Case report

Autoaggression syndrome resembling acute graft-versus-host disease grade IV after autologous peripheral blood stem cell transplantation for breast cancer

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Summary:

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Acute graft-versus-host disease (aGVHD) is a well-known complication of allogeneic bone marrow (BM) transplantation that typically presents with dermatitis, hepatitis and enteritis developing within 100 days after bone marrow infusion.1 Less frequently, aGVHD has been reported to be associated with blood transfusion, mainly in immunocompromised patients.2 Furthermore, particular clinical features of aGVHD have been recently described in some patients receiving syngeneic or autologous transplants. This spontaneous aGVHD after autologous BM or peripheral blood progenitor cell (PBPC) transplantation is usually less severe and has a better response to immunosuppressive treatment than allogeneic or transfusion-associated aGVHD.3 Similarly, autologous GVHD induced by cyclosporine is usually mild,4 although serious cases related to the concomitant administration of cytokines such as gamma-interferon have been described.5

Although an exponential increase of autologous BM and PBPC transplantation has been observed during the last decade, cases of severe spontaneous aGVHD are extremely unusual. Here, we report the first case of fatal grade IV aGVHD associated with autologous PBPC transplantation in a patient with breast carcinoma.

Case report

A previously healthy 40-year-old female was diagnosed in November 1994 with stage III breast carcinoma. Bilateral breast silicone prostheses were implanted for cosmetic reasons in 1984. Breast cancer treatment consisted of radical mastectomy, adjuvant chemotherapy with FEC (5-fluorouracil, epirubicin, cyclophosphamide), and chest wall and axillary irradiation (50 Gy). On evaluation no evidence of disease was found, but an elevated Ca 15.3. In this setting, autologous PBPC transplantation was scheduled as consolidation therapy. Apheresis was started after the patient had received G-CSF for 3 days (8 μg/kg/day) subcutaneously. Leukapheresis yield was 5.79 × 10^9/kg white blood cells and 2.04 × 10^9/kg CD34+ cells. In August 1995, after conditioning with STAMP-V (cyclophosphamide 6 g/m², carboplatin 800 mg/m², thiopeta 500 mg/m²), all the material collected was infused. Cytokines were not used and the patient engrafted granulocytes (>0.5 × 10^9/l) and platelet (>20 × 10^9/l) by days 14 and 11, respectively. During the procedure she received four packed red cell units and two platelet apheresis products. All blood products were irradiated (25 Gy) and transfused with white blood cell reduction filters. There were no complications except for gastrointestinal toxicity grade III (WHO), and the patient was discharged on day 15 in excellent health.

On day 23 post-transplant, she was admitted with a temperature of 38.5°C, diarrhea, myalgias, nasal discharge and a papuloerythematous rash on the face and trunk. Laboratory studies and chest radiographs were normal; microbiological cultures and serological test were negative.

On day 25, peripheral thrombocytopenia was noted (increased megakaryocyte numbers on the bone marrow aspirate plus positive anti-platelet antibodies). Prednisone (1 mg/kg/day) was started and the platelet count increased. Despite broad-spectrum antibiotic therapy the patient remained febrile, developed bilateral pulmonary infiltrates and mild elevation in liver function tests. The eruption became diffusely confluent, and then spread over almost the entire body. Virological and microbiological testing of
blood, urine and bronchoalveolar lavage (BAL) samples was negative. Ten days later the patient became afebrile, showed slow resolution of the rash and respiratory failure, the liver function tests had reverted to normal and steroid treatment was tapered.

By day 45, she suffered a new febrile episode, increase of diarrhea (1.5 l/day) and flare-up of the skin rash which involved the entire body including both palms and soles. Polymicrobial pneumonia was diagnosed (gram-positive and gram-negative microorganisms isolated in sputum and BAL) and several broad-spectrum antibiotics were administered, with improvement of the respiratory function. By this time neither fungus nor virus had been identified; particularly, cytomegalovirus (CMV) cultures from blood, throat, urine and BAL were negative.

After day 54 the patient’s condition deteriorated rapidly: the rash progressed to a toxic necrolysis-type picture, the diarrhea became bloody and jaundice appeared. Liver function tests disclosed the following values (day 55): total bilirubin, 5.51 mg/dl (normal, 0.2–1.1 mg/dl); aspartate aminotransferase, 890 U/l (normal 3–37); alanine aminotransferase, 1500 U/l (normal 3–37); alkaline phosphatase, 588 U/l (normal 98–279); lactate dehydrogenase, 1514 U/l (normal 230–460). Peripheral blood counts showed anemia (hemoglobin 7.5 g/dl), thrombocytopenia (platelet 35 × 10^9/l), and eosinophilia (eosinophils 2.3 × 10^9/l). Antinuclear antibodies were not detected.

