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Modifying NHL-BFM-90 and HLH-2004 Protocols for a Child with SPLTCL and HLH; Prompt Initiation of Dexamethasone and Etoposide

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Subcutaneous panniculitis-like T-cell lymphoma (SPLTCL) which is similar to lobular panniculitis is a subtype of skin lymphoma that is characterized by pleomorphic T cells and benign macrophages. The simultaneous presence of hemophagocytic lymphohistiocytosis (HLH) is the most important and adverse prognostic factor in SPLTCL. SPLTCL is a rare disease with no well-established standard treatment. We report a child with SPLTCL and HLH, who were successfully treated with the modified NHL (non-Hodgkin lymphoma)-BFM(Berlin-Frankfurt-Münster)-90 and HLH-2004 protocols. Patient had persistent fever and subcutaneous masses. SPLTCL with HLH was diagnosed by immunohistochemistry, radiology and laboratory results. SPLTCL with HLH has shown high mortality when treated with a combination of intensive anticancer drugs. Thus, we first administered dexamethasone and etoposide. After this, when we used the modified protocol of NHL-BFM-90 and HLH-2004, patient showed complete resolution of the subcutaneous masses and features of HLH, except for persistent hyperferritinemia. We tried etanercept to reduce high serum ferritin with some effects. In children with diagnosis of SPLTCL with HLH, initiation of immediate and appropriate treatment affects prognosis. Thus, prompt initiation of the agents that can simultaneously control underlying disease as well as secondary HLH could have lead to successful results.

Keywords: Etanercept, Hemophagocytic lymphohistiocytosis, Subcutaneous panniculitis-like T-cell lymphoma

Introduction

Subcutaneous panniculitis-like T-cell lymphoma (SPLTCL) which is similar to lobular panniculitis is a subtype of skin lymphoma that is characterized by pleomorphic T cells and benign macrophages which infiltrates to subcutaneous tissue. The simultaneous presence of hemophagocytic lymphohistiocytosis is the most important and adverse prognostic factor in SPLTCL [1]. SPLTCL is a rare disease with no well-established standard treatment. Various protocols have therefore been used. Successful treatment of SPLTCL with hemophagocytic lymphohistiocytosis (HLH) in children has rarely been reported [2–4].

We present a case of SPLTCL with HLH successfully treated initialy with dexamethasone and etoposide followed by modified NHL (non-Hodgkin lymphoma)-BFM(Berlin-Frankfurt-Münster)-90 and HLH-2004.

Case report

An eight-year-old boy was admitted to the department of pediatric surgery with a two-week history of fever and an abdominal mass. He continued to be

febrile with intravenous antibiotics, and because of bicytopenia, he was transferred to the department of pediatrics.

On physical examination, a tender, 15 cm round erythematous swelling on right mid-abdominal wall (Fig. 1) and hepatosplenomegaly (subsequently confirmed by computed tomography) were observed. Initial laboratory findings were: white blood cell count, $2.4 \times 10^9/dm^3$; hemoglobin, 99 g/dm^3; platelet count, $147 \times 10^9/dm^3$; C-reactive protein, 275.24 $nmol/dm^3$ (normal: 0.0–47.62 $nmol/dm^3$); triglycerides, 4.16 $mmol/dm^3$ (normal: 0.56–1.47 $mmol/dm^3$); fibrinogen, 1.7 g/dm^3 (normal: 2.0–4.0 g/dm^3); soluble interleukin 2 receptor, 14,991 pg/cm^3 (normal: 1,398–5,513 pg/cm^3); ferritin, 1,126.52 $pmol/dm^3$ (normal: 33.71–449.44 $pmol/dm^3$) and Epstein-Barr virus and cytomegalovirus immunoglobulin titers, negative. Biopsy of the abdominal mass showed subcutaneous infiltration by atypical lymphocytes rimming adipocytes.

Immunohistochemistry of the specimen was positive for CD3 and CD8, and negative for CD4, CD20, and CD56 (Fig. 2). T Cell receptor (TCR) gene rearrangement analysis revealed γ oligoclonality. Whole-body 18F-fluorodeoxyglucose positron emission tomography (PET) revealed increased contrast uptake in subcutaneous tissues of the right abdominal wall, left anterior chest wall, right upper quadrant abdominal wall, left pelvis, bilateral buttocks, and upper legs (Fig. 3). Taken together, these results led to a diagnosis of SPLTCL with HLH.

