Graft-versus-lymphoma effect after reduced intensity allogeneic hematopoietic stem cell transplantation from HLA-two loci mismatched father in a patient with refractory non-Hodgkin lymphoma

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SUMMARY: Suminoe A, Matsuzaki A, Koga Y, Hatano M, Hara T, Hara T. Graft-versus-lymphoma effect after reduced intensity allogeneic hematopoietic stem cell transplantation from HLA-two loci mismatched father in a patient with refractory non-Hodgkin lymphoma. Turk J Pediatr 2009; 51: 500-503.

A 10-year-old female developed a mediastinal mass and was diagnosed as mixed lineage lymphoblastic lymphoma. The tumor was extremely refractory, and she never achieved remission despite intensive therapy using 12 anti-lymphoma agents and local irradiation. She received reduced-intensity allogeneic peripheral blood stem cell transplantation from her HLA-two loci mismatched father, and achieved complete remission. However, the lymphoma relapsed four months later, and we abruptly discontinued immunosuppressive drugs. Concurrent with the development of grade III graft-versus-host disease, the lymphoma completely disappeared with an increase of activated T-cells in peripheral blood. The clinical course suggested the graft-versus-lymphoma effect against aggressive/refractory lymphoma.

Key words: graft-versus-lymphoma effect, HLA mismatch, child, non-Hodgkin lymphoma.

High-dose chemoradiotherapy and hematopoietic stem cell transplantation (SCT) is a potentially curative therapy for patients with refractory/relapsed non-Hodgkin lymphoma (NHL). The initial concept of SCT was to administer myeloablative doses of chemotherapy and radiation to eradicate malignant cells and to infuse hematopoietic stem cells as supportive therapy to restore hematopoiesis. However, an immune-mediated reaction was discovered to be involved in the antitumor activity of allogeneic SCT[1]. In lymphoma, the relapse rate was lower after allogeneic SCT than after autologous SCT[2,3], and T-cell depletion of the graft has been shown to have a negative therapeutic impact particularly on patients with aggressive lymphoma[4,5]. Immunotherapeutic potential of the allogeneic graft has recently been well recognized and is known as graft-versus-lymphoma (GVL) effect. Since the conventional high-dose chemoradiotherapy followed by SCT usually results in high incidence of regimen-related toxicity and treatment-related mortality, the intensive preparative regimens have recently been replaced by reduced-intensity or non-myeloablative conditioning regimens, which can reduce toxicity and induce GVL effect[6].

We here report a 10-year-old girl with refractory NHL who underwent reduced-intensity SCT and subsequently presented the clinical course suggesting the potent GVL effect.

Case Report

A 10-year-old Japanese female presented with persistent dry cough and dyspnea. Chest X-ray and computed tomography (CT) revealed a mediastinal mass with pericardial and bilateral pleural effusion (Fig. 1a). CT and scintigraphy detected no other masses. Pleural effusion contained many small sized lymphoblasts, which were positive for CD3, CD7, CD19,

T cell receptor (TCR)-γδ and cytoplasmic CD79a by flow cytometry. Cytogenetic analysis revealed TCR gene rearrangement, but not immunoglobulin gene rearrangement. The blasts had chromosomal abnormality with 46, XX, add(3)(p25), -5, -10, add(10)(p11.2), -11, add(14)(q24), +3mar. Her peripheral blood showed white blood cells 5,180/μL (blast 0%), hemoglobin 14.6 g/dl, platelets 351 x 10^3/μl, lactate dehydrogenase 222 U/L, uric acid 3.2 mg/dl, and C-reactive protein 2.1 mg/dl. Bone marrow (BM) examination revealed that blasts positive for CD3, CD7 and CD19 accounted for 2.1% of nucleated cells. No blasts were detected in cerebrospinal fluid. These findings indicated the diagnosis of mixed lineage lymphoblastic lymphoma, stage III.

Although the patient was treated with several combination chemotherapies consisting of vincristine (VCR), cyclophosphamide, l-asparaginase (ASP), prednisolone (PSL), intermediate-dose methotrexate (MTX), high-dose cytarabine (HD-AraC), etoposide (VP16) and idarubicin, the tumor responded poorly to these drugs. She then received local irradiation to the mediastinal mass (total 41.4 Gy) and additional chemotherapy using VCR, ifosfamide, daunorubicin, mitoxantrone, HD-AraC, VP16, ASP, and fludarabine (Flu, 20 mg/m^2 x 5). Despite this intensive chemoradiotherapy, the pleural effusion never disappeared and pleural infiltration developed (Fig. 1b). In addition, blasts appeared in the peripheral blood seven months after diagnosis.

