The Turkish Journal of Pediatrics
Volume 23, No. 1, January - March 1981

GRAFT-VERSUS-HOST REACTION MANIFESTED AS TOXIC EPIDERMAL NECROLYSIS IN A PATIENT WITH ACUTE LEUKEMIA*

*A. İzzet Berkel MD**, Keriman Tınaztepe MD****

Key words: acute leukemia, graft-versus-host reaction, toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN) is a cutaneous reaction pattern characterized by diffuse erythema and tenderness of the skin followed by desquamating sheets of epidermis. It is usually considered to be a staphylococcus or drug-induced condition, but cases associated with other diseases or conditions such as lymphoma, leukemia, aspergillosis and exposure to irradiation and fumigants have also been reported[1]. A pattern resembling TEN has been described in experimentally induced graft-versus-host (g.v.h.) disease[2-4]. It has also been observed following allogeneic bone marrow transplantation or plasma transfusion in patients with immunodeficiency[5-7] or leukemia[8] as a manifestation of g.v.h. disease.

We report a patient with leukemia who developed g.v.h. reaction manifested as TEN following chemotherapy and multiple blood transfusions.

Case Report

A 5-year-old male was admitted to the Hacettepe Children's Hospital with a history of pain in both knees for the preceding 4 weeks and the development of pallor, fever and petechiae over the last 10 days. Two days prior to hospitalization he had noted bleeding from his nose and gums. Physical examination revealed pallor, generalized lymphoadenopathy (0.5-1 cm in diameter), enlargement of the liver and the spleen (4 cm and 2 cm below the respective costal margins) and scattered petechiae over the neck and lower extremities, coarse rales and rhonchi over the lung fields.

* From the Pediatric Immunology and Pediatric Pathology Units, Hacettepe University Institute of Child Health, Ankara.

** Professor of Pediatrics, Director of Immunology Unit, Hacettepe University Institute of Child Health.

*** Professor of Pediatrics and Pediatric Pathologist, Hacettepe University Institute of Child Health.

Laboratory findings showed hemoglobin: 3.9 gm/dl, white blood cells: 6,000/mm^3 with a differential count of 61% lymphocytes, 29% polymorphonuclear leukocytes (PMN) and 10% blasts. The platelets were decreased on the smear. The bone marrow elements were replaced by blasts. The chest film did not show any mediastinal mass.

