Graft-Versus-Host Disease Limited to the Irradiated Skin
— Report of Two Cases —

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We present two very interesting cases of acute graft-versus-host disease (GVHD), whose skin rashes initially appeared on the localized area of total nodal irradiation (TNI) performed previously to prevent graft rejection and/or GVHD.

The histopathologic findings showed some dyskeratotic cells in the epidermis and perivascular mononuclear cell infiltration in the upper dermis. The immunohistochemical studies revealed that HLA-DR was diffusely strongly positive in a number of keratinocytes, whereas both CD4 and CD8 were focally weakly positive in the perivascular lymphocytes in the upper dermis.

Later on, liver dysfunction and diarrhea developed and skin rashes began to spread over the other parts of the body in those two patients. (Ann Dermatol 5(2) 125–129, 1993)

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Bone marrow transplantation (BMT) is used with increasing frequency for the treatment of life-threatening hematologic disorders such as aplastic anemia and leukemia¹. Graft rejection or graft-versus-host disease (GVHD) may occur as a serious complication following BMT. In an attempt to prevent graft rejection and/or GVHD, conditioning regimens including irradiation and immunosuppressive agents have been widely prepared before and/or after BMT.

However, on the other hand, it is also suggested that radiation among these modalities, may affect the epidermis in such a way as to alter its antigenicity by the reports on erythema multiforme², lichen sclerosus et atrophicus³, bullous pemphigoid⁴, and drug eruption⁵ in irradiated skin. Furthermore, Zwaan et al⁶ reported a very interesting case of GVHD in which skin changes followed the outline of portals from previous radiation therapy.

In this report, we present two cases of GVHD identical to Zwaan’s, and call attention to the fact that the skin manifestation of GVHD may initially appear on the irradiated skin.

REPORT OF CASES

Case 1. A 28-year-old man was referred because of the development of a erythematous maculopapular eruption in the limited skin area of the posterior neck and trunk that had been exposed to the previous TNI (Fig. 1). About 1 month ago, he received allogeneic BMT due to severe aplastic anemia. Prior to BMT, a conditioning regimen consisting of cytoxan (50mg/kg/day for 5 days) and TNI (850 cGy, single dose) was performed. After transplantation, a GVHD prevention program with cyclosporin and methotrexate was started. The post-transplant course was unremarkable up to day 30, when an erythema began to develop in the skin area that had been involved in the TNI. Skin biopsy specimens were obtained from the patient’s upper back. Histopathologic findings showed some dyskeratotic cells in the
epidermis and mild perivascular mononuclear cell infiltration in the upper dermis (Fig. 2). Immunohistochemical staining revealed that HLA-DR was diffusely strongly positive in a number of keratinocytes, whereas both CD4 and CD8 were focally weakly positive in the perivascular lymphocytes in the upper dermis. Within a few days, SGOT/

Fig. 1. Erythematous maculopapular rashes in the limited skin area of posterior neck and trunk that were exposed to the previous TNI on the 30th day of BMT in case 1.

Fig. 2. Dyskeratotic cells with eosinophilic cytoplasm in the epidermis on the 30th day of BMT in case 1 (H & E staining, x 400).

Fig. 3. Skin rashes (erythematous papules) that spread over the other parts of the back on the 50th day of BMT in case 1.

Fig. 4. Skin rashes that spread over other parts of the chest and abdomen and remained pigmentation on the 60th day of BMT in case 1.

Fig. 5. Erythematous scaly maculopapular eruption on the back, especially at the prior TNI sites on the 20th day of BMT in case 2.
SGPT levels markedly increased (156/274) units) and diarrhea developed. Under the impression of acute GVHD, he was treated with cyclosporin (3 mg/kg/day) and methylprednisolone pulse therapy. Later on, the skin rash progressed to affect the other parts of trunk and extremities and remained pigmentation (Fig. 3, 4). 76 days after BMT, he complained of a dry mouth and dry eyes as well as a generalized erythematous maculopapular skin rash. The findings of the second skin biopsy taken on the 83rd day were compatible with the early lichenoid stage of chronic GVHD. Antithymocyte globulin (ATG, 1.25 mg/kg/day for 5 days) treatment was started.

Case 2. A 32-year-old man, who had received allogeneic BMT due to severe aplastic anemia, developed an erythematous scaly maculopapular eruption on the posterior neck and trunk, especially at the prior TNI sites on the 20th day of BMT (Fig. 5). He was prepared with the same conditioning regimens as case 1. The biopsy specimen from the upper back showed individual cell dyskeratosis and spongiosis in the epidermis and perivascular lymphocytic infiltration in the dermis (Fig. 6). Immunoperoxidase staining revealed that HLA-DR was diffusely strongly positive in a number of keratinocytes, whereas both CD4 and CD8 were focally weakly positive in the perivascular lymphocytes in the upper dermis. Gradually, the skin rashes spread over the whole body and a rise in SGOT/SGPT (176/230 units) and bilirubin (total, 2.0 mg/dl) levels appeared several days later. Also, fever and diarrhea developed. Prednisolone (60mg/day) and cyclosporin (200mg/day) were alternatively given every other day. Thereafter, he managed to keep his improved state. But, on the 100th day of BMT, he complained of spiking fever, coughing & general malaise associated with generalized erythematous skin eruption. On the 105th day of BMT, the findings of a second biopsy obtained from his left forearm showed several scattered eosinophilic keratinocytes and basal cell necrosis in the epidermis and a perivascular mononuclear cell infiltrate with pigmented incontinence in the upper dermis, which were compatible with chronic GVHD. Chest X-ray film showed pneumatic infiltration in the left lower lung. In addition to chronic GVHD, pneumonia was suspected and antibiotics were started. However, in spite of overall efforts, his state was aggravated to adult respiratory distress syndrome (ARDS) and he was hopelessly discharged and expired about 2 weeks later.

