ORIGINAL RESEARCH PAPER

Volume-8 | Issue-4 | April-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

RARE INSTANCE OF CO-INFECTION WITH CYTOMEGALOVIRUS AND ASPERGILLUS IN A CASE OF H1N1: A CASE REPORT

Pathology

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ABSTRACT

Co-infections in H1N1 patients have higher complication rates. Our patient with H1N1 pneumonia presented with a unique combination of Aspergillus and CMV co-infections. Histopathological features of H1N1 were examined on the post-operative surgical specimen in our case, rather than on autopsy specimens as in the case of most studies in the literature. Features characterisitic of H1N1 virus were observed in the lobectomy specimen along with detection of fungal hyphae and incidental detection of cytomegaloviral inclusions. However, in the post-operative phase, the patient developed pneumatocoele and persistent air leak and finally succumbed. A high index of suspicion is necessary to identify such possible associations and prompt early appropriate management.

KEYWORDS

Alveolar haemorrhage, Aspergillosis, Coinfection, Cytomegalovirus (CMV), H1N1, necrotising bronchiolitis, Swine flu

INTRODUCTION:

In 2009, Mexico witnessed a respiratory illness caused by a novel influenza A virus of swine origin (S-OIV) which later evolved into a pandemic resulting in several thousand deaths.[1] As the laboratory tests specifically target H1N1 during epidemics, the clinicians may assume the etiological agent to be a single virus. However, other bacterial, viral and fungal co-infections may contribute to significant morbidity and mortality in such patients.

CASE REPORT:

A 5 year old boy presented with severe respiratory distress, for which high-frequency oscillatory ventilation (HFOV) support was given. The condition of the child improved in 48 hours. The endotracheal secretions submitted were positive for H1N1 following which oseltamavir was started. On the fifth day after admission, the child developed pneumothorax with persistent air leak and needed HFOV. Antifungals were started and autologous blood patch pleurodesis was done. Computed tomogram of the chest showed diffuse consolidation of left lung with pneumatocele and patchy consolidation of right lung (Figure1). In the third week of admission, bronchoscopy revealed white flakes over bronchi with mucus impaction which was cleared. On culture of bronchoalveolar lavage (BAL) fluid, Aspergillus was isolated. A repeat CT chest performed in the fourth week showed necrosis of the left lower lobe. CSF culture revealed Aspergillosis. The worsening prognosis was explained to the parents and left lower lobectomy was performed.

Macroscopic examination of the lobectomy showed exudate on the pleural surface and the cut surface showed variably sized firm, grey white and yellow necrotic areas. The parenchyma appeared solid and non-crepitant (Figure1).

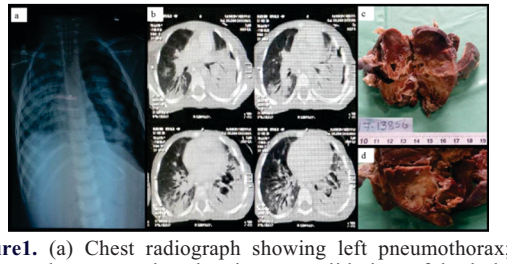

Figure1. (a) Chest radiograph showing left pneumothorax; (b) Computed tomography showing consolidation of both lungs, predominant in the left lung and pneumatocele in the left lung; (c,d) Gross photographs of lobectomy specimen –Cut surfaces show solid parenchyma with necrotic areas.

Histopathological examination of the lung parenchyma showed extensive alveolar haemorrhage and large foci of necrosis with associated neutrophilic infiltrate consistent witn necrotising alveolitis. Necrotising bronchiolitis with an ulcerated bronchiolar lining and neutrophilic aggregates within were noted. The interstitium and alveolar spaces showed a dense infiltrate of neutrophils, lymphocytes, plasma cells and foamy histiocytes. These features were consistent with changes seen in infection by H1N1 (Figure2). Few pneumocytes showed nuclear and cytoplasmic inclusions suggestive of cytomegalovirus (CMV) which was confirmed by immunohi stochemistry. Periodic Acid Schiff (PAS) and Grocott Methenamine Silver (GMS) stain showed few septate hyphae with acute angle branching suggestive of Aspergillus (Figure3).

A couple of days (4weeks after admission) after the surgery, the child developed air leak, bradycardia and hypotension, and could not be revived.

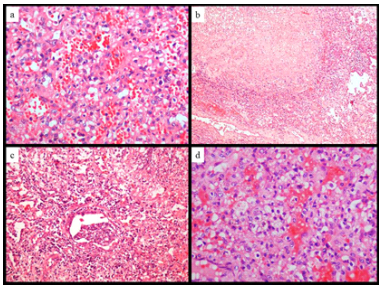

Figure2. Histopathological features: (a) Extensive alveolar haemorrhage (HE, 40x); (b) Foci of necrosis (HE, 10x); (c) Necrotising bronchiolitis (HE, 20x); (d) Aggregates of foamy histiocytes (HE, 40x).

