Invasive Aspergillosis Complicating Pandemic Influenza A (H1N1) Infection in Severely Immunocompromised Patients

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We report 5 cases of invasive aspergillosis occurring in severely immunosuppressed patients hospitalized with pandemic influenza A (H1N1). We suggest that infection with influenza A (H1N1) may predispose immunocompromised patients to develop invasive aspergillosis. Physicians should be aware of this potential association to allow early diagnosis and prompt treatment of aspergillosis.

Invasive aspergillosis (IA) is a significant cause of life-threatening infection in severely immunocompromised patients, especially those with acute myeloid leukemia (AML) and those who have undergone hematopoietic stem cell transplantation or solid organ transplantation. The clinical risk factors associated with this infection have been described elsewhere [1, 2] and include viral infections, specifically cytomegalovirus and some respiratory viruses, mainly parainfluenza 3 and respiratory syncytial virus.

Last year, a new strain of influenza A (H1N1) resulted in the first pandemic of the 21st century. This virus caused acute respiratory infection with considerable morbidity and mortality worldwide, especially in immunocompromised patients [3, 4]. Despite the extensive epidemiologic and clinical information collected in the first year of the pandemic, the association between influenza A (H1N1) 2009 infection and IA in immunocompromised patients has not been documented.

We aim to alert physicians to the possibility that pandemic influenza A (H1N1) infection could predispose immunocompromised patients to IA. To this end, we report 5 cases of IA that complicated infection with H1N1 in this population.

METHODS

We report 5 cases of IA occurring in severely immunosuppressed patients (patients with AML receiving chemotherapy or transplant recipients) hospitalized in 3 acute-care academic centers in Barcelona, Spain, during the 2 waves of the A (H1N1) influenza pandemic. A confirmed case of A (H1N1) influenza infection was defined as an influenza-like illness with laboratory-confirmed influenza A (H1N1) infection according to real-time polymerase chain reaction (PCR) or viral culture. For diagnosis of IA, we followed the criteria published by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC/IFICG) [5]. Only patients in whom IA was documented as proven or probable were considered case patients. Galactomannan antigen in serum and bronchoalveolar lavage (BAL) was measured using an immunoenzymatic sandwich microplate assay (Platelia Aspergillus; Bio-Rad; sensitivity, 97.4%; specificity, 90.5%).

RESULTS AND CASE REPORTS

Fifty-seven patients with AML or transplantation were hospitalized with pandemic A(H1N1) infection. Of these, 5 (8.8%) developed IA. Table 1 summarizes their characteristics. Additional information is provided in the case reports.

Case 1

Patient 1, a 57-year-old man, was admitted to undergo liver transplantation. Four days after transplantation, he developed a fever and cough and had purulent sputum. A chest radiograph showed unilobar pneumonia. A nasal swab sample was positive for influenza A (H1N1) by PCR. Oseltamivir was given (150 mg/12 hours). After showing no clinical improvement, the patient underwent bronchoscopy 2 days later. Aspergillus fumigatus was isolated from the BAL fluid. Thoracic computed tomography
<table>
<thead>
<tr>
<th>Patient</th>
<th>sex</th>
<th>age, years</th>
<th>Underlying diseases</th>
<th>Immunosuppressive therapy and chemotherapy</th>
<th>Previous H1N1 vaccination</th>
<th>Other risk factors for IA</th>
<th>Days from H1N1 to IA</th>
<th>Treatment (dosage, mg/12 hours)</th>
<th>Days to negative PCR results</th>
<th>IA diagnosis</th>
<th>IA treatment</th>
<th>30-day outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/57</td>
<td></td>
<td></td>
<td>Liver transplantation (cryptogenic cirrhosis); severe obesity; diabetes mellitus</td>
<td>Cyclosporine; tacrolimus</td>
<td>Unknown</td>
<td>Transplantation; immunosuppressive treatment (tacrolimus plus cyclosporine)</td>
<td>20</td>
<td>Oseltamivir (150)</td>
<td>10</td>
<td>BAL culture; thoracic CT; clinical findings</td>
<td>Amphotericin B lipid complex plus anidulafungin</td>
<td>Recovery</td>
</tr>
<tr>
<td>2/F/48</td>
<td></td>
<td></td>
<td>AML; breast cancer (2008)</td>
<td>Idarubicine; cytarabine; etoposide</td>
<td>No</td>
<td>Age (&gt;40 years); AML; pancytopenia</td>
<td>14</td>
<td>Oseltamivir (75)</td>
<td>12</td>
<td>Serum galactomannan; sputum culture; thoracic CT; clinical findings</td>
<td>Amphotericin B lipid complex followed by voriconazole plus caspofungin</td>
<td>Death</td>
</tr>
<tr>
<td>3/M/78</td>
<td></td>
<td></td>
<td>AML; diabetes mellitus</td>
<td>No</td>
<td>Age (&gt;40 years); AML; pancytopenia</td>
<td>13</td>
<td>Oseltamivir (75)</td>
<td>10</td>
<td>Serum galactomannan; thoracic CT; clinical findings</td>
<td>Voriconazole</td>
<td>Recovery</td>
<td></td>
</tr>
<tr>
<td>4/M/65</td>
<td></td>
<td></td>
<td>Liver transplantation (2004) (viral hepatic cirrhosis); hypertension; diabetes mellitus; stage IIA large B-cell lymphoma</td>
<td>Sirolimus; rituximab; cyclophosphamide; doxorubicin; vincristine; prednisone</td>
<td>No</td>
<td>Age (&gt;40 years); hypertension; diabetes mellitus</td>
<td>9</td>
<td>Oseltamivir (75)</td>
<td>7</td>
<td>BAL culture and serum galactomannan; thoracic CT; clinical findings</td>
<td>Voriconazole</td>
<td>Recovery</td>
</tr>
<tr>
<td>5/F/66</td>
<td></td>
<td></td>
<td>AML; hypertension; mild ulcerative colitis; rectal cancer (2005)</td>
<td>Idarubicine; cytarabine; etoposide</td>
<td>No</td>
<td>Age (&gt;40 years); AML; pancytopenia</td>
<td>23</td>
<td>Oseltamivir (75)</td>
<td>7</td>
<td>BAL culture and serum galactomannan; thoracic CT; clinical findings</td>
<td>Voriconazole plus caspofungin</td>
<td>Death</td>
</tr>
</tbody>
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**NOTE.** AML, acute myeloid leukemia; BAL, bronchoalveolar lavage; CT, computed tomography; LRTI, lower respiratory tract infection; PCR, polymerase chain reaction; URTI, upper respiratory tract infection; TCTS, thoracic computed tomography scanning.