DISCUSSION

GVHD is produced by immunocompetent donor blood cells that have been introduced to a host incapable of rejecting them. Acute GVHD is characterized clinically by dysfunction of the skin, liver and gastrointestinal tract. It usually appears two to five weeks after bone marrow transplantation. The initial manifestation is usually a skin rash, followed by liver and gut involvement several days later. Typical cutaneous features of acute GVHD are erythemas initially present on the cheeks, ears, neck, and upper chest and are often accompanied by itching and pain on the palms and soles. However, in fact, the features of the skin rash in acute GVHD are pleomorphic and may be influenced by a number of factors. Among them, the extent of the chemoradiation damage and its recovery undoubtedly affect skin manifestations.

Recently, we found two very interesting patients who received allogeneic BMT for the management of severe aplastic anemia and developed erythematous maculopapular skin rashes, initially exactly confined to the irradiated site about one
month and twenty days after BMT, respectively. They were prepared with a conditioning regimen composed of cytoxan and TNI, one week before BMT. At first glance, we diagnosed our cases as radiation dermatitis (RD) rather than acute GVHD, because the distribution of skin lesions were consistent with the previous TNI site.

Skin biopsy findings in our cases showed some dyskeratotic cells in the epidermis and perivascular lymphocytic infiltration in the upper dermis. But these findings were non specific and could be seen both in acute GVHD and in RD. Sale et al.¹⁰ expected to be able to distinguish the two by using criteria such as cytologic atypia (to identify cytotoxic effect) and eosinophilic bodies, satellitosis, and epidermal inflammatory infiltrates (to identify GVHD). However, instead, the two proved histologically indistinguishable when subjected to double-blind analysis. Therefore, they suggested that the two injurious stimuli produce nearly identical effects and that in the allografted patients with GVHD the effects of the two injuries are additive. In these cases, worsening changes on repeated skin biopsy specimens might have provided helpful evidence⁹.

Although the importance of immunohistologic findings for diagnosis of GVHD has been debated in the literature in recent years,¹⁰⁻¹² we performed the immunohistochemical studies to obtain further information. Out cases demonstrated that HLA-DR was diffusely strongly positive in a number of keratinocytes, whereas both CD4 and CD8 were focally weakly positive in the perivascular lymphocytes in the upper dermis. In acute GVHD, keratinocytes consistently express HLA-DR antigens,¹⁵ but, abnormal keratinocyte expression of MHC class II molecules has also been reported in a variety of skin diseases, all of which are characterized by lymphocytic infiltration within the epidermis.¹⁴ Therefore, expression of HLA-DR antigens on keratinocytes in our studies was non specific, but, at least, may help to make a diagnosis of acute GVHD in our cases. Paller et al.¹⁵ analysed T-lymphocytes subsets in the lesional skin of allogeneic and autologous BMT patients. In early mild GVHD lesion and drug reaction, CD4/CD8 ratio was 5.0 or more, whereas in acute GVHD and the majority of chronic GVHD, 0.8 to 3.0, due to increased numbers of cytotoxic cells. In our cases, the correct CD4/CD8 ratio could not be calculated because both CD4 and CD8 were only weakly positive. All in all, immunohistochemical findings as well as histologic features in our cases, gave little decisive information in distinguishing acute GVHD from RD.

However, there were several pieces of evidence that our cases might not be RD but acute GVHD initially limited to area of irradiated skin. Firstly, skin rashes in our patients slowly progressed to affect the other parts of the trunk and extremities, later on. Secondly, other clinical signs and symptoms of acute GVHD, including liver dysfunction and diarrhea, began to appear several days after the skin rashes did. Thirdly, another proposed aid for distinguishing between them, was the supposition that preparatory TNI dosage (850 cGy, single dose) can rarely cause RD. Although other factors of radiation therapy such as type of radiation, fraction and time, and anatomic location should be considered, in general, the amount of 1000cGy which is used as a guideline, is unlikely to show any of the effects of RD.¹⁶ Finally, the acute cutaneous reaction to radiation may appear within two days or as long as forty-two days after onset of treatment. It usually appears, however, eight to twenty-one days after onset of treatment is begun, and then fades with time².

In the literature, Zwaan et al.⁶ reported GVHD limited to the area of irradiated skin and briefly commented that the skin areas which were altered by irradiation were especially susceptible to GVHD reaction. Their case is well consistent to ours. Also, chronic GVHD and limited to areas of a previous measles exanthem were reported by Fenky et al.¹⁷ suggesting the predilection of GVHD to develop in areas of recently diseased skin.

On the other hand, LeBoit⁷ reported two cases of radiation dermatitis which resembled acute of multiple myeloma is about 15% per year¹¹. The standard treatment of multiple myeloma has consisted of intermittent pulse therapy of an alkylating agent (melphalan, cyclophosphamide or chlorambucil) and prednisolone for 4 to 7 days every 4 to 6 weeks². At present our case is being treated with intermittent chemotherapy composed
of melphalan, vincristine and prednisolone for 7
days every 4 weeks, and is in a remission state.
We report a rare case of malignant melanoma
with multiple myeloma.

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