CASE REPORT

TRANSFUSION ASSOCIATED GRAFT-VERSUS-HOST DISEASE (TA-GVHD) IN AN IMMUNOCOMPETENT PATIENT FOLLOWING ORTHOPEDIC SURGERY

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ABSTRACT

Transfusion associated Graft versus Host Disease (TA-GVHD) is a well-known but rare complication that follows infusion of histo-incompatible lymphoid cells, often seen in individuals with impaired cellular immunity. However, it may also occur in immunocompetent individuals. The clinical syndrome consists of fever, skin rash, diarrhea, hepatic dysfunction, and bone marrow aplasia. The outcome is nearly always fatal. We present here a case report of fatal TA-GVHD in a "presumed" immunocompetent patient after transfusion of whole blood from a first and a second degree relative following orthopedic surgery for right coxarthrosis.

Keywords: Transfusion-associated graft versus host disease, Immunocompetent, Rash

İMMUNKOMPETAN BİR HASTADA ORTOPEDİK CERRAHİ SONRASI GELİŞEN TRANSFÜZYONLA İLİŞKİLİ GRAFT VERSUS HOST HASTALIĞI

ÖZET

Transfüzyonla ilişkili Graft versus Host Hastalığı, genellikle hücresel immünitesi bozulmuş bireylerde histokompatibl olmayan lenfoid hücrelerin transfüzyonu sonrası gelişen, iyi bilinen fakat nadir bir komplikasyondur. İmmünitesi sağlam olan bireylerde de nadiren görülebilir. Ateş, cilt döküntüsü, diyare, karaciğer fonksiyon bozukluğu ve kemik iliği aplazisi bu hastalığın klinik tablosunu oluşturur. Hemen her zaman ölümcül seyreder. Burada, sağ koksartroz nedeniyle ortopedik cerrahi sırasında birinci ve ikinci derece akrabalarından kan transfüzyonu yapılan immünkompetan bir hastadaki ölümcül seyreden Transfüzyonla ilişkili Graft versus Host Hastalığı olgusu sunulmuştur.

Anahtar Kelimeler: Transfüzyonla ilişkili graft versus host hastalığı, İmmünkompetan, Döküntü

INTRODUCTION

Many transfusion reactions are not recognized as such, perhaps because signs and symptoms mimic other clinical conditions. TA-GVHD is a rare but dangerous and fatal complication of blood transfusion. It basically affects patients with impaired T-cell-related immunity. However, it may also occur in immunocompetent individuals. It is mainly reported after open heart surgery and almost always fatal. Risk of TA-GVHD caused by transfusion practice in any surgery should be appropriately recognized. The disease is characterized by fever, skin rash, liver failure and pancytopenia[1]. We present here a case report of fatal TA-GVHD in a "presumed" immunocompetent patient after transfusion of whole blood from a first and a second degree relative following orthopedic surgery for right coxarthrosis.

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Marmara Medical Journal 2006;19(1);36-40

CASE REPORT

A 58-year-old male patient who initially presented with fever, macular erythematous rash and pancytopenia was admitted to our clinic. He had no complaints until 2 days before admission when he noticed maculopapular rash on the dorsal aspects of his feet and over his chest. Later on, the rash spread to his arms and back (Fig. 1). The day before admission, he developed high fever (39.5ºC) and diarrhea.

