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Interesting post-mortem findings in a H1N1 influenza-positive pneumonia patient

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ABSTRACT

Reports of histopathological findings in a patient infected with H1N1 influenza virus are limited in the literature, although many deaths have occurred because of this viral infection. In an otherwise healthy individual with no underlying co-morbid conditions, this virus passes off as a very mild disease. However, it can be fatal in the presence of underlying risk factors. Here, we present the autopsy findings of a patient who died of H1N1 infection, but who was apparently healthy with no predisposing ailments. The autopsy revealed chronic kidney disease and caseating granulomatous lymphadenitis in addition to the known classical diffuse alveolar damage picture seen in this condition. These underlying co-morbidities may provide greater insight and a better understanding of this infection.

Keywords
Autopsy; Renal Insufficiency; Granuloma; Influenza A Virus, H1N1 Subtype

Key messages: Understanding the pathology of H1N1 influenza will give a better awareness of the novel unrecognized risk factors that will help reduce fatalities in the near future by triaging high-risk patients and preventing life-threatening complications.

INTRODUCTION

H1N1 is an influenza virus, which predominantly causes respiratory illness in humans. India reported its first case of H1N1 in July 2009.\textsuperscript{1}

Influenza has been well recognized as a human illness since the Middle Ages.\textsuperscript{2} Influenza affects the human race in two ways: periodic (the most common) and pandemic (the most dreaded). Pandemics are generally associated with the influenza A virus breeds, which express newer forms of the hemagglutinin (H) molecule.\textsuperscript{2,3}

The interesting aspect of the H1N1 pandemic is that the fatal cases have disproportionately affected young to middle-aged adults, and surprisingly, many of them lacked the known risk factors for life-threatening complications from influenza infection. The histopathological findings described concerning H1N1 are related exclusively to postmortem studies in the literature.\textsuperscript{4-8} We present the autopsy findings with their clinicopathological correlation in an H1N1-positive, healthy, middle-aged male, to further detail the features of this lethal but unique H1N1 influenza virus infection.

CASE REPORT

A 43-year-old man, a reformed alcoholic, presented to the hospital with complaints of sudden onset breathlessness and fever of 3 days’ duration.

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Examination showed the room air arterial oxygen saturation (SpO2) of 80%. All other vital parameters, such as blood pressure and pulse, were within normal limits. A chest x-ray revealed bilateral pneumonitis. After 2 days, with worsening respiratory distress, he was intubated and transferred, on a ventilator, to our tertiary care set-up with a working diagnosis of viral pneumonia, possibly H1N1 related.

At our hospital, he continued to be on mechanical ventilation and was given antivirals and antibiotics. On hematological evaluation, he had normal hemoglobin levels. However, he had leukopenia (leukocyte count = 2,700/mm³). The biochemical evaluation revealed normal liver and renal function (serum bilirubin 0.7 mg/dL; blood urea 37 mg/dL; serum creatinine varied from 0.9 to 1.1 mg/dL during the 4 days of hospitalization). Urinalysis was tested once and was unremarkable. The biochemistry parameters were repeated on a daily basis, and the tests were run on an automated analyzer after running the requisite daily internal quality control tests.

However, his health gradually deteriorated, and he was put on inotropic support owing to hypotension. An antemortem nasopharyngeal swab sent to a reference laboratory confirmed positivity for H1N1 virus via real-time polymerase chain reaction (RT-PCR). On day 6 of hospitalization, he suffered cardiac arrest.

AUTOPSY FINDINGS

The autopsy, which was performed on the day the patient died (prior to the availability of the RT-PCR results) showed the deceased to be averagely built and well nourished. The thoracic cavity drained two liters of serous pleural effusion bilaterally. Pre-tracheal and carinal lymph nodes were found to be enlarged, measuring 2 × 1 × 1 cm. However, there was no generalized lymphadenopathy. Both lungs were heavy and boggy; the heart and liver appeared grossly unremarkable; splenomegaly was present; and the kidneys were bilaterally scarred and contracted, measuring 9.5 × 4 × 3 cm (right) and 9 × 4 × 2.5 (left), with partially maintained cortico-medullary differentiation. Cytological analysis of the pleural fluid showed a predominant lymphocyte picture.

Histopathological examination of both lungs (Figure 1) showed septal inflammation, congestion, and thickening of alveolar septae. In addition, other features of diffuse alveolar damage (DAD) were seen, which included marked intra-alveolar hemorrhage, reactive hyperplasia of type II pneumocytes, and hyaline

Figure 1. Photomicrograph of the lung. A – A massive intra-alveolar hemorrhage (asterisk) (H&E, 40X); B – Desquamation of bronchiolar epithelium (arrowhead) and necroinflammatory slough in the lumen (H&E, 100X) (asterisk); C – Presence of hyaline membrane (H&E, 400X) (arrows); D – The sloughing off of the bronchial epithelium (H&E, 100X).
membrane formation. Evidence of bronchitis was present focally in the form of epithelial ulceration along with plugging of the lumen with necroinflammatory slough, and submucosal inflammatory infiltrates. No foci of granulomas were found in lung sections.

