RHINOCEREBRAL ASPERGILLOSIS IN PATIENTS UNDERGOING BONE MARROW TRANSPLANTATION

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Rhinocerebral aspergillosis (RA) is becoming increasingly common in patients undergoing bone marrow transplantation (BMT). The disease can involve nearly all major head and neck structures, including the nose, paranasal sinuses, and orbits. Intracranial extension of the infection is of major concern, since this is usually a fatal complication. Our study population comprised 423 consecutive BMT patients at Hadassah University Hospital from January 1986 to August 1992. Eight patients (1.9%) developed RA, 5 of whom had underlying hematologic malignancies, and 3 of whom had severe aplastic anemia. Only 2 of the 8 patients responded completely to therapy, with a follow-up of 15 months. It appears that RA is a fatal complication in immunocompromised patients post-BMT. Early diagnosis followed by extensive surgical debridement of necrotic tissue and systemic, as well as topical, antifungal therapy with amphotericin B or its new formulations and the patient’s recovery of bone marrow function may improve the outcome of this life-threatening complication.

KEY WORDS — aspergillosis, bone marrow transplantation, nose, orbit, paranasal sinuses, rhinocerebral aspergillosis.

INTRODUCTION

Deep or disseminated fungal infections are leading causes of morbidity and mortality in patients with hematologic malignancies and a compromised immune system. Bone marrow transplantation (BMT) recipients are prone to develop fungal infections because of profound immunosuppression, prolonged neutropenia, and the wide use of broad-spectrum antibiotics. Most fungal sinusitis in BMT patients is caused by Aspergillus species. Diagnosis of rhinocerebral aspergillosis (RA) is sometimes quite difficult, as presenting symptoms can be nonspecific, especially in BMT patients with leukopenia, fever, and concomitant infections. Computed tomography is an important diagnostic tool. Final diagnosis is confirmed by microbiologic and/or histologic examinations.

Only a few reports systematically evaluate fungal sinusitis in a large group of BMT patients. Treatment of RA usually involves surgical debridement, irrigation of the affected cavity, and systemic antifungal therapy with amphotericin B, currently the drug of choice for most systemic mycoses. In the present study we assessed the incidence, presenting symptoms, diagnostic procedures, treatment, and outcome of RA in 423 patients who underwent BMT between January 1986 and August 1992.

MATERIALS AND METHODS

Patients. There were 423 BMTs performed at the Israel National BMT Center at Hadassah University Hospital between January 1986 and August 1992. Of these, 256 were allogeneic, from a matched sibling donor, and 167 were autologous BMTs. The male patients numbered 249 and the female 174, with an average age of 21.9 years (range 3 months to 57 years). One hundred ten patients had acute myelogenous leukemia, 67 acute lymphoblastic leukemia, 12 myelodysplastic syndrome, 41 chronic myelogenous leukemia, 76 lymphoma (Hodgkin’s and non-Hodgkin’s), 30 severe aplastic anemia, and 87 other diseases. Of the 256 patients who underwent allogeneic BMT, 92 (36%) developed graft-versus-host disease (GVHD) of at least grade II. All patients were kept in rooms fitted with an air filtration system, and beginning in July 1992, a high-efficiency particulate air filter system was in use. The records of all patients who developed RA were retrospectively reviewed. Student’s t test was used for statistical analysis.

RESULTS

Of the 423 transplanted patients, 8 (1.9%) were found to have RA: 5 patients had hematologic malignancies (acute myelogenous leukemia 3, acute lymphoblastic leukemia 1, myelodysplastic syndrome 1), and 3 severe aplastic anemia (Table 1). Of interest, 3 of the 30 (10%) patients receiving transplants for severe aplastic anemia developed RA, while the incidence of the same complication among patients with acute leukemia was 2.25% (p < .05). Of the 8 RA patients, 5 underwent allogeneic BMT from a
fully matched, related donor, 2 underwent autologous BMT, and 1 developed RA at the beginning of conditioning, prior to BMT (Table 1).

The median interval between BMT and RA was 20 days (range 2 to 90 days). Six of the 8 patients had protracted neutropenia (median 11 days, range 4 to 60 days) with a median neutrophil count of 0.13 x 10⁹/L, while 2 had normal neutrophil counts at the time of RA diagnosis (Table 1). All patients received broad-spectrum antibiotics, and 2 were receiving amphotericin B empirically at the time of diagnosis of RA. There was no clustering of cases in terms of the month of year at onset of the infection, and there was no association between a nosocomial source of infection such as demolition works and the infection. There was no statistically significant difference in duration of neutropenia between patients with aplastic anemia and those with leukemia.

