Chest Radiograph Findings In Novel Swine-Origin Influenza A (H1N1) Virus (S-OIV) Infection: A UKMMC Experience

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SUMMARY

OBJECTIVE: 1.To evaluates and recognizes findings in chest radiograph in patients with laboratory-confirmed S-OIV (H1N1) infection treated at UKMMC. 2. To evaluate whether the findings on initial chest radiographs of influenza A (H1N1) patients can help to predict the prognosis.

MATERIAL AND METHODS: Total of 109 adult patients presenting to the Universiti Kebangsaan Malaysia Medical Centre (UKMMC) with flu-like symptoms who were positive for influenza A and these patients had underwent chest radiographs (CXR). The initial CXRs were evaluated for the pattern (consolidation, ground-glass, and reticulation), distribution, and extend of abnormality. The disease is classifies by the clinical severity (mild, moderate or severe illness) and adverse outcome (ventilated, death or recovered well).

RESULTS: The initial CXRs were normal in 56% of cases. The predominant radiographic finding was consolidation, most commonly involving the middle and lower zones (35% of cases). There is no significant association between initial CXR findings with the patient clinical outcome either fully recovered or death/ ventilated.

CONCLUSION: Normal chest radiographs is the most common radiographic finding in S-OIV (H1N1) infection and the most common abnormal lung finding is consolidation. Initial chest radiographs did not determine the patient clinical outcome and a normal initial radiograph could not exclude adverse outcome.

INTRODUCTION

Novel influenza A (H1N1) virus (also known as new influenza virus, swine-like influenza virus, swine-origin influenza virus, and colloquially as "swine flu") is a novel form of influenza A virus resulting from a combination of genes derived from 2 types of swine influenza, one of which is, in turn, a "triple reassortant" of human, avian, and swine influenza A strains. This new virus is not only anti-genically and genetically distinct from seasonal influenza A (H1N1) virus, but is also usually sensitive to oseltamivir, a neuraminidase inhibitor to which 10.9% of recent seasonal influenza A viruses were resistant. [1]

Novel influenza A (H1N1) virus first caused illness in Mexico and United State in March and April, 2009. [1, 2] The first novel H1N1 patient in the United States was confirmed by laboratory testing at CDC (Centers for Disease Control and Prevention) on April 2009. The second patient was confirmed on April 17, 2009. It was quickly determined that the virus was spreading from person-to person. On April 22, CDC activated its Emergency Operations Centre to better coordinate the public health response. On April 26, 2009, the United States Government declared a public health emergency and has been actively implementing the nation's pandemic response plan. [4]

On June 11, 2009, the World Health organization (WHO) indicated that a global pandemic of novel influenza A (H1N1) was underway by raising the worldwide pandemic alert level to Phase 6, on the basis of documented human-to-human spread of infection in at least three countries of two WHO regions. [2-4] This action was a reflection of the magnitude of spread of the new H1N1 virus, and not the severity of illness caused by the virus. [4]

Since the WHO declaration of the pandemic, the new H1N1 virus has continued to spread, with the number of countries reporting cases of novel H1N1 nearly doubling.[2] By July 11, 2009, there were 105304 confirmed cases and 463 deaths in 143 countries, including 627 cases in Malaysia. The first two cases in Malaysia were reported on 16th May 2009.The Ministry of Health (MOH) immediately responded with measures to contain disease spread. Contained focused on active cases finding and robust control of contacts. [3]

In the United States, significant novel H1N1 illness has continued to occur in the summer, with localized and in some cases intense outbreaks. The United States continues to report the largest number of novel H1N1 cases of any country worldwide. Given ongoing novel H1N1 activity to date, the CDC anticipates that there will be more cases, more hospitalizations and more deaths associated with this pandemic in the United States. The novel H1N1 virus, in conjunction with regular seasonal influenza viruses, poses a potential threat to the general public due to the significant illness it may cause, especially with associated hospitalization and deaths during the influenza season. The mortality rate of novel H1N1 is estimate to be round 0.01% .[4]

By case definition by WHO; a suspected case is a person with history of an acute onset of; high fever (38o), and dry cough and one or more of the flu ill like symptoms; with or without close contact with a person diagnosed with pandemic influenza (PI) within 10 days of the onset of symptoms or recent history of travel to areas reporting cases of PI. A

