Transfusion-Associated Graft-versus-Host Disease in Patients with and without Immunodeficiency: Report of Six Cases

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Key Words

Transfusion · Graft-versus-host disease · Fludarabine · Irradiation

Summary

Background: Transfusion-associated graft-versus-host disease (TA-GVHD) is extremely rare compared to transplant-associated GVHD. Mortality in TA-GVHD approaches to 100%. We report six cases with TA-GVHD that were seen during 1994–2004 and discuss the clinical characteristics. **Case Reports:** Two patients were immunosuppressed, and 4 patients were immunocompetent. All 6 patients were transfused with non-irradiated blood products from relatives before TA-GVHD had occurred. Diagnosis of TA-GVHD in all patients was made based on characteristic clinical manifestations and laboratory findings. All patients died due to TA-GVHD-related complications such as progressive pancytopenia and liver dysfunctions. **Conclusion:** Our data shows that TA-GVHD is a serious complication of transfusion of blood products among relatives.

Schlüsselwörter

Transfusion · Graft-versus-host-Erkrankung · Fludarabin · Bestrahlung

Zusammenfassung

Hintergrund: Die transfusionsassoziierte Graft-versus-host-Erkrankung (TA-GVHD) ist verglichen mit der transplantationsassoziierten GVHD extrem selten. Die Mortalität bei TA-GVHD beträgt 100%. Wir berichten hier über 6 Fälle, die wir in der Zeit zwischen 1994 und 2004 beobachtet haben, und diskutieren die klinischen Charakteristika. **Fallberichte:** Zwei Patienten waren immunsupprimiert, 4 immunkompetent. Alle 6 Patienten waren mit unbestrahlten Blutprodukten von Verwandten transfundiert worden, bevor es zur TA-GVHD kam. Die TA-GVHD-Diagnose wurde anhand typischer klinischer Manifestationen und Laborergebnisse gestellt. Alle Patienten verstarben an Komplikationen in Zusammenhang mit TA-GVHD wie fortschreitende Pancytopenie oder Leberversagen. **Schlussfolgerung:** Unsere Daten zeigen, dass TA-GVHD eine schwerwiegende Komplikation der Bluttransfusion unter Angehörigen ist.

Introduction

Transfusion-associated graft-versus-host disease (TA-GVHD) may be seen when blood products from relatives including viable donor T lymphocytes after engraft in immunocompromised recipients are transfused. However, it also may occur in immunocompetent patients following transfusion of blood products from first degree family donors and random donors

with similar HLA antigens. It includes the triad of dermatitis, hepatitis and gastroenteritis plus pancytopenia. TA-GVHD is extremely rare compared to transplant-associated GVHD. However, its mortality rate is almost 100% [1–6]. In the present study, we report of 4 immunocompetent and 2 immunocompromised patients suffering from TA-GVHD who received perioperative transfusion of cellular blood products from close relatives donors.

Table 1. General characteristics of patients

Patient no.	Age, years	Sex	Reason of transfusion*	Type of blood products	Number of units	Donors
1.	67	male	anemia, CLL	red cell	2	sons
2.	58	male	anemia, CLL	red cell	2	sons
3.	30	female	salpingectomy	whole blood	2	brother, brother's son
4.	50	female	anemia	whole blood	1	son
5.	55	female	CABS	red cell	1	sister
6.	80	female	femur fracture	whole blood	2	sons

CABS = Coronary artery bypass surgery.

*All blood products were given due to anemia.

Table 2. Laboratory, skin and bone marrow results of patients

Patient no.	Hb, g/dl	Platelets $\times 10^9/l$	WBC $\times 10^9/l$	Fever $> 38^\circ C$	Bilirubin*, mg/dl	ALT, U/l**	Skin biopsy	Bone marrow biopsy
1.	9.7	128	2.5	+	4.0	69	not done	hypocellular
2.	8.5	55	1.1	+	4.8	213	not done	hypocellular
3.	9.8	45	1.8	+	4.0	1103	GVHD	hypocellular
4.	9.2	123	3.6	+	6.0	380	GVHD	hypocellular
5.	10.6	43	1.2	+	3.1	809	GVHD	hypocellular
6.	10.3	78	0.3	+	5.0	274	GVHD	hypocellular

*Normal ranges 0.3–1.2 mg/dl.