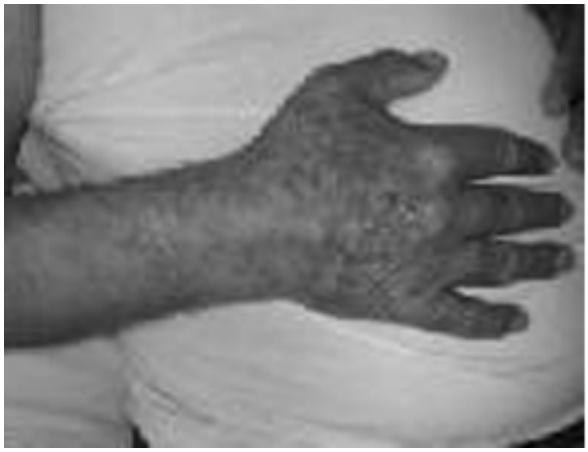


Fig. 1: Rash on his arms and hands

He had had a right total hip replacement operation for coxarthrosis 3 weeks previously. After the operation, 3 units of nonirradiated whole blood (one unit from his son, one unit from his cousin and another from an unrelated person) were transfused. His total blood count before the operation were within normal ranges [White blood cells (WBC): 7300 / mm^3, Hemoglobin (Hb): 14.9 mg/dL , Hematocrit (Htc): 33.8%, Platelets (Plt): 187000 / mm^3]. He had used nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen) and analgesics (paracetamol) for pain in the right hip joint. Cefazoline was given for surgical prophylaxis. Medical history of his family was unremarkable.

On admission, his temperature was 39.5ºC, pulse rate 88 / min, respiratory rate 20 / min and blood pressure 120/60 mmHg. On physical examination, the patient seemed fatigued and confused, erythematous macular rash was present on his abdomen, back, arms and purpuric rash with no bleach on pressure on his legs (Fig. 2). No lymphadenopathy was found. Hyperemia was observed on the pharynx and tonsils. The tonsils were also hypertrophic. Enanthems were observed on the hard palate. No abnormal breathing sound or pleural friction rub was heard. Examination of the heart and the abdomen revealed no abnormalities except for an erythematous rash on the abdomen. No costovertebral or suprapubic tenderness was detected. Both hips were mobile; no pain or limitation of motion was elicited. His hands and feet seemed edematous and erythematous (Figs. 3-5). Initial neurologic examination revealed no abnormalities except confusion.

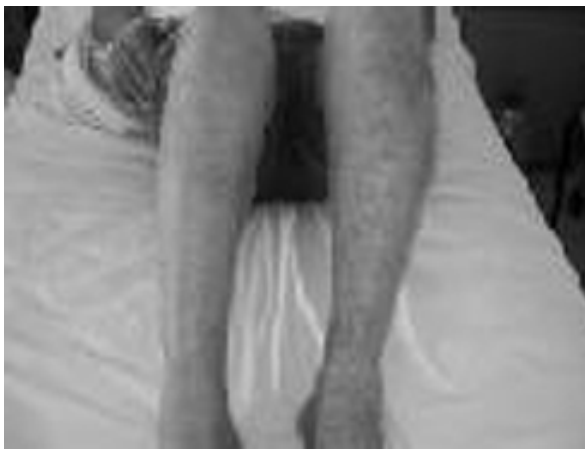


Fig. 2: Purpuric (Vasculitic) rash on his lower extremities

Fig. 3: Diffuse erythema and edema of his hands and rash on forearms

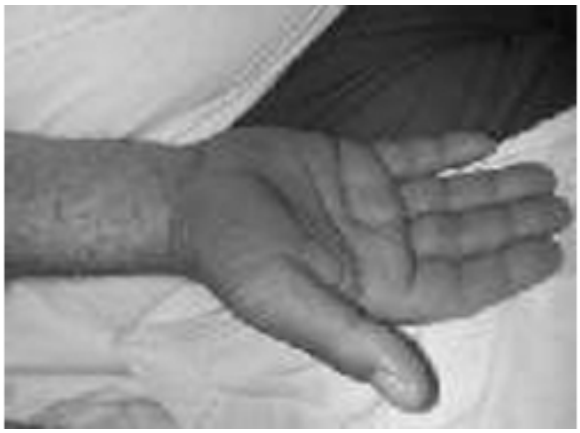
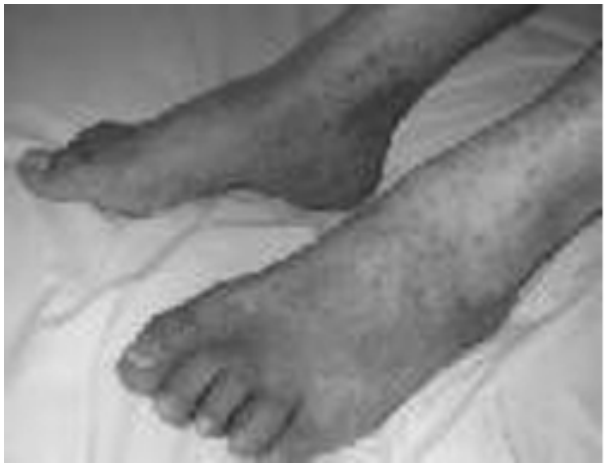


