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Review Article

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Transfusion-Associated Graft-Versus-Host Disease Confirmed by Human Leukocyte Antigen Typing in a Patient with Severe Combined Immunodeficiency and Review of the Literature

Daifulah ALZahrani[1]*, Meshab ALShamrani[2], Ahmed Kassar[3], Sami ALThubaiti[4], Khalid ALGamdi[2], Mehmet Guler[5], Alaa Iskandrani[6], Amir Shehzad[7] and Farzal Anwar[8]

[1]*Immunology and Allergy, King Saud Bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City – WR, Jeddah, Saudi Arabia*

[2]*General Pediatric Department, King Abdulaziz Medical City – WR, Jeddah, Saudi Arabia*

[3]*Laboratory Medicine Department, King Abdulaziz Medical City – WR, Jeddah, Saudi Arabia*

[4]*Pediatric Hematology/ Oncology Department, King Abdulaziz Medical City – WR, Jeddah, Saudi Arabia*

[5]*Pathology department, King Abdulaziz Medical City – WR, Jeddah, Saudi Arabia*

[6]*Pediatric Gastroenterology, King Abdulaziz Medical City – WR, Jeddah, Saudi Arabia*

[7]*Pediatric intensive care unit, King Abdulaziz Medical City – WR, Jeddah, Saudi Arabia*

[8]*Transfusion Medicine, Pathology department, King Abdulaziz Medical City – WR, Jeddah, Saudi Arabia*

***Corresponding author**

Dr. Daifulah M. ALZahrani, Assistant professor and Consultant Allergist, Immunologist and BMT, Pediatric department, King Saud Bin Abdulaziz for Health Sciences, King Abdulaziz Medical City – WR P.O.Box: 9515, Jeddah 21423, Saudi Arabia, Tel: +96626240000; EXT: 22069; Fax: +96626240000; EXT: 22579; E-mail: drdaif2003@yahoo.com

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Abstract

Background: *Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare, but often lethal complication of cellular blood component transfusion that produces a graft-versus-host clinical manifestation in immunodeficient patients. We report a patient who developed TA-GVHD and provide a review of the literature.*

Method: *We report an infant with severe combined immunodeficiency (SCID) who developed TA-GVHD. The patient received a nonirradiated, packed erythrocyte cell suspension and platelet transfusions from unrelated donors, before the diagnosis of SCID. The patient manifested symptoms and signs of TA-GVHD (fever, skin rash, diarrhea, icterus, eosinophilia and bone marrow failure) 3-weeks after blood product transfusions.*

Result: *Immunology investigation was consistent with T^- B^- NK^+ SCID. The recto-sigmoid biopsies confirmed the gold standard features of grade-II acute GVHD. HLA typing of the patient and his parents showed that the patient has an extra-parental-allele of major histocompatibility complex (MHC) class I B*53. He received high doses of methylprednisolone, IVIG and ursodeoxycholic acid, but he had progressive hyperbilirubinemia and bone marrow failure, then he developed candidemia and pseudomonas aeruginosa sepsis and multiorgan failure then he died.*

Discussion / Conclusion: *SCID is one of several risks for TA-GVHD. TA-GVHD develops when transfused blood-derived immunocompetent, alloreactive T lymphocytes able to engraft in the recipient's lymphoid tissues that fail to reject them. Those lymphocytes mediate immune response causing damage and dysfunction of the skin, gastrointestinal tract, liver and bone marrow failure. Our patient showed all features of TA-GVHD that was complicated by fulminant sepsis and multiorgan failure despite aggressive management. The diagnosis of this lethal condition needs high index of suspicion and the transfusion history must be questioned in all immunodeficiency patients. The disease is fulminate and rapidly fatal in majority of patients even with aggressive treatment, while irradiation of blood products that to be given to recipients at risk is the preventive method of choice.*

Keywords: Bone Marrow Transplantation (BMT); Human Leukocyte Antigen (HLA); Major Histocompatibility Complex (MHC); Polymerase Chain Reaction (PCR); Rectal Biopsy; Severe Combined Immunodeficiency (SCID); Transfusion-Associated Graft-Versus-Host Disease (TA-GVHD)

Introduction

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare, but often lethal, complication of cellular blood component transfusion that produces graft-versus-host clinical manifestations with bone marrow involvement in immunodeficient patients [1]. TA-GVHD develops when transfused blood-derived, alloreactive T lymphocytes that are viable and immunocompetent engraft in the recipient's lymphoid tissues, which fail to reject them. The engrafted donor T lymphocytes mediate a cellular immune response that attacks host tissues, causing damage and dysfunction of the skin, gastrointestinal tract, liver, and bone marrow [2, 3].

