Transfusion-Associated Graft-Versus-Host Disease in Two Patients at Yangon General Hospital

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Summary

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare complication of blood transfusion. Two male patients admitted to the Department of Clinical Haematology, Yangon General Hospital (YGH) diagnosed to have TA-GVHD in 2011 and in 2016 are presented. Both of the patients received blood donation from close relatives where neither leukoreduction nor irradiation was done. Both patients had fever, skin rashes, gastrointestinal symptoms, raised liver enzymes and pancytopenia. Skin biopsies of both patients showed characteristic histological changes. Unlike graft-versus-host disease that occurred after haemopoeitic stem cell transplantation, TA-GVHD involves the recipient's bone marrow leading to bone marrow aplasia.

Background

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare, usually fatal, complication of blood transfusion wherein donor lymphocytes in a transfused blood component mount an immunodestructive response against recipient tissues.[1]

Case presentation - Case (1)

A 54-year old farmer got left humerus fracture from an accident in July 2011, and underwent operation (fixation of fracture with intramedullary nail) for that. He received one unit of fresh whole blood donated by his son during operation. Leukoreduction and irradiation of blood product was not done. He was discharged from hospital three days later.

Seven days after getting blood transfusion, he got fever followed by appearance of erythematous rash all over the body. At that time he also had severe neutropenia for which he was referred to the Department of Clinical Haematology, YGH. He was medically, fit before he got humeral fracture. He received antibiotics and analgesics during perioperative period but was off medication after that. He was a non-smoker and a social drinker. There was no relevant family history.

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On examination, he had fever, puffy face, jaundice and generalized erythematous macular papular rash invading the whole body including palms and soles. Oral mucosa and eyes were normal at the time of hospital admission. (Figure 1 A, B and C)

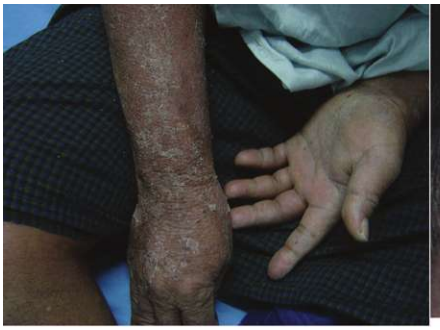

Figure 1 (A). Desqamatous erythematous rash in extremities involving palms in TA-GVHD Case 1

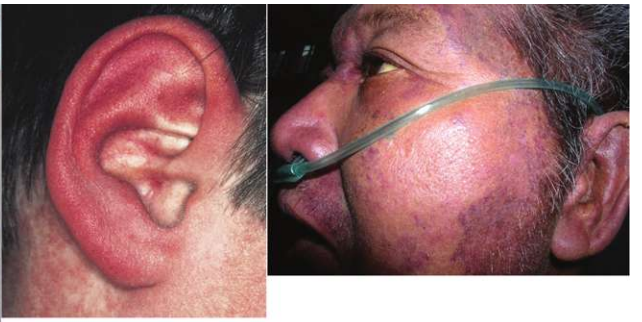

Figure 1 (B and C). Erythematous rash involving face and ears in TA-GVHD Case 1

Examination of respiratory, cardiac, gastrointestinal and nervous systems revealed no significant abnormality. Liver was just palpable and tender. There was no enlargement of spleen and lymph nodes.

Investigations

On the day of admission, he had haemoglobin 12 g/dL, white cell count 1.14 x 10^9/L, neutrophil 0.12 x 10^9/L, lymphocyte 0.8 x 10^9/L and platelet count 107 x 10^9/L. Serum bilirubin was 1.4 mg/dL, with alanine transaminase (ALT) 910 U/L, aspartate transaminase (AST) 959 U/L and alkaline phosphatase (ALP) 327 U/L. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were slightly prolonged. D-dimer was high. Lactate dehydrogenase (LDH) was raised (485 U/L). Urinalysis and renal function test were normal.

Viral serology for hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus HIV, cytomegalovirus, dengue virus and chikungunya virus were all negative. Blood for malaria parasite and immuno-chromatographic test for malaria were also negative. Blood and urine culture were sent. Chest X-Ray, ultrasound abdomen and echocardiogram were also normal.

Differential diagnosis

Since patient had fever, skin rash, hepatic involvement and pancytopenia, severe systemic infection with septicaemia was put as a first differential diagnosis. But with the history of blood transfusion from relative, TA-GVHD was considered as a possibility as well.

