Imaging Spectrum of H1N1 Influenza from a Tertiary Liver Hospital in India: First Ever Experience

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Abstract

Context: To review the imaging spectrum, clinical profile and disease outcome of patients with H1N1 influenza at a tertiary liver hospital

Aim: To review the imaging spectrum, clinical profile and disease outcome of patients with H1N1 influenza at a tertiary liver hospital

Settings and Design: A retrospective analysis of imaging findings of 21 patients with H1N1 flu, admitted to our hospital from September 2014-March 2015, was done.

Methods and Material: All patients with H1N1 virus infection were included. Mode of hospital admission, concomitant liver disease, clinical findings, liver function tests and viral markers for hepatitis B and C infections were studied. Chest imaging findings on CXR or HRCT were analyzed. Correlation with CLD, clinical course, mortality and morbidity was reviewed.

Statistical Analysis Used: Analysis was performed with SPSS version. Mean ± standard deviation (SD), number and percentage, chi-square or Fisher exact test, t-test and odds ratio were calculated as appropriate.

Results: The mean age was 43.52 ± 14.2 years (18 males, 3 females). Positive CXR and HRCT findings were found in 14/21 (66.7%) and 19/21 (90.5%) respectively. Commonest abnormalities observed were bilateral consolidation and ground glass opacities (9/21, 42.9% each). Mid zone distribution was seen in 15/21(71.4%). Underlying CLD was seen in 14/21 (66.7%) with positive findings in 11/14 (78.6%) on CXR and 13/14 (92.9%) on HRCT. Presence of pleural effusion (PE)(57.1%) and lymphadenopathy(50%) were statistically significant ($p<0.05$). Median length of hospital stay was longer: 12 days (IQR 1-30) with significant mortality rate in this group.

Conclusions: Imaging profile of patients with H1N1 influenza revealed that patients with underlying CLD were more likely to have imaging findings, pleural effusion, lymphadenopathy, receive intensive care and longer hospital stay with increased risk for mortality.

Introduction

The recent seasonal outbreak of influenza virus in India has been attributed to the pandemic strain of H1N1 (pdm H1N1).[1] This has claimed approximately 2000 lives in the country and led to a panic situation nationwide.[1-3] Although this has been circulating in India since 2010, a strong resurgence was seen in winter of 2014-15 with higher morbidity and mortality.[4] To our knowledge, this is the first study to correlate various parameters on imaging and clinical presentation in patients with CLD and swine flu. As observed previously, the chest imaging findings in swine flu patients have non-specific appearances varying with the severity of the disease. [5] The aim was to examine the pattern of consolidation, ground glass opacities (GGO's), interstitial-nodular thickening and presence of associated mediastinal nodes, PE in this unique patient population afflicted by H1N1 flu. The clinical outcome and mortality with underlying CLD was studied to discern the observations pattern in this population.

Subjects and Methods

The study was retrospective and included all H1N1 infected patients confirmed by the polymerase chain reaction test (RT-PCR) at our hospital from September 2014-March 2015. Our institutional review board approved the study and informed consent was waived as the study was retrospective and observational. The study period was September 2014-March 2015. Modes of admission were through emergency, outpatient, ward and ICU's. Underlying liver disease was based on clinical findings, liver function tests and viral markers for hepatitis B and C infections. Chest imaging (CXR or HRCT) was performed and findings were studied with respect to their growth during the patient's hospital stay. The radiologist was blinded to the final outcome of the study group. The impact of underlying presence or absence of CLD was analyzed with respect to intensive care, length of hospital stay, morbidity and mortality.

Laboratory Analysis

All CLD patients, who visited outpatient clinics (OPD's) or were admitted with clinical suspicion of H1N1pdm were included in the study. Two throat swabs in viral transport medium or endotracheal aspirate from mechanically intubated patients were collected and laboratory diagnosis was made by rRT- PCR as per CDC guidelines 2009.[6] All samples were tested for H1N1pdm virus using universal primers and probes for influenza A as well as H1N1pdm strain using specific primers and probes with Roche Light Cycler 2.0 rRT-PCR system, as described previously by Panning et. Al.[7] Samples were also tested for human RNAseP gene to rule out false negative cases. RT-PCR has good sensitivity and specificity compared to viral culture, with lower limit of this assay being 101.6 TCID50 /ml.

