Ann Hematol (1997) 75:235–237

CASE REPORT

W. Rabitsch · S.A. Brugger · W. Pirker
C. Baumgartner · E. Reiter · F. Keil · D. Prayer
P. Hoecker · K. Lechner · P. Kalhs · H.T. Greinix

Symmetrical necrosis of globus pallidus with severe gait disturbance in a patient with myelodysplastic syndrome given allogeneic marrow transplantation

Received: 9 June 1997 / Accepted: 10 September 1997

Abstract A 21-year-old Caucasian man received an allogeneic marrow transplant (BMT) from his HLA-identical brother because of myelodysplastic syndrome. He remained red blood cell (RBC) transfusion dependent with persistent antibodies against the donor's RBC. Six months following BMT the patient suddenly developed a severe akinetic syndrome with gait disturbance and frequent falls and bilateral symmetrical lesions in basal ganglia. Concomitantly, micrococcus species septicemia from an infected Hickman catheter developed. Despite antimicrobial therapy and withdrawal of cyclosporin A, neurologic abnormalities persisted and were unresponsive to various therapies. Ischemic damage due to a vascular event during severe infection could be the most probable reason for the lesions seen in our patient, although infectious or toxic complications cannot be ruled out.

Key words Globus pallidus necrosis · Allogeneic marrow transplantation · Myelodysplastic syndrome

Introduction

Neurologic complications after BMT affect 12–70% of patients and are the cause of death in up to 10% [1–3]. CNS infections and metabolic encephalopathies are the most frequent events, followed by CNS hemorrhage, toxicity of various drugs, CNS relapse of underlying malignancy, and vascular events [1–3]. We report a patient with a severe akinetic syndrome due to symmetrical, selective damage of basal ganglia, which occurred during severe infection after allogeneic marrow transplantation.

W. Rabitsch · S.A. Brugger · E. Reiter · F. Keil · P. Kalhs
H.T. Greinix (✉)
Department of Medicine 1, Bone Marrow Transplantation Unit, University of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria

W. Pirker · C. Baumgartner
Department of Neurology, University of Vienna, Austria

D. Prayer
Department of Radiology, University of Vienna, Austria

P. Hoecker
Department of Transfusion Medicine, University of Vienna, Austria

K. Lechner
Department of Hematology, University of Vienna, Austria

Case report

A 21-year-old male Caucasian in whom myelodysplastic syndrome (MDS) subclassified refractory anemia (RA) was diagnosed in May 1993 was referred to our center 6 month later for allogeneic marrow transplantation from his HLA-identical brother. He had a history of heavy smoking but no exposure to toxic agents. The patient had received 26 units of packed red blood cells (RBC). Besides seropositivity for parvovirus, virologic examinations were unremarkable. After conditioning with fractionated total body irradiation of 12 Gy and cyclophosphamide (120 mg/kg body wt.), 2.31×10^8 nucleated cells/kg or 2.56×10^6 CD34-positive bone marrow (BM) cells/kg were infused. Because of major AB0-major incompatibility between recipient and donor, RBC depletion was performed prior to BM infusion. GvHD prophylaxis consisted of cyclosporin A (CsA) and methotrexate according to the Seattle protocol [4]. Granulocyte colony-stimulating factor (G-CSF) was administered at a dose of 10 μg/kg as continuous intravenous infusion starting on day 1 after marrow grafting and continuing until recovery of absolute neutrophil counts (ANC).