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probable case is a suspected case with limited laboratory confirmation of influenza A / sub-type or a person with an unexplained respiratory illness resulting in death with history of close contact with a person diagnosed with PI within the last 10 days or recent history of travel to areas reporting cases of PI. [7]

The novel influenza A (H1N1) virus spreads in the same way as regular seasonal influenza viruses do, mainly through the coughs and sneezes of infected people and also spread by touching infected objects and subsequently touching the one's nose or mouth. [4] Most cases are mild and self-limited; however, S-OIV (Swine- Origin Influenza A (H1N1) Virus) infection in high-risk patients is more likely to have severe and complicated courses. [4]

About half of the patients were previously healthy individuals. The rest have co-morbidities include older age more than 65 years old, pregnancy, chronic lung disease, congestive heart failure, renal failure, immunosuppression (due to underlying disease or therapy), haematological abnormalities (anaemia, haemoglobinopathies), diabetes, hepatic disease, socially unable to cope (i.e., without personal support at home, such patients may need an alternative centre of care) and patients on long-term acetylsalicylic acid therapy (increased risk of Reye's syndrome). [7]

Novel H1N1 infection has been reported to cause a wide range of flu- like symptoms, including fever, cough, sore throat, body aches, headaches, chills and fatigue. In addition, many patients also have reported fits (infant), nausea, vomiting and/ or diarrhea. [4, 6,7]

A detailed history of the clinical, travel and contact history including occurrence of respiratory disease in contact patients during the last 10 days should be obtained thoroughly. This should be followed by the clinical workout measures stated in the Syndromic Approach Protocol for acute respiratory syndromes. 5 Nasopharyngeal aspirate (NPA) samples were collected from patients at presentation to test for the H1N1 virus, using a specific real-time reverse–transcriptions polymerase chain reaction (RT) PCR assay. [9]

Complications of H1N1 infection would include pneumonia, acute confusion, metabolic derangement, respiratory failure and acute cardiac deterioration. Seizure was the most common neurologic complication (7.5%). Others included encephalitis/encephalopathy (1.4%), confusion/disorientation (1.0%), loss of consciousness (1.0%), and paralysis/Guillain-Barré syndrome (0.4%). [12]

OBJECTIVE

3.1 To evaluate and recognize findings in chest radiograph in patients with laboratory-confirmed S-OIV (H1N1) infection treated at UKMMC.

3.2 To evaluate whether the findings on initial chest radiographs of influenza A (H1N1) patients can help to predict the prognosis.

METHODOLOGY

4.1 Method
- This is a retrospective & prospective study.

4.2 Study period
- Between May 2009 to May 2011

4.3 Venue
- Department of Radiology, Internal Medicine Department and Microbiology Department, UKMMC

4.4 Study samples;

4.4.1 Inclusion criteria;
- The study population included 108 adult patients presenting to the UKMMC between May 2009 and May 2011 with flulike symptoms who were positive for influenza A.
- Their respiratory specimens were tested with real-time reverse transcription polymerase chain reaction (rt-PCR) at the Microbiology Department, UKMMC and/or Institute of Medical Research of Malaysia (IMR) and confirmed to have S-OIV (H1N1) infection.
- These patients underwent chest radiographs forming the study population.

4.4.2 Exclusion criteria;
- Patients in paediatrics age groups were excluded.
- Negative H1N1 lab tests.
- No chest radiographs taken.

The inclusion and exclusion criteria are summarized in Appendix A.

4.5 Sample size

Formula of calculation of sample size

$$n = \frac{t^2 \times p(1-p)}{m^2}$$

$$n = \frac{(1.96)^2 \times (0.069)(0.93)}{0.05^2}$$

$$n = 99$$

- n= required sample size
- t= confidence level at 95% (std value 1.96) (std value 1.96) (for CI of 95%, t=1.96;normal distribution table)
- p= **6.9%** estimated prevalence of an attribute present in the population (based on 2 years duration of local data from UKMMC Radiology Department)
- m= margin of error at 5% (std value of 0.05)

By referring to the table in Lwanga and Lemeshaw, 1991, sample size determination studies page 25, with a prevalence (P) of 5%, precision of 0.05, the table indicated that the sample size required is 99.

