

Case Study

Subcutaneous Panniculitis-Like T-Cell Lymphoma (SPTCL) with Hemophagocytosis (HPS) : Successful Treatment Using High-Dose Chemotherapy (BFM-NHL & ALL-90) and Autologous Peripheral Blood Stem Cell Transplantation

Eiichi Sakurai,^{1,2)} Takashi Satoh,²⁾ Yashima-Abo Akiko,²⁾ Chihaya Maesawa,²⁾
Kanako Tsunoda,^{1,2)} Mikiya Endo,³⁾ Toshihide Akasaka,¹⁾ and Tomoyuki Masuda²⁾

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare form of non-Hodgkin lymphoma, in which lymphoma cells infiltrate preferentially into subcutaneous adipose tissue. Although various treatment trials for SPTCL have been attempted, no standardized therapy has been established. Here, we report a case of α/β^+ T-cell-phenotype SPTCL (SPTCL-AB) with hemophagocytosis (HPS) in a 14-year-old girl, who presented with low-grade fever, general fatigue and chest swelling. Laboratory examinations revealed leukocytopenia, and bone marrow aspiration cytology showed HPS. The diagnosis of SPTCL-AB was made by biopsy on the basis of thickened subcutaneous tissue in the chest wall. Following high-dose chemotherapy (HDT) of BFM-NHL & ALL-90, autologous peripheral blood stem cell transplantation (auto-PBSCT) was performed. The patient responded to the treatment and has remained asymptomatic for 2 years. Our results suggest that a combination of HDT of BFM-NHL & ALL-90 and auto-SCT treatment is effective for SPTCL associated with HPS. [*J Clin Exp Hematop* 53(2) : 135-140, 2013]

Keywords: SPTCL, hemophagocytosis, BFM-NHL & ALL-90, auto-PBSCT

INTRODUCTION

In 1991, the distinct clinicopathological features of a T-cell lymphoma in which the lymphoma cells preferentially invade the subcutaneous tissue were described by Gonzalez *et al.*¹ Under the term subcutaneous panniculitis-like T-cell lymphoma (SPTCL), this new condition was established as a distinct disease entity in the World Health Organization (WHO) classification.² Because of its peculiar pathological features, SPTCL may be initially misdiagnosed as Weber-Christian disease, a benign inflammatory panniculitis and a granulomatous disease.^{3,4} Recent studies have disclosed that cases with an α/β^+ T-cell phenotype (SPTCL-AB) and a γ/δ^+ T-cell phenotype (SPTCL-GD) can be distinguished within

the group of SPTCL.⁵ SPTCL-ABs have a $CD4^-$, $CD8^+$, $CD56^-$ phenotype, and SPTCL-GDs have a $CD4^-$, $CD8^-$ phenotype with frequent expression of CD56. Compared with SPTCL-ABs, SPTCL-GDs have a poor prognosis.^{6,7} On the basis of these observations, the term SPTCL is used only for SPTCL-ABs, and SPTCL-GDs are included within the cutaneous γ/δ^+ T-cell lymphomas.^{6,8} Although SPTCL-AB patients without hemophagocytic syndrome (HPS) have a favorable prognosis, the clinical course of cases associated with HPS is generally aggressive, and a delay in diagnosis or treatment may result in a fatal outcome. There have been few reports of successful treatment of SPTCL-AB patients with HPS, and no therapeutic regimen has been established.

Here, we report a case of SPTCL-AB with HPS that was treated successfully with a combination of high-dose chemotherapy (HDT) of Berlin-Frankfurt-Münster-non-Hodgkin lymphoma-90 (BFM-NHL-90) and autologous peripheral blood stem cell transplantation (auto-PBSCT).

CASE REPORT

A previously healthy 14-year-old Japanese girl visited a physician because of a 1-month history of chest swelling.

Received : January 4, 2013

Revised : March 12, 2013

Accepted : April 11, 2013

Departments of ¹⁾Dermatology, ²⁾Pathology and ³⁾Pediatrics, School of Medicine, Iwate Medical University, Morioka, Japan

Corresponding author: Eiichi Sakurai, MD, Departments of Dermatology and Pathology, School of Medicine, Iwate Medical University, Uchimarui 19-1, Morioka 020-8505, Japan

e-mail : sakkuei@iwate-med.ac.jp

She also had a 3-month history of general fatigue and low-grade fever. Initial laboratory examinations revealed a white blood cell count of $2.82 \times 10^3/\mu\text{L}$, hemoglobin of 11.6 g/dL, hematocrit of 33.8 g/dL and platelet count of $16.4 \times 10^4/\mu\text{L}$. Histopathologic examination of a biopsy specimen of subcutaneous adipose tissue from the chest wall revealed diffuse infiltration of medium-sized lymphocytes. Under a diagnosis of panniculitis due to lupus profundus, administration of low-dose prednisolone (PSL) was started. Several weeks later, the chest swelling expanded gradually. She was therefore referred and admitted to our hospital for further evaluation and treatment.