The diagnosis of this lethal condition requires a high index of suspicion, but its recognition is often difficult because the clinical manifestations are not specific [4-7]. There are several risk factors for the development of TA-GVHD, including congenital immunodeficiency syndromes, bone marrow transplantation (BMT), intrauterine transfusions, transfusion from descendant relatives, human leukocyte antigen (HLA)-matched platelet transfusions, and hematologic malignancies [1, 4-9]. The disease is fulminant and rapidly fatal in most patients even with aggressive treatment. The worldwide preventive measure for TA-GVHD is irradiation (to damage the DNA of donor lymphocytes) of all transfused blood products given to susceptible recipients, such as those who are immunodeficient or infants with an unclear diagnosis [10]. Herein, we report a patient with severe combined immunodeficiency (SCID) who developed TA-GVHD. The patient received a nonirradiated, packed erythrocyte cell suspension and platelet transfusions from unrelated donors. We also provide a review of the literature.

Case Description

A 4-month-old boy born of first-degree consanguineous parents was admitted to the local hospital with a history of persistent oral thrush, failure to thrive, fever, recurrent chest infections, and sepsis. He received Bacille Calmette-Guérin (BCG) vaccine after birth. His cousin died from SCID before transplant. His pulmonary infections were complicated by bilateral unresolved pleural effusion. He received intravenous immunoglobulin (IVIG), packed red blood cells, and platelet transfusions and was then transferred to our hospital. When he arrived, he was hypothermic and hypotensive. He received fluid resuscitation, intubation, inotropic support, and broad-spectrum IV antibiotics (piperacillin/tazobactam and gentamicin) and was then admitted to the intensive care unit. His initial physical examination was significant for generalized body wasting and bilateral decreased air entry in his chest. His initial complete blood count was as follows: leukocytes, 2.6 x 10^9/L; neutrophils, 0.9 x 10^9/L; lymphocytes, 0.6 x 10^9/L; hemoglobin, 10.9 g/dL; and thrombocytes, 385 x 10^9/L. The differential lymphocyte subset showed the following: $CD3^+$, 0.07 x 10^9/L; $CD3^+/CD4^+$, 0.04 x 10^9/L; $CD3^+/CD8^+$, 0.03 x 10^9/L; $CD3^-/CD19^+$, 0.00 x 10^9/L; and $CD3^-/CD16^+$, 0.54 x 10^9/L. His immunoglobulin levels (after one dose of IVIG) were as follows: IgG 2.8 g/L; IgA, 0.1 g/L; and IgM, 0.05 g/L. Thus, his immunologic investigation was consistent with T^- B^- NK^+ SCID. Cytomegalovirus (CMV) and HIV results by polymerase chain reaction (PCR) were negative. The results of his initial renal and liver function tests were normal. The workup for BMT was initiated, including HLA typing of blood samples, as required before any blood product transfusion in our institution.

The chest radiograph showed bilateral pleural effusion with pulmonary infiltrates. Pleural fluid was drained, an open lung biopsy performed, chest tubes inserted, and empirical anti-tuberculosis treatment initiated for the possibility of BCGitis. However, the pleural fluid and lung tissue biopsy specimens were negative for Gram stain, bacterial culture, histopathologic staining for *Pneumocystis jirovecii* pneumonia, acid-fast bacillus staining, and PCR for CMV and mycobacterium. The anti-tuberculosis treatment was discontinued.

One week after admission, the patient's fever spiked (37.8 °C axillary); the IV antibiotics were switched to meropenem and vancomycin. Two days later, he developed an erythematous symmetrical skin rash on both hands and feet that was progressive and that spread proximally, with swelling of both feet over several days. His complete blood counts showed severe neutropenia, lymphopenia, anemia, and eosinophilia (leukocytes, 3.0 x 10^9/L; neutrophils, 0.06 x 10^9/L; monocytes, 0.03 x 10^9/L; lymphocytes, 0.28 x 10^9/L; eosinophils, 0.84 x 10^9/L; hemoglobin, 10.1 g/dL; and thrombocytes 120 x 10^9/L). He also developed hepatitis on day 1 of the onset of fever; liver function results revealed the following: aspartate aminotransferase, 252 IU/L; alanine aminotransferase, 279 IU/L; alkaline phosphatase, 309 IU/L; gamma-glutamyl transpeptidase, 531 IU/L; serum protein, 45 g/L; and albumin, 22 g/L. Over 4 days, the patient developed generalized body edema. The clinical findings and related laboratory investigations were consistent with the diagnosis of acute GVHD (fever, skin rash, ongoing diarrhea, hepatitis, pancytopenia, and eosinophilia).

