenchymal abnormalities were more common among patients with dyspnoea than those without (51% vs 20%, $p<0.001$) (Table 2). Similarly, patients with hypoxaemia were more likely to have parenchymal abnormalities (77% vs 19%, $p<0.001$). Diabetes mellitus was also associated with the presence of radiographic findings, occurring in eight of 13 (62%) patients with diabetes and 30 of 109 (28%) without ($p=0.023$). A weaker trend towards positive CXRs was noted with morbid obesity ($p=0.078$). No significant associations in radiographic presentation on plain CXR were noted in patients who were pregnant, immunosuppressed or in children compared with adults (Table 3).

Among the 119 patients who had both an RIT and a plain CXR, a positive RIT was associated with less consolidation. Patients with a negative RIT had 0 (0–2) zones with consolidation on CXR (mean 1.83), compared with 0 (0–0) zones among those with positive RIT (mean 1.03, $p=0.013$).

Chest CT

Chest CT scans were performed on 21 patients 1 (0–4) day after presentation (Table 1). Patients were imaged on a Siemens® multidetector scanner (Siemens® Medical Solutions, Malvern, PA). Studies were performed using a standard (not high resolution) algorithm. Thirteen scans

were performed without intravenous contrast, with a reconstructed slice thickness of 5 or 6.5 mm. Eight were performed with intravenous contrast, with a reconstructed slice thickness of 2–5 mm.

The predominant finding was consolidation in nine (43%); GGO in eight (38%), tree-in-bud nodules in one (5%) and discrete nodules in one (5%). Two scans (8%) did not show parenchymal disease; one demonstrated only a small pleural effusion. Relatively small pleural effusions were present in eight patients (38%). Negative chest radiographs and positive CT scans were found in 4 (16%) of 21 patients.

Our cohort had five (24%) patients with GGO but without consolidation, four (19%) with consolidation but without GGO and nine (43%) with both. When present, GGO involved seven (4–9) lung segments and the distribution was predominantly lobular in 12 (86%) cases (Figure 1). Consolidation, when present, involved four (2–8) segments and five of these patients had air bronchograms. We found four patients (19%) with centrilobular nodules or tree-in-bud opacities; three had separate areas of both consolidation and GGO while one had neither. Bilateral lung disease was present in 15 (71%) patients while four (19%) had unilateral disease. Lower lobe predominance was demonstrated in eight of 19 patients with lung disease (42%) and 4 (21%) had upper lobe predominance; seven patients (37%) had neither. Seven patients (37%) showed peripheral distribution, two (11%) central and 10 (53%) neither.

Linear regression yielded the relationship:

$$(\text{predicted CXR zones}) = 0.60 \times (\text{CT segments}) - 0.33 \quad r^2 = 0.6775$$

Two patients were predicted by CT to have no involved zones on CXR.

When CXR sensitivity was quantified as the ratio of actual to predicted CXR zones with parenchymal abnormality, hypoxaemia and the need for mechanical ventilation were associated with high sensitivity ($p<0.01$ for each), while the presence of significant immunosuppression was associated with low sensitivity ($p=0.0072$) (Table 4).

Among the six immunosuppressed patients, two had AIDS, three had solid organ transplants, one had been receiving corticosteroid therapy, one was neutropenic and one had lymphoma. All six had less involvement on CXR than predicted by the CT scan (Table 4) (Figure 2).

The relationship noted between consolidation on CXR and RIT results was paralleled with CT scanning: 4 (1–7) segments with consolidation among the 14 patients with negative RIT, 0 (0–1) segments among the 5 patients with positive RIT ($p=0.017$).

Discussion

Multiple authors have published their clinical experience in the diagnosis and management of influenza A (H1N1) infection [1, 5–7], but less attention has been focused on the imaging findings [12].

In our cohort, consolidation was the most prevalent CXR finding of viral pneumonia, similar to most published studies of various viral influenzas [13–16]. Approximately 67% of the initial radiographs in our series were negative, similar to the 58% that were

Table 3. Chest radiographic findings in adult and paediatric H1N1 patients

CXR finding	Adult	Paediatric	p-Value
Main finding			0.38
Consolidation	16/81 (20)	12/42 (29)	
Effusion	1/81 (1)	0/42 (0)	
Ground glass	4/81 (5)	1/42 (2)	
Interstitial disease	4/81 (5)	0/42 (0)	
LAD	0/81 (0)	1/42 (2)	
Nodule	1/81 (1)	0/42 (0)	
No disease	55/81 (68)	28/42 (67)	
Consolidation	20/81 (25)	12/42 (29)	0.67
Air bronchogram	1/81 (1)	2/42 (5)	0.27
Ground glass	8/81 (10)	1/42 (2)	0.16
Nodule	2/81 (3)	0/42 (0)	0.55
Lungs involved			0.51
None	55/81 (68)	29/42 (69)	
Unilateral	9/81 (11)	7/42 (17)	
Bilateral	17/81 (21)	6/42 (14)	
Effusion	2/81 (3)	1/42 (2)	0.99
Upper/mid/lower predominance			0.06
Upper	0/27 (0)	1/13 (8)	
Mid	1/27 (4)	3/13 (23)	
Lower	14/27 (52)	7/13 (54)	
None	12/27 (44)	2/13 (15)	
Medial-lateral predominance			0.78
Medial	4/27 (15)	2/13 (15)	
Lateral	1/27 (4)	0/13 (0)	
None	22/27 (82)	11/13 (85)	

LAD

Numbers in parentheses represent percentages.

