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Influenza challenging the diagnosis and management of pulmonary coccidioidomycosis

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ABSTRACT

Lower respiratory infections are the most important cause of death due to a transmissible disease. We present a case of severe influenza and coccidioidomycosis lung coinfection in a 65-year-old Mexican migrant. This case highlights the challenges that respiratory viruses impose on the diagnosis of fungal infections and on the multidisciplinary management of these infections. In addition, this case shows how medical complications and superinfections could be potentially prevented if flu vaccination is provided.

1. Introduction

Lower respiratory infections are the most important cause of death due to a transmissible diseases [1]. Annually, influenza causes an average of 54 millions of lower respiratory tract infections (LRTIs) worldwide from which, 15% are severe LRTIs causing between 290,000 to 645,000 deaths [2,3]. Mixed infections or coinfections between influenza and bacteria occur in 11% to 35% of the cases of severe influenza [4]. Coinfection with bacterial pathogens complicates the management of influenza infection and also, increases the severity of the respiratory symptoms and the mortality. Multiple factors favour bacterial superinfections in severe influenza for example: pulmonary epithelial damage by the virus, increased receptor availability, virus effects on immunity to bacteria (impairing phagocytosis and killing) and, increased inflammation [5].

In recent years, a new influenza-associated infection has been reported. Influenza-associated pulmonary aspergillosis (IAPA) has been reported more frequently after 2009 influenza pandemic [6,7] and occurs between 14-28% of severe influenza cases [8–10]. IAPA increases the need of ICU admissions, renal replacement therapy and length of hospital stay in individuals with severe influenza [8,11]. In individuals with COPD and influenza, pulmonary aspergillosis is three times more frequent than in individuals with either only influenza or COPD alone [12].

We report a different influenza-associated fungal infection in a 65-year-old man admitted to ICU unit due to acute respiratory distress syndrome. Coinfection between influenza and coccidioidomycosis was diagnosed. During the ICU stay, the patient required invasive mechanical ventilation, a wide multidisciplinary approach, renal replacement therapy, broad-range spectrum antibiotics and antifungal agents. Coccidioidomycosis should be considered in the differential diagnosis of returning migrants and travellers from endemic regions. The role of influenza on the local immunity may play a major role on the severe reactivation of coccidioidomycosis.

2. Case presentation

On 30th January 2020, a Mexican 65-year-old man presented to the emergency department with 24 h progressive shortness of breath and was admitted to ICU unit for invasive mechanical ventilation. He was a previous resident of California (USA) and, he flew back to Michoacán (México) 3 months before admission. A month before admission, the patient had respiratory symptoms that partially improved over time. A week before admission, new fever, myalgia, arthralgias and, dyspnoea made the respiratory symptoms worst. At the admission, physical examination showed temperature of 37 °C, blood pressure 75/40 mmHg (norepinephrine at 0.2 μg/min was started after fluid IV infusion), pulse 125 bpm. Blood tests showed creatinine 1.7 mg/ml (patient was

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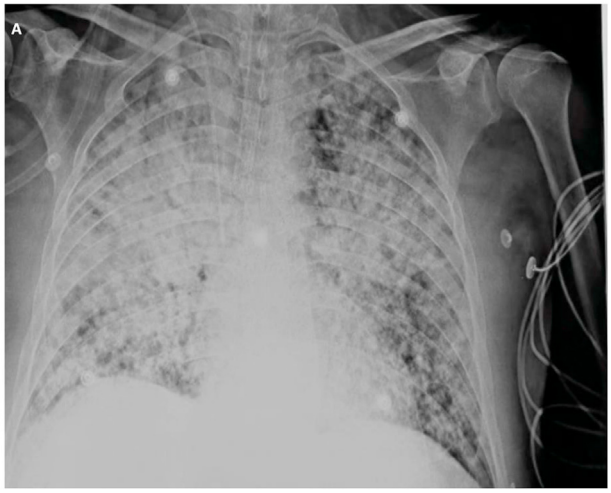