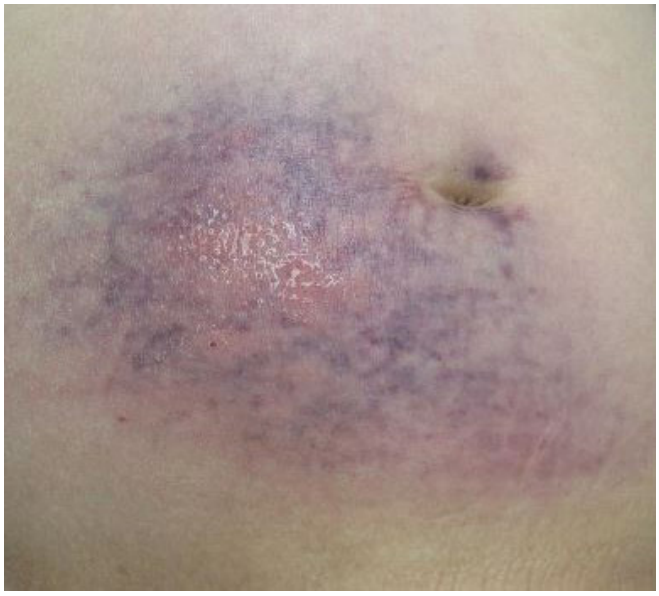

Fig. 1. Erythematous subcutaneous nodules on the right mid-abdominal wall.

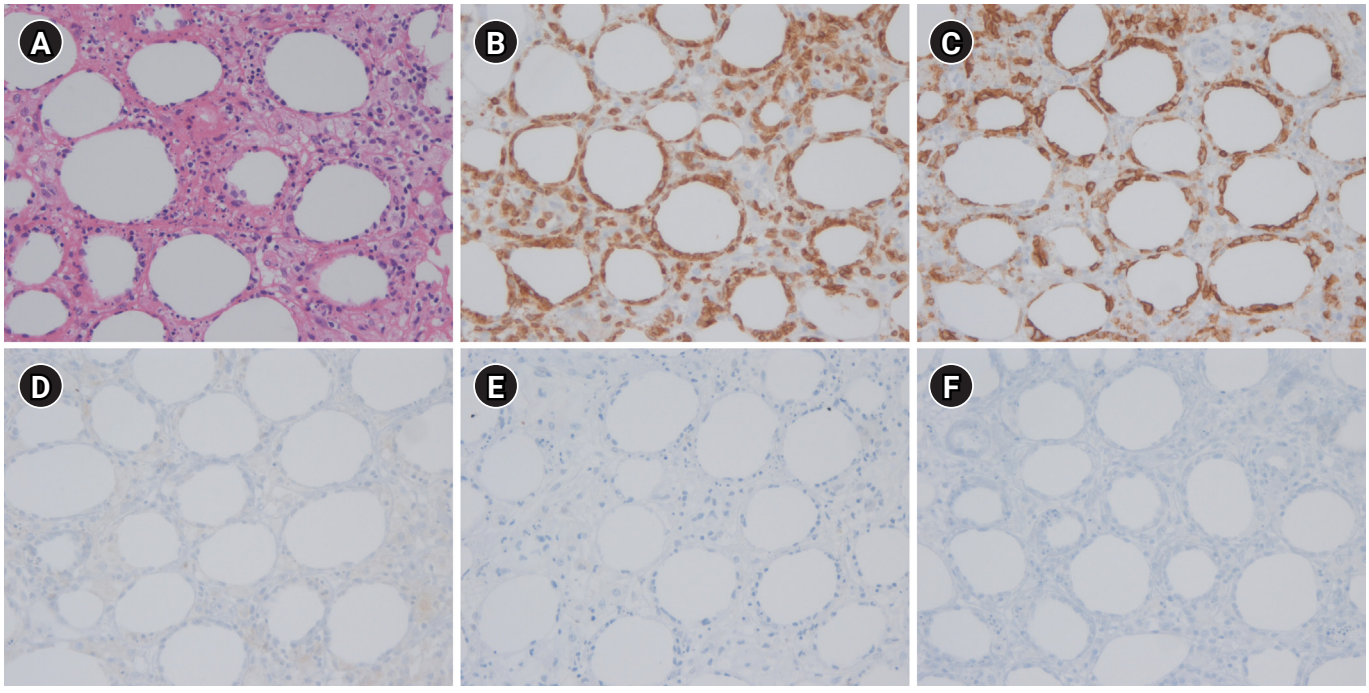

Fig. 2. Histopathologic findings of right mid-abdominal wall nodules. Hematoxylin and eosin stained specimen shows atypical lymphocytes infiltration in the subcutaneous tissue (A). Immunohistostainings are positive for CD3 (B), CD8 (C) and, negative for CD4 (D), CD20 (E), CD56 (F). (A-F, original magnifications: ×200).

