Invasive Pulmonary Aspergillosis in a Puerperant with Drug-induced Agranulocytosis

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Abstract

Invasive pulmonary aspergillosis (IPA) is an acute infection of Aspergillus species to the lungs. It generally occurs in immunocompromised hosts, especially with neutropenia. We report a 30-year-old puerperant, who developed IPA from agranulocytosis. She had been treated for threatened labor with ritodrine and cefepime, one of which induced agranulocytosis. After vaginal delivery of twins, pneumonia emerged in the right lower lobe. She was diagnosed to have IPA according to the halo sign on computed tomography (CT) and positive circulating antibody against Aspergillus, and was treated successfully with oral itraconazole followed by surgical resection. It is important to note that IPA might arise in otherwise immunocompetent hosts when neutropenia is long-standing.

Case Report

A 30-year-old pregnant woman had been well without any episodes of serious infection, and regularly visited a maternity hospital because of pregnancy of twins since the summer in 1999. She felt labor pain and was admitted to that hospital on December 15, when she was in the 32nd week of pregnancy. She was diagnosed to have threatened premature labor, and treated with intravenous injection of both ritodrine hydrochloride (100 μg/min, continuously) and cefepime dihydrochloride (1.0 g, b.i.d.). Thereafter, the same remedy was continued for more than 4 weeks. On January 14, 2000, because her body temperature rose to 39°C and hemogram revealed agranulocytosis, she was transferred to the obstetrical department of Social Insurance Gunma Chuo General Hospital.

At transfer, she was in the 36th gestational week, 163 cm tall and weighed 63 kg. Vital signs were as follows: body temperature 39.6°C, blood pressure 108/70 mmHg, pulse 93/minute. Auscultation of the chest was unremarkable. Laboratory data revealed that white blood cell count was decreased to 1,000/mm³, with 60/mm³ of neutrophils. Hemoglobin level and platelet count were also decreased to 11.3 g/dl and 77,000/mm³, respectively. Serum C-reactive protein (CRP) and lactate dehydrogenase (LDH) were increased to 4.4 mg/dl and 573 IU/l, respectively. Sputum culture was negative for bacteria, fungi, and mycobacteria.

Soon after the transfer, administration of ritodrine and cefepim was discontinued. Instead, subcutaneous injection of granulocyte-colony stimulating factor (G-CSF) and intravenous infusion of piperacillin and clindamycin were begun. On January 15, she gave birth to twins via normal vaginal delivery, but she still had a high fever with chilling. Because chest radiograph revealed faint opacity in right middle lung field (Fig. 1), the antibiotics were exchanged to imipenem-cilastatin (IPM/CS) and fluconazole (FLCZ) on January 17, when the neutrophil count was the lowest (12/mm³). Computed tomography (CT) of the chest on January 21 depicted a mass-like lesion with a “halo” in the apical segment of the right lower lobe (Fig. 1128

Key words: ritodrine, pregnancy, halo sign, surgery

Introduction

There are three different clinical presentations of pulmonary infection by Aspergillus: allergic bronchopulmonary aspergillosis, aspergilloma, and invasive pulmonary aspergillosis (IPA). Of these, IPA, an acute infection of Aspergillus species, occurs almost exclusively in immunocompromised hosts. Although long-standing neutropenia is the major risk of IPA (1), there have been no previous case reports of IPA, which developed during drug-induced neutropenia in otherwise healthy patients. Here, we report a 30-year-old pregnant woman, who developed drug-induced aganulocytosis and suffered from IPA soon after vaginal delivery.

For editorial comment, See p 1073.
Invasive Pulmonary Aspergillosis

2), which suggested pulmonary aspergillosis. IPM/CS and FLCZ were, however, continued, because her body temperature was gradually becoming lower. She became completely afebrile on January 24, with the rise of neutrophils to 5,451/mm³. The infiltration in the right lung, however, extended rapidly to form an air-crescent sign (Fig. 3). Because positive circulating antibody against *Aspergillus fumigatus* was proved by Ouchterlony method, she was diagnosed to have invasive pulmonary aspergillosis and treatment with oral itraconazole (ITCZ) was started. *Aspergillus* galactomannan antigen was not detected by Pastorex *Aspergillus*.

Despite the reduction of the halo after the initiation of ITCZ, a solid mass remained on CT (Fig. 4). The apical segment of the right lower lobe was surgically removed through mini-thoracotomy under the assistance of a videoscope on February 21, in order to eradicate fungal infection. In the resected specimen, a ball-shaped structure was found in a cavity. Microscopic examination revealed that the ball consisted of coagulation necrosis and scanty nucleated cells. In contrast, there were numerous neutrophils in the inner surface of the cavity, accompanied by a small number of calcified branching organ-

Figure 1. Chest radiograph on January 16 revealed faint opacity in the right middle lung field.

Figure 2. Computed tomography of the chest on January 21 depicted a mass-like lesion with a “halo” in the apical segment of the right lower lobe.

Figure 3. Chest radiograph on January 26 soon after neutrophil recovery showed that infiltration in the right lung extended rapidly to form an air-crescent sign.

