

## Unusual association of diseases/symptoms

## Cryptococcal meningoencephalitis after H1N1 influenza

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*Cryptococcus neoformans* is associated with a spectrum of diseases including meningoencephalitis, pneumonia and soft tissue infections. Incidence is higher in immunocompromised hosts like HIV-infected individuals and solid organ transplant recipients. The influenza virus is known to cause immunologic defects. Additionally, the 2009-pandemic H1N1 virus is associated with increased incidence of acute respiratory distress syndrome (ARDS) requiring treatment with systemic steroids. The authors present the first case of cryptococcal meningitis in a patient with flu A-associated ARDS (FLAARDS). In this patient, risk factors for invasive fungal disease included a combination of severe and prolonged H1N1-influenza virus infection, corticosteroid therapy and broad-spectrum antibiotics. While prolonged corticosteroid use is a known risk factor for development of invasive fungal disease, the authors postulate that by causing immunologic defects and FLAARDS, the 2009-pandemic H1N1 virus may represent an additional independent risk for the development of *C neoformans* meningitis in a previously healthy individual.

**BACKGROUND**

The pandemic H1N1-flu infection was associated with a wide variety of clinical manifestations. Mortality from respiratory failure was high compared with previous flu outbreaks. Our patient developed *Cryptococcus* meningitis while he was being treated for respiratory failure from severe lung injury. He was successfully treated for both infections with full recovery. There is no report in the literature of the association between *Cryptococcus* and the pandemic H1N1-influenza virus.

**CASE PRESENTATION**

Our patient is a 52-year-old previously healthy Caucasian male who was admitted to the hospital with fever and shortness of breath. He was a non-smoker and family history was negative for any major illness. A rapid deterioration in his respiratory status necessitated endotracheal intubation.

**INVESTIGATIONS**

A chest CT scan showed bilateral extensive pulmonary infiltrates (figure 1). 2009 influenza A (H1N1) virus infection was diagnosed by PCR from nasopharyngeal swabs. Tests for HIV were negative and the CD4 count was normal.

**TREATMENT**

Oseltamivir 75 mg twice daily was initiated. The patient had persistent fever along with respiratory failure, hence the course of oseltamivir was prolonged beyond the recommended 5 days. PCR for 2009 influenza A (H1N1) virus remained positive for 21 days. Nasopharyngeal swabs were sent to the Centre for Disease Control to evaluate for resistance. Testing did not reveal the viral H-275Y gene mutation often associated with oseltamivir resistance. Oseltamivir was continued until the patient became afebrile and PCR results were negative.

However, the patient had persistent lung infiltrates and remained ventilator-dependent. Respiratory cultures remained sterile. This triggered a lung biopsy on day 45 of hospitalisation. Pathology revealed extensive interstitial fibrosis with young fibroblasts, alveolar cell hypertrophy and patchy cellular infiltrates consistent with the organising phase of diffuse alveolar damage (figure 2). Based on bilateral extensive lung involvement, ventilator requirements and pathology findings, a diagnosis of flu A-associated acute respiratory distress syndrome (FLAARDS) was confirmed. At this stage high-dose corticosteroids were initiated.

Twenty five days later he developed a new fever of 103°F. Initially, blood and urine cultures were negative for bacteria, and bronchoalveolar lavage was negative for bacteria, fungus and pneumocystis.

However, 4 days later blood cultures revealed yeast in multiple sets. Serum cryptococcal antigen was positive at 1:512. Culture of cerebrospinal fluid revealed *Cryptococcus neoformans* with a cryptococcal antigen titre of 1:32. Antifungal therapy was initiated and steroids were gradually tapered. He was successfully treated with induction therapy of intravenous liposomal amphotericin B 450 mg daily and oral flucytosine 3750 mg four times a day for 4 weeks, followed by consolidation and suppressive therapy with fluconazole 400 mg daily.