TECHNIQUE

The study population was all adult patients presenting to the Universiti Kebangsaan Malaysia medical centre (UKMMC) between May 2009 and May 2011 with flu-like symptoms who were positive for influenza A. Their respiratory specimens were tested with real-time reverse transcription

polymerase chain reaction (rt-PCR) at the Microbiology Department, UKMMC and / or Institute of Medical Research of Malaysia (IMR) and confirmed to have S-OIV (H1N1) infection. All of these individuals underwent chest radiograph on admission. An experienced radiologist in cardiothoracic field who is blinded to the clinical outcome of the patients reviewed all the CXRs.

CXRs were obtained on admission using conventional radiography either in standard posteroanterior (PA) projection using departmental or in anteroposterior (AP) projection performed with bedside portable x-ray machine.

The CXRs were assessed for presence and distribution of parenchymal consolidation, interstitial opacities and ground glass opacity. Consolidation was defined as an opacification of the parenchyma with obscuration of the underlying anatomical structure (Figure 1). Ground glass opacities (GGO) were defined as hazy areas of increased attenuation with preservation of bronchial/vascular marking and without obscuration of the ribs (Figure 2). Interstitial opacity was defined as linear opacities forming mesh-like pattern, which may be thin or thick and coarse (Figure 3). A mixed pattern denoted a combination of consolidation, ground glass opacities and interstitial opacities.

Distribution was categorized as focal, patchy or diffuse. A single focus of abnormality was defined as focal while, patchy was defined as more than one abnormality and diffuse defined as abnormalities involving three or more lung zones. The predominant distribution was assessed as being in the upper, middle or lower lung zones of the patients by using imaginary horizontal lines traversing the lungs at levels that were one-third and two-third of the vertical distance between the apices and the hemidiaphragmatic domes. The presence of pleural effusion and adenopathy were also recorded.

Mild illness referred to patients who, in the absence of public health measures, could have been treated at home. They were prescribed antiviral therapy and symptomatic treatment. Patients with moderate illness required certain medical interventions beyond what could be provided at a primary care setting. These patients had stable parameters and were thus treated in a general ward setting. Severe cases referred to patients who were either hypoxemic, needed ≥ 4 L/min of oxygen and/or critically ill patients who required HD or ICU level of care. [13]

The outcome 'death' was defined as death of any cause that occurred during hospitalization. 'Adverse outcomes' were defined as the requirement of intensive care unit (ICU) admission for ventilatory and organ support and/or death that occurred during hospitalization, either in the ICUs or in the medical wards (i.e., 'ICU admission and/or death,' in contrast to patients who survived and did not require ICU admission). [8]

The statistical analysis on comparison of continuous variables between groups was performed by using Student t test. Frequencies of category were compared by using the Fisher exact test. All analyses were considered significant at P values of less than 0.05. All statistical evaluations were performed with SPSS Statistic 20.0.

Table I: Summary of radiographic findings in patients with S-OIV infection

Pattern of radiographic abnormality	No. patient (%)
Normal	61 (56) VS 48 (44)
Consolidation	24 (50)
Interstitial opacity	12 (25)
Ground glass opacity (GGO)	4 (8)
Interstitial opacity+ GGO	1 (2)
Interstitial opacity + consolidation	6 (12)
Mixed pattern	1 (2)
Extend on initial imaging	
Focal	10 (21)
Patchy	14 (29)
Diffused	24 (30)
Predominance	
Upper zones	3 (6)
Middle zones	4 (8)
Lower zones	12 (25)
Upper + middle zones	3 (6)
Upper + lower zones	2 (4)
Middle + lower zones	17 (35)
All zones	7 (15)
Pleural effusion	8 (16)
Adenopathy	1 (2)

Table II: Radiologic Findings of H1N1 Patients with Initial Chest Radiograph Findings.

Characteristics	No ventilation/Death	Ventilated/Death	P Value
Initial CXR			
Normal	92% (55)	8% (5)	0.095
Abnormal	81% (39)	19% (9)	
Distribution			
Focal	93% (65)	7% (5)	0.018
Patchy	71% (10)	29% (4)	0.261
Diffused	68% (15)	23% (5)	0.083
Lung Zone Involved			
Upper Zone	67% (2)	33% (1)	0.343
Middle Zone	50% (2)	50% (2)	0.081
Lower Zone	92% (11)	8% (1)	0.52
Upper and Middle Zones	100% (2)	0	0.76
Upper and Lower Zones	100% (2)	0	0.76
Middle and Lower Zones	82% (14)	18% (3)	0.38
All Zones	71% (5)	29% (2)	0.224
Pleural Effusion	63% (5)	37% (3)	0.066