Treatment and outcome

He was given broad spectrum antibiotics, steroid and liver support regimen but his blood counts fell progressively to haemoglobin 8.5 g/dL, white count 0.15 x 10^9/L, neutrophil 0.01 x 10^9/L, lymphocyte 0.22 x 10^9/L and platelet count 26 x 10^9/L. Blood and urine culture were sterile. Bone marrow aspirate showed hypocellular marrow with relative increase in number of macrophages in the bone marrow. (Figure 2 A and B) Trephine biopsy of bone marrow also showed severe hypoplastic marrow. Bone marrow flow cytometry showed no evidence of lymphoproliferative disorder. Lymphocytes comprised approximately 8.6% of all viable cells with 8% T lymphocytes, 0.2% B lymphocytes and 0.4% NK cells. B lymphocytes showed no overtly abnormal immunophenotypic features and had a kappa:lambda ratio of 0.28. T lymphocytes also showed no overtly abnormal pan-T antigen expressions with the CD4:CD8 ratio of 0.15.

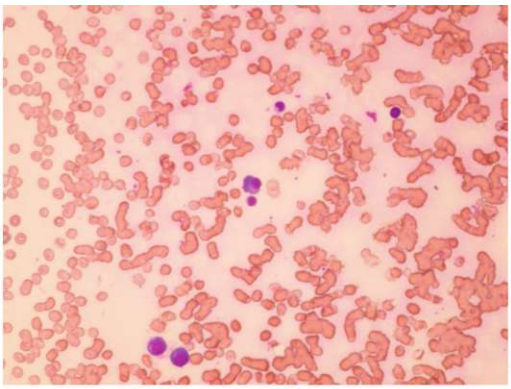

Figure 2 (A). Hypocellular bone marrow aspirate in TA-GVHD Case 1

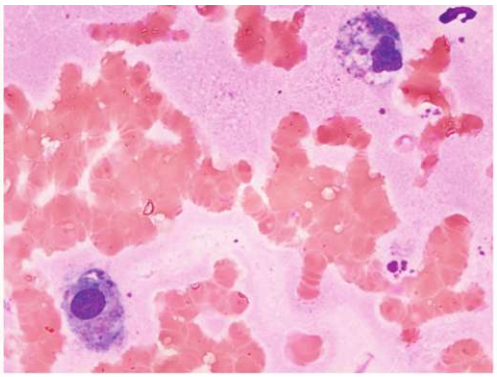

Figure 2 (B). Increased number of macrophages in bone marrow aspirate of TA-GVHD Case 1

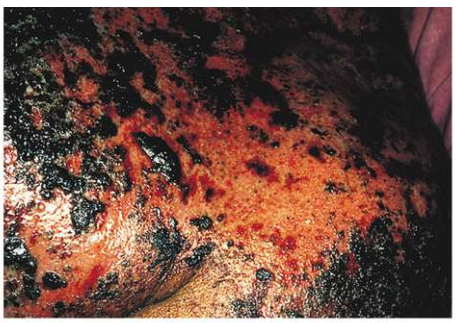

Figure 3. Haemorrhagic bullae in TA-GVHD Case 1

His liver enzymes were slightly improved with above treatment but cytopenia was progressive. His maculopapular rash became haemorrhagic bullae. (Figure 3) Fluid culture from blisters showed growth of Staphylococcus aureus. Later he developed mucositis with diarrhoea. Skin biopsy was taken from shin. Skin biopsy was reported as oedema of skin with dilated small blood vessels and extravasated red blood cells with focal few necrotic keratinocytes in the epidermis. Several blood vessels contained thrombi and some had fibrin in the wall. One portion of skin exhibited haemorrhage and full thickness necrosis. Pathological diagnosis was ischaemic necrosis of skin, probably related to post-transfusion GVHD. Pathologist also commented that the reaction was mainly caused by humoral antigen antibody reaction but the cell mediated reaction was a minor part of it. (Figure 4 A, B and C)

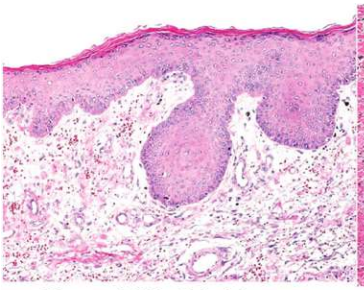

Figure 4 (A). Skin biopsy appearance in TA-GVHD Case 1

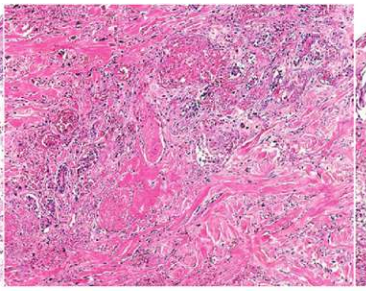

Figure 4 (B). Skin biopsy appearance in TA-GVHD Case 1

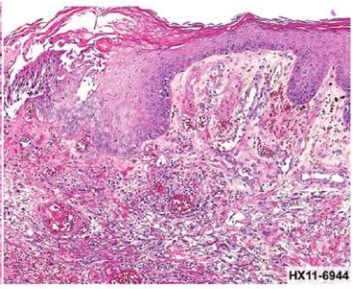

Figure 4 (C). Skin biopsy appearance in TA-GVHD Case 1

The patient was treated with antibiotics, steroid, cyclosporin, mycophenolate-mofetil and anti-thymocyte globulin but expired on day 15 after admission due to septicemia and multiorgan failure.

