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Severe respiratory failure in an immunocompetent host with invasive pulmonary aspergillosis and H1N1 influenza

Luigi Francesco Saccaro, Valentina Galfo, Simone Ferranti, Alessandro Russo, Francesco Menichetti

Infectious Diseases Unit, Azienda Ospedaliera Universitaria Pisana, University of Pisa, Italy

SUMMARY

Invasive pulmonary aspergillosis (IPA) is a life-threatening condition that usually occurs in immunocompromised hosts. However, according to recent reports it can affect immunocompetent hosts with severe influenza infection due to viral-dependent disruption of respiratory immune defenses. We present the case of a 61-year-old Caucasian man admitted to the Emergency Department with respiratory failure and fever, who was diagnosed with H1N1 influenza and IPA. Because of his poor general conditions, he was treated with a double antifungal scheme, although this lies outside the suggested treatment guidelines. This choice turned out to be extremely effective. He was discharged after one month and his clinical conditions showed rapid improvement, with nearly complete normalization of the radiological pattern in three months. IPA remains a life-threatening condition, even in immunocompetent hosts, and should therefore always be suspected; if necessary, a combined treatment should rapidly be started. We report this case as the interest in influenza-associated IPA is high, both due to the clinical severity of this condition, which is treatable if identified early, and the emerging importance of respiratory infections caused by viruses belonging to the SARS family, such as SARS-CoV-2.

Keywords: IPA, H1N1 influenza, immunocompetent, coinfection.

INTRODUCTION

In recent years, Invasive Pulmonary Aspergillosis (IPA) has been recognized as a serious complication of influenza H1N1, although the prevalence of this association may vary across different geographical regions [1]. IPA is a major cause of morbidity and mortality in immunocompromised patients [2]. Although the definition of "immunocompromised" is not always straightforward, the number of cases of aspergillosis in association with influenza A (H1N1) and B in immunocompetent hosts has increased, *i.e.* in previously healthy individuals [3, 4]. This increase might be explained by more aggressive and debilitating influenza strains (*e.g.* the pandemic H1N1), and/or the use of steroids to treat severe pneumonia [5]. Furthermore, there have also been cases of coinfection of SARS-associated Coronavirus influenza and IPA [6]. Different mechanisms have been proposed to explain the predisposing effect of influenza on IPA [2, 7].

In this scenario, response to antifungal therapy depends on several factors, such as the immune status of the host and the extent of infection at the time of diagnosis [2]. Combination antifungal therapy may be used for patients whose disease worsens while on monotherapy [8].

Further insights into the pathophysiological

Corresponding author
Francesco Menichetti
E-mail: menichettifrancesco@gmail.com

mechanisms underlying the predisposing effect of influenza on IPA, and the prompt identification of patients at risk for IPA will be key to improving patients' outcomes. For this reason, we present the following case of an immunocompetent patient with influenza H1N1 and IPA.

CASE PRESENTATION

A 61-year-old Caucasian man with a history of asbestos exposure and cigarette smoking (40 pack-years), without underlying disease, was admitted to the Infectious Diseases Unit of the Hospital of Pisa in Italy in February 2018, with hypoxic respiratory failure and pneumonia.

Before admission, the patient presented a history of recurrent low-grade fever for 1 month and non-productive cough with an abrupt onset of dyspnea, which did not respond to ceftriaxone, levofloxacin, or piperacillin/tazobactam. He had previously been admitted to the Emergency Department where a diagnosis of pneumonia had been made.

At admission to the Infectious Disease Unit, the patient was apyretic, dyspneic and vigilant with an increase in the vocal fremitus, hypophonesis, and crepitations localized in the left medium lobe. The chest X-ray demonstrated left medium-lower lobe infiltrations and laboratory examination showed a reduction of pO_2 (78 mmHg, normal value 80-100 mmHg), thrombocytopenia with 130^10^3/mm^3 platelets (NV 140-450 ^10^3/mm^3), hepatic sufferance with an increase of ALT (58 U/L, NV <40U/L) and ALP (141 U/L, NV<45U/L). The patient was also diagnosed with unknown and uncontrolled diabetes (139mg/dl, NV 60-110 mg/dl). Due to a high suspicion of influenza infection, empirical therapy with oseltamivir (75 mg x 2 orally) was started, associated with intravenous corticosteroids (60 mg IV) and antibiotics (ceftobiprole 500 mg x 3 IV and clarithromycin 500 mg x 2 orally).

On the third hospital day (HD), clinical symptoms did not improve. Worsening hypoxia required oxygen therapy (4 liters/minute). The chest X-ray and pulmonary CT scan showed a progression of bilateral multiple pulmonary nodules, with diffuse alveolar destruction and a ground-glass appearance.

PCR on broncho-alveolar lavage (BAL) fluid, taken on the fourth HD, confirmed the presence of influenza A H1N1.