Radiological Evaluation

Portable radiographs were performed using 14" x 17" flat panel

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Table 1: Clinical outcome and Imaging predictors for H1N1 influenza in the study group

Parameter	Patients with CLD	Patients without CLD	P Value
Age	48.6 ± 13.4	33.4 ± 10.0	0.01
Gender (M:F)	92.9%	71.4%	0.25
CXR positive	78.6%	42.9%	0.19
HRCT findings positive	61.9%	33.3%	0.16
Pleural effusion	57.1%	0.0%	0.02
Mediastinal Lymph nodes	50.0%	0.0%	0.05
Emergency admission	7.1%	42.9%	00.19
Ward admission	21.4%	14.3%	
ICU admission	71.4%	42.9%	
Hospital stay	Median 12 (Range 1-30)	Median 5 (2-45)	0.39
Mortality	64.3%	0.0%	0.007

Abbreviations: CLD- Chronic liver disease; HRCT- High resolution computed tomography; ICU- Intensive care unit

detector (Shimadzu) with scintillator & amorphous silicon method.

Multi detector CT scanner (Discovery 750HD, GE healthcare, USA) was used to perform HRCT chest scan from lung apices to the costophrenic sulci in helical mode with the given scanning parameters: 120 kVp, 90–115 mA, 4×2-3-mm collimation, 28–32cm field of view, 512×512 matrix size. Scan data was reconstructed at slice thicknesses and intervals of 1.5mm and displayed with high-spatial-frequency reconstruction algorithm, mediastinal (window width 350 HU; level 40 HU) settings.

Imaging Analysis

Pattern and symmetry of lung involvement in the form of GGO, dense consolidation, nodules and interstitial thickening was studied on each side of the chest, in relation to three zones (upper, middle and lower). The presence of mediastinal lymphadenopathy and PE (unilateral or bilateral) was recorded. Lung changes during admission and disease course during the hospital stay were recorded.

Statistical Analysis

Analysis was performed with SPSS version 16 (Released 2007. SPSS for Windows, Version 16.0 Chicago, USA). The quantitative variables were determined by mean ± (SD) and the

Table 2: Predictors of imaging findings in patients of H1N1 for patients with underlying Liver disease

Imaging Findings on CXR and CT chest	Patients without CLD N=7	Patients with CLD N=14
No consolidation	57.1%	35.7%
Bilateral Consolidation	28.6%	50.0%
Unilateral Consolidation	14.3%	14.3%
Upper zone	14.3%	21.4%
Middle zone	42.9%	85.7%
Lower zone	57.1%	57.1%
Ground glass opacities present	14.3%	57.1%
Dense air space opacification	28.6%	42.9%
Nodules	14.3%	28.6%
Progressive changes on Imaging	42.9%	64.3%
Symmetrical pattern	57.1%	50.0%
Asymmetrical pattern	42.9%	50.0%

categorical variables were shown with number and percentage. The comparison between CLD and non CLD groups was performed by chi-square or Fisher exact test as appropriate. The t-test was also applied to compare continuous data. Besides this, the odds ratio was also calculated. The p value < 0.05 was considered significant.

Results

Total of 21 patients were admitted to our hospital with confirmatory RTPCR for H1N1 flu and their clinical outcome and imaging predictors were analyzed (Table 1). The mean age of patients was 43.52 ± 14.15 years (18 males and 3 females). More number of males (13/18, 92.9% Vs 1/3, 33.3%) were found affected by swine flu compared to females (p>0.05). Swine flu patients with CLD were older than their non CLD counterparts (48.6±13.4 Vs 33.4±10 years) and this parameter was statistically significant (p<0.05). Fourteen (66.7%) of the above 21 patients had underlying CLD. Hospital admission and stay of 4/21 (19%) patients was through emergency, 4/21 (19%) into wards and 13/21 (62%) to (ICU's). Patients in ICU and wards were asymptomatic for respiratory infection at the time of admission and were found to be H1N1 positive after laboratory testing. Majority (71.4%) of the patient's admitted to ICU's were H1N1positive with underlying CLD, although this number was not statistically significant. Imaging predictors in H1N1patients with and without CLD were studied (Table 2).

