

Mucormycosis and hemopoietic transplants

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Mucormycosis is becoming recognized as a serious complication in patients undergoing hemopoietic transplantation (HT), because it is a major cause of morbidity and mortality. In our institution 4 cases of mucormycosis in post-HT period among 345 patients undergoing HT were diagnosed between 1984 and 1997. We studied the clinical characteristics of these cases and we conclude that mucormycosis is not a common infection in patients undergoing HT but that it is followed by a high morbidity and mortality. Maintained neutropenia is the most important risk factor.

Mucormycosis is becoming recognized as a serious complication in patients undergoing hemopoietic transplantation (HT), because it is a major cause of morbidity and mortality. Mucormycosis is a term used to describe the diseases caused by fungi of the family *Mucoraceae*, which includes the genera *Absidia*, *Apo-physomyces*, *Mucor*, *Rhizomucor* and *Rhizopus*.¹ Its wide clinical spectrum includes sinonasal, rhinocerebral, pulmonary, disseminated, gastrointestinal, cutaneous, and miscellaneous disease forms.^{2,3} The histologic findings are broad, non-septate hyphae that branch at right angles, vascular invasion, tissue necrosis and infarction. Prolonged neutropenia, extended steroid treatment and immunosuppression are implicated as risk factors for post-BMT mucormycosis.²

In our institution 32 cases of invasive mycosis (candidiasis 13, aspergillosis 14, mucormycosis 4 and cryptococcosis 1) were diagnosed between 1984 and 1997 in the post-HT period among 345 patients undergoing HT. The clinical characteristics of the four cases of mucormycosis are summarized in Table 1. The median age of the patients affected was 22 years (range 19-25). Two were male and two female. Primary disease diagnosis was CML (chronic phase), AML, aplastic anemia, and Fanconi's anemia (without previous treatment with deferoxamine). All had received allogeneic HT, three of them, bone marrow from an HLA-identical sibling donor, and the other umbilical cord blood. The diagnosis of mucormycosis was established by identifying the fungi in histologic samples and in one case (UPN 108), *Rhizopus spp.* was isolated in microbiological cultures. Autopsies were performed in two cases (UPN 20 and 314-partial). In three cases, the diagnosis was made in the early post-HT period (days: +4, +11, and +21). These patients had sustained neutropenia before HT. The remaining case was diagnosed at the same time as the development of acute GVHD and steroid therapy. The clinical presentations were: rhinocerebral

Table 1. Clinical characteristics and evolution of patients.

UPN	Age-Sex diagnosis	Hematopoietic source	Conditioning regimen / GVHD prophylaxis	Post-transplant evolution	Days after transplant / site of infection	Neutropenia	Treatment	Outcome
108	25-M CML	HLA-identical sibling donor	TBI (12Gy) + CY (120 mg/kg) / MTX+Csa	Cytogenetic relapse + 4 years post-transplant IFN treatment with partial cytogenetic response IDL with aGVHD development grade II and complete remission (morphologic and cytogenetic)	+6 years and 2 months / rhinocerebral	No	Liposomal amphotericin B (total dose 12 g) Surgical debridement	Alive
314	22-F Fanconi's anemia	UCB-UR	TBI (12 Gy) + CY (40 mg/kg) + ATG (90 mg/kg) PDN + Csa		4 days / thoracic wall + lung	Yes (> 6 months)	Liposomal amphotericin B Granulocytic infusion Surgical debridement	Dead +13 days post-transplant
20	23-F AML	HLA-identical sibling donor	TBI (12 Gy) + CY (120 mg/kg) / MTX		21 days / thoracic wall surrounding central venous access	Yes (+76 days)	Amphotericin B Surgical debridement	Dead +78 days post-transplant (CMV pneumonia)
38	19-M AA	HLA-identical sibling donor	TBI (12 Gy) + CY (120 mg/kg) / Csa		11 days / rhinocerebral	Yes (> 6 months)	Amphotericin B	Dead +20 days post-transplant

UPN: unique patient number; M: male; F: female; CML: chronic myeloid leukemia; AML: acute myeloid leukemia; AA: aplastic anemia; UCB-UR: umbilical cord blood - unrelated; GVHD: graft-versus-host disease; TBI: total body irradiation; CY: cyclophosphamide; MTX: methotrexate; ATG: antithymocyte globulin; Csa: cyclosporin; IDL: infusion of donor lymphocytes.

