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Case Report Open Access

Acute Respiratory Failure in Idiopathic Pulmonary Fibrosis: Co-Infection With H1n1 And Cytomegalovirus: An Unexpected Common Denominator

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Abstract

We described a case of persistent influenza AH1N1 and cytomegalovirus respiratory infection in a patient with chronic interstitial lung disease and multiple bilateral pulmonary opacities. An open lung biopsy revealed diffuse organizing alveolar damage, necrotizing bronchiolitis, necrotizing pneumonia and alveolar hemorrhage, compatible with H1N1 infection as well as usual interstitial pneumonia. Diagnoses of an idiopathic CD4+ T cell lymphocytopenia and immunoglobulin G deficiency were made as an unexpected co-denominator of H1N1 and CMV persistent infection changing our treatment approach.

Keywords: Respiratory failure; IPF exacerbation; Persistent CMV respiratory infection; Persistent H1N1 respiratory infection; CD4 T cell idiopathic deficiency

Case Report

AMCAL, female, fifty-nine years old Brazilian housewife, with five years history of stable interstitial lung disease and a Medical Research Council (MRC) *breathlessness* scale grade 1 dyspnea, breathing room air with a SpO_2 of 97% without previous medical treatment that was submitted to an abdominoplasty one month before admission (Figure 1). She had no rheumatologic symptoms and her Antinuclear Antibody (ANA) was negative.

After the surgical procedure she evolved with progressive worsening of dyspnea when a diagnosis of respiratory infection due to Influenza AH1N1 virus was made. Olsetamivir, *intravenous methylprednisolone* (40 mg/day) and respiratory support (Venturi mask with 50% FiO_2) were used for five days and the patient showed improvement that lasted for two days. She began to present a right eye conjunctivitis and respiratory failure refractory to non-invasive ventilation. Then, she was intubated and mechanically ventilated with FiO_2 of 70%, PEEP of 12 cm H_2O and PaO_2/FiO_2 of 130. Bronchoalveolar lavage, blood cultures, blood quantitative DNA-PCR for cytomegalovirus (CMV) was collected and broad-spectrum antibiotics including ganciclovir were introduced. Her physical examination at ICU admission showed diffuse fine crackles bilaterally, without other remarkable findings.

The initial workup showed leukocytosis (13,870 cells/mm^3, neutrophils 79% and bands 7%), hemoglobin level of 12.7 g/dL and C-reactive protein of 29 mg/L. The electrocardiogram showed no suggestive signs of ischemia; markers of myocardial necrosis and brain natriuretic peptide were within the normal range. Transthoracic echocardiogram showed normal cardiac function (left ventricular ejection fraction of 74%) with normal estimated systolic pulmonary artery pressure (27 mmHg).The initial chest X-ray is shown in Figure 2. A chest computed tomography (CT) scans revealed diffuse ground glass pattern, multiple nodular opacities, peripheral lung cysts and bronchiolectasis (Figure 3). Quantitative blood PCR for CMV revealed 27,000 virus copies/mL and nasal swab RT-PCR for influenza AH1N1 was positive. Bronchoalveolar lavage cultures were all negative, Herpes virus PCR detection was negative, but PCR for CMV detection was positive. Two blood analyses with an interval of one week revealed CD4 lymphocytes sub-population of 86 cells/mm^3 and 45 cells/mm^3, respectively (normal range 400 to 1,500 cells/mm^3). Serology for HIV-1/-

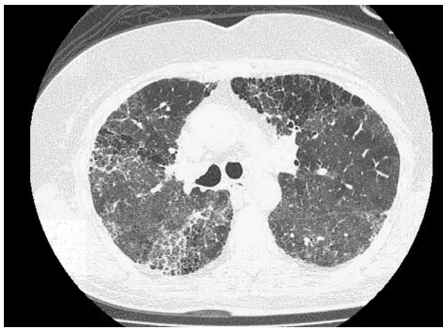

Figure 1: Chest computed tomography scan before interstitial lung disease exacerbation. Reticular opacities associated with traction bronchiectasis, architectural distortion and honeycombing can be noted.

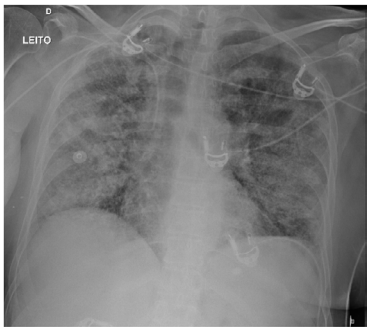

Figure 2: Initial chest X-ray showing bilateral asymmetric interstitial infiltrates associated with extensive areas of consolidation.

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2 was negative. Blood immunoglobulin G level was 578 mg/dL (normal range 700 to 1,600 mg/dL). Naso- enteral administration of olsetamivir was restarted and intravenous polyclonal immunoglobulin (500 mg/kg) was administered. Since the patient showed little improvement after 7 days of evolution, a new chest CT scan was performed. The CT scan revealed an increment of the multiple irregular nodular pulmonary opacities and an increase in ground glass infiltrate. Since Aspergillus antigen galactomannan, 1,3- beta-D-glucan, Crytococcus neoformans antigen blood detection and HIV detection were all negative, an open lung biopsy and a tracheostomy were indicated and performed.

