Transfusion Medicine and Hemotherapy

Case Report · Fallbericht

Transfus Med Hemother 2005;32:252–254
DOI: 10.1159/000087922

Received: December 29, 2004
Accepted: May 15, 2005
Published online: September 23, 2005

Rhino-Orbito-Cerebral Mucormycosis in Transfusion-Associated Graft-versus-Host Disease: Case Report

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Key Words
Transfusion-associated GvHD · Non-irradiated whole blood transfusion · Mucormycosis

Summary
Transfusion-associated graft-versus-host disease (TA-GvHD) is in most cases refractory to immunosuppressive therapy and fatal because of severe bone marrow aplasia. Mucormycosis is a rare invasive fungal infection, but it has clinical importance because of its often delayed diagnosis and high mortality. Invasive mucomycosis is frequently associated with diabetes mellitus, neutropenia, severe immunodeficiencies following steroid therapy, organ transplantation, cytotoxic chemotherapy, and AIDS. We present a case of lethal rhino-orbito-cerebral mucormycosis after TA-GvHD in an initially healthy patient.

Schlüsselwörter
Transfusionsassoziierte Graft-versus-Host-Erkrankung · Transfusion unbestrahlten Vollbluts · Mukor-Mykose

Zusammenfassung
Die transfusionsassoziierte Graft-versus-Host-Erkrankung (TA-GvHD) ist in den meisten Fällen refraktär gegenüber einer immunsuppresiven Therapie und von fatalem Ausgang wegen der schwerwiegenden Knochenmarkaplasie. Die Mukor-Mykose ist eine seltene invasive Infektion, aber sie hat eine klinische Bedeutung wegen der oft verspäteten Diagnosestellung und hohen Mortalität. Die invasive Mukor-Mykose tritt insbesondere auf bei Diabetes mellitus, Neutropenie, ernsthaften Immundefizienzen nach Steroid-Therapie, Organtransplantationen, zytotoxischer Chemotherapie und AIDS. In diesem Artikel wird ein Fall von letaler rhinoorbitozerebraler Mukor-Mykose nach TA-GvHD bei einem initial gesunden Patienten vorgestellt.

Introduction

Transfusion-associated graft-versus-host disease (TA-GvHD) may occur when viable donor T lymphocytes from transfused blood products engraft in a severely immunocompromised recipient [1]. However TA-GvHD has even been reported in immunocompetent patients following the transfusion of cellular blood products from close relatives or random donors with similar HLA antigens, especially when the donor is homozygous for an HLA haplotype [2–4].

Mucormycosis is a rare invasive opportunistic infection caused by fungi of the order Mucorales, family Mucoraceae, which includes the genera *Absidia*, *Mucor*, *Rhizomucor*, and *Rhizopus*. Invasive mucormycosis is particularly associated with diabetes

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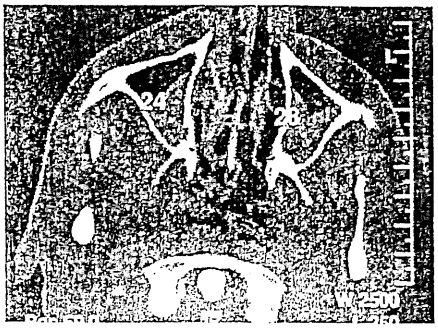


Fig. 1. Fluid and air density the paranasal sinuses extending to the nasal cavity.



Fig. 2. Oral, nasal and palatal black necrotic lesions increasing gradually.

mellitus and profound immunodeficiencies [5]. Mucormycosis of the central nervous system occurs as a consequence of penetrating growth of the fungus from its initial site of invasion in the nose or paranasal sinuses through the adjacent bones into the orbita and brain [6]. Once the infection has reached the orbita or the brain, the outcome of rhino-cerebral mucormycosis is mostly fatal [7]. We present a case of rhino-orbito-cerebral mucormycosis following long-term neutropenia due to TA-GvHD.

Case Report

A 30-year-old woman without previous medical illness had undergone urgent abdominal laparotomy for ruptured ectopic pregnancy. During the operation, 2 U of ABO/Rhesus-compatible non-irradiated fresh whole blood had been transfused from her brother and brother's son. Five days after surgery the patient developed fever and was transferred to our hospital on the 11th day because of continuous fever, skin rash, and deteriorating condition. At admission the blood pressure was 115/85 mm Hg, pulse 86/min, axillar temperature 39 °C, and breath rate 36/min. A non-itching, confluent erythema extending over the entire trunk and extremities was noted.