**Normal ranges 10–45 U/l.

Case Reports

Our cases included 4 females and 2 males ranging from 30 to 80 years of age. Two patients were immunocompromised due to treatment of chronic lymphocytic leukemia (CLL) with fludarabine; the other patients were immunocompetent. All patients received 1–5 units of fresh non-leukoreduced, non-irradiated blood products from relatives. Blood products were transfused due to major surgery such as left partial salpingectomy, femur fracture, coronary artery bypass surgery and anemia. Table 1 summarizes the general characteristics of the patients.

All patients were admitted to hospital with fever, diarrhea, and disseminated skin rashes (fig. 1). These symptoms appeared between the 5th and 15th day after transfusion. Laboratory studies at the time of hospital admission showed that all patients had different degrees of pancytopenia, with hemoglobin levels ranging between 8.5 and 10.6 g/dl, white blood cell counts between 0.3×10^9 and $3.6 \times 10^9/l$, and platelet counts between 43×10^9 and $128 \times 10^9/l$. Peripheral blood counts declined progressively in a couple of days. The levels of serum bilirubin (normal ranges between 0.3 and 1.2 mg/dl) and alanine aminotransferase (ALT; normal ranges between 10 and 45 IU/l) were elevated to 3.1–6.0 mg/dl, and 69–1,103 U/l respectively. Bone marrow biopsies revealed aplastic marrow, and Gram stain showed no organisms. Culture and serology results of these patients were negative for bacterial or viral infections, and there was no history of drug reactions. Table 2 summarizes the laboratory results. Results of skin biopsy specimens showed basal vacuolopathy, mild spongiosis, individual keratinocyte necrosis associated with mononuclear cell infiltration of epidermis and upper dermis (fig. 2). Considering these symptoms, clinical history and the skin rash biopsy results were highly suggestive of TA-GVHD. TA-GVHD can be diagnosed both by the clinical symptoms and

by the evidence of blood donor lymphocyte engraftment. The HLA types of the donor-recipient pair would have been of great value. However, because of some technical limitations, suitable laboratory methods such as HLA typing and DNA studies were not available. Treatment with high-dose methylprednisolone (HDMP) therapy (10 mg/kg/day) and antibiotics was started. In addition to HDMP and antibiotics, one patient received granulocyte colony stimulating factor (G-CSF). The patients continued to have pyrexia, worsening hepatitis, diarrhea, skin rash, and bone marrow failure. Despite antibiotics and high-dose steroid treatment and intensive medical care, the patients died due to febrile neutropenia and multiple organ failure 15–43 days after admission.

Discussion

There are three factors that influence the occurrence of TA-GVHD: the immune status of the host, the HLA match between the host and donor, and the dose and viability of transfused leukocytes [7]. If the donor and the patient share HLAs or a haplotype, transfused blood may produce fatal TA-GVHD even in immunocompetent recipients. Development of TA-GVHD in these patients shows similarities to the legend of Trojan horse; because the recipients' T-lymphocytes are haploidentical and the lymphocytes in the recipients' blood does not recognize the invading T lymphocytes, no host immune reaction occurs. Invading donor T lymphocytes cause

Fig.1. Patient disseminated skin rashes.

immune reaction at the recipients' skin, gastrointestinal system and bone marrow. Only 2 of our patients had a suppressed immunoreactivity as they received fludarabine treatment due to CLL while the other 4 patients were immunocompetent. All of them were transfused with non-irradiated blood products from first-degree family donors.