**Presenting Symptoms.** Fever was the most common finding, for which the patients were extensively investigated. This included, among others, routine sinus and brain computed tomography (CT) and otorlaryngological evaluation of the patient when sinusitis was evidenced on CT. Facial pain and tenderness over the involved sinus(es), hypesthesia, and localized pallor of the nasal septum or turbinate mucosa were the initial findings in all patients. Rhinorrhea was not a common finding, but when it was present, a turbid yellow or straw-colored nasal discharge was seen. The nasal mucosae were observed to be dry, crusted, pale, painless, and not bleeding easily even when irritated, despite the ease with which most of these patients bled because of associated thrombocytopenia. Obstruction of the involved nostril was an early finding that preceded frank necrosis. The obstruction was due to adherence between the septal mucosa and the mucosa of the involved turbinate, more commonly the inferior turbinate. Necrosis of the mucosa of the nasal septum and/or turbinate or palate manifesting as black crusts was a late finding and when present meant an already rapidly advancing disease. Periorbital swelling and redness, proptosis, and visual loss were ominous signs. Necrosis of facial skin (Fig 1), when it appeared, progressed very rapidly, ie, by the hour, especially in severely neutropenic patients. Disorientation, orbital apex syndrome, cavernous sinus syndrome, hemiparesis, and seizures were manifestations of intracranial spread of the infection.

**Diagnosis.** A CT scan of the brain and sinuses was performed on all patients. Air-fluid levels, frequently seen in immunocompetent hosts with sinusitis, were not encountered in these patients. Mucosal thickening was more commonly seen. Opacification of the sinuses represented extensive disease with tissue necrosis. Calcification of the involved sinus(es) or orbit was rarely seen, since this was not a chronic infection. There was a unilateral predilection of the infection of the sinuses and eventually the orbit. The

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**TABLE 1. CLINICAL CHARACTERISTICS AND HEMATOLOGIC FINDINGS OF PATIENTS WITH RA**

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age</th>
<th>Sex</th>
<th>Disease</th>
<th>BMT</th>
<th>GVHD</th>
<th>Days From BMT to RA</th>
<th>PMNs at RA Diagnosis (x10⁹/L)</th>
<th>Duration of Neutropenia (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>M</td>
<td>MDS</td>
<td>Allo</td>
<td>No</td>
<td>18</td>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>F</td>
<td>AML</td>
<td>Allo</td>
<td>No</td>
<td>68</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>M</td>
<td>AML</td>
<td>Auto</td>
<td>No</td>
<td>12</td>
<td>200</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>F</td>
<td>AML</td>
<td>Auto</td>
<td>No</td>
<td>20</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>M</td>
<td>ALL</td>
<td>Allo</td>
<td>Yes</td>
<td>90</td>
<td>1,500</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>F</td>
<td>SAA</td>
<td>Allo</td>
<td>No</td>
<td>22</td>
<td>2,000</td>
<td></td>
</tr>
<tr>
<td>7*</td>
<td>42</td>
<td>M</td>
<td>SAA</td>
<td></td>
<td></td>
<td>300</td>
<td>300</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>F</td>
<td>SAA</td>
<td>Allo</td>
<td>No</td>
<td>2</td>
<td>100</td>
<td>8</td>
</tr>
</tbody>
</table>


*Developed RA prior to BMT.

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Fig 1. (Patient 8) Fourteen-year-old girl with severe aplastic anemia who developed rhinocerebral aspergillosis. Note intranasal and right facial skin necrosis. Palate, right orbit, and right ethmoidal and maxillary sinuses, as well as intracranial soft tissues, were involved.
TABLE 2. MICROBIOLOGIC FINDINGS, TREATMENT, AND OUTCOME OF PATIENTS WITH RA