On physical examination, a massive tumor was evident in her chest subcutaneous tissue (Fig. 1). The findings from laboratory examinations were as follows: aspartate aminotransferase 27 IU/L (normal: 10-40 IU/L), alanine aminotransferase 15 IU/L (normal: 5-35 IU/L), lactic dehydrogenase 235 U/L (normal: 115-359 IU/L), soluble interleukin-2 receptor 641 U/mL (normal: 220-530 U/mL) and ferritin 56 ng/mL. Moreover, previous infection with Epstein-Barr virus was evident. Magnetic resonance imaging revealed noticeable thickening of the subcutaneous tissue, compatible with the region of the massive tumor in the chest (Fig. 2). Histopathology of skin biopsy specimens showed medium-sized lymphocytes diffusely infiltrating into the subcutaneous fat tissue (Fig. 3a). Rimming of the lymphocytes around individual fat cells was observed (Fig. 3b).

Immunohistochemical staining revealed that the infiltrating lymphocytes were CD3⁺, CD4⁻, CD5⁺, CD8⁺, CD20⁻, CD30⁻, CD45RO⁺, CD56⁻ and CD79a⁻ (Fig. 4). They were positive for T-cell receptor- β (Fig. 5a). Cytotoxic molecules such as granzyme B, T-cell intracellular antigen-1 (TIA-1) and perforin were positive (Fig. 5b). Latent membrane protein 1 (LMP-1) and EBER *in situ* hybridization were negative (Fig. 5c & 5d). Bone marrow smears showed hemophagocytosis.



Fig. 1. A massive tumor, indicated by *black dots*, was present in the subcutaneous tissue of the chest.



Fig. 2. Magnetic resonance imaging of the chest (T2-weighted). The subcutaneous tumor of the chest wall showed high signal intensity.

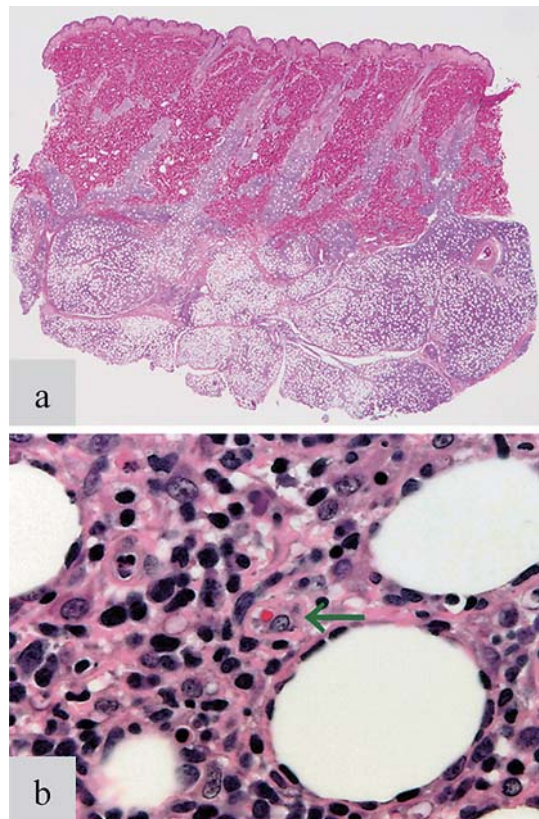


Fig. 3. Histopathology of the skin biopsy specimen (H&E stain). (3a) Diffuse cellular infiltration occurred in the subcutaneous fat tissue. (3b) Rimming of lymphocytes around fat cells was observed (*arrow*). Bean bag cells, phagocytosing erythrocytes, were found among the lymphocytes. (3a) $\times 10$, (3b) $\times 400$.