He underwent a rectosigmoid colonic biopsy that showed colonic mucosa with increased apoptosis, crypt necrosis, and atrophy consistent with mild to moderate acute GVHD (Grade II) (Figure 1). Immunostaining of colonic tissue specimens for CMV infection was negative. HLA typing of the patient and his parents (using PCR–DNA-based approaches) showed that the patient had an extra-parental allele of major histocompatibility complex (MHC) class I B*53 (Table I). Thus, the clinical manifestations, histologic findings on rectosigmoid biopsy specimens, and presence of an extra-parental allele in the patient on HLA typing confirmed the diagnosis of TA-GVHD. TA-GVHD was managed with methylprednisolone, 20 mg IV every 12 hours (10 mg/kg/day) for 3 days, which was then reduced to 15 mg every 12 hours (7.5 mg/kg/day) for 3 days and thereafter kept at 10 mg every 12 hours (5 mg/kg/day). He received five doses of IVIG (700 mg/kg/dose). Within 1 week of steroid treatment, the erythema of his skin rash resolved and the liver enzyme levels decreased, but his diarrhea became more frequent and watery, and his abdominal distension and generalized edema worsened with progressive hypoalbuminemia (albumin, 18 g/L), requiring frequent albumin infusion. He developed progressive hyperbilirubinemia, the highest bilirubin level being noted on day 17 of his TA-GVHD (total bilirubin, 138 µmol/L; direct bilirubin, 115 µmol/L), which was unresponsive to administration of ursodeoxycholic acid, 20 mg/kg/day divided every 12 hours. All signs indicated severe liver dysfunction.

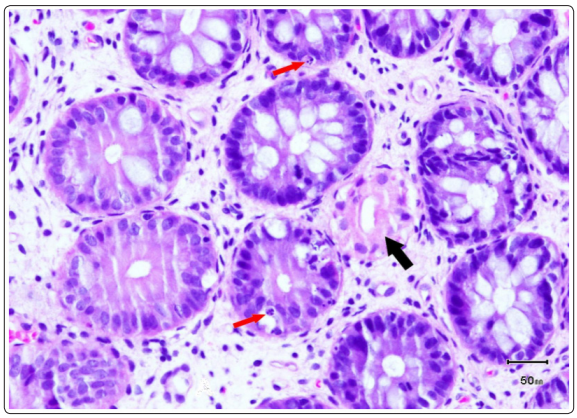

Figure 1: The histopathologic results of the recto-sigmoid biopsies showing the gold standard features of grade II acute GVHD of the gastrointestinal tract. Epithelial cell apoptosis (red arrows) and well developed crypt necrosis (black arrow). (Microscopic magnification x400).

Table I: HLA typing of the patient and his parents
HLA typing using PCR–DNA-based approaches showed that the patient had an extra-parental allele of major histocompatibility complex (MHC) class I B*53.

	Histocompatibility of human leukocyte antigens (HLA)						
	HLA-A		HLA-B		HLA-DRB DRB1		DRB3/5
Patient	*31	*68	*53	*73	1*01	1*03	3*
Father	*11	*68	*51	*73	1*01	1*15	5*
Mother	*31	*33	*51	*58	1*03	1*11	3*

On day 12, he manifested a full-blown picture of bone marrow failure with very low absolute reticulocyte counts (4.94 x 10^9/L; normal: 20–100 x 10^9/L) and his complete blood count showed progressively severe pancytopenia that required frequent red blood cell and platelet transfusions (leukocytes, 0.10 x 10^9/L; neutrophils, 0.02 x 10^9/L; monocytes, 0.00 x 10^9/L; lymphocytes, 0.07 x 10^9/L; hemoglobin, 6.8 g/dL; and thrombocytes, 6 x 10^9/L). On day 14 of TA-GVDH, he required maximum inotrops and high-frequency ventilation. The central and peripheral blood cultures grew multidrug-resistant *Pseudomonas aeruginosa* and *Candida tropicalis* within 24 hours of incubation. Ciprofloxacin, colistin, and lipid-complex amphotericin B were added to the drug regimen. Administration of granulocyte colony-stimulating factor was initiated (5 µg/kg/day), but the patient's condition deteriorated with fulminant sepsis and multiorgan failure. He died on day 18 of TA-GVHD.

