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Atypical skin graft-vs.-host disease following bone marrow transplantation in an infant

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Abstract: Herein, we describe an unusual presentation of acute graft versus host disease (GVHD) mimicking contact dermatitis in an infant who underwent 5/6 HLA-matched bone marrow transplantation (BMT) from his mother for malignant infantile osteopetrosis. The initial rash on day +32 simulated diaper rash, which progressed to a belt-shaped rash and then developed hyperkeratotic nodules on the hands. The acute GVHD was atypical and the course was progressive and fatal, with liver and gut involvement. This presentation of atypical initial skin involvement of acute GVHD may be useful for practicing clinicians in the BMT field who need to be aware of the early unusual signs of acute GVHD so that they can initiate prompt treatment.

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Key words: bone marrow transplantation – dermatitis – graft-vs.-host disease – skin GVHD

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Introduction

GVHD is one of the most important complications of allogenic HSCT, and despite tremendous efforts in prevention and treatment, it is still associated with significant morbidity and mortality. The skin, gastrointestinal tract, and liver are the organs primarily affected (1). The skin is typically the first site of involvement (2). Clinically, acute cutaneous GVHD is characterized by a maculopapular rash, reticulate rash, bullous lesions, and erythroderma that involves the palms and soles, and as the disease progresses, the upper trunk, neck, cheeks, and ears become involved (3–5). Early recognition of GVHD is of critical importance for undertaking necessary measures to prevent progression to a life-threatening condition. Herein, we present a five-month-old infant with osteopetrosis who developed localized skin acute GVHD, which initially mimicked contact dermatitis, and progressed to grade IV disease (involving skin, the gastrointestinal system, and liver) following bone marrow transplantation (BMT) from his 5/6 HLA-matched mother. To the best of our knowledge, there have been no previous reports of localized, belt-shaped acute GVHD.

Abbreviations: GVHD, graft-vs.-host disease; HSCT, hematopoietic stem cell transplantation; i.v., intravenous; G-CSF, granulocyte-colony stimulating factor; BMT, bone marrow transplantation; VOD, veno-occlusive disease; CyA, cyclosporin A; HLA-DR, human leukocyte antigen DR.

Case report

A five-month-old male infant with malignant infantile osteopetrosis underwent allogenic BMT from his HLA-5/6 (DRB1 mismatch) identical mother in January 2005. Molecular methods have been used for HLA typing of class I and class II. The patient had initially presented with hepatosplenomegaly, anemia, thrombocytopenia, leukocytosis, blindness, optic nerve involvement, and mild hydrocephalus. The diagnosis was based on X-ray findings consistent with diffuse osteosclerosis. The parents were first-degree relatives. The conditioning regimen consisted of i.v. busulfex (3.2 mg/kg ×4 d) and cyclophosphamide (50 mg/kg ×4 d). GVHD prophylaxis included CyA and methotrexate. CyA was initiated at a dose of 3 mg/kg/d (i.v.) on day −2 and was adjusted according to blood level. Methotrexate was given at a dose of 15 mg/m^2 on day +1, 10 mg/m^2 on day +3, and day +6. Infection prophylaxis consisted of weekly i.v. immunoglobulin at a dose of 400 mg/kg, antifungal (fluconazole), antiviral (acyclovir) prophylaxis, gut sterilization, and metronidazole. Cotrimoxazole treatment began after engraftment. Ursodeoxycholic acid and low-molecular-weight heparin

were both used for veno-occlusive disease (VOD) prophylaxis. Unmanipulated bone marrow cells, including 4.5×10^8 nucleated cells/kg and 2×10^6 CD34 cells/kg, were given. G-CSF was started at a dose of 5 μg/kg on day +8. Neutrophil and platelet engraftment $>20 \times 10^9$/L occurred on days +17 and +35, respectively. He received antibacterial treatment for neutropenic fever, including cefepime, amikasin, and imipenem. A rise in blood calcium levels during the peri-engraftment period suggested improving osteoclast function. On day 32, he developed a hyperemic erythematous skin rash over the diaper region that resembled diaper rash, and topical steroids and antifungal treatment were given. Soon after, a localized, belt-shaped hyperemic skin rash on his mid-lower abdominal region was observed, which was also confined to the diaper area (Fig. 1). Three days after the skin rash, hyperemic keratotic lesions developed on the patient's fingers and dorsum of the hands. Systemic methylprednisolone at the standard dose was initiated for possible acute GVHD, which was later confirmed by histopathological examination of skin biopsies obtained from the upper abdominal region and the keratotic lesions on the hand (Fig. 2). The pathological findings showed verrucous hyperplasia and prominent granular layer of the epidermis. There were also focal vacuolization of basal cell layer, spongiosis, scattered dyskeratotic keratinocytes and a few lymphocytes around dermal capillaries. No evident koilocytes or other signs of wart infection was found. The eccrine glands and vessels were normal. A histopathological diagnosis of acral keratotic acute GVHD was made. Although skin lesions regressed, jaundice and elevated liver enzymes were detected on day +37 and diarrhea developed the next day. Acute GVHD rapidly progressed to grade IV disease and the patient died of intractable acidosis despite aggressive treatment consisting of high-dose methylprednisolone, dose-adjusted CyA, anti-IL-2 receptor antibody, and daclizumab.