Histology sections showed acute or chronic changes (Figure 4). The acute lung injury had a diffuse alveolar damage pattern in the organizing phase with fibroblast proliferation, pneumocyte hyperplasia, immature squamous metaplasia and small vessels micro thrombi. Signs of alveolar hemorrhage with blood and hemosiderin filled alveolar spaces were focally seen. There are also extensive areas of necrotizing pneumonia and focal necrotizing bronchiolitis. The lung parenchyma not involved by acute disease had diagnostic features of Usual Interstitial Pneumonia (UIP). It shows architectural distortion with areas of dense collagenous scarring, predominantly in sub pleural and paraseptal regions, combined with areas of active or ongoing fibrosis (fibroblast foci).The pathology report conclusion was acute lung injury consistent with the clinical and laboratory diagnosis of H1N1 infection, associated with background of UIP.

The patient received 21 days of olsetamivir, ganciclovir, methylprednisolone (40 mg/day) and broad-spectrum antibiotics with stabilization of her clinical condition, but she became dependent on mechanical ventilation (FiO_2 of 40%, PEEP of 8 cm H_2O and support pressure of 10 cm H_2O).

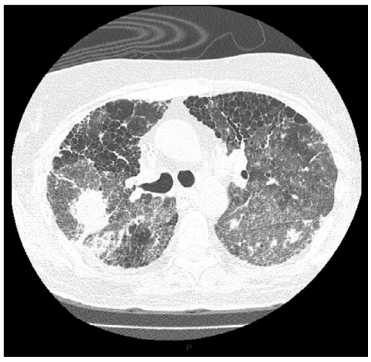

Figure 3: Chest CT scan showing diffuse ground glass opacities together with bilateral multiple irregular nodular opacities, peripheral cystic areas and bronchiolectasis.

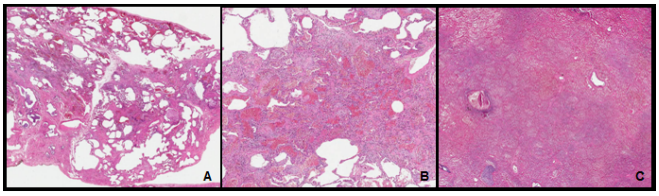

Figure 4: Open lung biopsy: anatomopathological findings. **A.** Low power field showing patchwork pattern of lung involvement of fibrosing interstitial pneumonia. **B**. Acute lung injury and hemorrhage: alveolar spaces filled with blood and septal thickening by fibroblasts. **C.** Necrotizing pneumonia: extensive areas of lung parenchyma necrosis. See text for more details.

Discussion

This case presents several interesting points to be discussed. The differential diagnosis of a patient with respiratory failure in a context of chronic interstitial lung disease is broad. The ground glass opacities may be attributed to an acute exacerbation episode of the disease and the identification of an infectious etiological agent doesn't rule out the possibility of concomitant acute exacerbation of the interstitial process. In this patient, the de novo identification of influenza A H1N1 virus accompanied by the identification of CMV virus indicates that these viruses might have played a role in the acute respiratory failure of this patient [1-3]. The H1N1 infection had been treated previously with oseltamivir, and its de novo identification was interpreted as persistence of H1N1, especially in the setting of an idiopathic CD4+ T cell lymphocytopenia (ICL) [4,5]. We measured the CD4+ cells twice in one-week interval. The first blood analysis revealed CD4 lymphocytes sub-population of 86 cells/mm^3 and the second blood analysis revealed CD4 lymphocytes sub-population of 45 cells/mm^3. Serology for HIV-1/-2 was negative. These findings suggested that our patient had the diagnosis of ICL. The etiology of ICL is still unknown. There is evidence for increased activation and turnover of CD4+ cells, as well as accelerated CD4+ cell apoptosis in patients with ICL. The most typical manifestations of ICL are cryptococcal, mycobacterial and other opportunistic infections, malignancies, and autoimmune disorders. These conditions are all believed to result from immune deregulation [4,5]. Infection with CMV is also described in these patients. In our case, it is highly probable that the ICL is the common denominator that explains persistent H1N1 and concomitant CMV infection. Persistent H1N1 infection is described in the literature and prolonged olsetamivir treatment is recommended, as it was done [1,2].

Another unusual aspect of this patient was the nodular opacities, which histologically corresponded to areas of necrotizing pneumonia probably due to the H1N1 pulmonary infection. Infection with H1N1 may present a histological picture of organizing diffuse alveolar damage, which resembles an organizing pneumonia, however, the nodular appearance is quite unusual [2]. Areas of usual interstitial pneumonia were also seen in the histological analysis of this patient but an acute exacerbation of IPF does not have such radiological presentation [6,7]. As our patient had a chronic and stable interstitial lung disease for more than five years before the acute exacerbation of the disease, it was unlikely that she had a respiratory virus infection before the acute exacerbation. As she had a persistent H1N1 infection (naso- pharyngeal swab PCR positive for H1N1) for more than one month despite prolonged olsetamivir treatment (21 days), we started to investigate her cellular immunity and detected these persistent low blood levels of lymphocytes, immunoglobulin G deficiency and two measurements of CD4 levels below 100 cells/mm^3 in a HIV negative woman. This suggests that this low CD4 levels contributed to the no-resolution of her respiratory viruses infections. The finding of a non-HIV CD4 deficiency in our patient explained the persistent respiratory influenza AH1N1 and CMV viral infections and changed our treatment approach.

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