

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

2) History of TA-GVHD

At first, TA-GVHD was observed only in immunodeficient patients. For example, Hathaway et al.¹⁾ reported first 2 cases in 1965 were immunocompromised. A review by Brubaker²⁾ in 1983 also stated that TA-GVHD develops only in patients with cell-mediated immune deficiency.

Apart from these studies, in 1955, Shimoda³⁾ reported 12 cases of POE (postoperative erythroderma) as a new disease that fell into severe condition with erythema on skin after surgical operation. Among these 12 cases, 6 cases died, and 5 cases of them showed leucopenia. These cases seem to be TA-GVHD. However, we should pay attention because not all patients with POE are TA-GVHD. After the report by Shimoda, many cases of POE, especially those who received cardiovascular surgery were reported as serious condition with unknown mechanism in Japan. In 1984, Aoki et al.⁴⁾ conducted biopsy of the skin and bone marrow of a patient of POE after surgery of aortic aneurysm and found that lymphocyte-like cells bound and attacked the damaged cells in skin and bone marrow by histological examination. They reported that this condition was caused by GVHD. This report gave a strong impact on the researchers of surgery who had investigated POE, and the researchers in transfusion medicine because they were shocked by discovery of such serious side effect of transfusion.

They started to collect evidences that POE developed by the same mechanism of GVHD. Sakakibara et al.⁵⁾ showed presence of lymphocytes having HLA type different from that of the patient, in the peripheral blood of the patient with POE. Ito et al.⁶⁾ demonstrated that postoperative erythema in immunocompetent patients is one of symptoms of TA-GVHD, because the lymphocytes in the peripheral blood of a patient changed from HLA haplotype heterozygote (phenotype of the patient) to homozygote (phenotype of the donor), when the patient had POE. This report demonstrates that TA-GVHD can develop in immunocompetent patients by one-way matching of HLA antigens. Matsushita et al.⁷⁾ reported 2 immunocompetent female patients with TA-GVHD, and demonstrated presence of lymphocytes having Y chromatin of male donors, adjacent to damaged cells on skin lesion of female patients.

The Japan Society of Transfusion Medicine⁸⁾ conducted a questionnaire survey regarding to 63,257 cardiovascular surgeries conducted during 6 years from 1980 to 1985 and found 96 cases of TA-GVHD. This result confirmed that 1 TA-GVHD occurs in 658 patients who have undergone cardiovascular surgeries. The Japanese Red Cross Society⁹⁾ conducted a questionnaire survey in physicians working for institutions that used more than 1000 blood products a year, to investigate recognition by physicians on TA-GVHD. The survey revealed that only half of 14,000 physicians

understood that TA-GVHD may developed even in immunocompetent patients. A secondary questionnaire survey in physicians having experience of post transfusion GVHD, was conducted to collect data of their suspected TA-GVHD cases. As a result, 171 cases were identified as TA-GVHD based on their clinical symptoms. These patients received surgical operations for cardiovascular diseases, cancer and others. In addition, 14 cases were neonates who received transfusion, and among these 14 cases, 13 cases received blood from their fathers. This finding warns risk of TA-GVHD by transfusion between close relatives.

Wang et al.¹⁰⁾ compared VNTR (variable numbers of tandem repeats) in DNA derived from lymphocytes in peripheral blood and that derived from nails of the patients, and showed that the genotype of the lymphocytes is different from that of the nail. This method was established as a method for definitive diagnosis of TA-GVHD. In this historical background, it was urgent to establish a system to investigate serious risk of side effect of transfusion including TA-GVHD. The Japanese Red Cross Society employed more than 150 MR (medical representatives) for Red Cross Blood Centers, who received special training to establish a system to collect clinical information, and blood samples of the cases that showed adverse reaction after transfusion from hospitals across Japan, and sent them to Central Blood Center of the Japanese Red Cross Society. At the same time, the Society established a research laboratory to analyze the adverse reactions in the Central Blood Center, to elucidate its mechanism. This is a hemovigilance activity that starts from 1993 in Japan. As mentioned above, 61 cases were confirmed by VNTR method as TA-GVHD, among more than 300 suspected cases of TA-GVHD, the data of which were collected in Japanese Hemovigilance System from 1993 to 1999. No case was immunodeficient, except 1 case of SCID (severe combined immunodeficiency). This finding indicated that the guideline stipulating that irradiated blood should be used for immunodeficient patient, was not clinically relevant in Japan. After discussion with the Ministry of Health, Labour and Welfare, it was decided that blood products containing cells should be universally processed with irradiation after 2000. Fortunately, during these 10 years after the implementation of universal irradiation, no TA-GVHD occurred by blood supplied from Japanese Red Cross Blood Centers.

References

- 1) Hathaway WE, Githens JH, Blackburn WR, Fulginiti V, Kempe CH. Aplastic anemia, histiocytosis and erythrodermia in immunologically deficient children, probable human runt disease. *N Engl J Med.* 273:953-958, 1965
- 2) Brubaker DB. Human posttransfusion graft-versus-host disease. *Vox Sanguinis* 45:401-420, 1983
- 3) Shimoda T. On postoperative erythroderma. *Geka* 17:487-492, 1955
- 4) Aoki Y, Nakamura H, Sakakibara Y. *Nippon Naika Gakkai Zasshi* 73: 1209-1216, 1984

- 5) Sakakibara T, Juji T. Post-transfusion graft-versus-host disease after open heart surgery. *Lancet* 2(8515):1099, 1986
- 6) Ito k, Yoshida H, Yanagibashi K, Shimada Y, Imamura M, Tobe T, Akiyama Y, Saji H, Maruya E, Hosoi T. Change of HLA phenotype in postoperative erythroderma. *Lancet* 1(8582):413-414, 1988
- 7) Matushita H, Shibata Y, Fuse K, Kimura M, Iinuma K. Sex chromatin analysis of lymphocytes invading host organs in transfusion-associated graft-versus-host disease. *Virchows Arch B Cell Pathol incl Mol Pathol* 55:237-239,1988
- 8) Juji T, Takahashi K, ShibataY, Ide H, Sakakibara T, Ino T, Mori S. Post-transfusion graft-versus-host disease in immunocompetent patients after cardiac surgery in Japan. *N Engl J Med.* 321:56, 1989
- 9) Takahashi K, Juji T, Miyamoto M, Uchida S, Akaza T, Tadokoro K, Shibata Y, Ino T, Hidano A. Analysis of risk factors for post-transfusion graft-versus-host disease in Japan. Japanese Red Cross PT-GVHD Study Group. *Lancet* 343(8899):700-702. 1994
- 10) Wang L, Juji T, Tokunaga K, Takahashi K, Kuwata S, Uchida S, Tadokoro K, Takai K. Polymorphic microsatellite markers for the diagnosis of graft-versus-host disease. *N Engl J Med.* 330:398-401, 1994