On the ninth HD, the patient developed worsening respiratory symptoms with an increased requirement of oxygen therapy (7 liters/minute); the BAL revealed positive fungal testing for *A. fumigatus* (positive culture) and galactomannan (GM, antigen >4, cut-off >1).

Thus, a co-infection with *A. fumigatus* was suspected and antifungal therapy was started (isavuconazole 200 mg x 2 IV, and micafungin 100 mg x 2 IV). It ought to be remembered that this double regimen is not among the first-line regimens recommended by the Infectious Diseases

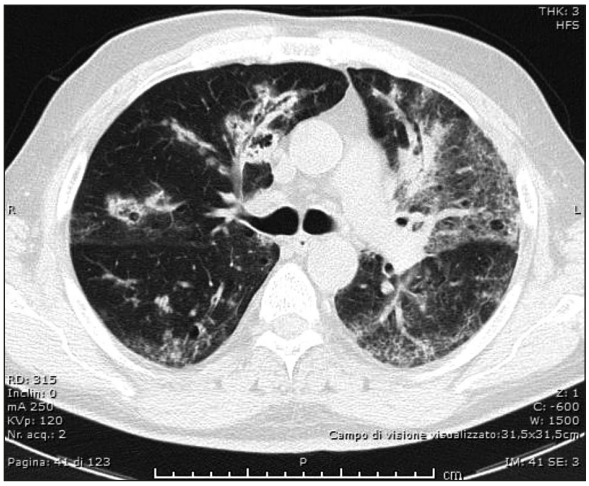

Figure 1 - Thoracic CT: consolidations and tree-in-bud sign.

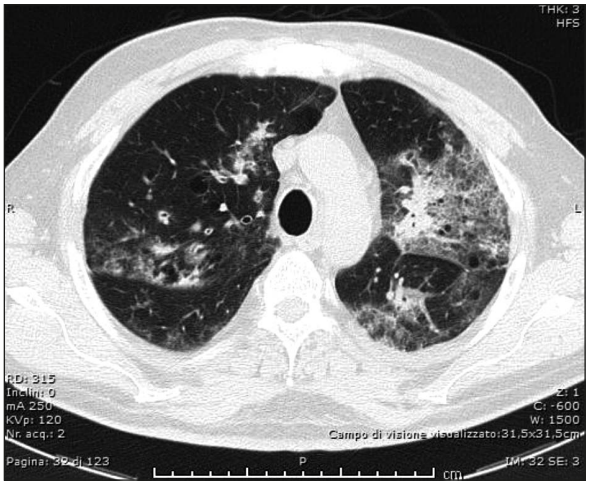

Figure 2 - Thoracic CT: multiple nodules and consolidations with air bronchogram and cavitary lesions.

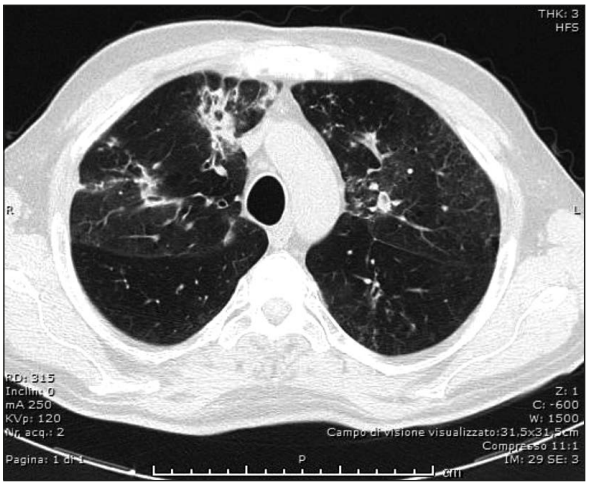

Figure 3 - Thoracic CT, at one-month follow-up: partial resolution of nodules and consolidations.

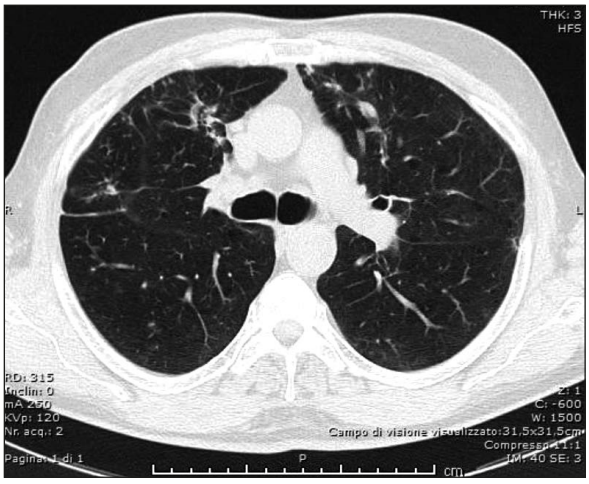

Figure 4 - Thoracic CT at four-month follow-up.

Society of America (IDSA). IDSA recommends voriconazole as IPA primary treatment and isavuconazole or liposomal amphotericin B as alternative therapies. In selected patients with documented IPA a double regimen with echinocandin and voriconazole may be used [9]. Corticosteroids administration was progressively reduced.