CXR was positive in 14/21 (66.7%) patients of which majority 11/14 (78.6%) had underlying CLD. Patients with positive findings on CXR without associated CLD were 3/14 (43%) in number. HRCT was performed in 11 patients in the total study group. Out of these, 9/11 (82%) patients showed positive findings. Of these, 8/9 (88.9%) patients had underlying CLD. Presence of PE and mediastinal lymphadenopathy on CXR and HRCT was statistically significant in the CLD group compared to the non CLD group (p<0.05). The average hospital stay was 12 (range 1-30) days for CLD group and 5 (range 2-45) days for non CLD group, hence significant.

The overall mortality was 9/21 (43%) patients. Out of these, all patients 9/9 (100%) had underlying CLD. This was a statistically significant (p=0.01) marker, predicting higher mortality and morbidity in this subgroup.

All patients were treated with antiviral therapy and antibiotics with corticosteroids based on clinical requirement and supportive measures. The patients who recovered were discharged in few days without any residual respiratory symptoms on follow up.

Discussion

H1N1strain of Influenza A was first recorded, 8years ago in Mexico, which soon expanded to various parts of the world where its severity and impact on mortality began to make a global impact. In 2009, WHO declared it as the highest level pandemic which was later considered to be manifesting in the post-pandemic form after a yearlong duration[5]. The presently ongoing resurgence in India observed in year 2014-15 was much more severe than the one observed in year 2009-10.[1] A recent subcontinent study found that the reasons for this could be related to northwestern states temperature in the winter months where the virus shows higher incidence in other parts of the country as well[1]. In addition, the role of host immunity, recommendation for vaccination and possibility of drift virus causing the above resurgence has been pointed out [1-3]. The present study was conducted to investigate the

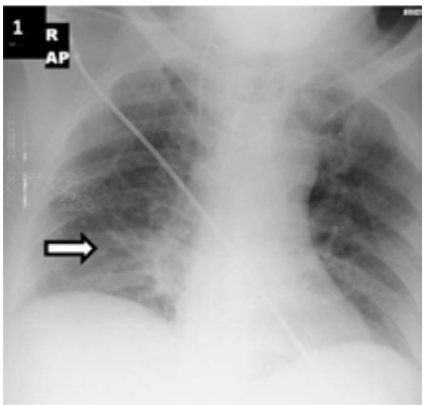

Fig. 1: 48 year old male with CLD admitted to the ICU for fever and constitutional symptoms for a period of 8 days. CXR showing an area of ill defined parenchymal opacity – likely consolidation (bold arrow) at day 4 of admission

pdm H1N1 strain impact on patients. The chronicity of liver disease, often leads to a state of immunocompromise within these patients. Currently, this flu is predicted to recur every 1-2 years with rise in mortality in the ongoing resurgence itself.[1] It is hence, essential to study the various indicators and predictors on imaging modalities such as CXR and HRCT, which are widely available at most of the centers where this patient population is referred.[5,7] Various international study groups have reported imaging findings of H1N1 flu in adult and pediatric populations with predominantly bilateral and extensive abnormalities on CXR and CT in majority of patients.[5,7]

Some groups reported lung zone predominance, of lower lobe and consolidation pattern as the commonest lung parenchymal involvement in their study.[8] Another group reported right upper lobe pneumonic presentation.[9] Pediatric studies showed a different spectrum of disease severity due to the vulnerable immune status of children 'per se' for the disease, however radiological findings showed variable areas of consolidation in both or single lung parenchyma with assisted ventilation required for severe disease in majority of cases.[10] Complications of H1N1 flu in the form of pneumothorax, cavitating lung and bronchiectasis has been reported in some studies.[11]

Recent reports portrayed that, in comparison to patients with non H1N1 flu, patients with swine flu had more severe, patchy, peripheral parenchymal

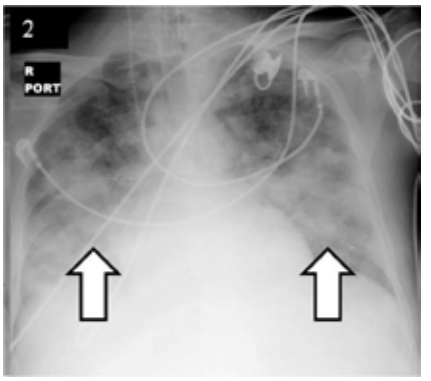

Fig. 2: 29 year old male patient with CLD admitted to the ICU for a week with rapidly progressive dyspnea. Sequential portable CXR's were performed: Bilateral extensive fluffy, consolidated air space opacities (vertical bold arrows) involving both and mid zones of the lung upper parenchyma on days 6-8 of admission with acute respiratory distress syndrome leading to death of the above patient on day 8