On day 5 after marrow infusion intravenous therapy with amphotericin B, imipenem, and teicoplanin was started because of persistent fever, moderate mucositis, and colonization of oral mucosa with *Candida albicans*. ANC above 0.5×10^9/l and platelet counts above 20×10^9/l without further transfusion requirement were achieved 19 and 20 days after marrow grafting. Acute self-limiting GvHD of skin and liver grade I developed 21 days after BMT. Morphological and cytogenetic analyses of BM samples performed on day 80 revealed hypocellularity with total absence of the erythroid lineage and normal male karyotype. At that time, both ANC and platelet counts in peripheral blood (PB) dropped and remained decreased. The patient remained RBC transfusion dependent and had persistent antibodies against the donor's RBC. he did not respond to erythropoietin treatment. Four months following BMT, plasmapheresis was performed on two consecutive days without success. Six months following BMT, the

patient developed severe gait disturbance with frequent falls. On admission he presented severely akinetic with repeated dystonic movements which were more pronounced in the upper than in the lower limbs. No meningeal or other focal signs, especially no corticospinal or cerebellar signs were found. Aside from these neurological findings, physical examination was unremarkable. The patient had no history of weight loss or nutritional deficiency. Blood pressure was 100/45 mm Hg. Other than tricytopenia in PB, serum chemistry and urine tests were normal, as were cytologic, chemical, bacteriologic, and virologic examinations of spinal fluid. CSA serum level was 150 ng/ml and serum ferritin was 2400 ng/ml. Serum vitamin B_{12} and folic acid were within the normal range. CT and MRI scans showed bilateral symmetrical lesions in both globi pallidi and cerebral peduncules. To avoid further toxicity, CsA medication was immediately withdrawn and no signs of GvHD were seen. Two days after being admitted, the patient showed spiked septic temperatures and micrococcus species were found in repeat blood cultures. There was no evidence of viral infection. Following removal of the Hickman catheter and intravenous antimicrobial and antifungal therapy fever, resolved within 5 days. In addition, RBC transfusion independency and increase of ANC and platelet counts above 100×10^9/l were observed on days 9 and 36, respectively, after admission. However, neurologic abnormalities persisted. L-DOPA/benserazide therapy for 6 weeks did not show any beneficial effect, whereas trihexyphenidyl therapy improved dystonia but did not affect the patient's akinesia. Four months later, MRI and CT scans showed a slight improvement in the size of lesions, but T_1-weighted hypointense and T_2-weighted hyperintense selective bilateral globus pallidus lesions indicated pallidal gliosis (Fig. 1). The patient remained severely akinetic and had episodes of head, trunk, and limb movement freezing. Therapeutic trials with amantadine sulfate and piracetam proved to be ineffective, as was high-dose L-DOPA/benserazide. More than 3.5 years after BMT the patient is in continuous hematological remission but severely disabled with a Karnofsky index [5] of 50%.

Discussion

We describe the development of a severe akinetic syndrome due to bilateral damage of basal ganglia in a BMT patient receiving cyclosporine, antimicrobial and antifugal therapy, and multiple RBC transfusions. CsA is well known to cause peripheral and central nervous system symptoms including seizures and subcortical white matter lesions [3, 6]. However, CsA-induced CNS toxicity usally responds to drug reduction or withdrawal.

Despite the fact that the spinal fluid examination was normal and an MRI scan showed no signs of encephalitis, a CNS infection has to be considered in our patient. Isolated basal ganglia lesions have rarely been seen in immunocompromised patients and were associated with infections such as toxoplasmosis, tuberculosis, cryptococcosis, or mucormycosis [7, 8]. There, mortalities as high as 97% [3, 7, 9] havebeen reported. In our patient clinical signs of infection resolved rapidly under antimicrobial and antifungal therapy. However, fever could have also been associated with the central venous catheter infection. In addition, PB cell counts increased rapidly after removal of the Hickman catheter, suggesting that tricytopenia could have been due to myelosuppression during infection, as previously reported [10].

Metabolic encephalopathy was ruled out in our patient since hepatic and renal function were normal and no main electrolyte and acid-base imbalances existed. Many antibiotics used after BMT have been associated with neurological toxicity including seizures, hearing loss, encephalopathy, or peripheral neuropathy [3]. In patients given amphotericin B, basal ganglia damage, together with cerebellar and cerebral damage as well as frontal and temporal lobe white matter involvement have been reported [11, 12]. Amphotericin B-associated leukoencephalopathy occurred under intravenous administration and was diffuse, unlike in our patient, where isolated basal ganglia lesions were seen 5.5 months after administration of amphotericin B.