Figure 1. 51-year-old male renal transplant recipient with cough and dyspnoea. (a) Chest radiograph demonstrates bilateral, predominantly lower lung zone opacities. (b) Coronal CT reformatted image shows bilateral, upper and lower lung zone ground-glass opacities in a lobular configuration (arrows). (c) Axial CT image at the lung bases shows bilateral consolidations with air bronchograms.

negative in the H1N1 study of Agarwal et al [12]. Bay et al [16] described lower lobe predominance, but Qureshi et al [15] did not. Most patients in our study did not have a radiographic zonal predominance, but of the minority that did 81% were in the lower zone. Most reports of the CT findings in patients with influenza virus pneumonia have described variable amounts of

centrilobular nodules, GGO and consolidation. A comparative study between bacterial and atypical pneumonias in immunocompetent patients described a case of influenza B pneumonia that showed GGO and consolidation in a lobular distribution [17]; these authors theorised that because the inflammatory change in atypical pneumonias first occurs in the respiratory tract,

Table 4. Chest radiographic sensitivity relative to CT scan, as a function of immunosuppression ($p=0.0072$)

Case no.	Immunosuppressed	CT segments with disease	Predicted CXR zones with disease	Actual CXR zones with disease	Ratio
20	Yes	5	2.67	0	0.00
35	Yes	1	0.27	0	0.00
90	No	7	3.87	0	0.00
18 8	Yes	3	1.47	0	0.00
176	No	12	6.87	2	0.29
105	Yes	17	9.87	7	0.71
4	Yes	5	2.67	2	0.75
80	No	11	6.27	5	0.80
72	Yes	17	9.87	8	0.81
98	No	11	6.27	6	0.96
38	No	17	9.87	11	1.11
71	No	2	0.87	1	1.15
12	No	6	3.27	4	1.22
109	No	6	3.27	4	1.22
101	No	18	10.47	13	1.24
5	No	18	10.47	16	1.53
94	No	3	1.47	3	2.05
31	No	2	0.87	2	2.31
3	No	4	2.07	8	3.87

CXR, chest radiograph.

Figure 2. 63-year-old female neutropenic patient with cough. (a) Chest radiograph is negative except for a right upper lobe granuloma (arrow). (b) Axial CT image obtained one day after the radiograph shows clustered peribronchovascular nodules in the right upper lobe.

the pathological changes are initially confined to the bronchiolar and peribronchiolar regions affecting certain lobules.

CT findings in H5N1 avian influenza A have also been reported. Qureshi et al [15] described three patients who showed predominantly GGO, in two; there was a mosaic (analogous to lobular) pattern and consolidation was also present in all three. However, unlike the GGO, consolidation was typically unilateral, segmental and primarily involved the dependent lung segments. Among immunocompromised patients, Oikonomou et al [14] reported three patients with haematological malignancies and influenza A virus pneumonia who underwent high-resolution CT. They exhibited GGO, consolidation, nodules and a tree-in-bud pattern. In two of the three patients GGO was the predominant finding, and one had a lobular distribution. In the CT scans of 15 patients with H1N1, Agarwal et al [12] identified GGO and consolidation as the major CT finding; one of their images showed a lobular distribution but this was not systematically reported in that study. Our CT findings confirmed a predominantly lobular distribution of GGO with relatively less nodular opacities than described in some of the aforementioned studies. It should be noted that we did not perform dedicated high-resolution CT, which may have been able to detect additional small nodular opacities. We did not identify pulmonary embolism (PE) on any of the CT scans. However, the majority of our studies were not performed with contrast or a dedicated PE protocol.

Although the total number of H1N1 patients with immunosuppressive conditions in our cohort was small, CXR was much less sensitive for detecting CT-identifiable disease among these patients than among immunocompetent patients. The threshold for CT scanning should be low for immunocompromised patients suspected of having H1N1.

Drexler et al [18] propose that increased viral shedding is associated with increased sensitivity of rapid influenza testing, but the level of viraemia can be affected by several factors. These includes timing

during the course of infection, when the sample was taken, patient age, storage and transportation. In our study, RIT was positive in 57% of the cases. However, patients with a positive RIT were less likely to be hospitalised and more likely to have a normal radiographic study.

Our study was limited by the lack of confirmatory RT-PCR or viral culture in some patients with a positive RIT who were considered to be positive for H1N1 infection by Centres for Disease Control and Prevention criteria [3]. Our outcome data are limited as we could document mortality in hospitalised patients but not in those treated as outpatients or patients who were discharged and did not return for follow-up within JHS.

In conclusion, our study identifies factors predisposing to a positive CXR, including hypoxaemia, dyspnoea and diabetes, and suggests that CT scanning may be highly useful for immunocompromised patients. The diagnosis of influenza should be considered in patients who present with consolidation or GGOs on chest radiography. Understanding the correlation between clinical presentation and imaging findings should assist in treating patients during the continuing pandemic.

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