Case presentation - Case (2)

A 72-year old farmer from Khayan Township was referred from ward 17/18 of YGH to the Department of Clinical Haemaotlogy in September 2016 with fever, skin rash, mucositis and pancytopenia.

Ten days before admission he got fever and took treatment at township hospital. There he was found to have anemia and received three units of whole blood from his two sons and a grandson. There was no leukoreduction and no irradiation. After two days of blood transfusion, he got fever and skin rashes all over the body and extremities including palms and soles. He also got loose stools the next day. He was first admitted to ward 17 and 18 of YGH and then referred to haematology department.

On arrival to haematology department, patient was ill, toxic, febrile and had jaundice. Diffuse confluent erythematous maculopapular rash covered the whole trunk, face and extremities and blanched on pressure. Mouth examination showed severe mucositis of oral mucosa. Liver was 3 cm below the costal margin and was tender. There was no enlargement of lymph node and spleen. (Figure 5 A, B, C, D and E)

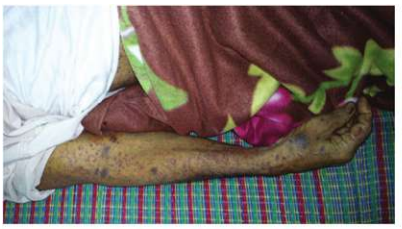

Figure 5 (A). Erythematous rash involving upper limb in TA-GVHD Case 2

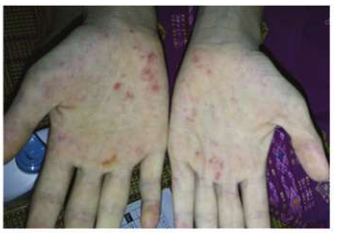

Figure 5 (B). Erythematous rash involving palms in TA-GVHD Case 2

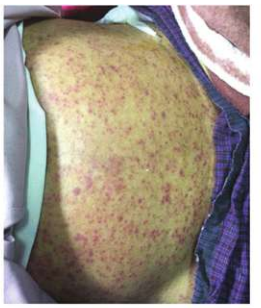

Figure 5 (C). Erythematous rash involving abdomen in TA-GVHD Case

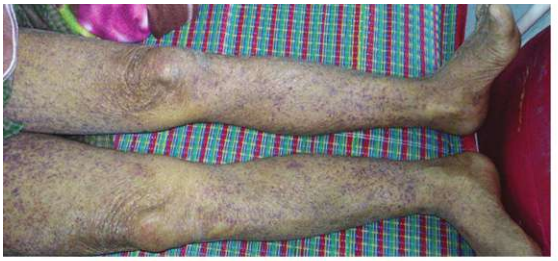

Figure 5 (D). Erythematous rash involving lower limbs in TA-GVHD Case 2

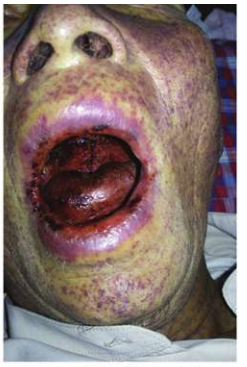

Figure 5 (E). Severe mucositis in TA-GVHD Case 2

Investigations

He had haemoglobin 8.5 g/dL, white blood cell 2.6 x 10^9/L, neutrophil 1 x 10^9/L, lymphocyte 1.3 x 10^9/L with platelet count 18 x 10^9/L. Erythrocyte sedimentation rate (ESR) was 70 mm per first hour. Serum bilirubin was 1.6 mg/dL with ALT 691 U/L, AST 981 U/L, and ALP 116 U/L. Serology for hepatitis B, hepatitis C, dengue, leptospira and HIV were negative. Serum creatinine was 136 µmol/L. Prothrombintime was slightly prolonged but APTT was normal.

Differential diagnosis

Since patient had fever, skin rash, mucositis, diarrhoea, hepatomegaly, raised hepatic enzymes and pancytopenia which all appeared after receiving blood from relative, the most likely diagnosis was TA-GVHD. Hepatitis-induced pancytopenia was excluded by the negative serologies for viral hepatistis B and C.

Treatment and outcome

The patient was treated with steroid, antibiotics, liver support measures and skin care. Skin biopsy was taken from right lower leg. The patient's condition deteriorated and he requested discharge. Patient expired after two days.