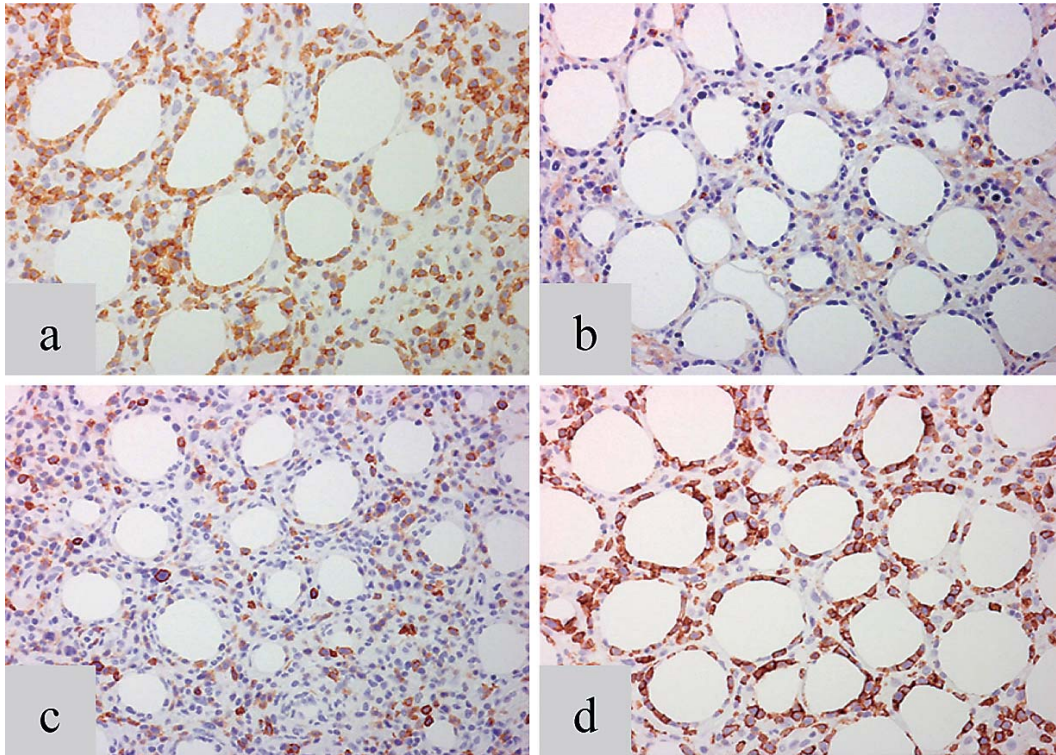


Fig. 4. Immunohistochemistry of CD3 (4a), CD4 (4b), CD5 (4c) and CD8 (4d). The infiltrating lymphocytes were positive for CD3, CD5 and CD8, but negative for CD4. $\times 400$.

tosis of red blood cells and neutrophils by histiocytes (Fig. 6).

On the basis of these results, the patient was diagnosed as having SPTCL accompanied by HPS in spite of the low levels of lactic dehydrogenase and ferritin, and was treated with high-dose PSL (75 mg/day internally), starting on day 9 of admission.

Nine days later (on day 17 of admission), despite the PSL therapy, the chest tumor was unchanged in size. Additional HDT of BFM-NHL-90 (protocol I) was therefore applied. After starting the first course of the chemotherapy, the tumor in the chest gradually decreased in size. During the phase of recovery from the chemotherapy, peripheral blood stem cells (CD34⁺ cells) were harvested. Moreover, chemotherapy of BFM-NHL-90 (Protocol M) was applied as a consolidation therapy. In addition, one course of the BFM-acute lymphoblastic leukemia (ALL)-90 regimen (HR3) was applied for further treatment.

Following pretreatment with the MCVAC (ranimustine, cytarabine, etoposide and cyclophosphamide) regimen, the patient was treated with auto-PBSCT. The clinical course thereafter was uneventful. She has been in complete remission for more than 2 years, and there was no evidence of local recurrence in the chest wall and HPS in the bone marrow at the final follow-up examination.

DISCUSSION

SPTCL is a type of skin lymphoma characterized by the infiltration of subcutaneous tissue by pleomorphic T cells and benign macrophages, mimicking lobular panniculitis. This malignancy typically presents in the form of skin nodules that involve the extremities and can become ulcerated.⁹ The clinical course associated with HPS is aggressive, and a delay in diagnosis and treatment may result in a fatal outcome.