At the start of antifungal therapy, the patient developed a brief progression of productive cough with concomitant hemoptysis and a higher requirement of oxygen therapy (10 liters/minute).

His vital signs revealed tachypnea (33 breaths/minute) and tachycardia (110 bpm) with alterations of ventricular repolarization at ECG. The patient also developed subscapular pain associated with cough and aphonia.

Another pulmonary CT scan imaging showed a progression of the pulmonary lesions: the initial ground-glass appearance had transformed into a tree-in-bud appearance (Figure 1) with the development of small diffused cavities (Figure 2).

One month after hospital admission, the patient was discharged with isavuconazole (200 mg/die, to complete 3 months of therapy) as antifungal therapy, without the need for oxygen, and a diagnosis of influenza complicated with IPA. At one-month and four-month follow-up, pulmonary CT showed a significant regression of consolidations, widespread micronodular findings, and interstitial involvement (Figures 3 and 4).

DISCUSSION

Influenza, and in particular H1N1, predisposes to IPA infections through various mechanisms. Up to a quarter of patients develop *Aspergillus* tracheobronchitis, probably as a superinfection of influenza-induced tracheobronchial ulcerations [4, 10]. Furthermore, both influenza A and B can cause ciliary stripping, hemorrhage, focal necrosis in the upper respiratory tract, diffuse alveolar damage and submucosal hemorrhage. These alterations may increase the risk of systemic fungal hyphae dissemination [11]. Moreover, influenza may lead to a shift in the Th1/Th2 balance and to lymphopenia, both of which facilitate fungal infection, ciliary hemorrhage, and focal necrosis in the upper respiratory tract [11]. More in general, many mechanisms that favor a post-influenza bacterial superinfection predispose to a mycotic one, as well. These involve interleukin (such as IL-10) secretion as well as macrophage, NK, and T cells deficiency [5, 12].

In immunocompetent and immunocompromised hosts, the most common influenza strain associated with IPA co-infection is influenza A H1N1, which is associated with better outcomes than non-H1N1 influenza A [13]. According to Shah et al., the mortality among patients with influenza and IPA co-infection is 24/34 (70%) patients, excluding two cases where the influenza virus was suspected but not demonstrated, and both died. Overall, 21 (81%) of the patients who died had

received antimycotic therapy. However, in the subgroup of patients with H1N1 infection, the mortality was 6/11 patients. Tobacco (14%), alcoholism (11%) and diabetes (11%) were the predominant risk factors [14].

In our case, IPA was strongly suspected because of the exemplary ground-glass radiological appearance, later evolving into a tree-in-bud appearance, and positive BAL (antigen and culture) for *A. fumigatus* five days after the diagnosis of influenza. It should be noted that positive serum or BAL GM antigen testing are not included in the revised proposed criteria for critically ill patients, due to poor sensitivity and specificity in immunocompetent hosts [15, 16]. The results can be falsely positive in patients taking beta-lactam antibiotics such as piperacillin-tazobactam and ceftriaxone, as in our case [17]. Increased incidence of truly positive GM has also been associated with air pollution, even though the evidence of causality remains weak [18].

Since corticosteroids have been associated with a negative outcome in IPA and acute respiratory distress syndrome, they were promptly reduced once IPA was suspected [13, 19]. In fact, our patient had other risk factors for aspergillosis: corticosteroid therapy, diabetes, broad-spectrum antibiotics, asbestos exposure, smoking and influenza A (H1N1) [7, 15, 20]. Diabetic patients with IPA can be particularly challenging [21]. Our patient did not have leukopenia, cirrhosis, alcoholism, chronic obstructive pulmonary disease, burn injury, or malnutrition, which are all risks factor for IPA in immunocompetent patients [14, 22].

To sum up, the elements in favor of a probable diagnosis of post-influenza IPA in our case were:

1) Compatible clinical signs and symptoms (recrudescent fever resistant to antibiotic therapy, cough, dyspnea).
2) Typical pulmonary CT images.
3) Aspergillus-positive culture of BAL fluid.
4) Host risk factors (glucocorticoid treatment) [15].

An antifungal combination therapy (isavuconazole and micafungin) was chosen due to our patient's poor clinical condition, which required high-dose oxygen and may have soon required sub-intensive care.

Even though *Aspergillus* findings in pulmonary samples of immunocompetent patients have largely been considered as a contaminant, increasing evidence underlines the inaccuracy of this statement [23]. Prompt diagnosis and prevention are crucial for successful treatment of IPA, therefore risk factors (*e.g.* steroids) should be identified and, when possible, limited. In particular, IPA should be considered as a differential diagnosis in immunocompetent patients with underlying influenza [14]. Due to the high mortality that affects immunocompetent patients with influenza and IPA, antiviral and antifungal treatment should be rapidly designed and initiated.

Conflicts of interest
None.

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None to declare.

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