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Graft Versus Host Disease after Transfusions of Non-irradiated Blood Cells in Patients Having Received Autologous Bone Marrow.

A Report of 4 Cases Following Ablative Chemotherapy for Solid Tumors

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Abstract—*In four patients with solid tumors (three small cell lung cancers, one germ cell cancer) high dose chemotherapy with autologous bone marrow infusion was given. Graft versus host disease (GVHD) was the cause of death in one patient and at autopsy signs of GVHD were found in the other three patients. In these four patients GVHD was caused by blood cell transfusion. Patients treated with aggressive chemotherapy for solid tumors are at risk for the development of GVHD after allogeneic blood cell transfusions and preventive measures are definitely needed.*

INTRODUCTION

GRAFT VERSUS HOST disease (GVHD) is a well-known syndrome in allogeneic bone marrow transplantations [1]. It occurs to some degree in about 70% of these patients despite careful selection of bone marrow donors. The immunocompetent lymphocytes of the marrow donor react with the tissues of the host, resulting in a syndrome with skin rash, liver function abnormalities and gastrointestinal disturbances.

GVHD has also been seen in infants with various primary immunodeficiency syndromes after transfusion of blood [2], and furthermore after intrauterine blood exchange and transfusion for hemolytic disease of the newborn [3]. Since the introduction of myelosuppressive therapy for hematologic malignancies GVHD has also been reported after transfusion of granulocytes, red blood cells and platelets to these patients [4].

Despite the intensification of chemotherapy in a steadily increasing number of patients with solid tumors GVHD has only been reported in two patients with neuroblastoma [5, 6].

In this report we describe acute GVHD in four patients with solid tumors, who received unirradiated blood cell transfusions after intensive chemotherapy and autologous marrow infusion.

CASE 1

A 53-year-old man was seen in March 1981 because of a röntgenologically detected tumor in the right lung. Small cell lung cancer of the right lower lobe was diagnosed; routine staging procedures showed no distant metastases. After two courses of CCE and two courses of VDP a partial remission was reached. Further tumor regression followed after 30 Gy to the area of the primary tumor. Till March 1982 maintenance chemotherapy (CCNU, HMM) was given. In May 1982 symptomatic brain metastases were irradiated (10 × 3 Gy). A brain CT in March 1983 showed no metastases. Hepatomegaly due to metastases was found in April 1983. A short-term remission was seen after one course of high-dose etoposide (3 g/m^2). Subsequently the patient was entered into a phase II trial of high-dose chemotherapy with autologous bone marrow infusion. During the auto-

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Abbreviations used: CCE = cyclophosphamide 750 mg/m^2 i.v. day 1, cisplatinum 75 mg/m^2 i.v. day 1, etoposide 100 mg/m^2 i.v. day 2, 5, 8; VDP = vincristine 1.4 mg/m^2 i.v. day 1 and 8, doxorubicin 60 mg/m^2 i.v. day 1, procarbazine 100 mg/m^2 days 1–10 orally; HMM = hexamethylmelamine; CCNU = lomustine; Gy = Gray; CT = computer tomography.

logous marrow sampling 3 units of leucocyte 'free' packed red cells (LFPC) were given. On July 5, 6 and 7 he received a total dose of cyclophosphamide 7 g/m^2 and etoposide 0.9 g/m^2. Reinfusion of the bone marrow was performed on July 12. Fever, erythema and diarrhea started on July 13 and continued till his death on July 22. Several unirradiated transfusions were given during this period; 8 units of LFPC and 4 units of single donor platelets. Despite intensive antibiotic and antifungal therapy his condition deteriorated with renal failure, respiratory insufficiency and confusion. Autopsy revealed generalized edema and signs of diffuse alveolar damage of both lungs. The heart showed a scar of an old postero-inferior cardiac infarct. There was no viable tumor tissue, but scars were present in right lower lobe and liver. Microscopy of skin and gastro-intestinal tract showed signs of acute GVHD with infiltration of lymphocytes in basal layers of the skin and intestinal crypts and degeneration of epithelial cells and so-called satellite necrosis.

CASE 2

In June 1981 a 55-year old man was referred for treatment of small cell lung cancer of the right upper lobe with bone marrow metastases. The induction treatment (two courses of CCE and two courses of VDP) resulted in a partial remission. Despite maintenance therapy (CCNU, HMM) the tumor progressed in March 1982. Reinduction with CCE failed and the patient was entered into a phase I study of high-dose cyclophosphamide (7 g/m^2) and etoposide (2.5 g/m^2) with autologous bone marrow transplantation. During the sampling of autologous marrow 3 units of LFPC were given. After the infusion of the chemotherapy on May 11, 12 and 13 a mild skin rash was present during 2 days and resolved spontaneously. The bone marrow was reinfused on May 18. Fever started on the same day and persisted till his death on May 31 despite antibiotic treatment. During this period 4 units of single donor platelets, and 3 LFPC were given. A mild erythema was first noted on May 25. The clinical situation deteriorated and on May 27 artificial respiration was necessary, at that time the patient was seriously confused and disoriented. During the following days multiple organ failure developed and resulted in death.

