Transfusion associated graft-versus-host disease (TA-GVHD)

TA-GVHD is one of the severest adverse reactions of transfusion and greatly feared because more than 95% of the victims die.
This serious transfusion associated adverse reaction will be described in this series of articles.
In Japan, since Aoki et al reported the first case of TA-GVHD in an immunocompetent patient in 1984, many cases of TA-GVHD had been reported, and it had been one of the most serious problems in transfusion medicine and surgery in Japan before the introduction of universal irradiation. At that time, TA-GVHD was considered as an adverse reaction that develops only in the patients with cell-mediated immune deficiency, as indicated in a review by Brubaker[1)] in Vox Sanguinis, the official journal of International Society of Blood Transfusion in 1983. However, most of the patients with this adverse reaction in Japan were immunocompetent patients. Thus, a study was conducted to demonstrate that this adverse reaction had evidences as TA-GVHD, and some findings were obtained. After that, an epidemiologic study was conducted to identify the incidence of this adverse reaction, and then Japanese Red Cross Society established a hemovigilance system to collect data and samples of patients with TA-GVHD and developed a method of definitive diagnosis for TA-GVHD, VNTR. As a result, several cases of TA-GVHD were identified in every year, and in 1997 the cases increased to14 per a year. The Japan Society of Transfusion Medicine made a series of guidelines, and recommended to use irradiated blood for patients with risk factors of TA-GVHD. The Ministry of Health, Labour and Welfare also supported this activity of the Japan Society of Transfusion Medicine. However, it was impossible to eradicate TA-GVDH only by recommendation. After discussions with the Ministry of Health, Labour and Welfare of Japan, universal irradiation was started in Red Cross Blood Centers across the nation from 2000 in Japan. Through these efforts, the annual incidence of TA-GVHD which had been estimated to 50 to 100 a year, decreased to zero.

This article summarizes pathogenesis of TA-GVHD, based on the 20 years experience in Japan and data of 64 cases with definitive diagnosis of TA-GVHD determined by VNTR.

1) Pathology

GVHD is a severe medical condition caused by attack of immune cells in transfused blood or in a transplanted graft, against a patient, through an immunologic mechanism. TA-GVHD is classified into acute GVHD and chronic GVHD, and most of TA-GVHD is acute GVHD. TA-GVHD and acute GVHD after bone marrow transplantation show markedly similar clinical symptoms. However, the mortality of GVHD after bone marrow transplantation is relatively low because bone marrow is not attacked through an immunologic mechanism since the bone marrow is derived from

the donor. On the other hand, TA-GVHD has a rapid fatal outcome due to infection or hemorrhage by pancytopenia, marked decrease in white blood cells and platelets.

The clinical feature of TA-GVHD is as follows. First, about 1 or 2 weeks after transfusion (mostly associated with a surgery), the patient, who almost has recovered from the surgery and ready for discharging from the hospital, shows fever around 38 ºC and a skin rash. A few days after onset of these symptoms, erythema spreads and the liver dysfunction become evident. After additional a few days, hematopoietic function is suppressed associated with damaged bone marrow, leading to marked decrease in granulocytes and platelets. The patient suffers remarkable infection and hemorrhage. The patients with GVHD after bone marrow transplantation show gastrointestinal symptoms such as diarrhea associated with injured gastrointestinal mucosa, but the incidence of these symptoms is 40% or less in the patients with TA-GVHD. After several days after onset of above symptoms, the blisters on skin become ulcer. No treatment can reverse the condition, and the result is death.

Among more than 300 suspected cases of TA-GVHD, which were collected by the hemovigilance system of Japanese Red Cross Society, 61 cases were confirmed as TA-GVHD by VNTR (variable numbers of tandem repeats) method developed by Wang et al [2]. With this method, T cells from blood of donors were identified in the patients' peripheral blood. Among these 61 cases, 60 cases died except one case that developed TA-GVHD after transfusion to treat massive bleeding by placenta previa. Therefore, the mortality of TA-GVHD is 95% or more. This exceptional case who recovered from TA-GVHD was a young woman in her thirties. When she had symptoms, lymphocytes in peripheral blood were those from the donor, but after recovery, genotype of lymphocyte was returned to that of her own.

In the terminal phase of TA-GVHD, the white blood cell count is markedly decreased: only few lymphocytes remain. Furthermore, these few lymphocytes come from the donor and have T-cell receptors consisting of extremely limited types of α-chain and β-chain gene subfamilies[3]. This observation may reflect the proliferation of specific clones that attack the patient's tissues.