**OUTCOME AND FOLLOW-UP**

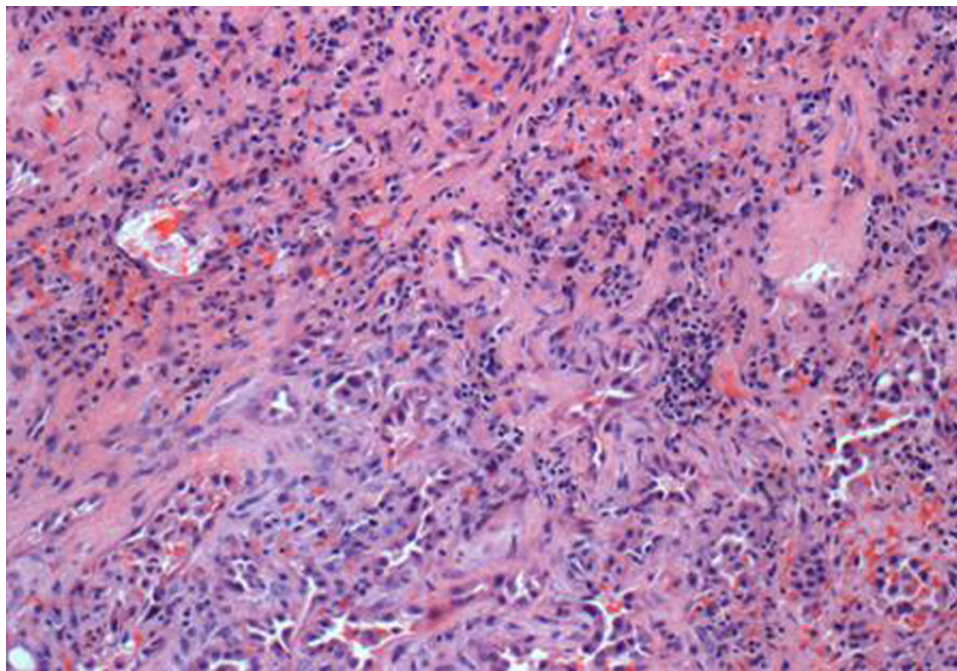
Follow-up blood and cerebrospinal fluid tests revealed clearance of the infection. Twelve months later he remains afebrile, has been weaned off the ventilator and has returned home after extensive pulmonary rehabilitation.

**DISCUSSION**

*C neoformans*, a yeast-like fungus, is associated with a wide-spectrum of diseases including meningoencephalitis,



**Figure 1** CT scan of the chest showing bilateral diffuse ground-glass opacities.



**Figure 2** Wedge biopsy of the lung revealing interstitial fibrosis, young fibroblasts, alveolar cell hypertrophy and patchy cellular infiltrates of lymphocytes, plasma cells and eosinophils.

pneumonia and soft tissue infections. *Cryptococcus meningoencephalitis* is the most frequent manifestation of cryptococcosis and is most often seen in the immunocompromised patient. Causes of immunosuppressed state include advanced HIV infection, prolonged corticosteroid therapy, solid organ transplantation, haematologic malignancies, sarcoidosis and hepatic failure.<sup>1</sup> The

novel 2009 influenza A (H1N1) virus outbreak was first reported in the USA in April 2009. Thereafter ensued a rapid spread and by June it was declared a global pandemic. While the majority of those infected had a mild illness, a small number developed a life-threatening respiratory syndrome described as FLAARDS.<sup>2</sup> Along with invasive and non-invasive ventilatory support, 2009

influenza A (H1N1) virus – associated ARDS is usually treated with high-dose corticosteroids.<sup>3 4</sup> This results in an immunocompromised state. In addition, the influenza virus itself has been known to cause cell-mediated immunologic defects, impairment of normal ciliary function and leucopenia.<sup>5</sup>

Fatal outcomes from other invasive fungal diseases like *Aspergillus* have been reported during the 2009 influenza pandemic season.<sup>6</sup> Our patient experienced a prolonged and severe flu infection. In spite of the fact that he received oseltamivir very early in the course of his illness, and there was no evidence for drug resistance, he remained febrile for a prolonged period and his PCR for the 2009 influenza A (H1N1) virus was negative at day 21 of hospitalisation, implying increased duration of direct immunosuppression by the virus. In addition, he developed FLAARDS that required further immunosuppressive therapy with systemic corticosteroids. We postulate that by causing immunologic defects and FLAARDS, requiring treatment with corticosteroids, prolonged 2009 influenza A (H1N1) virus infection may represent an emerging risk factor for the development of *Cryptococcus* meningoenzephalitis in previously healthy individuals.

To our knowledge this is the first case of *Cryptococcus* meningoenzephalitis in a patient infected with the 2009 influenza A (H1N1) virus. He was successfully treated with currently recommended antifungal regimen.

### Learning points

- ▶ The influenza virus is known to cause immune dysfunction. The pandemic H1N1 influenza virus may be associated with worse defects.
- ▶ *Cryptococcus* meningitis is seen in patients with immune defects caused by immunosuppressive medications, HIV and may be seen in cases with severe flu infection.

**Competing interests** None.

**Patient consent** Obtained.

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