Transfusion Associated Graft Versus Host Disease Following Whole Blood Transfusion from an Unrelated Donor in an Immunocompetent Patient

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Abstract Graft-versus-host disease (GVHD) is a well-known complication of allogeneic bone marrow transplantation. Transfusion associated graft-versus-host disease (TA-GVHD) is much less common and nearly uniformly fatal complication of blood transfusion. The risk factors underlying the development of TA- GVHD are incompletely defined, but it is commonly seen in individuals with congenital or acquired immunodeficiency, transfusions from blood relatives, intrauterine transfusions and HLA-matched platelet transfusions. Diagnosis of TA-GVHD may be difficult at a time due to rarity in occurrence and overlapping clinical features with various infections and drug reactions. We describe a case of transfusion-associated GVHD that occurred after transfusion of whole blood from unrelated donor in an immunocompetent patient.

Keywords Graft versus host disease · Blood transfusion · TA-GVHD

Introduction

Graft-versus-host disease (GVHD) is a well-known complication of allogeneic bone marrow transplantation and is increasingly being recognized after solid-organ transplantation and transfusion of cellular blood products [1–3]. Transfusion associated graft-versus-host disease (TA-GVHD) is

much less common and nearly uniformly fatal complication of blood transfusion. TA-GVHD follows 0.1–1.0% of transfusions in susceptible recipients [4]. As bone marrow failure is almost uniform in patients with TA-GVHD, the mortality rate of TA-GVHD is 87–100% [5]. It occurs due to transfusion of Immunocompetent lymphocytes into a recipient who is unable to mount a host response to the cells due to human leucocyte antigen (HLA) one-way compatibility and/or immunosuppression. This allows engraftment of the transfused cells, which then proceed to reject the host due to immunologic differences. The risk factors underlying the development of TA-GVHD are incompletely defined, but it is commonly seen in individuals with congenital or acquired immunodeficiency, transfusions from blood relatives, intrauterine transfusions and HLA-matched platelet transfusions [2, 3]. All cellular blood products, including red cells, platelet and granulocyte concentrates, and even fresh plasma have been implicated in TA-GVHD.

After the first case report of TA-GVHD in an immunocompetent individual was from Japan, there have been numerous reports of TA-GVHD in immunocompetent patients, the majority again from Japan or in patients transfused from family members [6–9]. TA-GVHD is rare after transfusion from unrelated donors due to genetic diversity. The genetic homogeneity of the Japanese population places them at significantly greater risk of developing TA-GVHD [10]. TA-GVHD is characterized by fever, skin rash, diarrhea and hepatitis, typically occurs much sooner (2–30 days after transfusion) and is frequently associated with bone marrow aplasia, which is fatal in most cases [2–4, 11–13]. Diagnosis of TA-GVHD may be difficult at a time due to rarity in occurrence and overlapping clinical features with various infections and drug reactions. High index of suspicion and association of a recent transfusion with clinical features is required for early diagnosis.

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We describe a case of transfusion-associated GVHD that occurred after transfusion of whole blood from unrelated donor in an immunocompetent patient.

Case Report

Fifty years old immunocompetent female had undergone vaginal hysterectomy before 15 days and had been transfused 2 units of whole blood on the day prior to surgery. Her complete blood count (hemoglobin: 10.5 g%, total count: 7250 cells/cmm, platelets count: 2.3 lacs/cmm) was normal and hepatitis B and HIV serology was non-reactive at the time of surgery. Post-operative course was uneventful and patient was discharged from hospital in normal condition after 4 days.