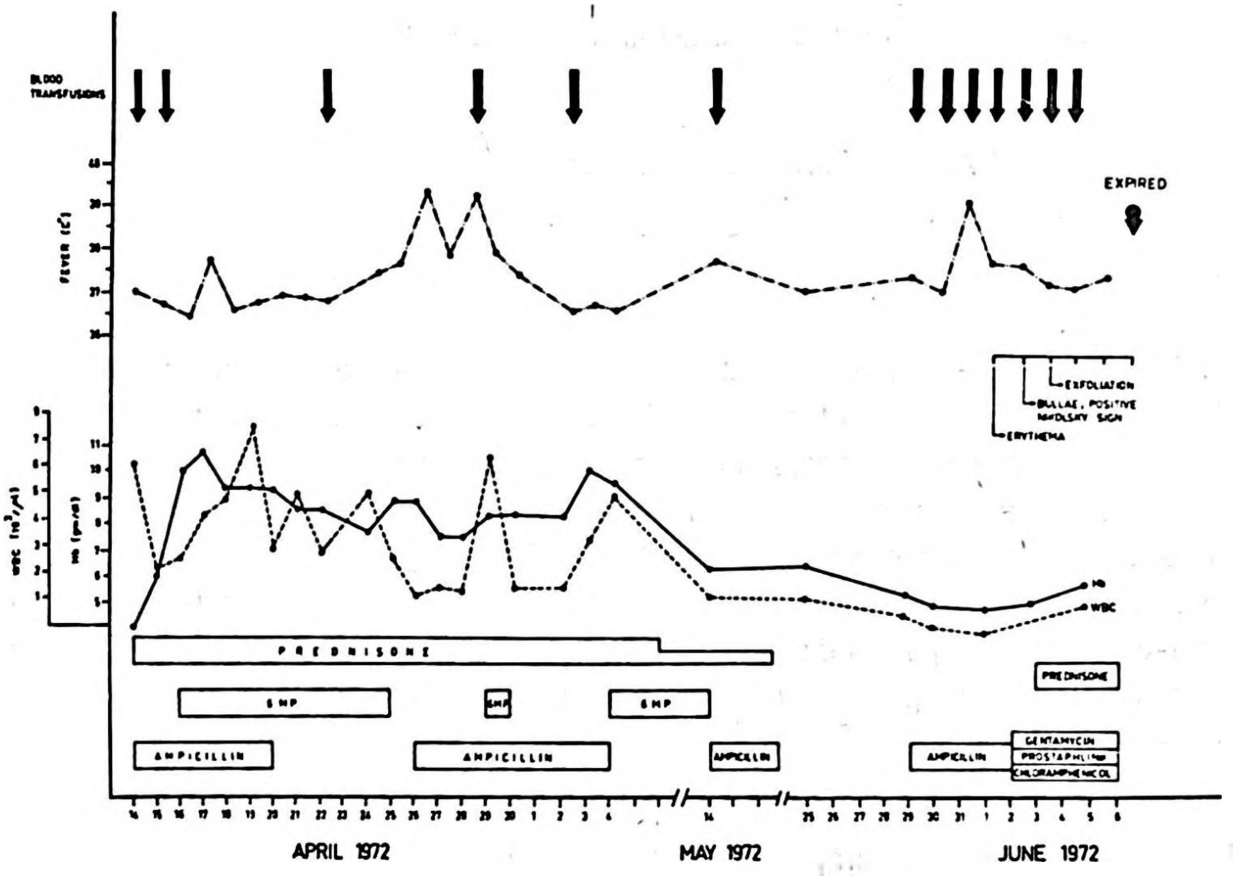

Figure 1.

The clinical course.

The diagnosis on admission was acute leukemia with respiratory infection. The patient was placed on oral ampicillin, prednisone and purinethol and received a whole blood transfusion on four occasions (Figure 1). He showed partial remission after the above treatment and was discharged on the 17th day of his hospitalization. Ten days later, the hemoglobin was 6.7 gm/dl, hematocrit 20%, white blood cells 1200/mm^3; the blood smear demonstrated 20% PMN, 4% bands, 60% lymphocytes, 16% blasts and an adequate number of platelets. Purinethol was discontinued and a whole blood transfusion was given. A week later physical examination revealed bilateral rhonchi and harsh breath sounds, and he was put back on ampicillin. Four days later he returned with complaints of fever, coughing and vomiting. Physical examination showed a temperature of 38.2°C, bilateral blepharitis, conjunctival hemorrhage in the right eye and crepitant rales over both lung fields. A chest x-ray showed left perihilar and right paracardiac infiltrations. After blood and throat cultures had been obtained he was again placed on oral ampicillin and

received another whole blood transfusion. Because of low hemoglobin levels, suspensions of packed erythrocytes were transfused for 7 successive days. The throat culture revealed non-pathogenic bacteria and the blood culture yielded no growth. On the fifth day of the second hospitalization he developed cellulitis and edema on the scalp. There was swelling of the face and neck and erythema throughout the skin. The next day bullae over the face and extremities were noticed followed by extensive exfoliation of the skin. This picture was interpreted as TEN. A punch biopsy of the involved skin was obtained. Antibiotics were changed to oxacillin, gentamicin and chloramphenicol; prednisone was also recommenced. The patient was isolated in a sterile environment to prevent further infection. The culture from the skin lesions grew E. coli sensitive to gentamicin and bactrim (trimethoprim and sulfamethoxazole). The patient died on the 7th day of hospitalization.