Although the mechanism of HPS in SPTCL has not been clarified, the phenomenon of HPS results from overproduction of cytokines, including interferon- γ , interleukin-2 (IL-2), IL-6, IL-12, IL-18 and tumor necrosis factor- α , produced by activated T cells (Th1 cells) and macrophages, which leads to a chain reaction of cytokines.¹⁰⁻¹³ Control of HPS in SPTCL-AB patients improves the prognosis.

Various therapies such as radiotherapy, PSL, CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone) (-like) chemotherapy and auto/allo-SCT have been applied for SPTCL-AB.⁹ For relapsed or refractory disease, various regimens have been attempted as salvage chemotherapy, including cladribine, DHAP (dexamethasone, cytarabine and cisplatin), ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin), FLAG (fludarabine, cytarabine and granulocyte-colony stimulating factor), mini-BEAM (carmus-

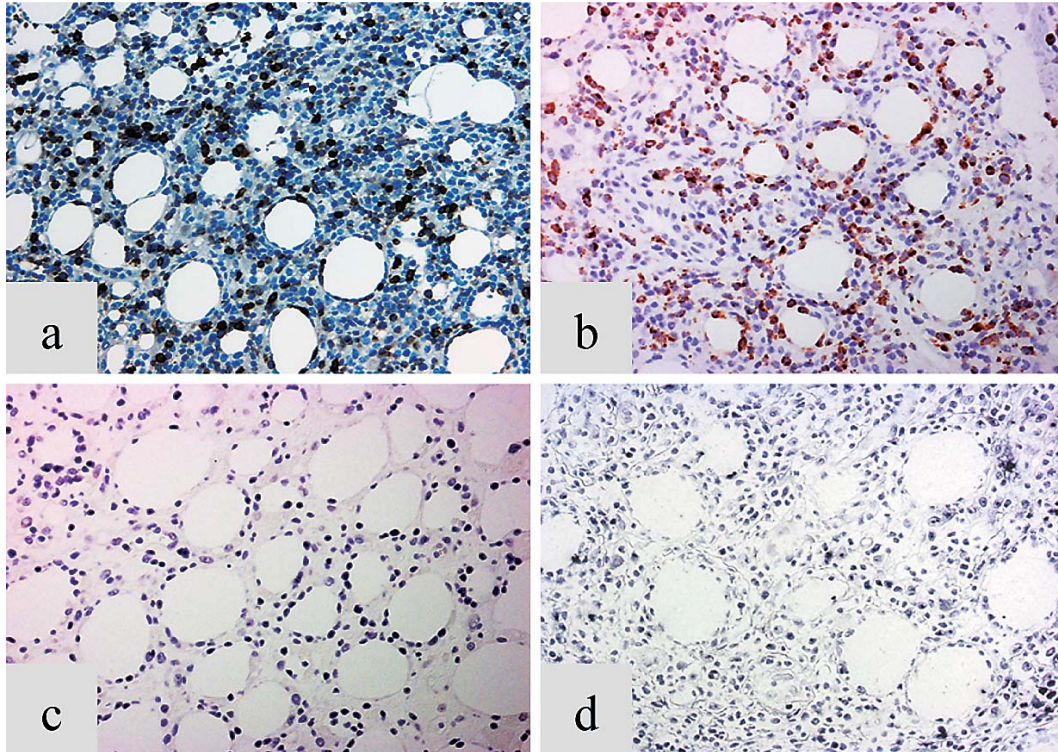


Fig. 5. Immunohistochemistry for T-cell receptor (TCR)- β (5a), granzyme B (5b), latent membrane protein-1 (LMP-1, 5c) and Epstein-Barr virus (EBV)-encoded RNA *in situ* hybridization (5d). Lymphocytes were positive for TCR- β , and expression of the cytotoxic molecule granzyme B was also found. LMP-1 and EBV were negative. $\times 200$.