Table III: Premorbidies and cause of death of died patients

Pre morbidity	Cause of Death	Number of sample
No premorbid	ARDS	1
Elderly (80 years old)	ARDS	1
Lymphoma/ ALL/ CML	Multi organ failure	3
Decompensated cardiac failure	Multi organ failure	1
Breast carcinoma	Multi organ failure	1
Lung carcinoma	Multi organ failure	1
Renal cell carcinoma	Multi organ failure	1
Ovarian carcinoma	Multi organ failure	1

Table IV: Comparison of disease severity of illness with co morbidity, CXR finding and adverse outcome.

	No. (%)			p value
	Mild	Moderate	Severe	
Severity of Illness	60 (56)	34 (32)	14 (13)	
Co morbidity present	42 (70)	29 (85)	13 (92)	
Abnormal CXR	17 (28)	17 (50)	14 (100)	<0.001
Adverse Outcome	2 (3)	2 (6)	10 (71)	<0.001

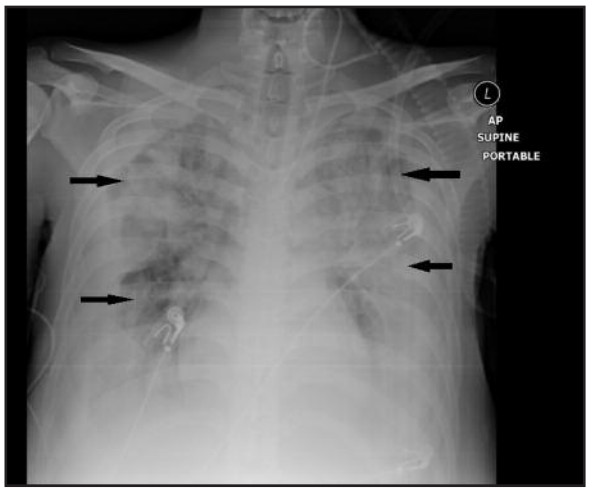

Fig. 1: A chest radiograph shows diffused bilateral lung consolidation involving more than three zones (arrow).

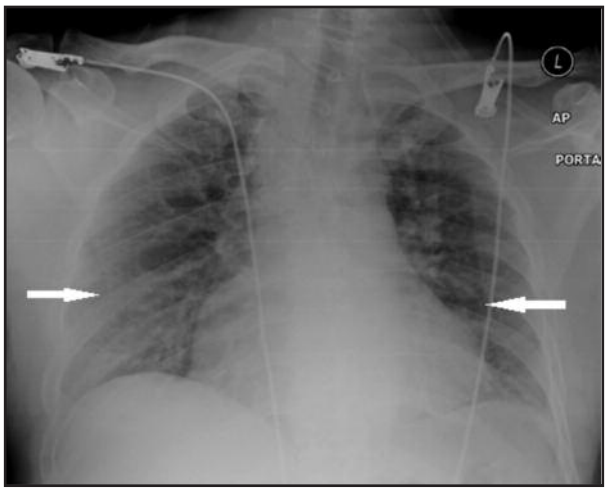

Fig. 2: A chest radiograph shows bilateral ground glass opacities involving both lungs predominantly in the lower zones (arrow).

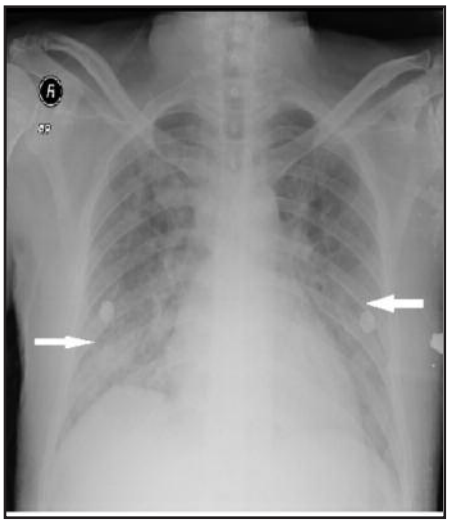

Fig. 3: A chest radiograph shows bilateral interstitial opacities predominantly involves both lower zones (arrow).