Fig. 1. Clinical findings in a patient with pulmonary coccidioidomycosis and Influenza A H1N1 mixed infection. Posteroanterior chest X-ray. After tracheal intubation on the first day in the ICU, the chest ray showed bilateral infiltrates and multiple opacities.

anuric), procalcitonin 58 ng/ml, pH 7.41, $PaCO_2$ = 21 mmHg, PaO_2 = 51 mmHg, HCO_3 = 16·9, lactate 8·4, haemoglobin 11·1 g/dl, WBC count 8800 per µl (lymphocytes 12%, 7% bands), platelet count 160,000 per µl. Control of these blood parameters were performed every other day. After tracheal intubation, a chest X-ray showed bilateral infiltrates and multiple opacities (Fig. 1). After cultures were recovered, antimicrobial treatment with carbapenem, clarithromycin, oseltamivir and voriconazole was initiated. Oral voriconazole (400 mg b.i.d on the first day, followed by 200 mg b.i.d) was administered via a nasogastric tube. A rapid test was positive for Influenza A. The patient never received previous influenza vaccination. Family denied the patient having a previous chronic disease but at ICU, HbA1c test was 8.4%, which leaded the ICU team to think the patient had an untreated undiagnosed diabetes condition.

On day 3 of ICU stay, bronchoalveolar lavage was performed, abundant and purulent secretions and biopsies were collected for cultures, PCR panel (to identify 16 viruses and 7 bacteria) and histopathological analyses. An HIV test resulted negative. At day 5, acute respiratory distress syndrome was diagnosed and amphotericin B deoxycholate (at 1 mg/kg/day) was added due to preliminary histopathological findings. On the 8th day of stay, the patient died.

Histopathology results reported structures compatible with spherules containing endospores, chronic inflammation in bronchi and pulmonary tissue. Also, focal oedema, vascular congestion, coagulative necrosis and multifocal haemorrhages were seen in tissue (Fig. 2). *Coccidioides* sp grew on three different culture media (blood, chocolate and Sabouraud agars) after two days of incubation (no bacteria were identified) and was confirmed by MALDI-TOF. The viral panel identified influenza A (H1N1). The final diagnosis of this patient was severe pulmonary coccidioidomycosis and influenza A (H1N1) mixed infection.

3. Discussion

To our knowledge, this is the first case reporting a coinfection between severe influenza and pulmonary coccidioidomycosis. The notification system in the United States has shown that, cases of coccidioidomycosis have increased in non-endemic (Washington state) and endemic regions specially in California and Arizona [13]. In Mexico, notification of coccidioidomycosis cases is not compulsory. However, up to 90% of the population in the neighbouring Northern Mexican states have a positive skin test for coccidioidomycosis, which allows an estimation on how frequent this fungal infection is in these areas [14]. Coccidioidomycosis is one of the infections that could potentially increase in frequency in the next coming years as result of climate change