lung opacities on CXR with longer hospital stay.[12] This disease spectrum with CLD was reported as a case series of 5 patients from the author's institute, who were admitted to the ICU and succumbed to the disease despite intensive care and anti viral therapy in the last annual flu outbreak.[13] This group could not, however, characterize the disease through radiographic findings because of the small sample size. The existing literature showed visible lacunae in study of H1N1 flu in patients with CLD. Amongst our patient group, symptomatic and RT-PCR proven group of H1N1 patients, without any lung parenchymal changes or consolidation on imaging constituted 36% of all patients (Figure 1) in the CLD group and 57% patients in the non CLD group. Hence lung changes are more common in the CLD group with H1N1; however it is not mandatory for all patients with swine flu to present with extensive parenchymal findings on imaging. This data also showed that patients with bilateral extensive consolidation were more commonly seen in CLD group (50%) versus non CLD group (30%) (Figure 2). Thus patients with immunocompromised status or CLD are l ? more prone to extensive consolidation, compared to rest of the population.

As reported by an Italian group, H1N1 cases show unilateral or bilateral

Fig. 3: Axial sections of a HRCT chest showing no obvious parenchymal abnormality in a 30 year old male patient admitted for fever and constitutional symptoms, without CLD, with H1N1 positive flu at day 3 of admission

GGO's on imaging which may or may not be associated with focal or diffuse areas of consolidation.[14-16] Contrarily our study revealed that bilateral lung consolidation was more common in 9/21 (43%) patients, whereas unilateral changes were present only in 3/21 (14%) patients. Another British report suggested that imaging findings are uncommon in swine flu; however we found that positive imaging findings were more often seen (54%) versus in (43%) patients who did not have any imaging abnormality[15,17] (Figure 3). Most studies have reported mid and lower zone lung parenchymal involvement with absence of PE or lymphadenopathy on imaging.[5,7,18] Our patient group manifested a definite overall preponderance of mid zone involvement (15/21, 71.4%) with odds ratio of 8.00 (0.96- 66.4)*, in the CLD Vs non CLD group. Overall involvement of lower and upper zone was 57.1% and 19% respectively. Odds ratio for lower and upper zone involvement of CLD versus non CLD were 1(0.16-6.3) and 1.6(0.1-19.4) respectively (Figure 4).

Presence of PE and lymph nodes showed statistical significance in the CLD versus non CLD group (Figures 5, 6), as compared to other studies which have shown absence of both in H1N1 patients.[19-21] A study even suggested that lack of both the above factors favors' the diagnosis of H1N1 infection.[7] This finding was unique since no previous groups found the above to be significant predictors in their disease population. Hence, our results indicate that pleural fluid and mediastinal nodes along with other parenchymal abnormalities should be considered when reporting cases of

swine flu in patients with concomitant CLD or immunocompromised status, to complete the checklist of thoracic imaging features.

Our study revealed that GGO's were present in 9/21(43%) patients. Odds ratio for GGO in CLD versus non CLD group was 8 (0.8-85.3)* (Figure 6b). Various groups have reported GGO as the commonest finding on chest imaging in H1N1 patients.[22] In our group, this finding was second to lung consolidation. Basically the CLD group showed a higher preponderance for both GGO and consolidation compared to the non CLD group.

Similar results were seen for dense air space opacities with odds ratio of 1.9 (0.3-13.2)* for CLD versus non CLD group and parenchymal lung nodules with odds ratio of 2.4 (0.2-26.8)* for the CLD group; however we have studied the unique profile of patients with H1N1 to our sub-specialized liver hospital.[22,23] A study from Italy regarding H1N1 in cirrhotic patients reported that the propensity to develop an influenza was no different in cirrhotic versus non cirrhotic groups, however mortality was higher in the cirrhotic group [24]. The number of patients in this group was minimal (mortality in 3/21 patients with cirrhosis). Another study group has discussed impact of Influenza on pre existing cirrhotic patients.[25] Progressive disease on radiographs was noted in 12/21 (57.1%) patients in our group.