(n=2), thoracic wall and lung (n=1), cutaneous involvement (surrounding a central venous access) (n=1). All patients received high doses of amphotericin B and surgical debridement was performed in three. One patient is alive, three are dead (two died of mucormycosis and one of CMV pneumonia).

We conclude that mucormycosis is not a common infection in patients undergoing HT but a high morbidity and mortality follow it. Sustained neutropenia is the most important risk factor. The early diagnosis followed by prolonged treatment with amphotericin B and surgical debridement, when possible, can improve the survival of these patients.

Key words

Mucormycosis, transplantation, hemopoiesis

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Transfusion-related acute lung injury associated with an NA1-specific antigranulocyte antibody

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Transfusion-related acute lung injury (TRALI) is an infrequent complication of hemotherapy. Antigranulocyte antibodies, most of them present in donor's serum, have been implicated in its pathogenesis. We describe a case of TRALI, following red blood cell transfusion, associated with an antigranulocyte antibody with NA1 specificity in the patient's serum.

A 70-year-old female with a history of previous transfusions was admitted for an elective prosthetic hip implant. Following surgery a single unit of non-buffy-coat deprived packed red blood cells with saline, adenine, glucose, mannitol, (SAG-M) was transfused. Thirty minutes later the patient developed acute respiratory failure. A chest X-ray revealed bilat-

eral alveolar infiltrates with a non-dilated heart, findings consistent with acute pulmonary edema. A Swan-Ganz catheter was placed, showing pulmonary and central venous pressures suggestive of TRALI. Systemic corticosteroids (prednisolone 2 mg per kg) were started, and the patient required mechanical ventilatory support. The clinical course was favorable with resolution within 48 hours. In order to establish a serologic diagnosis, antileukocyte antibodies were searched for in both the patient's and donor's serum. Anti-HLA antibodies were ruled out with a lymphocytotoxic test using the patient's serum and a lymphocyte panel (n=18) of known HLA phenotypes. The presence of specific antigranulocyte antibodies was studied with granuloagglutination and an indirect immunofluorescence (GIFT) test. Both tests showed the presence of an antigranulocyte antibody in the patient's serum, and when tested against granulocytes of known phenotype, the antibody was shown to be specific for NA1 (Table 1). The patient's and donor's granulocyte phenotypes were established by an immunofluorescence technique with flow cytometry (FACScan, Becton Dickinson, San José, CA, USA) using monoclonal antibodies specific for NA1, NA2 and CD16. The patient's phenotype was NA2/NA2, CD16⁺, while the donor's was found to be NA1/NA2, CD16⁺. Finally, once the antibody's specificity had been established, a confirmatory bidirectional cross-match was performed with a positive reaction with the patient's serum and the donor's granulocytes (Table 1). The diagnosis was TRALI associated with an antigranulocyte antibody with NA1 specificity in the patient's serum.

TRALI is a relatively infrequent transfusion-related complication, although it ranks second in transfusion-related mortality.¹ TRALI has been described following the transfusion of the majority of blood components;²⁻⁹ its incidence has been estimated as 1 in 5000 transfusions.² Clinically TRALI presents as an adult respiratory distress syndrome. Diagnosis requires a high index of suspicion and is made by exclusion. With appropriate supportive treatment, 80% of patients can be expected to recover fully, and mortality ranges from 5 to 10% in most studies.² The pathogenesis of TRALI is not fully understood,

Table 1.

Phenotype of tested granulocytes	NA1NA1	NA2NA2	NA1NA2 (Donor)	NA1NA2
Patient's serum	+++	-	++	++
Multispecific anti-HLA antiserum	+++	+++	+++	+++
AB serum	-	-	-	-