CORRESPONDENCE

Transfusion-Associated Graft-Versus-Host Disease with a Non-fatal Course

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Received: 30 January 2016 / Accepted: 8 April 2016 / Published online: 12 April 2016
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Dear editor,

Please find attached the article for correspondence.

Introduction

Graft-versus-host disease (GVHD) is a clinical syndrome ascribed to the inflammatory reaction mounted by the donor cells against the host organs [1]. Transfusion associated graft-versus-host disease (TA-GVHD) is a rare and a fatal complication of the transfusion of non-irradiated cellular blood components in susceptible recipients [2]. It has low incidence of 0.1–1 % in susceptible recipients with an extremely high mortality rate of 87–100 % [3]. The underlying pathogenesis of this dreaded condition is due to the donor T-cells that engraft, proliferate and mediate a cellular immune response against host tissues, resulting in

damage to skin, liver, gastrointestinal tract and bone marrow [2]. The existence of an atypical TA-GVHD, which does not follow a fatal course and exhibit all the manifestations of GVHD, has been suggested. English literature describes only two such published cases [4, 5]. The relative rarity of atypical TA-GVHD interested us to present this case report.

Case History

A 5 year old female child presented to the hospital in February 2014 with a high grade fever, petechial spots on trunk and lower limbs and bleeding per rectum since 5 days. A month before coming to the hospital, in view of decreasing platelet counts, she had received a course of steroids for 2 weeks from outside. At this time, physical examination showed severe pallor and multiple petechiae predominantly on trunk and lower limbs. Per abdomen examination revealed a mild hepatosplenomegaly (liver 5 cm below right costal margin and spleen 3 cm below left costal margin) and sub-centimetric cervical and inguinal lymphadenopathy. Complete hemogram showed pancytopenia with a hemoglobin of 44 g/L, total leucocyte count of $2.8 \times 10^9/L$ and a platelet count of $1 \times 10^9/L$. Clinical possibilities of acute leukaemia or autoimmune lymphoproliferative syndrome was considered. Peripheral blood film (PBF) showed a leucoerythroblastic blood picture with 66 % large granular lymphocytes. Bone marrow examination showed a myeloid preponderance with dense granulation and reduced thrombopoiesis. Trepine biopsy revealed hypocellular marrow spaces with relative granulocytic preponderance and multiple interstitial aggregates of mature lymphocytes. The serum biochemistry, including liver and renal function tests were within normal limits.

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The work-up for fever was negative and repeated blood cultures sent were sterile. In view of persistent cytopenias the patient was given a single unit of non-irradiated packed RBCs from an unrelated donor. On ninth day after blood transfusion the patient developed fever, purpuric rashes all over the body, persistent diarrhea and elevated liver enzymes. A clinical possibility of GVHD following blood transfusion was considered and a skin biopsy was advised which showed necrotic keratinocytes and exocytosis by neutrophils in the epidermis (Fig. 1) consistent with a grade II GVHD. Hemogram showed pancytopenia. Bone marrow trephine biopsy revealed markedly hypocellular marrow spaces with sinusoidal dilatation and interstitial aggregates of small mature lymphocytes (Fig. 2). Overall findings were consistent with blood transfusion related graft- versus-host disease. The patient was administered parenteral methyl prednisolone 30 mg/kg for 3 days followed by oral prednisolone 2 mg/kg/day along with G-CSF. She responded well to the treatment. Her skin rashes disappeared and elevated liver enzymes normalized. However, her pancytopenia persisted but the patient was clinically stable and afebrile. She was discharged and advised an out-patient follow-up. Subsequent follow-up for a period of 6 months shows that the patient is asymptomatic with a last documented platelet count of $47 \times 10^9/L$.

Fig. 1 Microphotograph of the skin biopsy showing exocytosis by neutrophils (arrow) and necrotic keratinocytes (arrow head) (H&E, 400×)

Fig. 2 Trephine biopsy shows markedly hypocellular marrow spaces with sinusoidal dilatation and interstitial aggregates of small mature lymphocytes (H&E, 200×)

Discussion

TA-GVHD is a rare and a potentially fatal complication of blood transfusion with a concomitant acquired bone marrow aplasia. It is an under-diagnosed entity due to its rare occurrence and overlapping clinical manifestations with viral exanthem or a drug reaction [2]. The risk of TA-GVHD is much more common in a genetic homogenous population as in Japan with the risk of transfusion of blood from HLA-homozygous donors [3]. The essential requirements for the development of TA-GVHD include immunologically competent cells in the graft, alloantigens in the host lacking in the donor graft, and an immunocompromised host. Signs and symptoms usually begin 2–30 days after transfusion [3]. The classical features of TA-GVHD include fever, pruritus, erythematous maculopapular skin rash progressing to generalized erythroderma or bullae formation, right side abdominal pain, abnormal liver function tests, diarrhea, nausea, vomiting, cough and dyspnea [3]. TA-GVHD is fatal within 3–4 weeks of transfusion, with most patients dying from hemorrhage and infections. TA-GVHD is poorly responsive to any available form of therapy [2]. As treatment is largely ineffective, prevention is of critical importance. Gamma irradiation of packed RBCs/whole blood is preferred to inhibit the proliferation of immunocompetent donor T-lymphocytes [3].

This patient developed GVHD following non-irradiated packed RBCs blood transfusion from an unrelated donor. The patient was administered steroids along with G-CSF. She responded well to the treatment and followed a non-fatal atypical course. The exact pathogenesis in atypical GVHD is unknown. It has been suggested that non-self lymphocytes surviving in hosts have a growth disadvantage, resulting in such non fatal cases [4]. A definitive

diagnosis of TA-GVHD requires documentation of presence of donor derived cells or DNA in the blood or affected tissues of recipient. HLA typing to demonstrate genetic homology with the recipient and VNTR/STR analysis for chimerism could not be done in this patient due to financial constraints.

To conclude, in resource constraint settings as seen in developing countries the elimination of risk of TA-GVHD is difficult due to non-availability of irradiated blood products at all centers. More so, TA-GVHD remains under-reported due to clinical mimicry with viral infections and drug reactions. Awareness of this entity is of utmost importance so that the patients at risk are identified early and TA-GVHD is prevented by giving them irradiated blood products. Novel techniques such as “pathogen inactivation” focuses at preventing transfusion of bacteria, protozoa and viruses via donor lymphocytes and monocytes and thus, can play a pivotal role in reducing the risk of TA-GVHD [3].

Compliance with Ethical Standards

Conflict of interest There is no conflict of interests among the authors.

Human and Animal Rights This study does not involve any human participants or use of animal. This correspondence involves retrospective report of clinical history, investigations and course of disease of a patient without any identification of index case.

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