She needed urgent treatment, but did not have an HLA-matched sibling donor. She thus received allogeneic peripheral blood SCT from her father eight months after diagnosis. HLA typing showed: patient: A24, B51, B52, DR1502, DR1403; father: A11.1, A24, B51, B52, DR1502, DR04. The conditioning regimen consisted of Flu (30 mg/m x 5 days) and melphalan (70 mg/m^2 x 2 days), and short-term MTX (15 mg/m^2 and 10 mg/m^2 x 3) and tacrolimus (0.03 mg/kg/day) were used for graft-versus-host disease (GVHD) prophylaxis. Grade I acute GVHD developed on day 13, and PSL was additionally administered. Engraftment was achieved on day 19. The karyotypic conversion from 46, XX to 46, XY was confirmed in all BM cells on day 28. Forty-nine days after SCT, hematological examination and clinical imaging (CT and scintigraphy) demonstrated no evidence of residual tumor (Fig. 1c).

Four months after SCT, however, she developed herpes zoster and subsequently pericardial and pleural effusion occurred (Figs. 1d, 2a), which contained blasts with the same surface markers as the initial presentation. Then, Flu (20 mg/m^2) was administered for five days and tacrolimus was abruptly discontinued. She developed grade III GVHD (generalized erythroderma, total bilirubin 2.6 mg/dl, and diarrhea of more than 1,500 ml/day). Concurrent with the development of GVHD, the pleural infiltration and effusion gradually decreased and completely disappeared 48 days after relapse (Figs. 1e, 2b). Hematological examination did not show any abnormalities, suggesting that she achieved remission again. The lymphocyte count at this time was 400/μL including HLA-DR+/CD3+ 63.0% and HLA-DR+/CD8+ 68.3%. Although she maintained complete remission for three months without any additional treatment, the mediastinal mass and pleural effusion appeared again as the GVHD disappeared, and she died of disease progression.

Discussion

In the present patient, the residual lymphoma refractory to intensive chemoradiotherapy completely disappeared concurrent with the development of GVHD after reduced-intensity SCT from the HLA-two loci mismatched father. Even though the GVL effect has been generally recognized, this case had a unique feature in that the radiological images clearly reflected the intensity of the GVL effect.

The clinical course of this patient strongly suggests the potent GVL effect.

Previous analyses of patients with NHL showed that the development of grade II-IV GVHD was significantly associated with a lower incidence of disease progression after transplantation, presumably through a stronger GVL effect[7-9]. The critical first step in the initiation of GVHD is antigen presentation to donor T-cells by recipient antigen presenting cells. The target antigens of cytotoxic T-cells may be divided into three categories: alloantigens broadly expressed on both malignant cells and normal epithelial cells; alloantigens expressed on both malignant cells and normal hematopoietic cells; and antigens expressed solely on malignant cells[10]. Alloantigens expressed on both malignant cells and normal epithelial cells