**Table 1.** Clinical Characteristics of Patients With Influenza A (H1N1) Infection and Invasive Aspergillosis (IA)
(CT) showed diffuse alveolar consolidation and nodular opacities. The patient was treated with amphotericin B lipid complex and anidulafungin. Five days later, he presented with allograft rejection and underwent a second liver transplantation. He had a slow but successful recovery.

**Case 2**
Patient 2, a 48-year-old woman, was hospitalized because of fever, dyspnea, and weakness. Laboratory tests showed leukocytosis, thrombocytopenia, and anemia, and chest radiography showed bilateral interstitial infiltrates. AML was diagnosed based on bone marrow aspirate findings, and influenza A (H1N1) infection based on PCR. Oseltamivir treatment (150 mg/12 hours) was initiated. Chemotherapy with idarubicin, cytarabine, and etoposide began 8 days later. Posaconazole prophylaxis was given during neutropenia. The diagnosis of influenza precluded isolating the patient in a room with positive pressure. On day 6, she showed worsening respiratory symptoms and high fever. Thoracic CT revealed bilateral multinodular pulmonary infiltrates. BAL fluid culture and serum galactomannan results were positive. She was treated with amphotericin B lipid complex. The posaconazol serum level was below the therapeutic range, and antifungal treatment was switched to voriconazol and caspofungin. The patient developed acute respiratory distress syndrome and hemodynamic instability requiring admission to the intensive care unit, vasopressors, and mechanical ventilation. She died 2 days later of multiorgan failure.

**Case 3**
Patient 3, a 78-year-old man, was hospitalized because of fever, cough, dyspnea, and pancytopenia. AML was diagnosed based on bone marrow aspirate findings, and influenza A (H1N1) infection based on PCR. Oseltamivir treatment (75 mg/12 hours) and azacytidine were administered. On day 13, the patient was febrile, the serum galactomannan result was positive, and thoracic CT revealed bilateral interstitial infiltrates. BAL fluid culture and serum galactomannan results were positive. She was treated with amphotericin B lipid complex. The influenza diagnosis precluded isolation of the patient in a room with positive pressure. On day 6, she showed worsening respiratory symptoms and high fever. Thoracic CT revealed bilateral multinodular pulmonary infiltrates. BAL fluid culture and serum galactomannan results were positive. She was treated with amphotericin B lipid complex. The posaconazol serum level was below the therapeutic range, and antifungal treatment was switched to voriconazol and caspofungin. The patient developed acute respiratory distress syndrome and hemodynamic instability requiring admission to the intensive care unit, vasopressors, and mechanical ventilation. She died 2 days later of multiorgan failure.