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Aspergillus Species</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Flavus</td>
<td>Caldwell-Luc, topical AmB, AmB</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>Quadrilineatus</td>
<td>EE + Caldwell-Luc, turbinectomy, GT, ABCD</td>
<td>Resolution</td>
</tr>
<tr>
<td>3</td>
<td>Flavus</td>
<td>EE + antrotomy, turbinectomy, topical AmB, ABCD</td>
<td>Resolution</td>
</tr>
<tr>
<td>4</td>
<td>Flavus</td>
<td>EE + antrotomy, septectomy, GT, ABCD</td>
<td>Death</td>
</tr>
<tr>
<td>5</td>
<td>Flavus</td>
<td>AmB, topical AmB</td>
<td>Death</td>
</tr>
<tr>
<td>6</td>
<td>Flavus</td>
<td>EE, Caldwell-Luc, AmB</td>
<td>Death</td>
</tr>
<tr>
<td>7</td>
<td>Flavus</td>
<td>AmB</td>
<td>Death</td>
</tr>
<tr>
<td>8</td>
<td>Flavus</td>
<td>Degloving approach to nose, sinuses, and palate, topical AmB, GT, ABCD</td>
<td>Death</td>
</tr>
</tbody>
</table>


most frequently affected sinus was the maxillary, followed by the ethmoidal, the sphenoidal, and then the frontal sinuses.

The responsible fungal pathogens were Aspergillus species: Aspergillus flavus in 7 patients and Aspergillus quadrilineatus in 1. The pathogenic fungi were detected by histologic examination and tissue culture in all patients.

_Treatment._ Six of the 8 patients underwent surgical debridement. Extensive sinusectomy procedures were carried out in order to remove all necrotic soft tissue and bone to create a wide cavity appropriate for local irrigation with amphotericin. Surgical procedures included the Caldwell-Luc operation, external ethmoidectomy, sphenoidectomy, nasal septectomy and turbinectomy, and a degloving approach to the nasal cavity, maxillary sinus, and palate for the excision of gross necrotic soft tissue and bone (Table 2). More than one surgical debridement was required for each patient as new necrotic tissue appeared.

Postoperative complications such as massive bleeding were minimal, because adequate preoperative, intraoperative, and postoperative transfusion of thrombocytes and cryoprecipitate was given. Also, excessive bleeding was prevented by adequate packing of newly created nasomaxillary, ethmoidonasal, or ethmoido-orbital cavities with antibiotic-impregnated gauze that was left in place for 24 to 48 hours before removal.

Six patients received local amphotericin lavage or irrigation through a catheter left in the newly created surgical cavity. All patients received, at least initially, systemic treatment with amphotericin B (Fungizone). Two patients were initially given conventional amphotericin B, but were then switched to amphotericin B colloidal dispersion (ABCD) because of treatment failure and/or toxic side effects, and 2 patients who were receiving conventional amphotericin were switched to ABCD after the diagnosis of invasive Aspergillosis was confirmed. The patients were treated for a median of 4.0 weeks (range 0.5 to 20 weeks) and received amphotericin B (both conventional and ABCD) at a daily dose of 1 mg/kg and at a median dose of 1,840 g (range 152 to 4,600 g). Three of the patients were treated concomitantly with granulocyte transfusions for an average of 11 days.

_Outcome._ Only 2 patients recovered (follow-up of 15 months). The other 6 died, a median of 30 days after diagnosis of the fungal infection (range 5 to 60 days). Three of those died because of the extensive rhinocerebral fungal infection and 3 because of cytomegalovirus pneumonitis, acute respiratory distress syndrome, and bone marrow failure, respectively.

**DISCUSSION**

Life-threatening fungal infections are becoming increasingly common in immunocompromised patients receiving intensive chemoradiotherapy, especially patients with leukemia and patients who have had BMT. Fungal infection of the paranasal sinuses in these patients is relatively rare, but is significant because of the rapidity with which adjacent vital structures such as the orbit and intracranial tissues are invaded, usually with fatal results. The _Aspergillus_ fungus is the most common pathogen found in sinus disease. The maxillary antrum is the most common sinus involved, followed by the ethmoidal as well as the sphenoidal and frontal sinuses. Infection of the sphenoidal and frontal sinuses is found not usually in isolation, but in association with either maxillary or ethmoidal sinus infection.