Discussion

Hathaway et al. first described TA-GVHD in 1965 in immunodeficient children [11]. In 1966, Billingham first described the criteria required to diagnose GVHD, including immunologically competent graft cells, alloantigens in the host that are lacking in the donor graft, and a host that is unable to mount an effective immunologic reaction against the graft. The incidence of TA-GVHD was about 0.1% to 1%, with a high mortality rate in immunocompromised patients [12-14]. However, with the use of irradiation and leukoreduction of blood products, a significant reduction in its incidence occurred, as in Japan; there were no reported cases in early 2000 [15]. In addition, no cases of TA-GVHD in patients with SCID were reported between 2003 and 2010, but in 2010, Sebnem Kilic et al. described two cases of SCID patients who developed TA-GVHD as a result of receiving transfusions of nonirradiated fresh erythrocyte suspension from unrelated donors [16, 17].

Pathology

If the recipient is unable to recognize and eliminate the transfused blood-derived, alloreactive T lymphocytes, then they will be able to escape immune recognition and engraft in the recipient's lymphoid tissues; thus, TA-GVHD develops. Escape from immunologic recognition occurs if the donor and recipient are homozygous for an HLA class I haplotype, in which case, donor lymphocytes may engraft. This mechanism is well known to contribute to the high incidence of TA-GVHD in populations with restricted HLA diversity, e.g., those of Japanese origin, after blood product transfusions to immunocompetent patients from their relatives [18-21]. Another well-known mechanism for the development of TA-GVHD is the immune incompetency of the recipient who is incapable of recognizing and/or eliminating the donor T lymphocytes; however, the degree of risk from the recipient's immune incompetence is still unclear [5, 15, 20-22]. The engrafted foreign viable T lymphocytes proliferate to produce $CD4^+$ and $CD8^+$ T-cell lines that react against the second haplotype on HLA that is not shared [15, 23, 24]. TA-GVDH manifests when cellular activation, via recipient HLA class II antigens, causes the release of cytokines and the direct effects of cytotoxic donor T lymphocytes against host tissues [25-27]. Ultimately, this immune-mediated response causes damage and dysfunction to the skin, gastrointestinal tract, and liver, as well as bone marrow failure [3].

Risks for TA-GVHD

GVHD occurs most commonly after allogenic bone marrow transplantation and less often after transfusion of nonirradiated cellular blood components, especially when the blood donor and recipient share similar HLA antigens. The patients considered at risk for TA-GVHD following transfusions of nonirradiated blood products include neonates and fetuses, patients with primary immunodeficiency syndromes, those receiving immunosuppressive chemotherapy or radiotherapy, and those receiving directed blood donations from partially HLA-identical and HLA-homologous donors [1, 2, 4-9] (Table II).

Table II: Patients considered at risk for TA-GVHD

Primary immunodeficiency syndromes:
SCID,
Combined immunodeficiency,
T- lymphocyte defect,
DiGeorge syndrome,
Wiskott-Aldrich syndrome,
Ataxia telangiectasia
BMT * and stem cell transplantation recipients
Solid organ transplantation recipients
Hematologic Malignancies §: HD, NHL, AML, ALL
Patients receiving immunosuppressive chemotherapy or radiotherapy
Patients receiving purine analogue drugs
Intrauterine transfusions - fetuses
HLA-matched platelet transfusions
Transfusions from blood relatives
Granulocyte transfusions
Infants receiving exchange transfusion
HIV/AIDS ¶
Neonates

* BMT; bone marrow transplantation.
§ HD; Hodgkin disease, NHL; non-Hodgkin lymphoma, AML; acute meyloid leukemia, ALL; acute lymphocytic leukemia.
¶ HIV/AIDS; human immunodeficiency virus / acquired immunodeficiency syndrome.

Primary immunodeficiency syndromes that have been reported to be associated with TA-GVHD include SCID, Combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome, and ataxia telangiectasia [16, 28-33]. Newborns with SCID should be considered at higher risk of developing TA-GVHD because they are often transfused before the underlying disease has been recognized [14].

In addition to the family history of SCID, our patient had significant recurrent pneumonia and sepsis that should significantly raise the index of suspension for SCID. From the complete blood count and differential, the presence of persistent lymphopenia (lymphocyte counts less than the normal 3000 cells/mm^3 in infants) can be a sign of cellular immunodeficiency. A total immunoglobulin screen will most likely decline rapidly because of recurrent infections in patients who are humoral immunodeficient. The diagnosis of SCID requires lymphopenia, a $CD3^+$ T-cell count of less than 20%, and severe hypogammaglobulinemia (IgG <150 mg/dL) [34]. Our patient was given a nonirradiated erythrocyte suspension and platelet transfusions in the local hospital before being diagnosed with SCID.