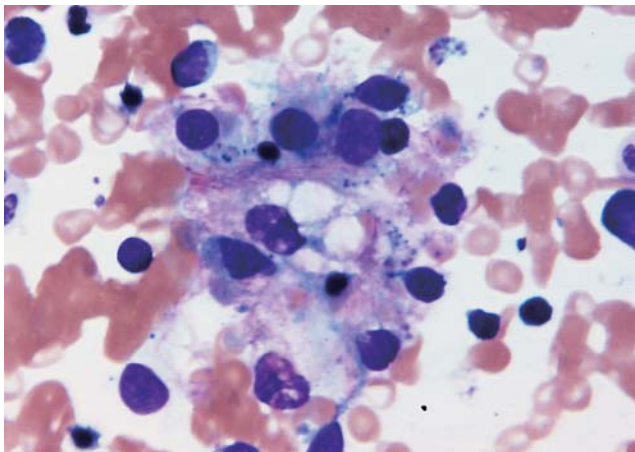


Fig. 6. Hemophagocytosis was seen in a smear of the bone marrow. Giemsa stain, $\times 1000$.

tine, etoposide, cytarabine and melphalan) and VEPPB (vincristine, etoposide, prednisone, pocarbazine and bleomycin).⁹ However, no standardized treatment has yet emerged. In SPTCL-AB patients with HPS, a recent report has indicated that CHOP (-like) chemotherapy is not very effective. Auto-SCT or allo-SCT following HDT has been suggested as an

important option for patients with refractory or recurrent SPTCL.^{4,14}

In the present case, high-dose PSL was initially used, but no response was obtained. Therefore, we treated the patient according to the BFM-NHL & ALL-90 protocol.

BFM-NHL-90 is a protocol for pediatric malignant lymphoma and yields a significantly better outcome for non-Hodgkin lymphoma at stage I or II.¹⁵ BFM-NHL-90 is also effective for pediatric anaplastic large-cell lymphoma. BFM-ALL-90 is a superior regimen for high-risk childhood T-cell acute lymphoblastic leukemia.¹⁶

The present case was treated successfully with a combination of HDT of BFM-NHL & ALL-90 followed by auto-PBSCT, and achieved clinical complete remission (CR). This result suggests that the BFM protocol is applicable and can yield complete remission in cases of SPTCL with HPS. Medhi *et al.* have also reported the value of the BFM-90 protocol for the treatment of patients with SPTCL and HPS.¹⁷

To date, there have been few reports of effective treatment for SPTCL using HDT following SCT. In almost all of the reported cases, the patients underwent HDT-allo-SCT and its effectiveness was impressive, 92% achieving CR, with a median response duration of ≥ 14 months.⁹ In intermediate- and high-grade lymphomas, myeloablative allo-SCT is associated

with a lower relapse rate than auto-SCT for the graft-versus-leukemia effect.^{18,19} However, chronic graft-versus-host disease (cGVHD) is a very common complication, with a reported incidence of between 40% and 70%,²⁰ and is the leading cause of late death in allo-SCT survivors.^{20,21}

The median age of patients with SPTCL-AB at diagnosis is 36 years (range: 9-79 years), and about 19% are in the second decade or younger.⁸ In children, cGVHD may reduce the quality of life because of the induction of growth irregularity. Mukai *et al.* described a patient with SPTCL and HPS who received HDT of BFM-NHL & ALL-90 and auto-SCT.⁴ The present case received a combination of HDT of BFM-NHL & ALL-90 and auto-SCT, and has been in complete remission for more than 2 years. This suggests that auto-SCT might be a feasible option following HDT.

In summary, we have reported a case of SPTCL complicated by HPS, which responded to treatment with HDT of BFM-NHL & ALL-90 and auto-SCT. Although the value of the BFM-NHL & ALL-90 protocol has to be further evaluated in SPTCL cases, our findings suggest that a combination of HDT of BFM-NHL & ALL-90 and auto-SCT is applicable for the treatment of SPTCL with HPS.

ACKNOWLEDGEMENTS

The authors express their thanks to Prof. Shigeo Nakamura, Nagoya University, Nagoya, Japan, for his advice.

DISCLOSURE/CONFLICT OF INTEREST

The authors state that they have no financial interest in the products mentioned within this article.