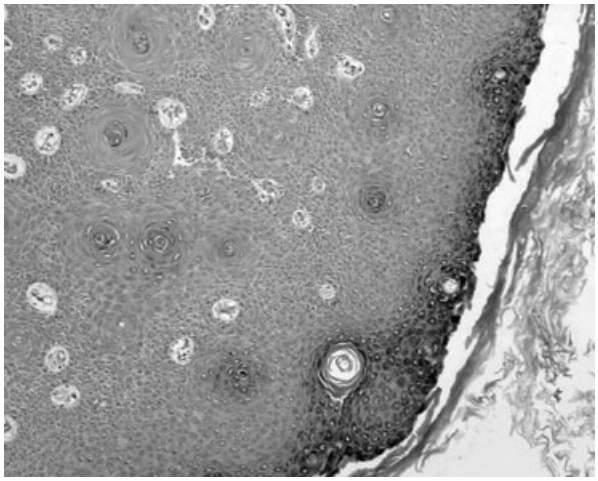

Fig. 2. Vacuolization of basal layer, spongiosis and dyskeratotic keratinocytes in epidermis of tangential section of skin biopsy.

Discussion

Acute GVHD is the primary or associated cause of death in up to 45% of BMT patients (6). Acute cutaneous GVHD reaction has been shown to develop in 50–80% of allogenic BMTs. GVHD following allogenic BMT is an immunological process in which activated donor lymphocytes mount an attack on recipient tissues (4). In acute GVHD, skin manifestations are usually the first and most frequent findings (7). Arslan et al. reported a 96.5% rate of skin involvement in acute GVHD (8). In acute GVHD, the most frequent skin manifestation is erythematous eruption with pruritus, and/or a burning sensation involving the palms, soles, earlobes, neck, and upper back. Early lesions are characterized by folliculocentric erythematous pale maculae and papules, and may involve broad areas. In severe acute GVHD, exfoliative dermatitis or toxic epidermal necrolysis-like lesions may also develop (9, 10). Unusual dermatological findings such as lichenoid papules, generalized erythema multiforme-like eruption, pustular acral erythema have rarely been reported in acute GVHD

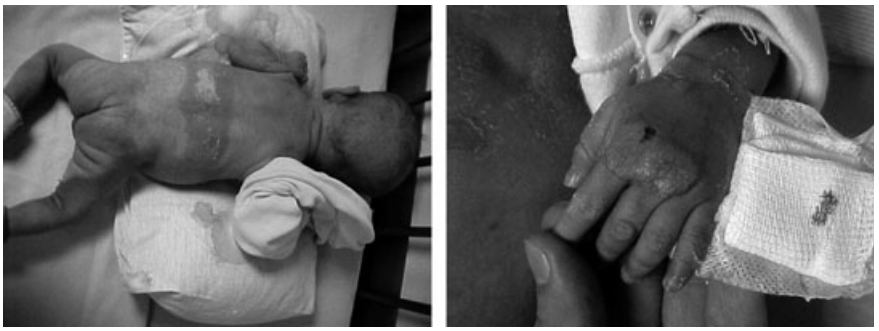

Fig. 1. Belt-shaped hyperemic skin rash and hyperemic keratotic lesions on the fingers and dorsum of the hands.

(7, 11). Multiple keratotic lesions resembling warts on the fingers, palms, and soles, resembling our patient's symptoms, have been described in a case in which skin manifestations were observed as a part of chronic GVHD (12). However, the diagnosis in the present case was acute, not chronic GVHD. The initial skin involvement consisting of hyperemic belt-shaped skin lesions on the mid-abdomen resembled diaper rash/contact dermatitis. Although systemic steroids at a standard dose were given three days after the initial rash and intensive immunosuppressive treatment was administered, progression to a fatal course could not be prevented. The stormy course of acute GVHD in the present case was attributed to HLA-DRB1 allele mismatch with his mother. The presentation of this unusual and fatal case of GVHD with atypical initial skin involvement may be useful for practicing clinicians in the BMT field who need to be aware of the early unusual signs of acute GVHD so that they can initiate prompt treatment.

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