Fig. 4: Diffuse erythema and edema of hands



Fig, 5: Rash and edema of his feet

Initial complete blood count revealed pancytopenia (WBC: 700 /mm^3, Hb: 8.5 mg/dL, Htc: 24%, Plt: 138000/mm^3.) Erythrocyte sedimentation rate (ESR) was 139 mm/hr and C-reactive protein (CRP) was 189 mg/L .

Biochemical investigation of the patient's blood revealed AST: 70 U/L , ALT: 123 U/L, ALP: 321 U/L, GGT: 285 U/L, total protein: 5 g/dL, albumin: 2.6 g/dL, globulin: 2.4 g/dL, total bilirubin: 1.7 mg/dL, glucose: 159 mg/dL, urea:41 mg/dL, creatinine: 0.8 mg/dL, uric acid: 2.3 mg/dL, sodium: 131 mEq/L, potassium: 3.6mEq/L, iron: 104 µg/dL, total iron binding capacity: 127µg/dL, prothrombin time: 16 sec, prothrombin activity: 69 %, INR: 1.4, aPTT: 29 sec.

On a peripheral blood smear, the lymphocytes were 97%, monocytes were 3%, no leukocytes, eosinophils, basophils, blasts or atypical cells were seen. The urine test was 2 positive (++) for bilirubin; the sediment contained 5-6 erythrocytes per high power field and no bacteria or casts.

Radiographs of the chest were unremarkable. Ultrasonography of the abdomen revealed no abnormalities. Normal bacterial flora was isolated from the throat culture. Urine and blood cultures remained sterile.

Serologic tests for hepatitis markers (HbsAg, anti-HBc IgM, anti-HCV, anti-HAV IgM), anti-HIV, anti-HSV 1-2 IgM, anti-CMV IgM, anti-Parvovirus B19 IgM were all negative. Serologic tests for Brucella (STA= standard tube agglutination) and monotest were also negative.

Because the patient was febrile and pancytopenic; after obtaining specimens of blood, urine and throat for culture, intravenous antibiotic therapy with ceftazidime (3x2gr) was started. Based upon the persistence of fever after 48 hours, amikacin (1x1gr) was added to the therapy regimen. At the same time, prednisolone 1 mg/kg/day was started. In spite of this therapy, the fever persisted (40ºC maximally). Thus, ceftazidime plus amikacin therapy was switched to meropenem 3x1 gr/day IV. On the 10th day, the patient developed sore throat and dysphagia suggesting fungal esophagitis. Fluconazole 200 mg IV daily was started. Total blood count measurement was performed daily. Irradiated and filtered platelets and erythrocytes were transfused accordingly. No underlying immunodeficiency was identified.

The diagnostic procedure was a punch biopsy of the skin from the lesions on his lower leg. The specimen stained with hematoxylin and eosin was examined histopathologically under the light microscope. Hyperkeratosis and parakeratosis within the epidermis, spongiosis in the spinal layer cells and focal vacuolisation within the basal cell layer were seen. There was lymphocyte infiltration within the papillary dermis. Lmphocytes were also seen in the epidermis (exocytosis). Taking the clinical findings into consideration, the histopathological findings could be consistent with grade I-II of acute phase of GVHD[2].

Bone marrow aspiration and biopsy were performed on the 9th hospital day. Erythrophagocytosis and hypocellular bone marrow with histiocytic reaction characterized by loss in the three series were reported. These findings could be consistent with immune system diseases, viral infections and the use of some drugs (e.g: chloramphenicol, phenylbutazone, anticonvulsants, sulfonamides etc.). During follow-up, his complete blood count values progressively decreased. Despite intensive follow-up and therapy, the patient died on the 13th hospital day (that is nearly five weeks after the implicated transfusion). Autopsy was planned but could not be carried out as the family members refused permission.

