

## ■ CASE REPORTS

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### Transfusion-associated Graft-Versus-Host Disease Caused by Leukocyte-filtered Stored Blood

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THE incidence of transfusion-associated graft-versus-host disease (TA-GVHD) is low, but the mortality rate is very high.<sup>1,2</sup> TA-GVHD is caused by viable or immunocompetent lymphocytes from transfused blood products. Transfusion of fresh blood products is well recognized to be a risk factor for this disease. In fact, the majority of reported cases of TA-GVHD have been associated with transfusion of fresh blood products, but only a single case has been reported after transfusion of unirradiated, nonfiltered, stored (5-day-old) packed red cells in an immunocompetent patient.<sup>3</sup> Because there is no effective treatment for TA-GVHD, its prevention is important.  $\gamma$ -Irradiation of blood products before transfusion is the most effective method of prevention.<sup>1</sup> A leukocyte filter is also used as an alternative method for the purpose of eliminating the lymphocytes in blood products. Herein, we report the first clinical case of TA-GVHD that developed after cardiac surgery after transfusion of unirradiated, stored (7-day-old) packed red cells despite leukocyte filtering.

#### Case Report

A 72-year-old man (height 156 cm, weight 54 kg) underwent aortic valve replacement and coronary artery bypass graft surgery at Osaka National Hospital for effort angina caused by aortic valve disease and coronary artery stenosis. Anesthesia was induced and maintained with fentanyl, diazepam, and pancuronium. Aortic valve replacement and coronary artery bypass graft surgery using an internal mammary artery were performed using cardiopulmonary bypass. Hemostasis after bypass was not easy, in part, supposedly, because of preoperative anticoagulant therapy. The patient was transfused with two units of unirradiated packed red blood cells (stored for 7 days; 1 unit is from

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400 ml whole blood) using a leukocyte filter (RC-100, PALL, East Hills, NY), and five units of fresh frozen plasma were added to control bleeding.

The early postoperative course was uncomplicated until the sixth day after surgery, when he developed a persistent fever (38°C). His postoperative hemodynamic state was stable. On the ninth day after surgery, he developed a diffuse skin rash. An allergic reaction caused by antibiotics was initially suspected, and the antibiotics were withheld. Two days later, however, the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels markedly increased to 485 and 761 U/l, respectively, and the platelet count decreased. Blood, urine, and sputum cultures and viral titers were all unrevealing. His skin lesions progressed to a generalized papular erythematous rash, so-called generalized erythroderma. Biopsy of the skin demonstrated necrotic keratinocytes with eosinophilic cytoplasm, the vacuolar degeneration of basal cells, and a lymphocytic infiltrate, all compatible with a diagnosis of TA-GVHD.

The patient was treated with methylprednisolone. On the 14th day after surgery, the leukocyte count decreased to  $1400 \mu\text{l}^{-1}$  (74% granulocytes and 19% lymphocytes). Despite treatment with granulocyte colony-stimulating factor, the leukopenia and thrombocytopenia worsened. The patient died of coagulopathy, sepsis, and multiple organ failure on the 16th day after surgery. Autopsy was not performed.

#### Discussion

TA-GVHD develops when donor lymphocytes from transfused blood products engraft in the recipient, and initiate an intense immune reaction against host tissue. Its early manifestations are fever and a skin rash (erythematous maculopapular eruption). The skin rash spreads and may progress to generalized erythroderma. Leukopenia and thrombocytopenia develop later. Sepsis and death are the usual end result of TA-GVHD. TA-GVHD is basically diagnosed from its typical clinical course and histologic examination of skin biopsy. Although the definitive diagnosis is based on proving a change of HLA phenotype, the so-called chimerism of circulating lymphocytes,<sup>4-6</sup> it is often difficult because of severe leukopenia.<sup>7</sup> In our case, the skin biopsy findings and typical clinical course strongly indicate that TA-GVHD was the diagnosis, although the proof of chimerism is lacking.

The majority of reported cases of this disease have been associated with transfusion of fresh blood prod-

## CASE REPORTS

ucts, and, thus, transfusion of fresh blood products is well recognized to be one of the risk factors for TA-GVHD. In particular, use of fresh blood from the recipient's family members is extremely risky, because the homogeneity of HLA-haplotypes between a patient and donors increases the chance for TA-GVHD to develop.<sup>5</sup> In contrast, stored blood products are considered to be much safer than are fresh blood products, because they contain fewer viable lymphocytes. Only a single case of TA-GVHD has been reported after intraoperative transfusion of unirradiated, nonfiltered, stored packed red cells.<sup>3</sup>

To date, the precise number of lymphocytes required to cause TA-GVHD in humans has not been determined. However, it is estimated from data in mice<sup>8</sup> that more than  $10^7$  lymphocytes per kilogram of the recipient's body weight need to be transfused to cause TA-GVHD in humans. From this viewpoint, a leukocyte filter is used as a preventive method to eliminate the lymphocytes in blood products. Akahoshi *et al.* reported a case of TA-GVHD that occurred in an immunocompromised patient after transfusion of platelet concentrates, despite leukocyte filtering.<sup>9</sup> There is, however, no report of TA-GVHD caused by transfusion of leukocyte-filtered stored blood products in an immunocompetent patient.