The pre-tracheal and carinal lymph nodes showed caseating epithelioid cell granulomas (Figure 2A and 2B). No acid-fast bacilli or fungal elements could be demonstrated on Ziehl-Neelsen or fungal stains, respectively, and reticulin stain ruled out the sarcoid origin. We found focal myofibril degeneration and interstitial fibrosis in the sections from the heart (Figure 2C and 2D).

Microscopic examination of the liver showed areas of centrilobular necrosis, spotty necrosis, and mild periportal lymphocytic inflammation (Figure 3A). Sections from the spleen revealed congestive splenomegaly with red pulp expansion. Sections from both the kidneys showed evidence of renal tissue injury in the form of glomerulosclerosis in many glomeruli (around 50-60%), thyroidization of the renal tubules, and lymphocytic interstitial infiltrate (Figure 3B). The large vessels in the renal parenchyma revealed Monckeberg medial sclerosis.

**DISCUSSION**

Our patient was a middle-aged, apparently healthy male with no known underlying co-morbid conditions, such as obesity, chronic airway diseases, hypertension, smoking, or malignancy, which could have predisposed him for the development of severe, life-threatening H1N1 disease. Therefore, the main goal of the autopsy was to identify any antecedent risk factors or cryptic co-morbidities.

In a study of 21 patients by Mauad et al., features of DAD were found in 20 of them, of which 6 were associated with necrotizing bronchiolitis, and 5 with extensive hemorrhage. They also discovered viral cytopathic effects in the bronchial and alveolar epithelial cells along with the expression of markers, such as TLR-3, IFN-γ, CD-8, and granzyme.

In a study of 15 patients of H1N1 pneumonia in Pune, India, Prasad et al. emphasized that the histopathological findings were typically localized to the lungs, which included features of DAD in the form of mononuclear and neutrophilic infiltrates, thickened alveolar septae, intra-alveolar hemorrhage, congested pulmonary vessels, pulmonary edema, hyaline membrane formation, and desquamation of the epithelium of the bronchioles.

![Figure 2: A and B – Photomicrograph of a carinal lymph node showing caseating granuloma (arrow) with a multinucleate giant cell (arrowhead) (H&E, 100X); C and D – Photomicrograph of the heart showing myofibril degeneration (arrowhead) and fibrosis (arrow) (H&E, 100X and 400X, respectively).](image-url)
The pulmonary pathology findings in our patient are corroborative. However, the only extra-pulmonary finding reported by Prasad et al. was fatty change along with mild portal triaditis of the liver.1

Bal et al.5 studied a series of nine autopsies of proven H1N1 pneumonia and discovered that apart from lung involvement, the majority of their patients showed centrilobular hemorrhagic necrosis in the liver; and two of them showing changes of acute tubular necrosis in the kidneys. They also found hemophagocytosis in the reticuloendothelial system. We did not find any histopathological evidence of hemophagocytosis in our patient.

In a study of 46 patients by Shelke et al.,4 areas of spotty or focal hepatic necrosis and acute tubular necrosis were observed in addition to the classical picture of DAD lungs. As well as spotty necrosis of the liver, we found centrilobular necrosis. We did not find any association of chronic kidney disease with H1N1 influenza on a detailed review of the literature; neither have we come across a case of H1N1 influenza being reported along with an underlying caseating granulomatous lymphadenitis. Our case seems to be the first one reported with such an extrapulmonary histopathological feature.

H1N1 infection is associated with the classical picture of DAD in the lungs. In our patient, the underlying medical renal disease and caseating granulomatous pathology may have significantly contributed to the progression of the disease, possibly by acting as inciting factors. More studies are required to find out if there is any association at all between the renal pathology and the chronic caseating granulomatous lymphadenitis, as either of these or both may, at some point, have led to immunosuppression.

**Figure 3.** A – Photomicrograph of the liver showing centrilobular necrosis (asterisk) (H&E, 100X); B – Photomicrograph of the kidney showing glomerulosclerosis (arrow) and thyroidization of the tubules (arrowhead) (H&E, 100X).
H1N1 infection, being superimposed on a case of caseating granulomatous lymphadenitis possibly tuberculosis infection in an Indian setting, leading to a rapidly fatal outcome should be kept in mind in our country. It is suggested that, in India, tuberculosis be considered as a high-risk factor in H1N1-positive patients.

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