Autopsy revealed viable tumor tissue in the right upper lobe and tracheo-bronchial lymph nodes. Microscopy showed *Candida* organisms in multiple organs. The skin showed subtle signs of GVHD with sporadic infiltration of single cells or small groups of lymphocytes and degeneration of individual epithelial cells with sporadic dyskeratosis. Liver and intestinal tract were free of signs of GVHD.

CASE 3

A 25-year old woman presented in September 1981 with an endodermal sinus tumor of the right ovary with intraperitoneal, supraclavicular, retroperitoneal and splenic metastases. She was treated with four 3-monthly courses of cisplatinum 150 mg, vinblastine 22 mg and bleomycin 45 mg. This treatment was complicated by serious electrocyte disturbances, status epilepticus, pulmonary embolism due to thrombosis of the right leg and cerebral infarction. In March 1982 a complete remission was found at laparotomy with normalization of alpha-1-fetoprotein (AFP). In August 1982 blood AFP levels increased and at laparotomy a metastasis was found in the liver. Second line chemotherapy, actinomycin D 2.5 mg/m^2, etoposide 400 mg/m^2 and *cis*-platinum 100 mg/m^2, was started; after the second course this treatment had to be stopped due to severe side-effects. In December 1982 macroscopic residual tumor was resected by partial hepatectomy. Consolidation therapy with cyclophosphamide 7 g/m^2, etoposide 1.5 g/m^2 with autologous bone marrow transplantation (ABMT) resulted in only short-term normalization of AFP levels. During the sampling of autologous marrow 3 units of LFPC were given. In February 1983 etoposide 2.5 g/m^2 gave again a decrease of AFP and on March 8, 9 and 10 1983 high-dose cyclophosphamide (7 g/m^2) and etoposide (2 g/m^2) was given, followed by autologous marrow infusion on day 7, on March 14.

On March 13 septicemia (*Str. viridans*) was found, fever over 40°C with rash persisted despite broad-spectrum antibiotics and antipyretics. From March 15 till 18 she received 4 units of non-irradiated granulocytes from unrelated donors, 6 LFPC and 2 times single donor platelets.

Despite signs of bone marrow regeneration on March 22 the patient's condition deteriorated with respiratory insufficiency; artificial respiration with PEEP was started on March 22. Multiple organ failure followed and the patient died on March 24 due to irreversible shock.

Autopsy revealed severe changes of diffuse alveolar damage. There was no indication of opportunistic infections. Viable tumor tissue was not present. Microscopy of the liver showed scattered necrosis and thrombosis of several intrahepatic portal veins. The bone marrow was aplastic. Clear signs of GVHD were seen in liver, pancreas, oesophagus and intestinal tract (Fig. 1).

CASE 4

A 53-year old man was seen in January 1983 for a superior caval vein syndrome with an IADH syndrome. He was treated with four courses of CCE and restaging showed a complete remission. A routinely made brain CT however showed two

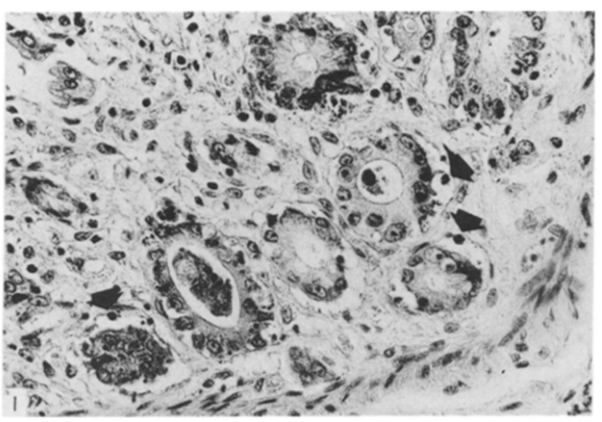

Fig. 1. Graft versus host disease of small intestine. Lymphocytes infiltrating bases of crypts indicated by arrows. There is also necrosis of epithelial cells and the crypts are filled with degenerated cells. (*H&E* × 214.)

