A Case of Invasive Maxillary and Orbital Aspergillosis Inhematopoietic Stem Cell Transplantation Recipient with Severe Aplastic Anemia

Young Don Joo, M.D.[1], Won Sik Lee, M.D.[1], Jung Lim Kim, M.D.[2], Jae Wook Yang, M.D.[2], Hyun Woong Kim, M.D.[2], Seong Kook Park, M.D.[3] and Chang Hak Sohn, M.D.[1]

Departments of [1]Internal Medicine, [2]Ophthalmology, [3]Otorhinolaryngology, College of Medicine, Inje University, Busan, Korea

Invasive aspergillosis (IA) of the paranasal sinuses is a rare infectious complication associated with allogeneic hematopoietic stem cell transplantation (HSCT). However, immunocompromised patients are particularly at risk of fulminant IA. The high risk of an invasive fungal infection (IFI) following allogeneic HSCT is due to several factors, including neutropenia before engraftment, disruption of mucosal barriers by various preparative regimens and the use of broad-spectrum antimicrobial agents, as well as the immunosuppressive effects of prophylaxis and treatment of GVHD. As the therapy for an IFI following allogeneic HSCT is often unsuccessful, the mortality rate is increased by 95%. Therefore,early diagnosis is important to overcome the high mortality of this destructive disease. In previous studies, high risks for the early onset of IA were demonstrated in patients with severe aplastic anemia (SAA), independent of the day of engraftment. Here, we report a case of invasive aspergillosis of the maxillary sinuses and orbit in a 50 years old man with SAA,who underwent an allogeneic HSCT from a HLA-matched sibling conditioned with Cytoxan/Fludara/ATG. ***(Korean J Hematol 2005;40:205-209.)***

Key Words: Maxillary sinus, Orbit, Aspergillosis, Severe aplastic anemia, Allogeneic hematopoietic stem cell transplantation

INTRODUCTION

Aspergillus is a spore-forming fungus, commonly found in soil and decaying vegetable matter.[1)] When the spores are inoculated into anaerobic sinuses, they may become pathogenic. In a immune compromised host, *Aspergillus* species can differentiate into hyphal forms producing toxins that destroy epithelial tissues.[2,3)] The clinical manifestations of diseases caused by *Aspergillus* species are both the results of tissue invasion and destruction by the fungus, and the physiologic effects of the patients' immune response. Identification of hyphal forms characteristic of *Aspergillus* species in tissue biopsies is often required

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㉾ 614-110, 인제의대 부산백병원 혈액종양내과 조혈모세포이식센터
Tel: 051-890-6076, Fax: 051-892-0273
E-mail: yjoo@inje.ac.kr
2005년 제주조혈모세포이식학회 하계학술대회 포스터발표 하였음.

Correspondence to : Young Don Joo, M.D.
Department of Internal Medicine, College of Medicine, Inje University
633-165 Goeguem-dong, Jin-gu, Busan 614-110, Korea
Tel: +82-51-890-6076, Fax: +82-51-892-0273
E-mail: yjoo@inje.ac.kr

for the diagnosis. The most important risk factor for invasive aspergillosis has been neutropenia.[4] The incubation period of invasive aspergillosis is highly variable. The manifestation of invasive fungal sinusitis is often serious.[5,6] Hyphae in sinus can invade mucous and bone, leading to hemorrhagic infarction, and spread into adjacent critical structures, such as the orbit and brain. We report a clinical case of a patient with early invasive aspergillosis of maxillary sinus and orbit in the setting of engraftment failure following allogeneic BMT from a sibling for the treatment of severe aplastic anemia, who underwent second PBSCT from the same donor.

CASE REPORT

A 50 year old male with severe aplastic anemia underwent an allogeneic HSCT after conditioning with cyclophosphamide/fludarabine/ATG from his HLA-matched older brother in December 2004. Until 4 months before admission, the patient had been managed with supportive care including blood transfusion. On admission, the patient was afebrile with no bleeding tendency. The physical examination was negative except for pallor. Plain radiographs showed no abnormalities of paranasal sinuses, chest and abdomen. Routine base line studies before transplantation were negative aside from severe pancytopenia with WBC count of 2,440/μL (ANC 309/μL), hemoglobin value of 7.8g/dL, and platelet count of 10,000/μL. The patient received donor bone marrow stem cells containing 0.5×10^8 MNCs/kg and 0.6×10^6 $CD34^+$ cells/kg on December 22, 2004. GVHD prophylaxis consisted of cyclosporine A and short course of methotrexate. He was housed in single room equipped with HEPA filters until recovery from neutropenia. Prophylactic antimicrobial agents were given during the neutropenic period. He began to complain of the left facial edema, tenderness, and nasal stuffiness on day 5 post HSCT. His facial edema progressed involving the left conjunctiva with ocular pain on day 13 (Fig. 1). Computed tomography scan showed inflammation of the left maxillary and frontoethmoid sinus extending into inferior part of the left orbit (Fig. 2). A provisional diagnosis of acute fulminant sinusitis was made based on the clinical findings. He was prescribed empirical broad spectrum antibiotics. The engraftment of neutrophil and platelet was achieved on day 21 and day 25, respectively. On day 30, full donor chimerism was documented on MNCs and neutrophils through the VNTR study. Despite the engraftment, symptoms of acute fulminant sinusitis persisted. Endoscopic