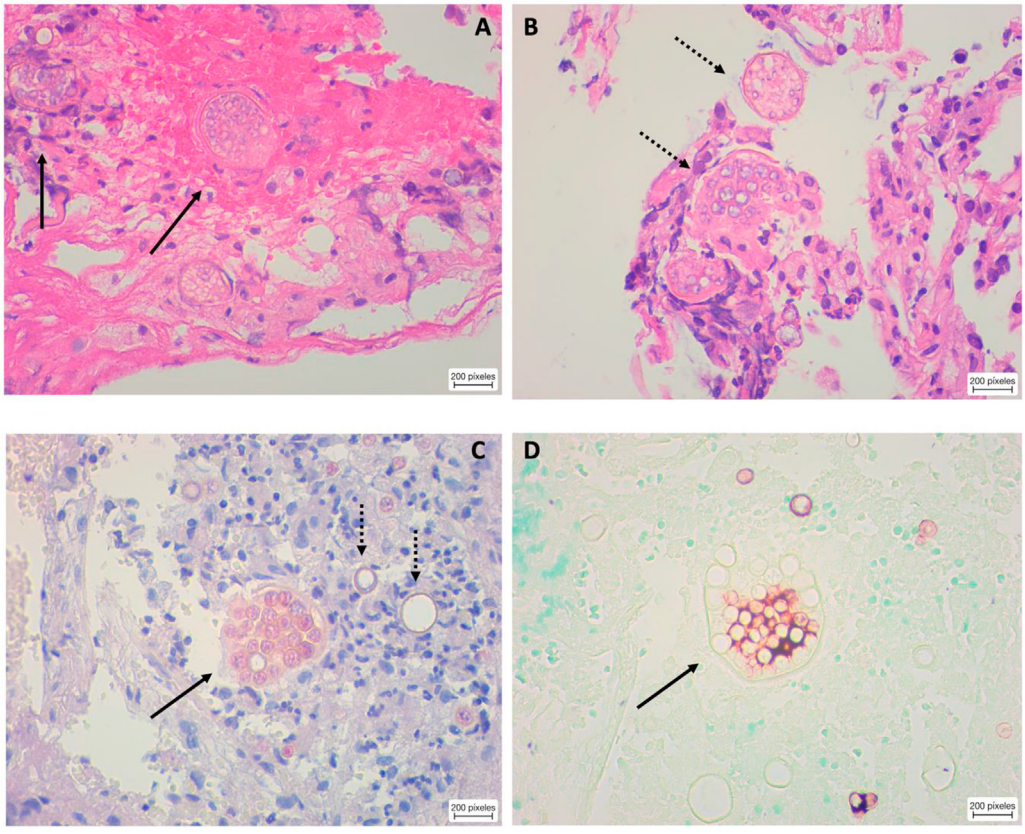

Fig. 2. Histopathological findings in bronchial and pulmonary tissue. Three different staining techniques were used. Haematoxylin and eosin staining (A, B) showing chronic inflammation characterised by infiltrating cells (lymphocytes, histocytes, plasmatic cells). (A) Vascular congestion, oedema, coagulative necrosis and multifocal haemorrhages are seen, incomplete granulomas surrounding spherules (black arrows), and (B) spherules containing endospores (punctate arrows). Periodic acid staining (C), show several forms of spherules, empty spherules (punctate arrows), spherules containing endospores (black arrows). (D) Methenamine silver staining shows a big spherule containing endospores stained in brown (black arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

as the frequency of this fungal infection is closely correlated with dust storms [15]. Coccidioidomycosis is also an infection to be considered in the differential diagnosis of returning migrants and travellers [16]. Usually, 60% of the coccidioidomycosis cases are asymptomatic and, severe pneumonia with ARDS and/or dissemination occurs in < 2% of the cases [16]. Diabetic individuals with extensive pulmonary coccidioidomycosis have higher risk of dissemination; in this group of patients, antifungal treatment is recommended with an orally absorbed azole [16]. Only few cases of tuberculosis and blastomycosis in co-infection with coccidioidomycosis have been rarely reported and worse outcomes are seen in HIV/AIDS individuals [17,18].

As mentioned above, it is thought that influenza virus would favour bacterial superinfection by damaging the pulmonary epithelial cells. In the current case it is possible that the patient had first coccidioidomycosis and then the influenza superinfection. Hence, the role of influenza on the local immunity could be playing the major role on a potential severe reactivation of coccidioidomycosis occurring in this patient. After inhalation of arthroconidia and spherule production in the lung, the response to coccidioidomycosis consists essentially on fungal containment by phagocytosis carried out by macrophages and neutrophils, high production of TNFα, IFNγ, and IL-17 and $CD4^+$ T cell response [19]. One of the effects of influenza on local immunity is the induction of type I interferon responses, which has a paradoxical effect on macrophages and neutrophils functions, especially on phagocytosis and early killing [5]. An *in vitro* study showed that viral infection triggers interferon-induced expulsion of live *Cryptococcus neoformans* previously phagocyted by macrophages [20]. This could be a potential triggering factor for reactivation of fungal infections such as coccidioidomycosis.

This clinical case illustrates the new diagnostic and therapeutic challenges that respiratory viruses impose on fungal infections, and also highlights the importance of flu vaccination in preventing not only more severe influenza but also severe superinfections.

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Declaration of competing interest

All authors declare that they have no conflicts of interest regarding this manuscript.

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