We diagnosed TA-GVHD in our patients based on both clinical manifestations and laboratory findings including bone marrow and skin biopsies. The classical clinical features of TA-GVHD are widespread rash, diarrhea, increased liver function tests and progressive pancytopenia occurring 7–14 days after transfusion of non-irradiated cellular blood products [1, 2, 5]. In our patients, symptoms of TA-GVHD appeared between the 5th and 15th day after transfusion. Disseminated skin rashes, progressive pancytopenia and elevated liver function tests were observed in all patients. In viral infections and drug reactions, fever, skin rash, diarrhea, pancytopenia, and liver dysfunction seldom occur simultaneously. The simultaneous occurrence of these symptoms and clinical findings after transfusion of non-irradiated blood products and/or blood products from relatives may be a useful clue to rule out other diagnoses than TA-GVHD. TA-GVHD should be kept in mind in patients having fever and rash after transfusion. Skin biopsy could be used as an alternative method of diagnosis if HLA typing and DNA studies are unavailable.

In our study two of the patients had received fludarabine treatment due to CLL. Fludarabine is the most widely used nucleoside analogue in the treatment of CLL. Its major toxicity resulted in severe myelosuppression requiring blood product support and antimicrobials. A profound fall in T cell subpopulations has been reported in all patients treated with fludarabine, and low counts persist for about 11–13 months. The

Fig.2. Mononuclear cell infiltration of epidermis and upper dermis.

occurrence of TA-GVHD in CLL and systemic lupus erythematosus patients receiving fludarabine rarely has been reported [4, 9, 10]. As in our study, all patients in the study of Leitman et al. [9] had blood product transfusions before TA-GVHD occurred. It is suggested that T cell decrease and immune deficiency during fludarabine treatment and in the follow-up period plays a major role in the development and progression of TA-GVHD and that TA-GVHD is a frequent complication in patients receiving fludarabine due to persistent immunodeficiency. However, in most CLL patients using fludarabine, TA-GVHD is not reported. This might be due to the use of irradiated blood products or to the fact that TA-GVHD symptoms are not recognized.

The incidence of TA-GVHD in immunocompetent recipients is not known, but it appears to be highest in Japan. The genetic homogeneity of the Japanese population together with the common use of the fresh blood for transfusion in patients undergoing coronary artery bypass graft surgery place them at a significantly higher risk of developing TA-GVHD [7]. Aoun et al. [3] reported 10 cases of TA-GVHD due to the transfusions of blood products from relatives during a 10-year period. The incidence of TA-GVHD in Turkey, is not known. However, in the international literature 3 studies can be found ad-

addressing this subject [6–8]. In our country patients insist on transfusions of their relatives as they believe to receive healthier products. Moreover, in Turkey irradiation and leukocyte reduction of blood products is only rarely done. Irradiation is not usually performed, except for university and central state hospitals. As a matter of this fact, four patients from close provinces and from other hospitals were admitted to our hospital when clinical symptoms and signs occurred.

Treatment of established TA-GVHD is rarely successful. Although corticosteroid, methotrexate, anti-thymocyte globulin, various monoclonal antibodies and new immunosuppressive agents are successfully used in the treatment of transplant related-GVHD, none of these treatment options is effective in the treatment of TA-GVHD [1]. We used high-dose methylprednisolone treatment, but none of our patients responded. Because TA-GVHD cannot be treated successfully and irradi-

ation is the only plausible method of preventing it, clinicians must request irradiated products. As patients receiving leukoreduced but non-irradiated blood were found to also suffer from TA-GVHD, leukocyte reduction filters should not be used as prophylaxis against TA-GVHD. The exact number of leukocytes needed to produce TA-GVHD is not known [11]. Physicians should be aware of this devastating complication of blood transfusion in the differential diagnosis of fever accompanied by pancytopenia, elevated liver enzymes, skin rash and diarrhea in a patient with a history of transfusion of non-irradiated blood products from relatives.

In conclusion, avoiding donations from first- and second-degree relatives without performing the required procedures and obligation of using irradiated cellular blood products are recommended as a practical approach to prevent TA-GVHD.

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