Most of the patients have received transfusion associated with a surgery, and TA-GVHD is rare in transfused patients without surgical operation. This finding may suggest that the stress by invasive surgical operation is one of the risk factors contributing development of TA-GVHD. Among our patients, 4 cases had no surgical operation: 1 case was with immunodeficient SCID (severe combined immunodeficiency), 1 case had hemorrhage by a traffic accident and 2 cases had massive hematemesis by gastric ulcer. Strong stress was imposed on the latter 3 cases. Also, among 61

cases with TA-GVHD we examined, only 6 cases were aged below 60: 16 cases were aged 60 to 70, 27 cases were aged 70 to 80 and 12 cases were aged above 80. Even after adjusting these figures by population of patients who received transfusion in each age group, age is one of statistically significant risk factors of TA-GVHD. As to history of transfusion, 8 cases had unknown history, 2 cases had history and 51 cases had no history of transfusion. Transfusion for the first time is another risk factor.

As shown in an experiment in rats conducted by D. B. Wilson et al[4)], resistance to GVHD can be induced by immunization with little amount of lymphocytes, under a condition where GVHD is likely to occur. He suggested that this is caused by immune response to T-cell receptors of the donor lymphocytes. It is suggested that the reasons why patients in internal medicine fields, especially those receive transfusion repeatedly to treat hematological disorders, seldom develop TA-GVHD, are that they are free from stress of surgery, and immune response against GVHD has been induced by repeated transfusion, as shown by Wilson et al.

References

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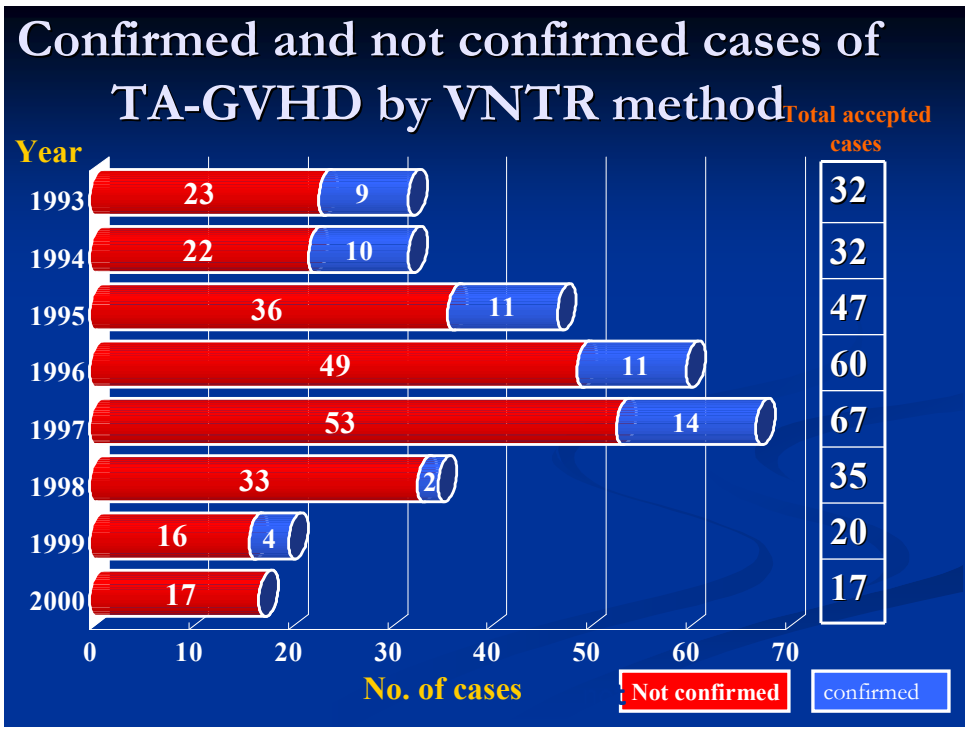
Confirmed and not confirmed cases of TA-GVHD by VNTR method
Year
Total accepted cases
1993
1994
1995
1996
1997
1998
1999
2000
23
9
22
10
36
11
49
11
53
14
33
2
16
4
17
32
32
47
60
67
35
20
17
0
10
20
30
40
50
60
70
No. of cases
Not confirmed
confirmed