Retrospective Analysis of Necropsy Findings in Patients of H1N1 and their Correlation to Clinical Features

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Abstract
India reported its first case of H1N1 in July 2009 in Pune and since then, the number of reported cases and deaths exploded in India. Since very little data is available about histopathological findings in patients of H1N1 fatal cases in India, a retrospective chart analysis of necropsy findings of 15 cases of 2009 H1N1 fatal cases was performed. Common clinical features were fever, cough, and breathlessness followed by sore throat and rhinorrhea. Common lung findings were mononuclear cell infiltration, thick alveolar septa, intraalveolar hemorrhage. The other findings were congested pulmonary blood vessels, pulmonary edema, cytomegaly, fibrin accumulation and formation of eosinophilic membrane. These findings are suggestive of diffuse alveolar damage (DAD) and DAD with hemorrhage. All patients who underwent necropsy had radiographic findings suggestive of unilobar or multilobar pneumonia. This clinical finding can be correlated pathologically in these patients as all of them had either polymorphonuclear or mononuclear infiltrate. Furthermore, necrotizing pneumonitis pattern seen on these patients is the likely cause of mortality in these patients. Although clinical ARDS pattern was noted in all these patients, it was well correlated in lung pathology in all these cases.

Introduction
The first two cases of H1N1 influenza were confirmed by the centers of disease control and prevention (CDC) on April 21, 2009 in children from California who reported febrile respiratory illnesses.1 When the Mexican Ministry of Health reported an increase in severe pneumonia cases and deaths in young adults in April of 2009, CDC confirmed that it is due to the same strain of the virus.2-3 On June 11, 2009, the World Health Organization raised the pandemic alert level to phase 6, indicating that a global pandemic had began.4 As of September 20, 2009, human infection with 2009 H1N1 virus had been identified in 191 countries and territories.5

A recent meta-analysis showed that 2009 pandemic influenza has affected 30% of children less than 18 years and has resulted in ICU admissions and deaths in 35% and 13% of patients respectively.6 Evaluations by CDC of lung specimens of 77 fatal cases revealed that 29% had a bacterial co-infection.7 A recent autopsy report from Brazil also showed that in fatal H1N1 cases, pathology is restricted to lungs.8

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Methods
We conducted a retrospective chart analysis of all 15 fatal cases of H1N1 influenza over the age of 12 years who had necropsy performed between August 2009 and November 2009 in BJ Medical College (BJMC) and Sassoon General Hospital (SGH), Pune, India. Institutional ethics committee approval was obtained.

Data Collection
All clinical data were collected by reviewing the medical charts from BJMC-SGH. We collected demographic and clinical characteristics of all fatal cases of H1N1 influenzae during the study period. A person was defined as infected with 2009 H1N1 influenza based on laboratory confirmation of the presence of H1N1 specific viral nucleic acid in a sputum or nasopharyngeal specimen collected at any time during hospitalization. All patient specimens were sent to the National Institute of Virology (NIV), a national reference virology laboratory in Pune, India, where reverse-transcriptase PCR assay was performed, according to the protocol recommended by the U.S. Centers for Disease Control and Prevention (CDC).9

Tissue Preparation
Necropsy was performed in BJMC-SGH pathology department. Both lung and liver tissue was processed to identify pathology. Tissue fragments were formalin-fixed, paraffin-embedded, and hematoxylin and eosin-stained.

Results
Fifteen patients died during the study period and necropsy of lung and liver were performed. The demographic and clinical characteristics of these patients are shown in Table 1. The median age was 34 years (range 13-50 years), and 40% were females and 60% males. Sixty percent of patients had one or more of co-morbidities. The most common co-morbidity noted in fatal cases were pregnancy, obesity, Rheumatic Valvular Heart Disease (RVHD), Chronic Obstructive lung disease (COPD), and Cerebrovascular Accident (CVA). The most common symptoms at presentation in decreasing order were fever, cough and shortness of breath. The most common radiologic findings were fluffy infiltrates followed by confluent opacities. Most of the patients had PO2 < 60 on admission and 2 patients had PO2 > 60 while PO2/FiO2 ratio in all patients was less than 150 suggestive of (acute respiratory distress syndrome) ARDS.