A post-mortem skin biopsy was obtained. Histological section of the material showed acute epidermal necrolysis and bullae formation located both in the intra-epidermal and dermo-epidermal zones. In the areas of the skin without bullae, the upper dermis revealed perivascular and periadnexal cuffing consisting of lymphocytes and plasmacytoid cells with some associated histiocytes. Most strikingly, single cell necrobiosis, with or without satellite cell, and lymphotic infiltration were present in the epidermis. The basal layer showed vacuolar degeneration in places (Figure 2). All these histological findings were consistent with g.v.h. reaction.

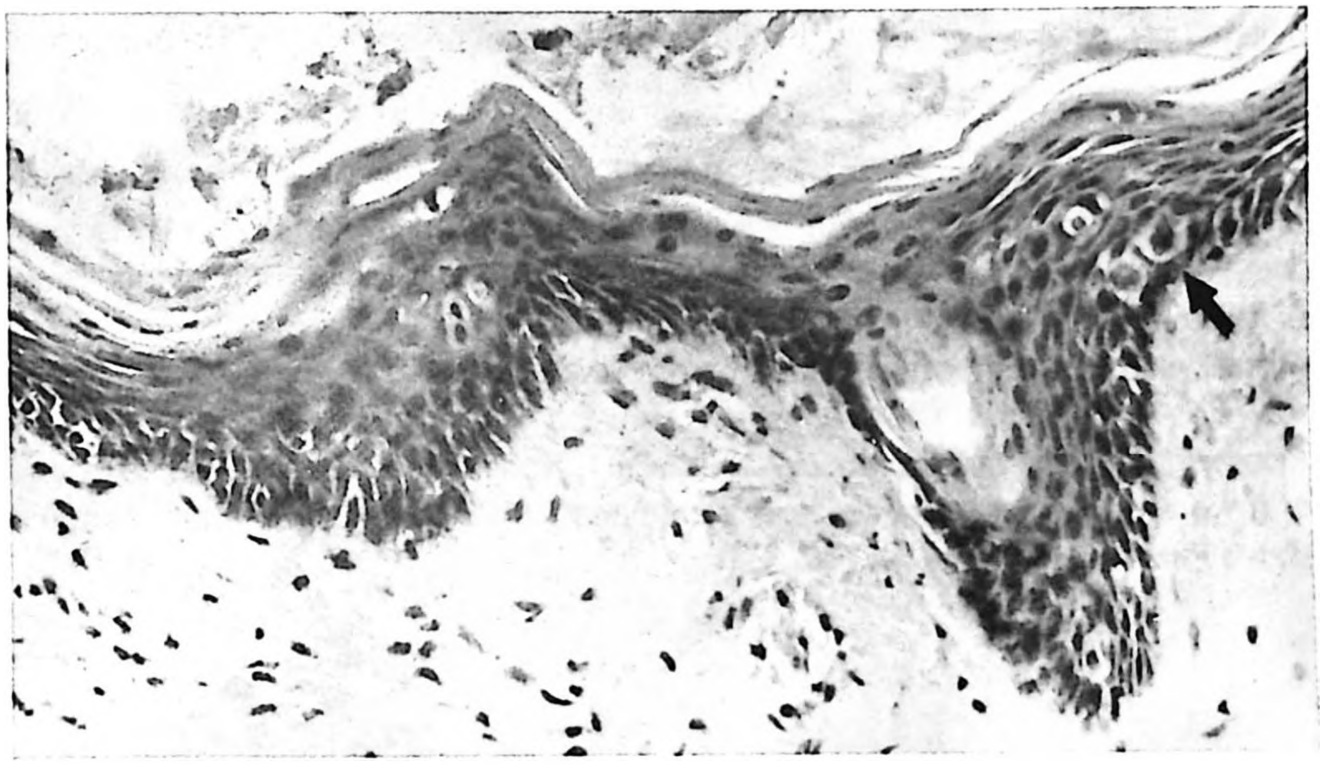

Figure 2.