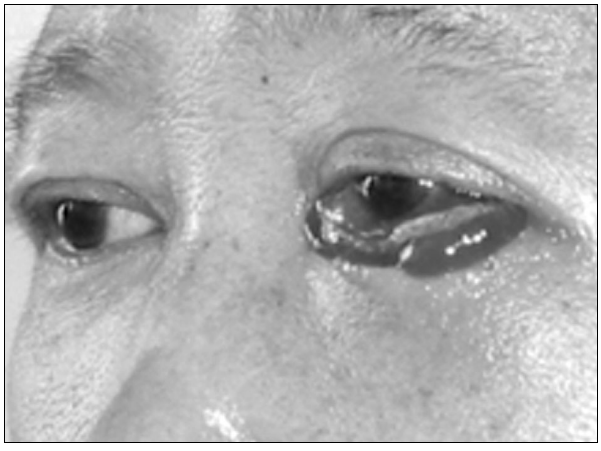

Fig. 1. The gross appearance of the patient showed a slight left exophthalmos, protrusion of lower conjunctival mucosa, left periorbital and cheek swelling.

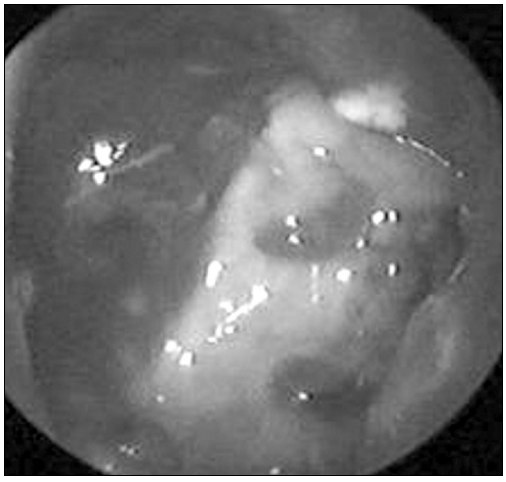

Fig. 2. Endoscopic findings of left maxillary sinus showed brownish white discoloration and edematous necrotic mucosa which were suggestive findings of fungal infection.

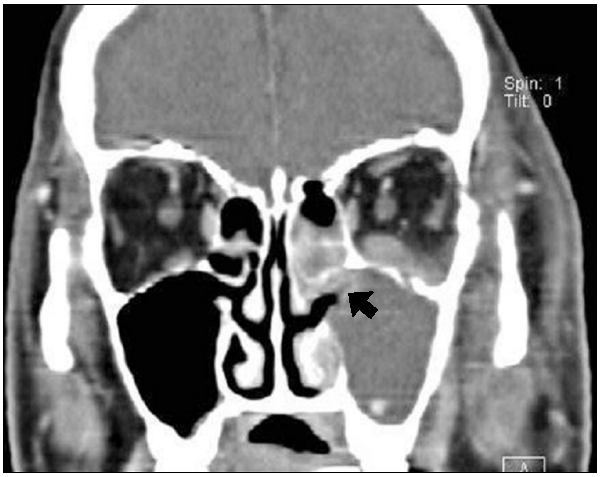

Fig. 3. Computed tomography scan showed left maxillary and frontoethmoid sinus inflammation with extension into inferior part of left orbit.

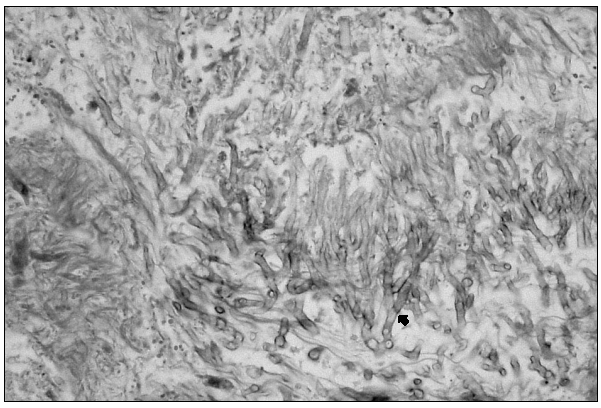

Fig. 4. Histologic examination of surgical specimens showed abundant neutrophilic fibrinoid exudative material containing *Aspergillus* hyphae which was broad, septate, and branch at about 45° (Gomori Metanamine Silver stain, original magnification ×400).