Diagnosis and management

The diagnosis of TA-GVHD requires clinical manifestations of the disease and relevant laboratory findings, but the gold standard tests are biopsy of the skin, gastrointestinal tract, or liver, or a bone marrow aspirate [14]. The most commonly affected organ systems in TA-GVHD are the skin, liver, and intestines. Fever is the first symptom that usually appears on day 10 after transfusion, followed by a skin rash on the trunk, palms, and soles. The spreading skin lesions can range from erythematous maculopapular to hemorrhagic bullae. Gastrointestinal and liver dysfunction causes nausea, vomiting, diarrhea, jaundice, elevated liver enzymes, and hypoalbuminemia [35]. Within 2 weeks of transfusion, our patient developed fever, erythematous skin rash, diarrhea, and liver dysfunction (hepatitis and icterus). The histopathologic result of the rectosigmoid colonic biopsy was consistent with grade II acute GVHD (Fig.1). The gastrointestinal manifestation of TA-GVHD is a well-recognized entity [36-43].

The gold standard and cardinal diagnostic criterion of acute gastrointestinal GVHD is the histopathologic features of epithelial cell apoptosis with or without associated increased inflammation in the lamina propria, typically mononuclear cells and reactive epithelial changes [37, 42, 44, 45]. The well-developed apoptotic cells contain intracytoplasmic vacuoles with nuclear material and debris that are prominently seen in the gland or crypt regenerative compartments [41] (Fig. 1). Rectal biopsy samples have been shown to have a high diagnostic yield for GVHD in several studies [41, 46, 47]. Viral infection can also cause apoptotic bodies, but immunohistochemical staining for CMV can clarify the diagnosis in such a setting [48].

The clinical manifestations of TA-GVHD are nonspecific; therefore, a definitive diagnosis requires confirmation of the presence of donor-derived cells, or donor DNA, in the recipient's blood [49, 50]. Among several methods, PCR is the most advanced technique used to detect the presence of donor DNA in the patient's blood [49, 51-54]. The clinical picture of TA-GVHD mimics GVHD seen in patients post-BMT; however, the most important differences between them are bone marrow hypoplasia, pancytopenia, and an increased risk of infection and hemorrhage in the former [3, 20].

The early manifestations of TA-GVHD and GVHD from maternal T cells being transplacentally engrafted in SCID patients may be similar; however, there are variations in the presentation of GVHD disease. Although both diseases have foreign circulating T cells, the significant difference is that TA-GVHD is progressive and rapidly fatal within 1 month of transfusion in most patients [3, 21, 22, 55, 56]. The use of HLA typing by means of the PCR technique for the patient and the parents is a quick method of identifying the presence and nature of foreign-donor DNA [57]. The presence of donor lymphocytes in the recipient's circulation is not enough to make a diagnosis of TA-GVHD without clinical features, because the immunocompetent recipient ultimately eliminates those foreign cells [49, 58]. HLA typing (using PCR–DNA-based typing approaches) confirmed TA-GVHD in our patient, consistent with the clinical manifestations of the disease and its histopathologic findings on rectosigmoid biopsy, but subsequently, he deteriorated and died on day 18 of TA-GVHD, despite aggressive management.

Even though, there are few reported cases to support aggressive therapies, if there is a match donor available for patient with SCID, a confirmed TA-GVHD could be treated with BMT or stem cell transplantation [16, 59]. Other treatment modalities may include autologous peripheral blood progenitor cell infusion combined with cyclophosphamide or antithymocyte globulin, methylprednisolone, IVIG, azathioprine, cyclosporine and methotrexate [60-62].

Conclusion

TA-GVHD is still encountered in SCID patients today after transfusion of nonirradiated blood products. It is unresponsive to immunosuppressive therapy, universally fulminant, and rapidly fatal, with mortality rates exceeding 90%. The transfusion history must

be questioned and TA-GVHD must be considered in the differential diagnosis of patients who manifest fever, diarrhea, skin rash, icterus, and bone morrow failure after blood transfusion. Prompt recognition of the underlying immune incompetence and avoidance of administering nonirradiated blood products to those patients are life-saving precautions, especially in the case of neonates and when there is a family history of immunodeficiency. Leukoreduction has been reported to not completely eliminate the risk of TA-GVHD. Irradiation of blood products, which inhibits the proliferation of donor lymphocytes by damaging the DNA, is the method of choice for prevention, with a preferred irradiation dose of 2500 cGy [63]. Prevention remains the key in reducing the incidence of TA-GVHD [17, 64].

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