Multiple Morphea-like lesions Associated with Chronic Graft-versus-host Disease after Cord Blood Transplantation

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Sir,

Chronic graft-versus-host disease (GVHD) is a systemic multi-organ syndrome associated with haematopoietic cell transplantation that occurs in 25–50% of long-term transplant survivors (1). Commonly involved organs are skin, mouth, liver, eyes, oesophagus, and upper respiratory tract. Although morphea-like skin lesion is one of the diagnostic manifestations of chronic GVHD (2) its evaluation is difficult due to its rarity, especially when it occurs alone. We report here a case of chronic GVHD presenting with multiple morphea-like lesions localized to the trunk after allogeneic cord blood transplantation (CBT). Compared with the previous reported cases, this case was unique for displaying no preceding acute GVHD, and absence of other specific clinical manifestations of chronic GVHD.

CASE REPORT

A 2-year-old Japanese boy with chronic granulomatous disease received an allogeneic CBT from an unrelated 1-locus HLA-mismatched female donor (HLA haplotypes; donor: A 3/24, B 7/35, DR 13/4, recipient: A 3/24, B 7/35, DR 13/15) in December 2004. Neither the patient nor the donor had any apparent history of morphea. On day +18 post-CBT (all date numbers refer to the transplantation day), engraftment was confirmed. The infant experienced no symptoms of acute GVHD under systemic treatment with methotrexate (6 mg on days 1, 3, 5 and 7), 2.5 mg tacrolimus hydrate (FK506), and systemic corticosteroid (hydrocortisone sodium succinate, 100 mg per day for 2 weeks followed by 20 mg per day oral prednisolone) as GVHD prophylaxis. On day +210 all the immunosuppressants were withdrawn. On day +650, he developed asymptomatic skin lesions on his abdomen, which gradually increased in size and number. Clinical examination on day +896 showed 8 oval plaques on his chest and abdomen, sized from 1 to 3 cm in diameter. Each plaque had shiny, ivory-coloured surface with lilac-coloured edge (Fig. 1). His general condition was stable. Abnormal laboratory findings were slightly elevated level of AST 37 U/l (normal, 13–33 U/l), and positive antinuclear antibody (ANA) (1:160, speckled). Other routine laboratory investigations were normal, and anti-DNA, topoisomerase-I, U1-RNP, and centromere antibodies were negative. A biopsy specimen from the abdomen demonstrated mild liquefaction degeneration without necrotic keratinocytes in the epidermal basal cell layer, sclerotic change with proliferation of collagen fibres extending throughout the dermis and surrounding sweat glands (Fig. 2a), and perivascular and interstitial infiltrates of lymphocytes in the reticular dermis (Fig. 2b). Immunohistochemical studies demonstrated infiltration of CD4 or CD8-positive T lymphocytes in the upper dermis and a mixed population of predominant CD20-positive B lymphocytes and CD4 or CD8-positive T lymphocytes in the reticular dermis (Fig. 2c). The clinicopathology was consistent with morphea. According to the National Institute of Health consensus development project on criteria for clinical trials in chronic GVHD (2), he was diagnosed as mild chronic GVHD. The skin lesions were treated with topical steroid, which resulted in poor response and the plaques have slightly increased in size, although they were still confined to his chest and abdomen, 8 months after initial diagnosis. We are considering systemic immunosuppressive therapy as the next line of treatment.

DISCUSSION

There are various kinds of clinical phenotypes in chronic cutaneous GVHD. In addition to the diagnostic skin lesions, such as poikiloderma, lichen planus-like eruptions, systemic deep sclerotic features, morphea-like superficial sclerotic features, and lichen sclerosus-like lesions (2), its clinical and histological spectrum is suggested to be wider, including panniculitis and fasciitis (3). Chronic GVHD has been classified into three patterns according to its clinical presentation: progressive, quiescent, and de novo late onset. In the progressive type, active acute GVHD progresses gradually into chronic GVHD. In the quiescent type, resolution of acute GVHD occurs with a phase with no clinical GVHD activity, and then follows the onset of chronic GVHD. In de novo late-onset type, chronic GVHD occurs without prior onset of acute GVHD (4). In spite of such precise classifications, articles describing clinical aspects of morphea-like or localized sclerodermatous GVHD are limited (4–7). According to Peñas et al. (6), who described 5 patients with localized sclerodermatous GVHD, mean onset of chronic GVHD was 581 days (range 299–1001 days). One patient (20%) was not preceded by acute cutaneous GVHD, whereas the other...
4 patients (80%) had previous history of acute cutaneous GVHD. The distributions were limited to the trunk in 3 patients, and to the legs in 2 patients. Three patients showed high titres of ANA, whereas anti-topoisomerase-I and centromere antibodies were negative in all patients. All 5 patients had involvement with the other organs, such as liver, gastrointestinal tract, or lung. Compared with these, our case was unique for \textit{de novo} late onset and absence of involvement with the other organs except for mild elevated serum level of AST.

Although clinical presentation of multiple morphea in our case was indistinguishable from ordinary morphea, which is not associated with chronic GVHD, pathological findings were distinct, displaying mild liquefaction degeneration of basal layer in addition to the common findings of morphea. Since liquefaction degeneration of basal cell layer has been observed in most patients with sclerodermatous GVHD, even in patients without previous history of acute or lichenoid cutaneous GVHD (6), it might be helpful to differentiate from non-GVHD. The precise mechanism for the development of morphea is unknown; however, immunological abnormalities, such as the presence of ANA (8), anti-histone antibodies (9), and anti-DNA topoisomerase II$\alpha$ (10) have been reported. Likewise, about 60% of patients with chronic GVHD have circulating autoantibodies, such as ANA or antimitochondrial antibody (4). In addition, donor B-cells combined with donor CD4-positive T cells are required to induce chronic GVHD in a mouse model (11). This evidence suggests that B-cell mediated immune response might play a part in the pathogenesis of both morphea and chronic GVHD.

In conclusion, we report here a case of multiple morphea associated with chronic GVHD, but without other organ involvement. Further accumulation of similar cases is needed in order to establish a more appropriate approach to the management of such an abnormal condition.

REFERENCES


Fig. 2. Histopathology of the skin. (a) The specimen obtained from the abdomen showed mild liquefaction degeneration in the epidermis, and sclerotic change with proliferation of collagen fibres surrounding sweat glands (haematoxylin and eosin (H&E) ×50). (b) The reticular dermis showed perivascular and interstitial infiltrates of lymphocytes (H&E ×200). (c) CD20-positive B cells were present in the perivascular inflammatory cell infiltrates of the reticular dermis. (CD20 staining ×200).