Skin biopsy revealed fragments of skin covered by stratified squamous epithelium and fibroconnective tissue stroma. There was mild hyperkeratosis of epidermis and basal cells vacuolar degeneration. Apoptotic keratinocytes were seen as acidophilic bodies at the tip of the rete ridges and whole layer of epidermis. Epidermis showed mild dysplastic changes. Pigment laden macrophages were seen. Dermis contained mild perivascular lymphocyte infiltrate and extravasated red cells. There were no cleft or epithelial separation. Hair follicles were not seen in given specimen. There was no feature of granuloma or malignancy. Histology features were suggestive of cutaneous GVHD. (Figure 6 A and B)

Bone marrow examination, anti-HLA antibodies, HLA typing of patient and donors and chimerism studies were not done.

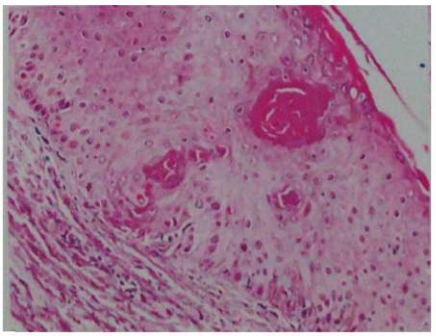

Figure 6 (A). Skin biopsy appearance in TA-GVHD Case 2

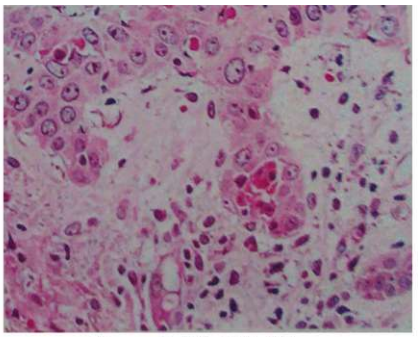

Figure 6 (B). Skin biopsy appearance in TA-GVHD Case 2

Discussion

According to the National Health and Safety Networks' criteria, definitive TA-GVHD is a clinical syndrome occurring from 2 days to 6 weeks after cessation of transfusion characterized by: (1) characteristic rash (erythematous, maculopapular eruption centrally that spreads to extremities and may, in severe cases, progress to generalized erythroderma and hemorrhagic bullous formation), (2) diarrhoea, (3) fever, (4) hepatomegaly, (5) liver dysfunction (i.e., elevated ALT, AST, Alkaline phosphatase, and bilirubin), (6) marrow aplasia, (7) pancytopenia **and** characteristic histological appearance of skin or liver biopsy. Probable TA-GVHD are cases that meet definitive criteria except biopsy negative or not done. The presence of white blood cell chimerism in the absence of alternative diagnoses can be used for imputability.[2]

Based on these criteria, both of the patients presented here were definitive TA-GVHD cases and death occurred in both definitely as a result of the adverse transfusion reaction.

Blood transfusions can trigger immune responses. These immune responses can include donor's anti-recipient immune responses as well as recipient's anti-donor immune responses induced by the donor leukocytes acting as antigen-presenting cells or as a source of antigen. Most of the time, recipient's anti-donor responses are usually able to eliminate donor leukocytes, but when the recipient's anti-donor responses are impaired, unabated donor anti-recipient responses occurred, resulting in TA-GVHD.[1]

A transfusion from a human leukocyte antigen (HLA) homozygous donor into a recipient who shares one haplotype with the donor would be a scenario in which the recipient's anti-donor elimination responses are compromised.[3]

This is because the recipient's immune cells, especially alloreactive CD8+ and NK cells, would see the donor cells as self, and therefore not be expected to generate alloreactive responses toward the donor cells, while the donor cells would recognize the non-shared HLA haplotype on recipient cells as allogeneic and generate strong alloreactive responses.[4,5]

The majority of cases in a systematic review were attributed to cellular, non-leukoreduced, non-irradiated blood components that were stored for less than ten days. The mortality of TA-GVHD is 89.7% at a median of 24 days after implicated transfusion in that review.[6]

Bone marrow aplasia induced by TA-GVHD makes it difficult to reverse the course of TA-GVHD once it has begun. Thus, the focus for the prevention of TA-GVHD has been to prevent donor T cell proliferation. Currently, leukoreduction and/or γ-irradiation are used to prevent TA-GVHD. Pathogen reduction protocols would provide an alternative method for overcoming the increasing number of constraints placed on the use of cesium source irradiators.[7]

Learning point

- TA-GVHD is rare and can be confused with drug allergy or severe infections.
- TA-GVHD is preventable but almost invariably fatal.
- TA-GVHD can occurr with transfusion of blood from relative which is non-leukoreduced, non-irradiated and is less than ten days old.

Reference

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