Laboratory data at admission revealed a white cell count of 1.8 G/l, hemoglobin level of 98 g/l, platelet count of 208 G/l, lactate dehydrogenase level of 2,514 U/l, total bilirubin of 3.8 mg/dl, aspartate aminotransferase level of 556 U/l, and alanine aminotransferase level of 1,103 U/l. Erythrocyte sedimentation rate was 30 mm/h. Prothrombin time was 18.2 s, partial thromboplastin time 34.5 s, and international normalized ratio 1.63. Direct Coombs test was negative, haptoglobulin was within normal limits, and D-dimers were high (830 µg/ml; N 0.0–0.5 µg/ml). Blood urea nitrogen, creatinine and electrolytes were within normal limits. Serologic tests for hepatitis, other viral infections, and antinuclear antibodies were negative. The blood smear revealed target cell, macrocytosis, fragmented erythrocytes, giant platelets, 12% granulocytes, 68% lymphocytes, and 20% monocytes. Abdominal and pelvic ultrasonographic examinations were normal.

A painful erythema on the palms and soles occurred the following day. Bone marrow biopsy revealed severe aplasia. The patient remained febrile despite a broad antimicrobial regimen. The skin rash progressed, the patient became lethargic and confused and developed jaundice. A skin biopsy revealed hyperkeratosis, parakeratosis, few apoptotic bodies, and lymphocyte infiltrates suggestive of a grade-1 GvHD; no evidence of male origin (Y-chromosome) of the infiltrating lymphocytes could be detected. We diagnosed a TA-GvHD as a consequence of the transfusion of non-irradiated fresh whole blood and proceeded with the immediate administration of methyl prednisolone 1,000 mg/day. After 3 days the patient had become afebrile, the liver function improved, skin rash decreased, and leukocytes and platelets had returned to normal levels, thus the steroid therapy was tapered off.

One week later oral, palatal and nasal black necrosis became apparent, and biopsies were performed. Microbiological analysis revealed broad, non-septate hyphae consistent with mucormycosis. Culture results were later known to be positive for mucormycosis. The patient complained of a rapid loss of vision on the right eye, and a bilateral proptosis developed within 2 days. CT images revealed fluid and air throughout the paranasal sinuses extending to the nasal cavity (fig. 1). Additionally, in post-contrast study the orbitas and cavernous sinuses appeared invaded and pathologic enhancement was detected in the nasopharyngeal soft tissues. Magnetic resonance imaging of the brain, paranasal sinuses and orbitas displayed opacification of the maxillar and ethmoid sinuses, nasal cavities and cavernous sinuses consistent with a pansinusitis, and an enhancement within the orbitas suggestive of a retrobulbar edema. An invasive mucormycosis was diagnosed and liposomal amphotericin B therapy (5 mg/kg/day) was initiated. Despite antifungal therapy, the black necrotic lesions gradually increased (fig. 2). In view of the rapid clinical deterioration a surgical intervention was not undertaken and the patient died 26 days after admission.

Discussion

TA-GvHD is characterized by fever, skin rash, diarrhea, hepatitis and bone marrow aplasia, does not respond well to immunosuppressive therapy, and is therefore most often fatal [10]. Although rare, TA-GvHD may occur in immunocompetent patients who inadvertedly receive donor lymphoid cells through non-irradiated blood products or from passenger lymphocytes in organ allografts. The recipients' marrow is typically targeted by T cells of donor origin [11]. Mucormycosis has been associated with numerous predisposing clinical factors, including diabetes, diabetic ketoacidosis, neutropenia, uremia, severe malnutrition, leukemia, lymphoma, organ transplantation, acquired immunodeficiency syndrome as well as steroid and immunosuppressive therapy [5–9]. In the case presented here neutropenia due to bone marrow aplasia, prolonged treatment with broad-spectrum antibiotics, and steroid thera-

py must be considered as predisposing factors for the rapid progression of mucor infection. Furthermore, neutrophils are the primary defense against fungal infections, and as such neutropenia is bound to further increase the risk of mucormycosis [5].

While the CT scan revealed sinus involvement resembling benign mucosal thickening, bone destruction is usually a late finding [12]. The MRI is especially useful for evaluating the intraorbital and intracranial infiltrations as seen in mucormycosis [13]. In our patient, we revealed rhino-orbito-cerebral invasion of mucormycosis by MRI and CT.

For invasive mucormycosis amphotericin B is the standard therapy. Doses typically range from 1.0 to 1.5 mg/kg/day for most patients. There are some data indicating that lipid-based amphotericin B preparations are also effective in doses of 3–10 mg/kg daily. In general, antimicrobial therapy is followed by repeated surgery, removing devitalized tissue [5]. Unfortunately the patients' deleterious condition did not allow for surgical interventions.

This case report shows the importance of standardized transfusion medicine procedures, which should avoid transfusion of blood products of closely related relatives unless irradiated with no less than 25 Gy or for transplantation purposes. Additionally, mucormycosis should be kept in mind when immunosuppressed patients are diagnosed with refractory sinusitis. The management of invasive mucormycosis depends on an early diagnosis, control of underlying diseases, treatment with systemic antifungal agents, and if possible the removal of necrotic tissue.

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October 2005
2005;32:241–288
ISSN 1660–3796
E 1385 F

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