All these patients were mechanically ventilated, 40% of patients died within 48 hours of hospitalization while 60% of patients were mechanically ventilated for >48 hours before death.

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The changes on patients who died within 1-4 days of hospitalization were mononuclear cell infiltration, congested pulmonary blood vessels, large giant cells, pulmonary edema, fibrin accumulation, desquamation and ARDs. Common histopathological findings beyond 4 days of hospitalization were thick alveolar septae, lung collapse, polymorphonuclear infiltration.

Upon comparing the clinical features with necropsy, 33% patients who presented with hemoptysis also had intraalveolar haemorrhage. All patients had mono or polymorpho nuclear infiltrates consistent with pneumonia on radiography. All the cases showed ARDS on blood gas examination, with involvement of more than 3 segments on radiography in 80% of cases but on necropsy only 2 patients had ARDS.
Discussion

Our report on necropsy findings of fatal cases of H1N1 influenza shows that these patients had mononuclear cell infiltration, thick alveolar septae, and intra alveolar haemorrhage. The other findings were congested pulmonary blood vessels, pulmonary edema, cytomegal, fibrin accumulation and formation of eosinophilic membrane. These findings was suggestive of diffuse alveolar damage (DAD). This report is the first report from India describing lung and liver pathology in patients who died secondary to 2009 H1N1.

The median age of our fatal cases were 34 years and is similar to prior reports. The clinical features of these patients were comparable with previous reports of 2009 H1N1influenza.8,9 In consistent with previous reports, 60% of our fatal cases had a co-existing condition. Majority of our patients showed clinical picture consistent with ARDS.

Viral infections can cause bronchitis, bronchiolitis and pneumonia. Most viruses that cause pneumonia infect epithelial cells exclusively or in addition to infecting other cells. The predominant tissue response is interstitial pneumonia. The walls of air spaces are thickened by edema, congestion and an infiltrate of mononuclear cells. The air spaces contain edema, fibrin and scanty cellular exudates of monocytes, macrophages, occasional neutrophils and sloughed epithelial cells.10

In fatal cases, hyaline membrane are usually present along alveolar spaces. Alveolar epithelial cells are enlarged and hyperplastic. Patients who have been ill for some days show signs of repair and organization similar to organizing bacterial pneumonia such as exudate in alveolar space being invaded by fibroblasts and converted to buds of fibrous tissue similar to bacterial pneumonia. Foci of hyperplasia and metaplasia to a squamous or bronchiolar type are found in alveoli. Discrete foci of necrosis are also seen.10

The present study shows that H1N1 caused extensive involvement of the lungs, and the changes range from mononuclear cell infiltration to formation of hyaline membrane and thick alveolar septae. These findings are suggestive of diffuse alveolar damage (DAD). As a result most of the patients presented with extensive pneumonia and ARDS. These findings were also reported in previous autopsy report from Brazil as well as previous pandemics.8,11-19 The liver changes noted in our series are mainly limited to fatty changes and portal triaditis which is not a primary consequence of viral infection.

In our series, 4 women were pregnant and showed evidence of extensive lung involvement. The major pathology noted was same as non-pregnant patients. These changes were also noted in prior reports.6

All patients who underwent necropsy had radiographic findings suggestive of unilobar or multilobar pneumonia. This clinical finding can be correlated pathologically in these patients as all of them had either polymorphonuclear or mononuclear infiltrate. Furthermore, necrotizing pneumonitis pattern seen on these patients is the likely cause of mortality in these patients. Although clinical ARDS pattern was noted in all these patients, it was not well correlated in lung pathology in all these cases.

The main limitation of our study is that we do not have data on the presence of bacterial co-infection on necropsy specimens. However, the correlation between presence of neutrophils and bacterial infection is established.10,11 The other main limitation is that we did not perform complete autopsy of these fatal cases. Since the study is retrospective in nature thus clinical comparison may be limited and biased. Despite these limitations, to our knowledge, our study is the first study describing the lung pathology in adult H1N1 fatal cases in India.

In summary, the extensive lung involvement in H1N1 infection is the likely cause of mortality in adult H1N1 cases. Our report adds to the current literature on natural progression of H1N1 infections as well as lung pathology in fatal H1N1 infection cases.

References

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