Figure 4. Computed tomography of the chest on February 15 after the initiation of itraconazole depicted a solid mass with an air crescent sign. The “halo” was reduced.
Figure 5. Microscopic view to the inner surface of the cavity. Numerous neutrophils were found along with a small number of calcified branching organisms, which were regarded as denatured Aspergillus. A: HE stain, ×400, scale bar=50 μm. B: PAS (periodic acid schiff) staining ×1,000. scale bar=50 μm.

Discussion

Invasive pulmonary aspergillosis (IPA) developed in a puerperant with agranulocytosis, which was induced by either ritodrine or cefepime. We have found no previous report in that an otherwise healthy patient developed IPA during drug-induced neutropenia. It is, however, not surprising for IPA to occur during transient leukocytopenia, because there have been some reports of non-immunocompromised hosts who have suffered from IPA (2, 3). It is important to note that anyone with neutropenia is at risk for IPA.

Invasive pulmonary aspergillosis is most commonly found among patients with leukemia and organ transplantation. The major risk factors are long-standing neutropenia of less than 500/mm^3 and treatment with glucocorticoids and/or cytotoxic drugs. Although we could not precisely define the duration of neutropenia in the present case, the nadir of granulocyte count was as small as 12/mm^3. Therefore, we propose that profound drug-induced granulocytopenia was the main cause of IPA in this woman.

Pulmonary aspergillosis was suspected from the characteristic radiographic findings, and diagnosed by serum antibody to Aspergillus in this case. The first CT study on January 21 revealed ground-glass opacity around the mass-like lesion. This halo sign on CT is an important clue for early diagnosis of IPA in immunocompromised hosts (4). We considered IPA, but continued FLCZ, because her body temperature was lowering and a CT halo sign had been observed not only in IPA, but also in various pulmonary lesions including neoplasms, tuberculosis, and other inflammatory processes (5). However, the later formation of an air crescent, which is pathognomonic in pulmonary aspergillosis, prompt us to replace FLCZ with ITCZ on January 26. Aspergillus infection was finally confirmed by positive serum antibody against Aspergillus fumigatus by the Ouchterlony method, while Aspergillus galactomannan antigen was not detected by Pastorex Aspergillus, which has been reported to be inadequate for early diagnosis of IPA (6). Consequently, in this case, administration of ITCZ was delayed for several days after the first CT study. We, however, did not think this suspension profoundly affected the clinical outcome, since her symptoms and serum CRP improved conspicuously over this period with the recovery of the neutrophil count.

Agranulocytosis was induced by either ritodrine or cefepime. Ritodrine hydrochloride is a beta-sympathomimetic agent, which has been widely used for tocolysis in cases of premature labor. There have been several reports stating that prolonged intravenous infusion of ritodrine induces agranulocytosis (7–10). Cefepime is a new cephalosporin antibiotic that was administered in this case under the supposition that the participation of bacterial infection threatened the labor. Although agranulocytosis has not been definitely associated with the use of cefepime, two possible cases of cefepime-induced neutropenia have been described (11). It is plausible that hematopoiesis was affected by the continuous long-term administration of ritodrine rather than cefepime.
Pregnancy might predispose *Aspergillus* infection. Although neutrophil alkaline phosphatase levels of pregnant woman are high in the puerperal period, the impaired ability for neutrophils to kill *Candida* and the reduction of myeloperoxidase activity has been reported (12). It is also well known that cell-mediated immunity is suppressed in pregnancy.

In this case, IPA was treated with oral itraconazole and surgical excision. Initial treatment with intravenous amphotericin B has been recommended in cases of rapidly progressing IPA (13). Since her white cell count was recovering, we had elected itraconazole, which is less toxic and has comparable efficacy to amphotericin B against aspergillus (14). Although itraconazole reduced “halo”, the formation of mycetoma was speculated on the second CT study. Therefore, we decided to remove the lesion in order to eradicate fungal infection and to prevent future hemoptysis.

Air crescent, a diagnostic sign of pulmonary aspergillosis, is found both in its saprophytic and invasive infection. In the former, *Aspergillus* first infects the preexisting cysts or cavities. When aspergilloma, a ball of hyphae, is formed, air crescent sign is visible on chest X-ray or CT. In the case of invasive pulmonary aspergillosis during chemotherapy-induced bone marrow suppression, air crescent formation usually follows the recovery from neutropenia. Although the rise of neutrophil count generally leads to the resolution of IPA, life-threatening pulmonary complications including hemoptysis, pneumothorax and death have been closely associated with rapid granulocyte recovery (15, 16). These observations suggest that neutrophils play a crucial role in the formation of cavities in IPA. In this case, the inner surface of the cavity contained numerous neutrophils and the elastolytic enzymes released from these cells would damage the surrounding tissues to form a cavity. Too rapid increase of granulocytes, which is induced by extended use of G-CSF, might jeopardize the host, although the use of G-CSF seems mandatory during severe neutropenia in order to avoid fatal infection. Therefore, in the case of IPA from granulocytosis, precipitate withdrawal of G-CSF under close monitoring of the leukocyte count is recommended. Additional use of ulinastatin might be useful to inhibit the elastase released from both neutrophils and *Aspergillus* (17).

References