**Case 4**
Patient 4 was a 65-year-old male liver transplant recipient who developed lymphoma. He was hospitalized because of fever, cough, and dyspnea. A chest radiograph showed multilobular pneumonia. A nasal swab sample was positive for influenza A, according to PCR. Oseltamivir (75 mg/12 hours) was administered. Seven days later, the patient’s respiratory symptoms worsened. A new influenza A PCR test was negative. Thoracic CT showed nodular infiltrates. The patient had 2 consecutive positive serum galactomannan tests. Voriconazole was given and the patient had a successful recovery.

**Case 5**
Patient 5, a 66-year-old woman, was hospitalized because of fever, asthenia, and pancytopenia. AML was diagnosed based on bone marrow aspirate findings, and influenza A (H1N1) infection was diagnosed based on PCR of a nasopharyngeal swab sample. Oseltamivir treatment was initiated (75 mg/12 hours). Chemotherapy with idarubicin, cytarabine, and etoposide was given 3 days later. Posaconazole prophylaxis was administered during neutropenia. The influenza diagnosis precluded isolation in a positive-pressure room. On days 20 and 21, serum galactomannan and BAL culture results were positive. The patient was treated with amphotericin B lipid complex. Posaconazol serum levels were below the therapeutic range. Two days later, she suddenly presented with hemiparesis. Brain CT showed a 1.2 inch thalamic nodule with signs of bleeding. The antifungal treatment was changed to voriconazol plus caspofungin. The patient’s clinical condition worsened, with a progressive decrease in her level of consciousness, followed by death a few days after IA diagnosis.

**DISCUSSION**
Based on these case reports, patients with AML or transplant recipients who contract H1N1 appear to have a high risk of IA. In our series, the frequency of IA in this population was 8.8%, much higher than reported elsewhere, especially given that we did not observe any cases among hematopoietic stem cell transplant recipients [1, 2].

Respiratory viral infection caused by parainfluenza 3 or respiratory syncytial virus has been described as a risk factor for developing IA [1, 6]. Furthermore, it has been suggested that influenza could also be related to a greater susceptibility to developing IA [7], although evidence of this association is scarce. Interestingly, the association between pandemic influenza A(H1N1) and IA has recently been reported in 2 immunocompetent adults with no classic risk factors for IA [8]. This association could arise for different reasons. The virus alters the bronchial mucosa, with the resulting epithelial disruption facilitating fungal invasion. More importantly, pandemic influenza A(H1N1) causes more disruption of the epithelium of the lower respiratory tract than the seasonal influenza virus [9]. In addition, infection caused by influenza A (H1N1) may affect local defenses against *Aspergillus*. It has recently been reported that this virus impairs the levels of pulmonary and systemic cytokines and the function of pulmonary phagocytes, producing a state of host adaptive immune deficiency [10]. Pandemic influenza A(H1N1) infection also leads to prolonged and increased levels of
interleukin-10 in the plasma [9, 10]. This cytokine is a known signature cytokine for the Th2 response [11], and adaptive immunity mediated by Th2 is associated with an increased risk for the development of IA [11].

In our patients, most IA cases occurred some days after influenza A (H1N1) infection. The clinical presentation was mainly that of a worsening of respiratory symptoms once the patient’s condition had initially improved. Some of the complications that arose after H1N1 infection, such as acute respiratory distress syndrome, secondary bacterial infections, selection of oseltamivir-resistant strains of the virus, or pulmonary hemorrhage, could lead to a torpid clinical course in immunocompromised patients. Clinicians should bear in mind that Aspergillus infection must be included in the differential diagnosis for these patients.

High-risk hematologic patients usually require a specialized patient care area with a positive airflow relative to the corridor, high-efficiency particulate air filtration, and frequent air changes to prevent infections, especially aspergillosis. However, one of the most critical factors in the management of those immunocompromised patients who are admitted to hospital with influenza A (H1N1) infection is that admission into a room with positive airflow is strongly discouraged to avoid nosocomial spread of the virus.

Our findings reinforce the need to maximize prevention measures against influenza infection in immunocompromised patients. The most effective strategy is annual influenza vaccination. However, the efficacy of vaccines could be compromised in this population due to an insufficient antigenic response. Gueller et al [12] recently reported that the rate of seroconversion after the first dose of influenza A vaccine was poor in patients with hematologic malignancies after hematopoietic stem cell transplantation but increased after a second dose. Further information is needed regarding the usefulness of influenza vaccine in this population. Another important measure that would minimize the risk of influenza in this setting is vaccination of health care personnel and family members against influenza early in the season.

In summary, we would like to draw attention to the increased risk of IA in immunocompromised patients with pandemic influenza A(H1N1) infection, as occurs with other respiratory viruses. Narrow monitoring with serum galactomannan determinations should be performed. In patients with worsening respiratory symptoms, prompt thoracic CT and bronchoscopy should be considered to ensure early diagnosis and treatment of IA.

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