Two weeks after surgery she presented with complaints of fever, nausea, vomiting, upper abdominal discomfort, diarrhea, skin rash and petechiae all over the body. She did not complain of cough, chest pain, breathlessness and active bleeding from any site. On examination, her look was toxic. General examination revealed tachypnea (respiratory rate: 18/min, SpO₂: 97% at room air), tachycardia (pulse 96/min), fever (100°F), normal blood pressure (120/78 mmHg), oral mucosal erythema with extensive oropharyngeal candidiasis, ankle edema, icterus and skin rash all over the body. The rashes were diffuse confluent erythematous maculopapular rash over trunk and extremities, which blanches on pressure and few vasculitis like lesions at places over lower limbs (as

Fig. 2 Diffuse confluent erythematous maculopapular rashes over trunk, blanch on pressure

shown in Figs. 1, 2). There were no palpable lymph nodes in neck, axillae and groins. Systemic examination revealed upper abdominal tenderness, hepatomegaly (3 cm below costal margin, firm, tender) and mild ascites. Her respiratory, cardiovascular and central nervous system examination was normal.

Laboratory investigations on current presentation revealed pancytopenia (Hb: 10.2 g%, total WBC counts: 63 cells/cmm and platelet count 1.2 lacs/cmm), reticulocyte count: 0.5%, negative direct coombs' test. Biochemistry parameter showed: total bilirubin: 7.6 mg%, direct: 6.9 mg%, indirect: 0.7 mg%, SGPT: 186 IU/l, SGOT: 74 IU/l, serum alkaline phosphatase: 74 IU/l, LDH: 448 IU/l, CPK total: 238 IU/l, ferritin: 1285 ng/ml, total protein: 4.4 g%, albumin: 1.8 g%, globulin: 2.6 g%, s. creatinine: 0.87 mg%, s. Na: 118 mmol/l, s. K⁺: 3.16 mmol/l, C-reactive protein: 23.4 mg%, (<1 mg%), s. amylase: 52 IU/l, s. lipase: 19 IU/l and normal arterial blood gas analysis. Urine examination showed +1 proteinuria, 8–10 pus cells and 2–3 RBCs. Her serological tests for HIV (HIV EIA), hepatitis A, hepatitis B, hepatitis E and leptospira were non-reactive. Cytomegalovirus antibodies titer was reactive for IgG antibodies and non-reactive for IgM antibodies. X-ray chest was normal; ultrasonography of abdomen showed mild ascites, hepatomegaly, reactionary gall bladder wall edema, bulky kidneys and dilated small bowel loops with present peristalsis.

Fig. 1 Erythematous maculopapular rash with vasculitis lesions

Fig. 3 Skin Biopsy: epidermis shows scattered necrotic keratinocytes at all levels, lymphocytic exocytosis, patches of parakeratosis and basal cell vacuolization: Acute graft versus host disease Grade 2

She was hospitalized and treated with IV fluid, cefipime 2 g IVq8h, vancomycin 1 g IVq12h, fluconazole 200 mg IVq12h, G-CSF, IV leucovorine, IV B12 and other supportive treatment. On the next day of hospitalization bone marrow (aspiration and trephine) and skin biopsies were performed. Bone marrow aspirate revealed hypercellular marrow with poor cell trait, decreased megakaryocyte, relative lymphocytosis, increased RE activity with few of them engulfing mature RBCs and decreased iron store. Intravenous immunoglobulin 400 mg/kg/day was added to her treatment regimen. Next day her blood culture grew *Candida albicans* (Sensitive to Fluconazole) and *Staphylococcus aureus* (MSSA). She had persistent pancytopenia with further decrease in hemoglobin and platelets requiring packed cells and platelet transfusion. She developed septic shock, paralytic ileus, renal failure, respiratory failure and died on the third day of hospitalization. Bone marrow trephine and skin biopsies were available to us after her death.

Bone marrow trephine biopsy revealed cellular marrow with adequate megakaryocyte, decreased hematopoiesis, increased macrophage activity and increased reticulin. On skin biopsy examination (Fig. 3) epidermis in skin showed scattered necrotic keratinocytes at all levels, lymphocytic exocytosis, patches of parakeratosis and basal cell vacuolization. There were also follicular involvement, upper dermal perivascular inflammation and internal hemorrhages, all above features were suggestive of Acute Graft Versus Host Disease, grade II.