Leukocyte filters will deplete more than 99% of white blood cells from blood products in an optimal condition.<sup>10</sup> In intraoperative use, however, their efficiency is affected by the type and amount of blood products being filtered, and by the flow rate. Efficiency may also decrease because of inadequate priming of the filter, which leads to channeling of blood, and so-called "pumping" manipulation, which manually forces blood to pass through a filter. It is reported that the efficiency of the leukocyte filter (RC-100) can decrease to less than 95% for processing two units of packed red blood cells.<sup>10</sup> Thus, it is likely that lymphocyte depletion in intraoperative transfusion using a filter may not be as effective as expected. Furthermore, although it has not been studied, the removal efficiency for granulocytes and lymphocytes may be different, so that lymphocyte depletion may be insufficient. Currently, it is not proven whether the leukocyte reduction by filter treatment would decrease the risk of TA-GVHD.<sup>1</sup>

Because the mechanism underlying the development of TA-GVHD remains poorly understood, and because there is no effective treatment for TA-GVHD, its prevention is essential. Anesthesiologists bear a responsibility for the prevention of GVHD associated with intraoperative transfusion, and should make every effort

to prevent it. The primary preventive measure is minimizing the transfusion of donated blood. Hypotensive anesthesia can be used in some types of operations to decrease operative blood loss and thereby diminish the need for transfusion. The use of autotransfusion should be considered when the need for transfusion is expected in advance.  $\gamma$ -Irradiation of blood products before transfusion is the only currently proven effective method of preventing TA-GVHD.<sup>1</sup> Button *et al.* examined the function of blood components after irradiation of 5–200 Gy, and demonstrated that doses as high as 50 Gy decreased mitogen stimulation by 98.5%, but did not compromise the function of cells other than the lymphocytes.<sup>11</sup> Another study indicates that irradiation at doses of 15–20 Gy can reduce mitogen-responsive lymphocytes by  $10^{-5}$ - to  $10^{-6}$ -fold compared with nonirradiated controls.<sup>12</sup> It has been recommended that the lowest radiation dose capable of inhibiting lymphocytes proliferation (15–20 Gy) should be used to irradiate blood components before transfusion.<sup>1</sup>

In view of the rarity of TA-GVHD, and although irradiation of blood products has been recommended for immunocompromised patients, the routine irradiation of blood products may not be justified. However, the incidence of TA-GVHD after cardiac surgery has been reported to be as high as 1 in 660 Japanese patients,<sup>2</sup> and it is likely that the homogeneity of HLA-antigens in the Japanese population contributes to this incidence. Thus, routine irradiation of all donated blood products containing viable lymphocytes should, perhaps, depend on the specific population of surgical patients until a more precise method of identifying susceptible patients is identified.

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## CASE REPORTS

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## Diffuse Oral Facial Cavernous Hemangioma Causing Severe Airway Obstruction after Intramuscular Ketamine

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SUCCESSFUL prevention of airway-related catastrophes begins with recognizing the potential problem.<sup>1</sup> In this paper, we describe a patient with diffuse oral facial cavernous hemangioma in whom severe airway obstruction occurred unexpectedly, soon after intramuscular ketamine injection.

### Case Report

A 3-yr-old boy weighing 12 kg was scheduled for digital subtraction angiography and embolization of diffuse oral facial cavernous hemangioma. He had no previous exposure to anesthesia or surgery. Coughing, crying, vomiting, or straining was often associated with minimal generalized swelling of the hemangioma, but swallowing and breathing were never affected, and spontaneous resolution generally took no more than a few minutes. He had no history of obstructive sleep apnea, hemoptysis, or bleeding in the oral cavity.

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General examination was unremarkable. Laboratory investigations were within normal limits. Local examination revealed: (1) an everted lower lip with a rough surface and bluish discoloration; (2) normal facial contours with slightly boggy cheeks; (3) patchy bluish discoloration of skin over the cheeks and lower jaw; (4) minimal macroglossia with discolored margins; (5) sparse and patchy bluish discoloration of entire oropharyngeal mucosa; (6) class I airway<sup>2</sup> and a normal voice; and (7) normal head and neck mobility. To the examiner, signs and symptoms did not appear to indicate any potential airway difficulty.

After oral triclofos, 50 mg intramuscular ketamine with 0.3 mg atropine was given. About 5 min later, when the child appeared to be drowsy, peripheral vein cannulation was attempted, and the stimulation caused transient breath holding. Soon thereafter, the hemangioma suddenly enlarged, leading to airway obstruction and distorted facial contours (fig. 1A and B).

At this stage, the patient's tongue, lips, and cheeks were greatly swollen to a thickness of an inch or more, and the oral cavity, including the hypopharynx, was reduced to a potential space after rapid inward expansion of all the structures in and around the oral cavity. Airway patency could not be restored by inserting either an oropharyngeal or a nasopharyngeal airway. The heart rate increased to 140-150 beats/min, and cyanosis appeared. Orotracheal intubation was performed immediately under direct laryngoscopy, and low-flow oxygen was given *via* "T" connector.

The tracheal intubation was atraumatic except for slight bleeding from the glossoepiglottic mucosal fold. The hemangioma was found to extend into the tonsillar bed, soft palate, and posterior pharyngeal wall; however, the vocal cords, epiglottis, and aryepiglottic folds were not involved.

Subsequently, the oro-tracheal tube was replaced by a nasotracheal tube. Vital signs gradually returned to within normal limits. The pa-