RESULTS

The total of 109 patients with PCR-confirmed H1N1 infection was studied. This includes 71 (65%) women and 38 (35%) men; median age is 38 + 18 year old. Of 109 patients who presented with H1N1 related symptoms in this study, all had at least one CXR done.

The initial CXRs were normal in 56% of cases. Out of the 48 patients with CXR abnormalities, consolidation was the common abnormality observed in CXRs present in 50% of cases. The findings from initial CXRs are summarized in Table I.

DISCUSSION

We report a case series of 109 patients with H1N1 infection (2009) of varying radiological findings, degree of severity of illness and disease outcome. In this study, approximately 56% of the initial CXRs in our study were normal, similar to other H1N1 studies. [4,7,8, 10]

The radiographic findings in this viral pneumonia consisted of consolidation, ground glass opacity and interstitial changes. These findings were variable, overlapped and reflect variable extent of the underlying histopathological features. The literature data shows that in S-OIV related pneumonia, the radiographic pattern is consistent with non-specific pattern of viral pneumonia (11). In our study the major radiological abnormalities were consolidation, followed by interstitial opacities and ground glass opacities and mostly located in lower zones. This data is similar to those reported in previous literatures. [4, 7, 8, 10] However our data differ considerably from literature data in which the most prevalent pattern is patchy ground glass opacities followed by consolidation and ground glass opacities but similarly located in lower zones. [5, 6,9]

Consolidations were detected in half of cases in our study and these may represent either a severe viral infection or superimposed bacterial infection.[11] The presence of possible superimposed infection might be the explanation why consolidation was the main radiographic finding in our study instead of patchy ground glass. However, sputum and/or blood culture are not done in majority of our patients to confirm this finding. In our centre empirical antibiotic was given depends on clinical assessment and radiological finding of possible bacterial pneumonia.

The majority of S-OIV infection demonstrated in our study was mild illnesses. However, the pandemic strain of H1N1 virus can cause severe illness, including pneumonia and ARDS. Consistent with experiences elsewhere, co morbidities were more common with increased severity of illness. [13] However 15% patients with moderate illness and 8% with severe illness reported to have no pre-existing medical conditions or risk factor suggesting that prior good health is not necessarily a good discriminator against severe disease. [13]

Data from our study suggests that the symptom of dyspnoea at presentation warrants caution, and may help to predict the severity of illness as well as the need for in-patient care at triage. Thus, clinical finding of tachypnea, low pulse oxymeter and abnormal chest auscultations should also alert the clinician the potential of severe disease.

8 out of 13 patients, who were ventilated, died because of other causes rather than H1N1 infection. Only 3 out of 13 patients died due to ARDS, a complication of the disease. Total of 7 deaths were of various cancer patients. These patients died as a result of multi-organ failure. It is beyond the scope of this study to determine whether chemotherapy can be considered as a risk factor for H1N1 infection. However it is an established fact that a patient receiving chemotherapy is immune-suppress making them susceptible to any form of infection. It is then a possibility that chemotherapy may be a risk factor for H1N1 infection.

This study showed that there is no association between diffused radiographic findings with poor clinical outcome (p=0.083). This is different from other study. [6] However, there is significant association between focal lungs finding in initial CXR and patient with good clinical outcome. An increased severity of illness is associated with abnormal CXR and adverse outcome of disease (p<0.001).

LIMITATION

Our study had several limitations. Only an experienced radiologist in cardio-thoracic field reviewed the chest radiographs. Preferably, two radiologists should review the CXRs and inter observer agreement could be performed. We evaluated only patients with confirmed H1N1 infection, so the group may not be representative of hospitalized patients who may not be tested.

No laboratory confirmation of superimposed bacterial pneumonia was done to the study samples. Thus, superimposed bacterial pneumonia as the cause of lung consolidation cannot be excluded.

CONCLUSION

We conclude that in S-OIV (H1N1), a normal chest radiographs is the most common radiographic finding in S-OIV (H1N1) infection and the most common abnormal lung finding is consolidation. Majority of H1N1 patients have mild illness, a subgroup, which can become critically ill. Co morbidities were more common with increased severity of illness. The presence of dyspnoea and desaturation at triage should heighten the index of suspicion for H1N1 related complications. Initial chest radiographs did not determine the patient clinical outcome and a normal initial radiograph could not exclude adverse outcome. Understanding the correlation between clinical presentations and imaging findings should assist in treating patients during the continuing pandemic.

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