Influenza A (H1N1) in a Pediatric Patient With Newly Diagnosed Acute Promyelocytic Leukemia and Invasive Pulmonary Aspergillosis

Stefano Vallero, MD, Francesca Carraro, MD,* Franca Fagioli, MD,* Anna Maria Postini, MD,* Elisa Rivetti, MD,* Stefania Bezzio, MD,† and Mareva Giacchino, MD**

Summary: Influenza A (H1N1) pandemic reached its peak in Europe in autumn 2009. H1N1 infection can be a serious complication in patients with comorbidity or immunodepression. Here, we report of a boy with newly diagnosed acute promyelocytic leukemia with a very severe respiratory distress caused by influenza A (H1N1) infection in pulmonary aspergillosis, successfully treated with antifungal therapy, oseltamivir, and extracorporeal membrane oxygenation.

Key Words: acute promyelocytic leukemia, immunodepression, influenza A (H1N1), aspergillosis

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In April 2009, a novel influenza A (H1N1) virus outbreak was reported in Mexico. Subsequently, several cases were reported worldwide[1]; by June 11, 2009, the World Health Organization declared the phase 6 "pandemic" alert level.[2]

Differently to seasonal influenza, mortality from influenza A (H1N1) is worse in infants, young adults, pregnant women, and pathologically obese patients.[3]

Neuraminidase inhibitors, such as oseltamivir and zanamivir, have been proposed as adequate treatment for patients with severe infection or relevant risk factors such as obesity, pregnancy, and immunodepression. Oseltamivir has been widely used among the pediatric population, too.[4,5]

Influenza A (H1N1) infection has been a matter of concern in the setting of the pediatric hemato-oncologic patient care owing to concomitant morbidity and mortality risk factors in children treated for cancer. Any severe viral infection can be dangerous in such patients, especially during the induction phase, when intensive chemotherapy, tumor lysis, and deteriorated patient's general conditions may impair immunity and favor infection.[5,6]

Invasive aspergillosis is one of the most threatening fungal infections in patients who are being treated for cancer owing to immunodepression and prolonged neutropenia.[7]

We describe the case of a patient with influenza A (H1N1) and *Aspergillus fumigatus* pulmonary infection, diagnosed during induction treatment for acute promyelocytic leukemia (APL). In this patient, multiple severe risk factors coexisted: acute leukemia, induction chemotherapy, hemorrhage, poor general conditions, and continued hospitalization.

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From the *Onco-hematology Unit; and †Infectious Disease Unit, Pediatric Hospital "Regina Margherita," Torino, Italy.
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Reprints: Stefano Vallero, MD, Oncoematologia Pediatrica, Ospedale Infantile Regina Magherita, Piazza Polonia Torino, Italy (e-mail: stefano.vallero@gmail.com; stefanogabriele.vallero@unito.it).

CASE REPORT

A 10-year-old-boy was admitted to our onco-hematology unit for fever and hemorrhagic diathesis. The patient had previously been healthy, and was not obese, his body mass index being at 75th centile.

Complete blood count showed white blood cell count (WBC) 30.15×10^9/L, hemoglobin 7.2 g/L, and platelet 18×10^9/L. Coagulation examinations were altered (prothrombin time 53%, international normalized ratio 1.47, activated partial thromboplastin time 38.5 s, D-dimer 33.91 mg/L). Peripheral blood smear showed 90% myeloid blasts, consistent with acute promyelocytic leukemia (APL), French-American-British classification M3. The diagnosis was confirmed on bone marrow (BM) aspiration (95% blasts). Rearrangement *t*(15;17)(PML-RARalpha) was found to be positive (breakpoint bcr1) at molecular analysis. The karyotype on BM was 46,XY,*t*(15;17)(q22;q21).

The patient was then enrolled in the International Children Cancer APL Study 01 protocol, high-risk group. Chest x-ray was normal at diagnosis.

Antibacterial and antifungal prophylaxis with beta-lactam and fluconazole was started. One week after the diagnosis, the patient presented high temperature (40°C), mild dyspnea, and cough; the patient was neutropenic (WBC 0.2×10^9/L, neutrophil 0.03×10^9/L); a computed tomography scan showed whole inferior right lobe parenchymal consolidation, multiple hyperdensity areas on both lungs, with a slight bilateral pleural effusion. Urine *Pneumococcus* and *Legionella* antigen search was negative.

Antigenemia for *Aspergillus* (Platelia) was found to be positive on 2 subsequent controls. Owing to the possible interaction between 13-all-trans-retinoic-acid (used in APL in induction phase) and azoles, liposomal amphotericin B at 3 mg/kg/d was chosen as antimycotic therapy.

Fifteen days after the diagnosis, the patient worsened further, with severe dyspnea, tachypnea, tachycardia, and supraclavicular and sternal retraction. Blood oxygen saturation values were in the range of 75% to 85% in air and 90% with O_2 therapy at 8 L/min. Chest x-ray showed severe bilateral perihilar and inferior lobe congestion and condensation, which was more evident on the right side, with aerial bronchogram. Blood SeptiFast examination[8] was positive for *A. fumigatus* infection, thus antimycotic combination therapy (liposomal amphotericin B at 3 mg/kg/d plus caspofungin at 50 mg/m^2/d) was started.[9]

The chemotherapy was then interrupted and the patient was transferred to the intensive care unit (ICU). At ICU admission, blood count showed WBC 0.4×10^9/L (neutrophils 0.1×10^9/L).