REFERENCES

- Gonzalez CL, Medeiros LJ, Brazier RM, Jaffe ES: T-cell lymphoma involving subcutaneous tissue. A clinicopathologic entity commonly associated with hemophagocytic syndrome. *Am J Surg Pathol* 15:17-27, 1991
- Jaffe ES, Gaulard P, Ralfkiaer E, Cerroni L, Meijer CJLM: Subcutaneous panniculitis-like T-cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, *et al.* (eds): *World Health Organization Classification of Tumours, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed, Lyon, International Agency for Research on Cancer (IARC), pp.294-295, 2008
- Tsukamoto Y, Katsunobu Y, Omura Y, Maeda I, Hirai M, *et al.*: Subcutaneous panniculitis-like T-cell lymphoma: successful initial treatment with prednisolone and cyclosporin A. *Intern Med* 45:21-24, 2006
- Mukai HY, Okoshi Y, Shimizu S, Katsura Y, Takei N, *et al.*: Successful treatment of a patient with subcutaneous panniculitis-like T-cell lymphoma with high-dose chemotherapy and total body irradiation. *Eur J Haematol* 70:413-416, 2003
- Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, *et al.*: WHO-EORTC classification for cutaneous lymphomas. *Blood* 105:3768-3785, 2005
- Massone C, Chott A, Metzger D, Kerl K, Citarella L, *et al.*: Subcutaneous, blastic natural killer (NK), NK/T-cell, and other cytotoxic lymphomas of the skin: a morphologic, immunophenotypic, and molecular study of 50 patients. *Am J Surg Pathol* 28:719-735, 2004
- Massone C, Lozzi GP, Egberts F, Fink-Puches R, Cota C, *et al.*: The protean spectrum of non-Hodgkin lymphomas with prominent involvement of subcutaneous fat. *J Cutan Pathol* 33:418-425, 2006
- Willemze R, Jansen PM, Cerroni L, Beriti E, Santucci M, *et al.*: Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood* 111:838-845, 2008
- Go RS, Wester SM: Immunophenotypic and molecular features, clinical outcomes, treatments, and prognostic factors associated with subcutaneous panniculitis-like T-cell lymphoma: a systematic analysis of 156 patients reported in the literature. *Cancer* 101:1404-1413, 2004
- Imashuku S: Advances in the management of hemophagocytic lymphohistiocytosis. *Int J Hematol* 72:1-11, 2000
- Akashi K, Hayashi S, Gondo H, Mizuno S, Harada M, *et al.*: Involvement of interferon- γ and macrophage colony-stimulating factor in pathogenesis of haemophagocytic lymphohistiocytosis in adults. *Br J Haematol* 87:243-250, 1994
- Osugi Y, Hara J, Tagawa S, Takai K, Hosoi G, *et al.*: Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohistiocytosis. *Blood* 89:4100-4103, 1997
- Aricò M, Danesino C, Pende D, Moretta L: Pathogenesis of hemophagocytic lymphohistiocytosis. *Br J Haematol* 114:761-769, 2001
- Alaibac M, Berti E, Pigozzi B, Chiarion V, Aversa S, *et al.*: High-dose chemotherapy with autologous blood stem cell transplantation for aggressive subcutaneous panniculitis-like T-cell lymphoma. *J Am Acad Dermatol* 52 (Suppl):121-123, 2005
- Kavan P, Kabicková E, Gajdos P, Koutecký J, Smelhaus V, *et al.*: Treatment of children and adolescents with non-Hodgkin's lymphoma (results based on the NHL Berlin-Frankfurt-Münster 90 protocols). *Cas Lek Cesk* 138:40-46, 1999
- Schrauder A, Reiter A, Gadner H, Niethammer D, Klingebiel T, *et al.*: Superiority of allogeneic hematopoietic stem-cell transplantation compared with chemotherapy alone in high-risk childhood T-cell acute lymphoblastic leukemia: results from ALL-BFM 90 and 95. *J Clin Oncol* 24:5742-5749, 2006
- Medhi K, Kumar R, Rishi A, Kumar L, Bakhshi S: Subcutaneous panniculitis-like T-cell lymphoma with hemophagocytosis: complete remission with BFM-90 protocol. *J Pediatr Hematol Oncol* 30:558-561, 2008
- Ratanatharathorn V, Uberti J, Karanes C, Abella E, Lum LG: Prospective comparative trial of autologous versus allogeneic bone marrow transplantation in patients with non-Hodgkin's lymphoma.

Sakurai E, *et al.*

- Blood 84:1050-1055, 1994
- 19 Jones RJ, Ambinder RF, Piantadosi S, Santos GW: Evidence of a graft-versus-lymphoma effect associated with allogeneic bone marrow transplantation. *Blood* 77:649-653, 1991
- 20 Lee SJ, Klein JP, Barrett AJ, Ringden O, Antin JH, *et al.*: Severity of chronic graft-versus-host disease : association with treatment-related mortality and relapse. *Blood* 100:406-414, 2002
- 21 Socié G, Stone JV, Wingard JR, Weisdorf D, Henslee-Downey PJ, *et al.*: Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. *N Engl J Med* 341:14-21, 1999