Skin showing discrete epidermal spaces with degenerating epithelial cells and associated lymphocytes (arrows) and vacuolar degeneration of the basal layer. (hematoxylin-eosin stain X 160)

Discussion

Graft-versus-host reaction in man frequently follows the administration of foreign immunocompetent cells to an immunoincompetent recipient. In practice, following an allogeneic bone marrow transplantation a g.v.h. reaction develops frequently. It is manifested by fever, anorexia, wasting, diarrhea, hepatic dysfunction, dermatitis, lymphopenia, eosinophilia, susceptibility to infections and characteristic histopathological findings[6,8,9]. In some cases, g.v.h. reaction may appear in the form of TEN[5-8]. It has been observed in two leukemic patients after bone marrow transplantation from histocompatible siblings[6,8] and in a patient with thymic hypoplasia following plasma transfusions[7]. Ammann et al[1] reported two cases of g.v.h. reaction with TEN, one following bone marrow transplantation and the other after an exchange transfusion in a newborn with immunological deficiency. They were unable to demonstrate a staphylococcal etiology in skin lesions[5]. Our case is another example of the g.v.h. reaction manifested as TEN in an immunosuppressed host who had received immunocompetent cells by blood transfusion. Although the cultures from the skin lesions grew E. coli in our patient, the histological findings were compatible with TEN. In addition, the presence of focal single cell necrobiosis with satellite intraepithelial lymphocytes, mild perivascular and periadnexal cuffing of lymphocytes and plasmacytoid cells were consistent with g.v.h. reaction as previously reported[9].

We recommend the use of irradiated blood for transfusions in immunosuppressed patients since they are good candidates for g.v.h. reaction as observed in our case.

Summary

A fatal graft-versus-host (g.v.h.) disease was observed in a 5-year-old male with acute leukemia who was treated with corticosteroids, purinethol and blood transfusions. A typical picture of toxic epidermal necrolysis showing intense erythema, bullous lesions and a positive Nikolsky's sign was observed 7 weeks following the diagnosis of leukemia. The skin biopsy revealed acute epidermal necrolysis and focal single cell necrobiosis with intraepithelial lymphocytes, which is characteristic of g.v.h. reaction described mainly in patients after allogeneic bone marrow transplantation.

REFERENCES

1. Ammann AJ, Tooley WH, Hong R. Toxic epidermal necrolysis. *Lancet* 2:484, 1972.
2. Balner H, DeVries MJ, Van Bekkum DW. Secondary disease in rat radiation chimeras. *J Natl Cancer Inst* 32:419, 1964.
3. Graw RG Jr, Rogentine GN Jr, Leventhal BG, et al. Graft-versus-host reaction complicating HL-A matched bone-marrow transplantation. *Lancet* 2:1053, 1970.
4. Grogan TM, Odom RB, Burgess JH. Graft-vs-host reaction. *Arch Dermatol* 113:806, 1977.
5. Lyell A. A review of toxic epidermal necrolysis in Britain. *Br J Dermatol* 79:662, 1967.
6. McCarty JR, Raimer SS, Jarratt M. Toxic epidermal necrolysis from graft-vs-host disease. Occurrence in a patient with thymic hypoplasia. *Am J Dis Child* 132:282, 1978.
7. Merritt CB, Darrow CC II, Vaal L, Rogentine GN Jr. Bone marrow transplantation on rhesus monkeys following irradiation; modification of acute graft-vs-host disease with antilymphocyte serum. *Transplantation* 14:9, 1972.
8. Peck GL, Herzig GP, Elias PM. Toxic epidermal necrolysis in a patient with graft-vs-host reaction. *Arch Dermatol* 105:561, 1972.
9. Streilein JW, Billingham RE. An analysis of graft-versus-host disease in Syrian hamsters. I. The epidermolytic syndrome: description and studies on its procurement. *J Exp Med* 132:163, 1970.