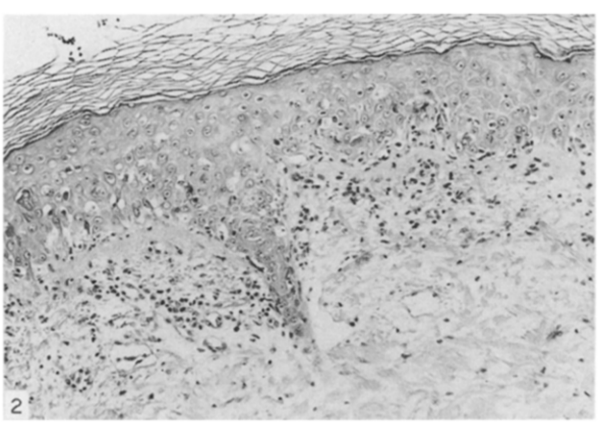

Fig. 2. Graft versus host disease of skin. (*H&E* × 85.)

small lesions, probably metastases. Radiotherapy (10 × 3 Gy) was given followed by one course of high dose etoposide (2.5 g/m^2). The patient was well till July 1984, at that time a large tumor was found in the right adrenal gland, a biopsy showed small cell lung cancer. In August 1984 high-dose cyclophosphamide (7 g/m^2) and etoposide (0.9 g/m^2) with autologous bone marrow transplantation was given. During the sampling of autologous marrow 3 units of LFPC were given. During the aplastic period fever due to septicemia with *Streptococcus viridans* was found and successfully treated. A skin rash resolved spontaneously and after bone marrow regeneration a partial remission was found on the CT scan. Radiotherapy of the residual tumor was started in October 1984. After 15 × 2 Gy leuco- and thrombocytopenia developed. Bone marrow biopsy showed tumor metastases. On November 1 6 units of allogeneic platelets were given. Skin rash and fever started on November 12, the leucocyte number decreased further. A skin biopsy taken on November 14 showed signs of GVHD (Fig. 2). Despite high doses of corticosteroids the patient's condition became worse and he died of gastrointestinal bleeding on November 27. Autopsy revealed lymphogenic dissemination of small cell cancer in both lungs. There was widespread seeding of *Candida* organisms in multiple organs. The skin showed signs of GVHD. These were less impressive than those found in the skin biopsy. Retrospectively a Cytomegalovirus (CMV) infection was serologically documented and had taken place in October 1984.

DISCUSSION

There is no doubt that GVHD can occur after the transfusion of blood cells to immunosuppressed hosts, even outside the situation of allogeneic bone marrow transplantation. Besides children with severe congenital immune deficiency, patients with bone marrow aplasia are at risk but it can also develop in non-leucopenic patients, as was seen in patient 4 in this report.

The clinical diagnosis of GVHD is often very difficult. Symptoms such as fever, skin rash, liver and gastro-intestinal disease are not characteristic. For this syndrome differential diagnostic alternatives are: disseminated viral syndromes, side-effects of cytotoxic treatment as well as complications of antibiotic therapy usually given because the fever is presumed to be of infectious origin. This complex of symptoms is rather often observed in patients after treatment with more or less myelosuppressive regimens with or without radiotherapy. The majority of these patients also have received transfusion of red blood cells and sometimes platelets or even granulocytes.

The risk of developing GVHD following the transfusion of blood cells is suggested to be very low by the case reports in the literature. The incidence of GVHD in patients with hematologic and lymphoproliferative malignancies is probably low, workers at the Roswell Park Memorial Institute estimate it between 0.1 and 1% [4]. The incidence in solid tumor patients seems to be even lower since only in two neuroblastoma patients GVHD has been reported [5, 6]. The explanation for this low incidence could be the degree and duration of myelosuppression caused by the chemo- and radiotherapy regimens used for most solid tumors. Another explanation might be the minimal tumor-related immunosuppression in these patients.

On the other hand the incidence of mild GVHD could well be higher than reported. The above described complex of symptoms might, in a fraction of those patients without a known explanation, represent a mild form of GVHD with a rather benign course. Since the diagnosis of GVHD ultimately rests on characteristic findings in the skin, liver and intestine, it might be worthwhile to investigate skin biopsies of patients with fever of unknown origin and rashes after blood cell transfusion. At present almost only GVHD cases with a fatal outcome have been reported and it is therefore considered to be a dangerous complication, however less ferocious forms could easily be missed. Also in the first three patients GVHD was not detected before death and it is uncertain how important it was in these patients and if it was co-responsible for their death. It is tempting to speculate on the role of mild GVHD as beneficial complication because the infused immunocompetent cells may have a certain anti-tumor effect in the tumor-bearing patient [7].

The risk of developing GVHD is in very aggressively treated patients probably high. In our institute it was proven in 4 out of a group of 34 comparably treated patients (12%). Prevention could be achieved by for instance the use of cryopreserved autologous blood cells, especially platelets [8]. For all other transfusions, also those given during marrow donation, irradiation with 15 Gy or more is necessary to eliminate the engraftment potential of the infused donor lymphocytes [9]. For other patients receiving donor blood cells the real incidence of GVHD has to be determined by further investigations in patients supposed to be at risk. This risk has to be outweighed against the small disadvantages of routine irradiation of all transfusions [10].

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