Discussion

GVHD is commonly seen in patients with hematologic malignancy undergoing bone marrow transplant.

Transfusion associated GVHD is a rare and fatal complication of blood transfusion occurring 2–30 days after transfusion as a result of engraftment in the recipient of viable transfused lymphocytes from cellular blood products. It is usually seen in individuals with defective cell mediated immunity, but it has been reported in apparently immunocompetent individuals. In immunocompetent individual it is commonly seen in individuals undergoing coronary artery bypass grafting and other cardiovascular surgery in which cardiopulmonary bypass is required. The reasons for increased risk in patients undergoing is not known exactly, but probably use of fresh blood during procedure and transient immunosuppression post surgery allowing more viable lymphocytes to engraft in recipient's bone marrow. The classical clinical features of TA-GVHD include fever, pruritus, skin rash, right upper quadrant pain, abnormal liver function tests, diarrhea, nausea, vomiting, cough and dyspnea. Illness progress rapidly to multiorgan failure and death occur in more than 90% of patients.

Our patient presented with clinical features consistent with that of GVHD. In view of history blood transfusion before 15 days, we were prompted to think about transfusion associated GVHD in this patient. Important differential diagnosis to be excluded in this case was to rule out active viral infection (community acquired or transfusion related) leading to similar illness like GVHD. Transfusions associated viruses like HIV, hepatitis B and cytomegalovirus can cause similar type of illness. Acute seroconversion illness due to HIV infection can present with similar features like fever, skin rash, diarrhea, abdominal discomfort, jaundice and lymphadenopathy, but it is usually associated with positive EIA test for HIV and indeterminate western blot test. Repeat HIV serology was non-reactive in our patient. Acute viral hepatitis can present with similar illness and is associated with progressively rising AST and ALT levels and positive serologic tests. Our patient had initial $4 \times$ ULN rise in AST and ALT, which then decreased to near normal with normal alkaline phosphates and stable bilirubin levels, and serology for HBV, HAV and HEV were also non-reactive excluding acute viral hepatitis. Dengue fever and leptospirosis are another important differential diagnosis for a person living in endemic area, which were excluded by negative serology for dengue and leptospira respectively. Exclusion of these infections with supporting clinical features and history of recent blood transfusion had favored our suspicion of TA-GVHD, which was later on confirmed on skin biopsy. Our patient does not have any immunosuppressive disease or history of consumption of immunosuppressive medications recently or in the past. Probably transient immunosuppression following surgery and blood transfusion may be responsible for engraftment of donor lymphocytes in host marrow [14]. We could not trace the donor to carry out

HLA typing to demonstrate genetic homology with the recipient.

The reported frequency of one way matching or sharing HLA haplotype in a non-first degree relative in Japan ranges from 1 in 312 to 1 in 874, which increases the risk of developing TA-GVHD in immunocompetent individuals even after receiving transfusion from unrelated donors. Use of fresh blood and directed donation also contributes to increased risk of TA-GVHD in Japanese population.

In our patient blood used was stored blood and was from unrelated donor. The data regarding genetic homogeneity in our populations are not available, but TA-GVHD has not been reported previously from Gujarat, so the frequency of sharing haplotypes in general population may not be very high. This is probably the first case of TA-GVHD reported from Gujarat.

TA-GVHD is under diagnosed because the disease appear and progress rapidly, clinical features are often misleading and overlapping with infection or drug reaction. However, the diagnosis should be suspected in a patient who develops cytopenias within 30 days of transfusion of blood products. TA-GVHD is a very rare complication of transfusion and although its true incidence is not known, the risk of this fatal complication is a strong argument against permitting directed blood donations from first degree relatives, unless the donation is irradiated to prevent lymphocyte proliferation.

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