Cerebral hypoxia-ischemia typically produces lesions of the globus pallidus. The resultant movement disorders respond poorly to therapy [13]. Carbon monoxide, hydrogen disulfide, and cyanide poisoning, anesthetic accidents, and chronic cerebral hypoperfusion may lead to the above lesions [13, 14]. In animal studies basal ganglia, the hippocampus, and cerebral cortex were affected with varying severity during cerebral hypoperfusion [14]. MRI scans revealed that changes due to ischemia occurred more rapidly in basal ganglia than in the cortex [15]. Thus, ischemic damage due to a vascular event during severe infection could be the main reason for the observed bilateral gliosis of the globus pallidus in our patient, although infectious or toxic complications cannot be ruled out.

Acknowledgements We thank the dedicated nurses of our stem cell transplantation program, our fellows and house staff, the medical technicans, and the staff of the blood bank, for their technical assistance in bone marrow harvesting and their support with blood products.

References

1. Patchell RA (1994) Neurological complications of organ transplantation. Ann Neurol 36:688–703
2. Graus F, Saiz A, Sierra J et al. (1996) Neurological complications of autologous and allogeneic marrow transplantation in patients with leukemia. Neurology 46:1004–1009
3. Openshaw H, Slatkin NE (1994) Neurological complications of bone marrow transplantation. In: Forman SJ (ed) Bone marrow transplantation. Blackwell, Cambridge, pp 482–496
4. Storb R, Deeg HJ, Whitehead J et al. (1986) Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. New Engl J Med 314:729–735
5. Karnofsky DA et al. (1948) Eastern Cooperative Oncology Group (ECOG) performance status scale. Cancer 1:634
6. Reece DE, Frei-Lahr DA, Shepherd JD et al. (1991) Neurologic complications in allogeneic bone marrow transplant recipients receiving cyclosporin. Bone Marrow Transplant 8:393–401
7. Hopkins RJ, Rothman M, Fiore A, Goldblum SE (1994) Cerebral mucormycosis associated with intravenous drug use: three case reports and review. Clin Infect Dis 19:1133–1137
8. Gaziev D, Baronciani D, Galimberti M, Polchi P et al. (1996) Mucormycosis after bone marrow transplantation. Report of four cases in thalassemia and review of the literature. Bone Marrow Transplant 17:409–414

9. Hagensee M, Bauwens J, Kjos B, Bowden R (1994) Brain abscess following marrow transplantation: experience at the Fred Hutchinson Cancer Research Center 1984–1992. Clin Infect Dis 19:402–408
10. Torok-Storb B, Simmons P, Przepiorka D (1987) Impairment of hematopoiesis in human allografts. Transplant Proc 19:29–32
11. Mott SH, Packer RJ, Vezina LG, Kapur S et al. (1995) Encephalopathy with parkinsonian features in children following bone marrow transplantation and high-dose amphotericin B. Ann Neurol 37:810–814
12. Walker RW, Rosenblum MK (1992) Amphotericin B-associated leukoencephalopathy. Neurology 42:2005–2010
13. Hawker K, Lang AE (1990) Hypoxic-ischemic damage of the basal ganglia. Mov Disord 5:219–224
14. Hattori H, Takeda M, Kudo T, Nishimura T, Hashimoto S (1992) Cumulative white matter changes in the gerbil brain under chronic cerebral hypoperfusion. Acta Neuropathol Berl 84:437–442
15. Matsumoto K, Lo EH, Pierce AR et al. (1995) Role of vasogenic edema and tissue cavitation in ischemic evolution on diffusion weighted imaging: comparison with multiparameter MR and immunohistochemistry. Am J Neuroradiol 16:1107–1115