The clinical manifestations of RA are often subtle, and a high degree of suspicion should be maintained. The most frequent clinical features are persistent fever without a known source, neutropenia, nasal obstruction, focal facial tenderness over the involved sinus(es), and localized pallor or necrosis of the nasal septum or turbinate. Periorbital swelling and redness followed by proptosis, ophthalmoplegia, and orbital apex syndrome signify orbital invasion. Cavernous
Fig 2. (Patient 7) Forty-two-year-old man with severe aplastic anemia who developed rhinocerebral aspergillosis. Note chemosis of left orbit. There was visual loss and intracranial extension.

Immune suppression with antineoplastic chemotherapy, bone marrow transplantation (BMT), and other factors such as splenic sequestration eventually results in sinus syndrome with eventual brain involvement rapidly follows. Further intracranial extension may be signaled by focal or diffuse brain dysfunction or by the involvement of additional cranial nerves. We observed these clinical findings in 4 of our patients, who had evidence of intracranial involvement in the form of seizures and multiple cranial nerve palsies.

Diagnosis of Aspergillus fungal infection of the nose and paranasal sinuses is confirmed by a biopsy of the suspected lesion and pathologic or microbiologic evidence of septate hyphae (as compared to nonseptate hyphae in mucormycosis). Computed tomography is yet the best imaging modality to detect the presence of sinus infection and to determine the extent of the infection. It is our policy to submit all patients to CT evaluation of the head, including the sinuses, before transplant. Any patient detected as having a sinus infection or any other infection is treated prior to transplantation. One of the patients (No. 7; Table 1) developed RA during conditioning just before BMT. The procedure was delayed until the infection could be eradicated, because the presence of any infection, including fungal, is an added risk for BMT. Computed tomography may show complete or partial opacification of the nasal airway and one or more sinuses. Destruction of bone may be clearly seen. When aspergillosis penetrates the lamina papyracea, invasion of the orbit occurs. When the entire orbit is involved, the muscles and the optic nerve are obliterated. Ultimately, the globe itself is destroyed (Fig 2).

Treatment of RA includes systemic antifungal therapy and surgical debridement of necrotic tissue. Currently, amphotericin B is the drug of choice for treating most systemic mycoses caused by opportunistic fungi. Recently, new preparations of liposomal amphotericin B and ABCD have been developed. Preliminary experience with the new preparations has shown less nephrotoxicity even at larger doses, but it is not known whether they are more effective.

Extensive surgical debridement of necrotic tissue with a margin of healthy tissue is necessary. However, mutilating procedures should be avoided, because the infection is angioinvasive and adequate excision of all necrotic tissue, even with a wide margin of healthy tissue beyond, is difficult. Also, residual granulomas next to vital structures such as dura or sclera have been observed to regress and heal by fibrosis following concomitant drainage and aeration of the involved sinus, in addition to recovery of bone marrow function and the production of adequate circulating neutrophils.

All of our patients were treated with conventional amphotericin B, and 4 patients with ABCD. Three patients received granulocyte transfusion concomitantly. Granulocyte transfusion along with amphotericin B has been sporadically reported in the literature. However, this is the first report of the administration of ABCD along with granulocyte transfusion. We observed no evidence of pulmonary infiltrates, a previously reported complication. We were not able to identify specific reasons for the favorable outcome of the 2 patients (Nos. 2 and 3). One patient was infected with A. quadrilineatus, and the other with A. flavus as were all the other patients. They were both treated with ABCD, as were 2 other patients, and did not have GVHD (nor did most others who did not recover). However, these 2 surviving patients had good neutrophil recovery eventually.

Rhinocerebral aspergillosis in BMT patients is an increasingly common fatal complication. Early diagnosis and aggressive multidisciplinary therapy, including systemic treatment with new preparations of amphotericin B, particularly ABCD, in conjunction with granulocyte transfusion and the administration of granulocyte-colony stimulating factor, may improve the outcome of this life-threatening complication in these patients. Prospective randomized trials in larger groups with long-term follow-up are needed in order to confirm our limited experience. However, ultimate recovery may be achieved only when the patient’s bone marrow function recovers and adequate circulating neutrophils are produced.

REFERENCES


31st WORKSHOP ON INNER EAR BIOLOGY

The 31st Workshop on Inner Ear Biology will be held in Montpellier, France, September 10-13, 1994. For further information, please contact Dr Guy Rebillard, INSERM U-254, Laboratoire de Neurobiologie de l'Audition, CHU Hopital St Charles, 34295 Montpellier cedex 05, France; telephone (33) 67 33 69 75; fax (33) 67 52 56 01.