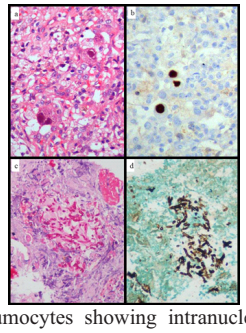

Figure3. (a) Pneumocytes showing intranuclear and cytoplasmic inclusions (HE, 40x); (b) Pneumocytes positive for cytomegalovirus

immunohistochemistry (40x); (c) Septate fungal hyphae showing acute angle branching (Periodic acid Schiff, 40x); (d) Fungal hyphae (Grocott Methenamine Silver, 40x).

DISCUSSION:

A wide spectrum of co-infections like bacterial, fungal and viral infections in patients with H1N1 has been reported in literature. Our patient with H1N1 pneumonia presented with a unique combination of Aspergillus and CMV co-infection.

The histopathological features were examined mostly on post-mortem lung tissue in literature. However, in our case, the surgical resected specimen of lobectomy was obtained for evaluation which was helpful in identifying co-infections of Aspergillus aand CMV, thereby facilitating further management of the patient. Mauad *et al.* identified three distinct histological patterns: diffuse alveolar damage, necrotising bronchiolitis and extensive alveolar haemorrhage, all of which were observed in our case. Other findings in their study include hyaline membrane/ fibrinous exudate, interstitial inflammation, intra-alveolar edema, granulation tissue, squamous metaplasia, perivasculitis, microthrombi and pulmonary thromboembolism. Extensive involvement of lung can be life-threatening. Similar virus-related changes were however not observed in other organs, placenta or fetus of pregnant patients.[2]

CMV pneumonitis is an uncommon complication in H1N1. Susceptible population like children, immunocompromised individuals following bone marrow or solid organ transplant, pregnant women etc. tend to be at a greater risk for acquiring infections during outbreak of epidemics as in H1N1. In transplant recipients, CMV is one of the most common opportunistic pathogen. Immunosenescence, which is associated with ageing is also implicated in the pathogenesis of CMV infection.[3]

Bonatti *et al.* reported a case of a 65-year old female renal transplant recipient who developed simultaneous CMV disease and H1N1 pneumonia diagnosed by blood PCR for CMV and H1N1 on bronchoalveolar lavage (BAL). Treatment with oseltamivir and gancyclovir and appropriate immunosuppression improved the patient's condition and graft survival.[4] Marchiori *et al.* studied the histopathological findings of lung in four known H1N1 patients confirmed by RT-PCR of nasopharyngeal aspirate out of which co-infection with CMV was reported in a pregnant patient.[5] Magira *et al.* examined 33 patients with pulmonary infection admitted in intensive care units of whom 13 were diagnosed with H1N1 by PCR testing and/or influenza A rapid antigen testing. Out of the 13 cases, 3 patients tested positive for CMV by PCR performed on BAL.[3]

Among the fungal infections aspergillosis is a common co-infection in H1N1 patients and a few cases of Candidial infection have also been reported.[6,7] It is postulated that epithelial disruption caused by H1N1 facilitates fungal invasion. The impaired phagocytic function and altered levels of cytokines due to H1N1 infection is another contributing factor to immune suppression predisposing to aspergillosis. In Spain, Garcia-Vidal *et al.* evaluated 57 immunocompromised patients who were receiving chemotherapy for acute myeloid leukemia (AML) and hospitalised for H1N1 infection and detected co-existing invasive aspergillosis in 5 of them with an incidence rate of 8.8%. The aspergillus infection was detected by galactomannan assay in serum and BAL.[7] Co-infection of H1N1 influenza with Pneumocystis jeroveci has also been reported in an immunocompetent patient.[8]

Co-infections with other viral infections like dengue and other influenza and para-influenza viruses have been reported.[9]

Bacterial co-infections were more common in the elderly and were associated with increased complications. Among these, co-infection of H1N1 with Streptococcus pyogenes, Streptococcus pneumonia, Staphylococcus aureus, Mycoplasma pneumoniae, Moraxella catarrhalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Streptococcus agalactiae and Mycobacterium tuberculosis have been reported in the literature.[10,11,12] Among 77 autopsy specimens studied in 2009, 22 had simultaneous bacterial infection with Streptococcus pneumonia infection being the most common. Dhanoa *et al.* evaluated 50 H1N1 patients and detected a co-infection rate of 34% with 28% bacterial infections and 6% viral infections and Mycoplasma pneumonia being the most common bacterial infection. Mycobacterium tuberculosis co-infection is rare with only a few case reports in immunocompromised patients especially in tuberculosis endemic areas.[10]

Table 1 summarises the various bacterial, fungal and viral co-infections observed in H1N1 patients reported in the literature.

Table 1. Co-infections reported with H1N1

Co-infections with H1N1		
Bacterial	Viral	Fungal
Streptococcus pyogenes Streptococcus pneumonia Staphylococcus aureus Mycoplasma pneumoniae Moraxella catarrhalis Klebsiella pneumoniae Pseudomonas aeruginosa Streptococcus agalactiae Mycobacterium tuberculosis	Cytomegalovirus Dengue virus Other influenza and para-influenza viruses	Aspergillus Candida Pneumocystis jeroveci

Co-infections in H1N1 patients have higher rates of complications and mortality. Therefore, the incidence of multiple co-infections should be borne in mind in order to initiate appropriate timely management and to avoid fatal outcomes.

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