The patient's progressive respiratory failure was unresponsive to noninvasive ventilation and his conditions gradually worsened. Two days after the ICU admission, and 9 days after the beginning

of respiratory symptoms, real-time polymerase chain reaction (PCR) search for influenza A (H1N1) viral genome resulted positive on the throat swab. Thus, the patient was intubated, and antiviral therapy with high-dose oseltamivir (150 mg bid) was started. As conventional ventilation and high-frequency oscillatory ventilation were ineffective, and because of refractory hypoxia, extracorporeal membrane oxygenation (ECMO) was performed and gas exchange gradually improved.

Aspergillus infection was confirmed on bronchoalveolar lavage both with antigen assay and cytologic examination. After the first week, oseltamivir was reduced to conventional dose (75 mg bid).

One month after presentation and 14 days after ECMO and oseltamivir beginning, ECMO was discontinued and the patient was extubated. His clinical condition improved progressively; the chest x-ray showed a reduction of the right medio-basal consolidation areas, and the patient was transferred again to the onco-hematology unit 40 days after diagnosis and 25 days after entering into ICU. At that moment, WBC was 7.48×10^9/L (neutrophils 4.43×10^9/L).

Oseltamivir was discontinued as soon as a negative H1N1 swab was obtained, 22 days after entrance into ICU.

Combination antifungal therapy was withdrawn 23 days after entrance into ICU; monotherapy with liposomal amphotericin B was continued. The last *Aspergillus* antigenemia positivity was recorded 14 days after entering the ICU.

Chemotherapy was started again 48 days after presentation with oral all-trans-retinoic acid; 5 days later, the first consolidation course was administered.

BM examination performed 51 days after presentation showed a morphological complete remission; rearrangement *t*(15;17)(PML-RARalpha) was still positive only in nested PCR, but after I consolidation phase became negative even in nested PCR.

The patient is currently in good general conditions. Multidisciplinary evaluation was performed to ascertain possible pathological consequences related to the infection and the ECMO therapy. So far, the patient does not present any impairment from the neurological, behavioral, or cardiopulmonary point of view. Hepatic and renal functions are normal. Lansky functional score is estimated at 90%.

DISCUSSION

The 2009 pandemic influenza A (H1N1) has affected mostly young adults and children; in the majority of cases it is indolent, although in very rare cases it can lead to respiratory insufficiency and may require intensive care in previously healthy subject.

At our center, approximately 130 children are diagnosed with cancer every year. About one-third of them have leukemia.

During 2009, 36 patients from our center with symptoms and signs compatible with influenza A (H1N1) were screened for the presence of viral genome in the pharyngeal swab. Among them, 16 were affected by acute leukemia, the others being affected mainly by neuroblastoma and Hodgkin lymphoma. Twelve out of 36 patients were neutropenic; 16 out of 36 patients resulted positive for the search of influenza A (H1N1) and received therapy with oseltamivir.

In our experience, influenza A (H1N1) infection management in uncomplicated pediatric cancer patients was successful with the prompt initiation of antiviral therapy. None of our patients, except the case described, needed respiratory intensive care and in most cases all symptoms disappeared after a few days of conventional treatment with oseltamivir.

To our knowledge, this is the first pediatric report of a concomitant infection of influenza A (H1N1) and *Aspergillus fumigatus*. Among our cases, the patient described was the only one with an acute and complicated course, probably owing to the coexistence of 2 infectious complications. Influenza A (H1N1) infection might have been contracted either before admission or during the first hospitalization days, when the patient was visited by his younger brother, who presented flu-like symptoms a few days later.

The viral shedding was particularly prolonged (pharyngeal swab had been consecutively positive for 26 d), as reported elsewhere in literature.[10]

The fact that our patient was on APL chemotherapy induction represented a further challenge in his clinical management. Recently, *Aspergillus* infection was demonstrated to be particularly frequent in acute myeloid leukemia patients, especially during induction therapy, in both adult and pediatric patients.[11]

It is difficult to weigh the contribution of H1N1 to the very severe picture of respiratory insufficiency experienced by our patient. In the first week of treatment for aspergillosis, despite treatment with liposomal amphotericin B, respiratory insufficiency worsened. After the initiation of oseltamivir therapy and ECMO, it was possible to notice a progressive clinical improvement, although it can be argued that during that period chemotherapy had been interrupted and WBC levels had started rising.

Indeed the patient was neutropenic when respiratory symptoms appeared, and when he entered ICU unit. Nadir was reached 5 days after ICU admission (WBC 0.19×10^9/L, neutrophils 0.03×10^9/L). The patient was not given any granulocyte-colony stimulating factor, being a myeloid leukemia in the induction phase.

This case represents a paradigmatic example of how multiple coexistent risk factors can worsen an infectious condition-influenza A (H1N1) infection—otherwise mostly indolent. A concomitant viral respiratory infection might accelerate the worsening of the pulmonary function, and sometimes precipitate a more ordinary and manageable situation.

Antifungal treatment undoubtedly played a primary role in our patient's recovery. It is reasonable to hypothesize that ECMO partially contributed to the respiratory improvement. Indeed, the contribution of oseltamivir remains unclear; we can only theorize its effectiveness in helping the patient overcome the pulmonary infection. Oseltamivir can be administered at higher doses or for a longer time in patients with critical conditions or major risk factors (as recommended by WHO Guidelines on Pharmacological Management of Influenza Virus).

In conclusion, the multidisciplinary treatment approach allowed us to overcome the pulmonary fungal and viral infection, on one hand, and to continue successfully the specific oncologic therapy for APL, on the other.

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