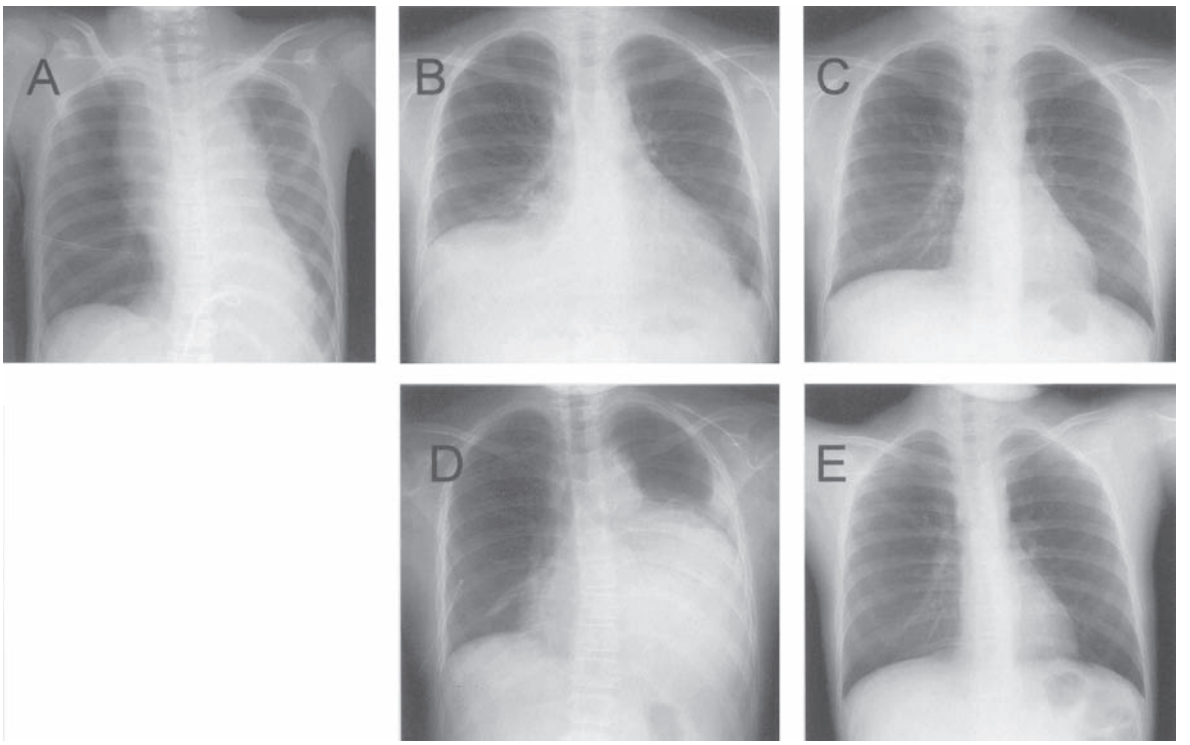

Fig. 1. The chest X-ray findings at initial presentation (a), just before stem cell transplantation (SCT) (b), 49 days after SCT (c), at relapse (d), and 48 days after relapse (a).

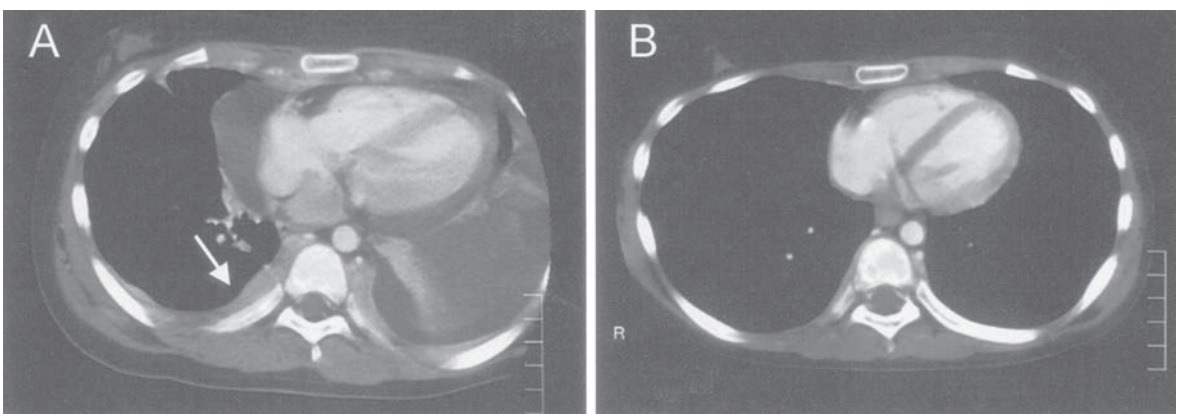

Fig. 2. Computed tomography images of the chest at relapse (a) and 48 days after relapse (b). The arrow indicates the pleural infiltration of the lymphoma.

would induce GVL effect in close association with clinical GVHD. In the present patient, the development of GVHD and tumor regression was accompanied with marked increase in activated T-cells (HLA-DR+/CD3+ 63.0% and HLA-DR+/CD8+ 68.3%), and the lymphoma relapsed as GVHD disappeared. In addition, the first relapse was preceded by the development of herpes zoster, suggesting the association of lymphoma relapse and severe weakening of donor T-cell mediated immunity. Similar cases with simultaneous leukemia relapse concurrently with varicella-zoster virus reactivation after SCT were reported[11]. These findings suggested the regression of refractory lymphoma in our case was attributed to the GVL effect.

The clinical relevance of GVL effect on lymphoma is controversial. Some reports demonstrated NHL regression after withdrawal of immune suppression or the donor lymphocyte infusion

(DLI) posttransplantation[12,13], while another report did not demonstrate detectable GVL effect in NHL patients who received an allogeneic SCT[14]. The extent of the GVL effect could vary according to histologic subtypes. Generally, the GVL effect is considered to be more potent against indolent or low-grade lymphoma compared with aggressive lymphoma[5,13,15,16]. In extremely chemotherapy-refractory patients, GVL effect may not be detectable because the tumor growth rate exceeds the ability of the immune effect to eradicate malignant cells[10,16]. These observations might explain why the GVL effect was only transient in our patient.

In patients with refractory lymphoma, some immune modulation to enhance and sustain the GVL effect might lead to a more favorable outcome, including prophylactic administration of DLI, lymphocyte activation by interleukin-2, transfer of in vitro expanded lymphoma-specific T-cells, and immunization of the donor with tumor-specific protein before DLI[8,17,18].

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