DISCUSSION

Most cellular blood products, including red cell, platelet, and granulocyte products, contain viable, immunocompetent T lymphocytes [3]. When transfused into immuno-incompetent recipients, these donor lymphocytes may proliferate in the patient and lead to the clinical syndrome of TA-GVHD[4,5]. TA-GVHD has also been reported in immunocompetent patients, especially those who

receive transfusions from family members or from random donors who share HLA antigens, as is the case when the donor is homozygous for an HLA haplotype [6,7]. In these cases, the recipient does not recognize the donor cells as foreign, allowing the transfused lymphocytes to proliferate and cause TA-GVHD[1].

Fever is the most common symptom followed by a typical erythematous, maculopapular skin rash that begins centrally and spreads peripherally to the hands and feet. Abnormalities of hepatic function, nausea and bloody diarrhea often occur as the process progresses. Leukopenia followed by pancytopenia due to marrow failure is quite common in TA-GVHD and is seen most often 2 to 3 weeks after the onset of symptoms. Diagnosis of TA-GVHD is difficult, and it is based on the clinical picture and can be confirmed histologically with a skin biopsy[1]. Immunohistochemical analysis of skin biopsy tissue is a useful investigation in pancytopenic patients presenting with unexplained rashes.

TA-GVHD is usually rapidly fatal despite aggressive treatment. The fatality rate has been reported to be greater than 90% [8]. Severe systemic infections are the most common cause of death, which often occurs within 3 to 4 weeks from the time of the implicated transfusion.

Corticosteroids, antithymocyte globulin, cyclosporine and growth factors have all been used with minimal success in the treatment of TA-GVHD. Because of the lack of effective treatment regimens, TA-GVHD should be prevented by pretransfusion irradiation of all blood products administered to patients at risk. Irradiation inhibits proliferation of donor lymphocytes but has no significant adverse effect on red cell, platelet, or granulocyte function[1].

Based primarily on case reports and reviews, a number of immunosupressed and immunocompetent patient groups can be stratified according to risk of developing TA-GVHD [8] (Table I). Although our patient was presumably immunocompetent, because of transfusion from blood relatives, he was at high risk of developing GVHD according to this categorization.

Since the effective standard therapy of TA-GVHD has not been established, the prevention by gamma irradiation of cellular blood components is most important. All blood products are irradiated in the blood banking center in our hospital. But the patient had been transfused with blood obtained from another blood bank.

Table I: Risk groups to develop TA-GVHD.

High Risk
Bone marrow transplant (allogeneic & autologous)
Intrauterine transfusions
HLA-matched platelet transfusions
Transfusions from blood relatives
Severe congenital immunodeficiency
Hodgkin disease
Moderate rİsk
Hematologic malignancy (AML, ALL, NHL)
Patients treated with purine analogue drugs (Eg: CLL)
Malignancies treated with intensive chemo-/radiotherapy
Solid organ transplant recipients
Preterm infants
Neonates receiving exchange transfusion
Low / Theoretical Risk
HIV/ AIDS
Healthy term neonates

In the differential diagnosis, viral infections leading to bone marrow suppression, adverse drug reactions and hematologic malignancies were considered, because the features characterizing GVHD may mimic drug reactions or viral infection. Some viral infections were excluded as the ELISA test results were negative. Examination of the bone marrow aspiration and biopsy specimen excluded any hematologic malignancy. Although the patient had used nonsteroidal anti-inflammatory drugs for months, repeated preoperative total blood counts (before transfusion) were within normal limits. Therefore, bone marrow suppresion due to drug use was also excluded.

Of the possible diagnoses, TA-GVHD would most comprehensively explain the clinical picture in this patient.

Any unexpected symptoms in a transfusion recipient should at least be considered as a transfusion reaction and be evaluated. TA-GVHD which usually occurs in the setting of an

immunocompromised recipient receiving nonirradiated blood components may also occur in immunocompetent recipients. A typical presentation includes skin rash, liver function abnormalities, and pancytopenia. It is almost invariably fatal. Preventive measures include exclusion of 1st and 2nd degree relatives as blood donors, and / or irradiation of blood to be transfused.

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