

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

3) Pathogenesis and treatment

Billingham¹⁾ suggested 3 conditions necessary for the development of GVHD: 1) the graft has immunocompetent cells; 2) the host has alloantigens those are absent in the graft; 3) the host lacks effective immune response to the graft.

When these conditions are satisfied, the immune cells (T cells) of the donor in the graft can survive in the recipient. The donor cells are not rejected when the recipient is immunodeficient, and when there is one-way matching between the donor and the recipient, in major histocompatibility antigens (in human, HLA antigens) that trigger rejection. One-way matching is a state in which the donor is homozygote (AA) of HLA antigens, and the recipient is heterozygote (AX). In this case, the immune cells of the donor circumvent immune system of the recipient and survive in the recipient, recognize HLA antigens on unshared X haplotype of the recipient as a foreign substance, and begin immune response to generate cytotoxic T cells. In the history of immunology, GVHD was identified as immune response in 1950s. Experiments at that time used inbred parental strain as a donor, and immune cells of the parental strain were injected to F1 (first filial generation) of this parental strain and a different inbred strain with different MHC antigens to make experimental GVHD. Ito et al.²⁾ described a case in which blood of HLA haplotype homozygote was transfused to a patient with heterozygote of donor's haplotype and another haplotype, and after the development of GVHD, the HLA phenotype of the recipient was replaced with that of the donor. This fact was confirmed in many cases collected by Hemovigilance system of Japanese Red Cross Society. This mechanism is identical to that of the above described experimental animals. When there is one-way matching of HLA, the immune cells of the donor is not rejected by the recipient. The immune cells of the donor surviving in the recipient recognize MHC (HLA) antigens that are present in the recipient but absent in the donor, as a foreign substance. A reaction to attack these antigens is manifested as transfusion associated GVHD.

HLA haplotype consists of a series of loci of HLA antigens: HLA-A, B, C, DR, DQ and DP. These loci so closely link to each other. that the combination of antigens is inherited from parents to their children. Each HLA antigen deeply associates with immune response. Haplotypes of each race have been built through long history of adaptation and development of that race in particular environment and infectious organisms. The most frequently observed haplotype is A1-B8-DR3 (5% to 8%) in Caucasians, while it is A24-B52-DR2 (7% to 10%) in Japanese. It is suggested that Japan has more cases of transfusion associated GVHD because the frequency of HLA haplotype homozygotes is higher in Japanese compared with Caucasian. .

Also, in Japan, it had been a common practice to ask a father of a neonate to provide his blood when the neonate needs transfusion before Aoki et al reported a case of TA-GVHD in a patient without immunodeficiency in 1984. This practice is extremely dangerous because a chance of one-way matching of HLA antigens extremely increases in transfusion between parents and their siblings compared with transfusion between unrelated. The system of blood donation from voluntary non-remunerated donors was established in the 1970s in Japan and enough amount of blood from these donors can be obtained in 1980s. However, a practice to obtain blood from relatives of patients that undergo surgery or platelet apheresis remained. Since 1984, transfusion between relatives is not conducted because the risk of transfusion associated GVHD comes to be known.

Transfusion associated GVHD does not appear soon after transfusion: it appears 1 to 2 week later. This is because after the immune cells of donors recognize HLA antigens of recipient, which is not present in donor's blood, as a foreign substance, they need some time to proliferate and differentiate to cytotoxic T cells to destroy cells of the recipient. Nishimura et al.³⁾ demonstrated 3 types of T cell clones from peripheral blood of patients with transfusion associated GVHD. These clones were : 1) cytotoxic CD8+ T cells that target HLA class I antigens of the patients, 2) cytotoxic CD4+ T cells that target HLA class II antigens of the patients, and 3) CD4+ T cells that lack cytotoxicity by direct contact, but divide and proliferate under presence of HLA class II antigens of the patient, produce and release TNF α to indirectly damage cells of the patient. These 3 types of T cells play important roles during effector phase of transfusion associated GVHD. Cytotoxic T cells divided and proliferated as above start attack to the skin, the liver and the bone marrow of the patients. In the end stage, the white blood cells of the patient are almost replaced with cytotoxic T cells with specific T cell receptors derived from donors.

Nafamostat mesilate (NM), a serine protease inhibitor, and an antimalarial agent, chloroquine were found to inhibit cytotoxicity and TNF- α production of these 3 types of T cell clones, thus these inhibitory activities of these agents were investigated *in vitro*⁴⁾. These agents with the concentration of 1 – 10 $\mu\text{g}/\text{mL}$ can totally inhibit the cytotoxicity and TNF α production. Therefore, NM was administered to 4 patients with TA-GVHD⁵⁾. After administration of NM, accompanied with disappearance of fever and skin rash, damaged liver function and bone marrow suppression improved dramatically. However, the administration of NM had to be terminated because of the appearance of NM induced hyperkalemia. The agents prolonged survival of the patients by several weeks, but could not reverse the condition. After this study, since we had no case of transfusion associated GVHD by the implementation of universal irradiation in all the JRC blood centers, we could not conduct further study. If we can prevent hyperkalemia by NM, the treatment of TA-GVHD may be possible in near future.

References

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