findings of left maxillary sinus showed brownish white discoloration and edematous necrotic mucosa which were suggestive of fungal infection (Fig. 3). He was taken to the operation room for the exploration of the maxillary sinuses under general anesthesia on day 40. A Cadwell-Luc procedure was performed on the left maxillary sinus which revealed granulation tissue and bony maxillary sinus erosion. Histopathologic examination under Gomori Metanamine Silver stain of surgical specimens showed abundant neutrophilic fibrinoid exudative material containing *Aspergillus* hyphae with broad septation and branching at about 45° (Fig. 4). He was started on intravenous amphoterecin B right after the surgical resection. The signs of maxillary sinusitis, conjunctival edema and intermittent fever persisted. On day 61, pancytopenia began to get worse. The chimerism study confirmed impending engraftment failure. A full donor chimerism was changed to a mixed chimerism with 26.44% of recipient cells. For the conversion of mixed chimerism into full donor chimerism, a second peripheral blood stem cell was infused on day 94 from the same donor after less intensive preparation consisting of cyclophosphamide alone. Infused peripheral stem cells were 5.0×10^6 $CD34^+$ cells/kg. He had been placed on intravenous amphoterecin B (1.0～1.5mg/kg/day, cumulative dose 3,242mg) for 36 days and later on liposomal amphoterecin B (3mg/kg, cumulative dose 2,700mg) for 15 days as he developed renal insufficiency. His condition continued to deteriorate in spite of the second HSCT. The pancytopenia persisted with WBC count of 210/μL, hemoglobin 7.9g/dL, and platelet 14,000/μL. On the day 6 post 2nd HSCT, uncontrollable severe hypoxia developed. Chest X-ray showed a total haziness of both lungs. Mental obtundation and renal failure followed. On day 8 post 2nd HSCT, the patient died.

DISCUSSION

Aspergillus spp spores are prevalent in the human environment, especially in air, are often inhaled explaining the respiratory tract as the most common primary site of infection. Occasionally, the fungus can enter the body through skin contacting or skin wound, which represents secondary transmission routes of infection.[7,8] Walsh et al.[9] found the fungus colonizing patients principally via aerogenic transmission and secondarily by contact transmission. Depending on the patient's defense mechanism, aspergillosis may take one of the following clinical courses: noninvasive form, include-

ing the allergic and saprophytic features affecting immunocompetent patients with low morbidity and mortality, and invasive form, in which there is invasion of the fungus into viable tissues resulting in severe necrosis. The latter feature is more likely to occur in immunocompromised patients with higher morbidity and mortality.[10,11] In the head and neck region, both forms of aspergillosis have been reported, with invasive form affecting tissue of the sinus and orbit region. Some investigators have pointed the fact that nosocomial source acquisition of aspergillosis is increasingly recognized as an important source of the invasive form of the disease.[12,13] Invasive aspergillosis of the paranasal sinus in an immunocompromised patient is uncommon, however, its incidence is increasing in the recent years. Early diagnosis is essential for early intervention to avoid the high morbidity and mortality. Housing the patient undergoing hematopoietic stem cell transplantation in a protective environment equipped with high-efficiency particulate air filtration does not guarantee prevention of aspergillosis. Careful anterior rhinoscopy followed by computed tomography of the sinus is of help in establishing the diagnosis, which should be confirmed by histologic study. Biopsy through the maxillary sinus, the more accessible site, demonstrated the typical septate hyphae of *Aspergillus* species. Histologic evidence of tissue invasion by fungal hyphae is also of help in identification of invasive nature of aspergillosis. Recovery from invasive aspergillosis on immune compromised state depends on immune reconstitution in this case. Marr et al.[14] a tendency for early IA among patients with aplastic anemia, independent of day of engraftment, and a tendency for late IA among patients with multiple myeloma, independent of GVHD. Invasive sinonasal disease caused by *Aspergillus* can be very aggressive and tends to spread to contiguous structures with mucosal invasion resulting in tissue infarction. When disease involves the paranasal sinuses, lateral nasal wall, orbits, or intracranial structures, extensive surgical debridement is mandatory.[15] In this case, shortly after the diagnosis of a invasive maxillary asperogillosis, a full course of parenteral amphoterecin B administration was carried out. Interestingly, the patient was housed in a high-efficiency particulate air-filtered positive-pressure airflow room during the treatment period, and there was no other documented case of aspergillosis in our unit. The case might have come from an endogenous source, i.e., colonization before transplantation. Despite the existence of powerful broad-spectrum antifungal drugs, the prognosis of proven invasive aspergillosis in allogeneic stem cell transplant recipients continues to be very poor. The role of new multiple antifungal drugs, need to be defined by large, well-designed clinical trials. Finally, this case further emphasizes the need for prompt diagnosis of invasive aspergillosis of the paranasal sinus in stem cell transplant recipients for early therapeutic intervention.

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