The average hospital stay was longer in the CLD group 12(IQR 1-30) versus 5 (IQR 2-45) days. The mortality rate was found significantly higher ($p<0.05$) in the CLD group (64.3% Vs 0.0%).

The above markers of morbidity and mortality indicate that CLD patients versus non CLD are more likely to develop prolonged illness and succumb to disease complications despite intensive care in the hospital.

Our study limitation, was the small number of observations during the study period, due to the sub specialized group of patients presenting to our Institute.

Conclusion

The imaging profile revealed that CLD patient with H1N1had higher probability of positive imaging findings, more widespread consolidation (predominantly in the middle zones) and showed significant association with PE and lymphadenopathy. Patients with CLD showed higher odds ratio for presence of GGO's, dense consolidation, lung nodules, asymmetrical pattern and disease progression on imaging. These patients were also more likely to receive intensive care, had longer hospital stay and despite intensive therapy showed a higher risk for mortality.

*Not statistically significant but clinically important observation.

Key Message

The recent seasonal outbreak of influenza virus in India in the year

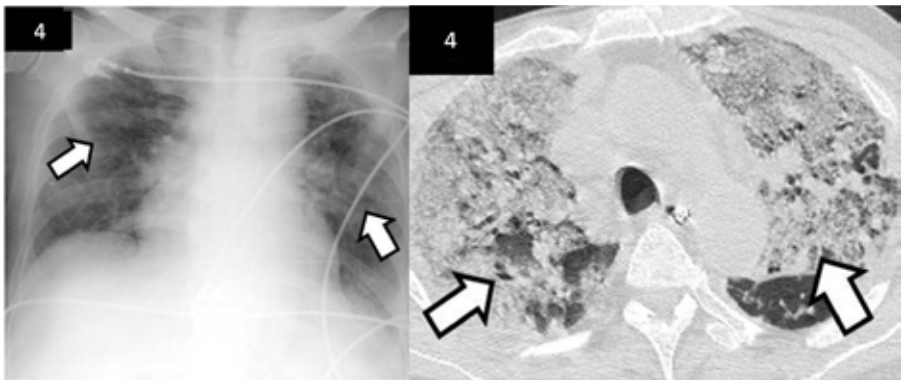

Fig. 4: CXR showing bilateral mid and upper zone involvement (bold white arrows) and axial section of a HRCT showing dense air space opacification in both upper and middle lobes of lung parenchyma (white with black outlined arrows) in a 50 year old male who presented with respiratory distress and underlying CLD admitted to ICU with H1N1 positive

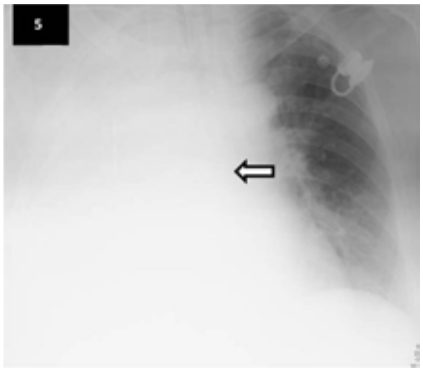

Fig. 5: CXR of a 30 year old male patient with underlying CLD, admitted to the general ward for constitutional symptoms of swine flu with positive H1N1 results, showing opaque hemithorax on right side (arrow) due to massive pleural effusion and underlying lung collapse

Fig 6: Axial sections of CT of the chest and upper abdomen in a 45 year male who presented with mild cough, fever and constitutional symptoms with underlying CLD admitted to general ward with H1N1 positive results showing mediastinal lymph nodes (white arrow with bold black outline), mid zone ground glass air space opacification on the right side (bold white arrow) and irregular liver contours (black arrow)

2014-15 showed a strong comeback in the form of resurgence in winter by the pandemic strain of H1N1 flu with higher morbidity and mortality experienced than ever before. The outbreak claimed approximately 2000 lives in the country as a whole and led to a panic like situation nationwide. On this backdrop, we have tried to analyze the impact of underlying liver disease on imaging findings and clinical course of patients affected by Swine flu at our tertiary liver care hospital. To our knowledge, this is the first study to correlate various parameters on imaging and clinical presentation in patients with concomitant liver disease and swine flu. The clinical outcome and mortality of the patients with and without chronic liver disease have been studied to compare the pattern of observations in this population.

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