Histological diagnosis of skin punch biopsy (day 54) and gut biopsy (day 62) was aGVHD (Figure 1). A clinical diagnosis of spontaneous grade IV aGVHD was made. Therefore, therapy with methylprednisolone intravenously (3 mg/kg/day) was initiated at 58 day and cyclosporine after day 68 post-transplant. Despite immunosuppressive treatment the patient died of progressive multiorgan failure on day 70. Post-mortem liver biopsy (day 70) confirmed aGVHD (Figure 1). CMV was excluded by immunohistochemical analysis in skin, gut and liver biopsies.

All transfused blood products were irradiated. However, in order to exclude the presence of allogeneic cells in the patient, we performed PCR amplification of two highly hypervariable loci, DIS80 and SE33, on peripheral blood (day 55), skin (day 63) and liver (day 70). The band pattern described in these samples was identical to that found in the apheresis products but different from the amplification of these loci in the six blood donors. No additional bands were identified in these samples (Figure 2).

Discussion

Acute GVHD is a frequent complication of allogeneic BM transplantation, and is a consequence of failure by the immunocompromised host to achieve an effective immunological reaction against graft reaction to patient alloantigens. Although the graft-versus-host reaction requires the presence of allogeneic cells, a similar syndrome has been described in autologous BM or PBPC transplantation. The manifestations are generally mild or subclinical, and they occur during the early phase of the engraftment process. This clinical entity has been called autologous engraftment syndrome6 or autoagression syndrome,7 and usually presents with fever, skin rash, and less frequently thrombocytopenia, autoimmune hemolytic anemia and diarrhea. Remarkably, this syndrome never affects liver or gut. The skin rash occurs earlier in autoagression syndrome but clinical and pathological findings are similar to allogeneic GVHD grades I–II.8 All these data suggest that spontaneous GVHD in autologous transplantation might be a common
phenomenon which is misdiagnosed because the mild clinical course does not necessitate histopathological diagnosis.

Our patient developed classical clinical signs of grade IV aGVHD. The severity of the clinical manifestations and her unresponsiveness to immunosuppressive treatment mimicked the picture of allogeneic transplantation or transfusion-associated aGVHD. In order to exclude both possibilities, we first checked that all blood components administered were irradiated before transfusion (25 Gy). However, irradiation of cellular blood components does not completely exclude transfusion as the cause of GVHD. Therefore, we undertook PCR analysis of polymorphic markers in peripheral blood and tissues of the patient, but we did not detect exogenous DNA derived from blood donors.

A role of the intensive chemotherapy might be suggested in the etiology of this aGVHD. However, both the induction and the conditioning regimens used in this case are associated with low toxicity and hematologic and extrahematologic toxicities were mild in the early post-transplant phase. Neither total body irradiation (TBI) nor immunotherapy were used.

During the transplantation procedure, we used no purging technique which could alter T cell subpopulations in the leukapheresis product, neither was it possible to demonstrate significant alterations in the natural killer cell count or in the CD4/CD8 ratio (data not shown). The hypothesis of reinfusion of autoreactive mononuclear cells released into circulation during mobilization, has been proposed by other authors, but remains speculative.

We did not test for human herpes virus type 6, herpes simplex virus, adenovirus or human herpes virus type 8. However, CMV is the most frequent virus related to development of aGVHD in allogeneic BM transplants, and we can exclude CMV infection because serological tests, CMV cultures and CMV identification on tissue biopsies from this patient were negative.

Finally, a distinctive feature of this patient was the presence of bilateral breast silicone prostheses inserted 10 years before the transplant. The existence of immune responses induced by silicone implants has been demonstrated, and could have played a role in the unusual severity of this case of GVHD, but this remains speculative.

In conclusion, this case is the first pathologically documented case of grade IV acute spontaneous GVHD after PBSC autologous transplantation not induced by cyclosporine, in which an exogenous origin has been rigorously excluded. The increase in the number of autologous transplants being carried out and the possibility of a fatal outcome (as in our case) make it necessary to understand all factors involved in the aGVHD process in the autologous setting.

References
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