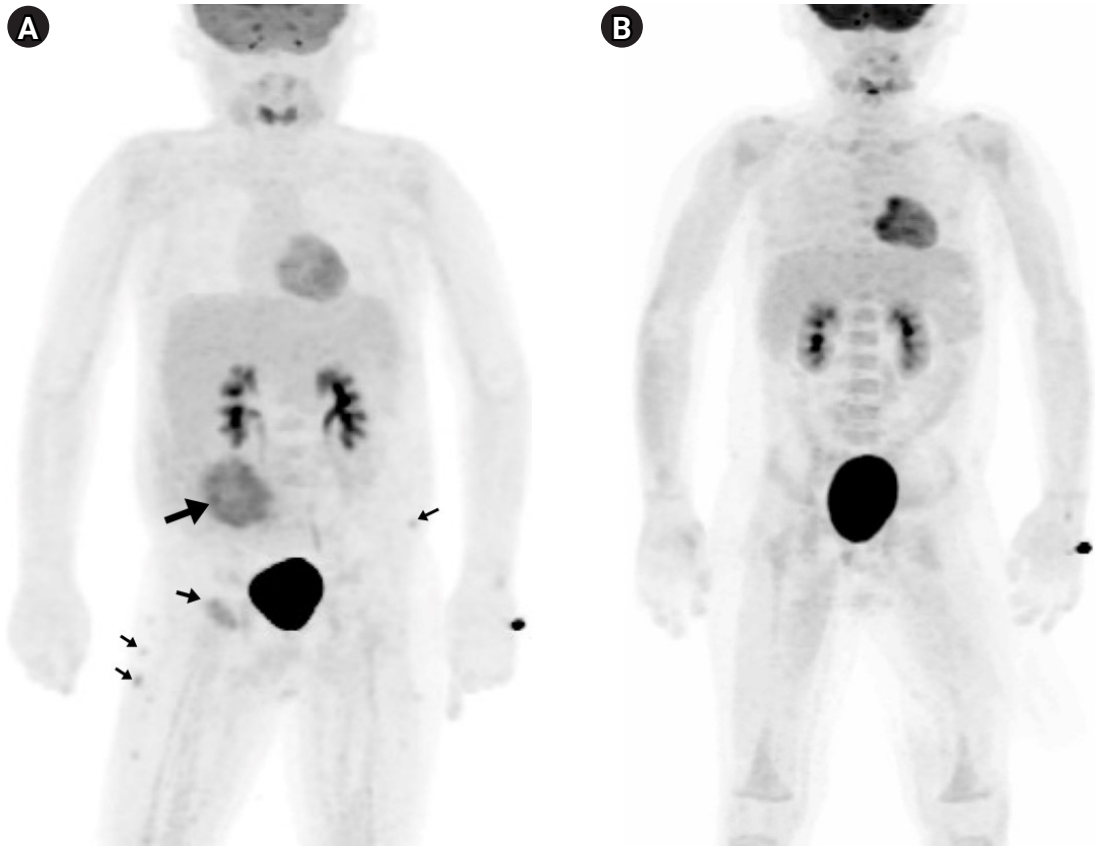

Fig. 3. (A) Whole-body positron emission tomography (PET) scan at diagnosis reveals multiple increased fluorodeoxyglucose uptakes in the subcutaneous tissues of right abdominal wall, left anterior chest wall, right upper quadrant abdominal wall, left pelvis, both buttock and upper legs. (B) Follow-up PET scan after the course B-A-B-A-B of the Non-Hodgkin Lymphoma-Berlin-Frankfurt-Münster-90 protocol shows resolution of most of the lesions.

Treatment with dexamethasone and etoposide was started immediately, and the patient defervesced the next day. After four weeks of HLH induction therapy with dexamethasone and etoposide, NHL-BFM-90 course A was started. When serum ferritin subsequently became elevated above 4,494.38 pmol/dm^3, we considered the possibility of HLH aggravation. Thus, four weeks of HLH-2004 induction treatment was repeated with dexamethasone, etoposide, and added cyclosporine A. Thereafter, per protocol, NHL-BFM-90 courses B-A-B-A-B were administered, leading to complete remission with normalized PET results. High ferritin persisted (up to 3,315 pmol/dm^3), however. The sustained ferritin elevation was worrisome and suspicious for incomplete control of HLH. A maintenance course of HLH-2004 was therefore continued for a total of 40 weeks. The tumor necrosis factor α (TNF- α) inhibitor etanercept was then administered for a further year. On regular follow-up, the patient has been doing well, except for a ferritin level of approximately 2,247 pmol/dm^3.

Discussion

SPLTCL is a type of skin lymphoma characterized by pleomorphic T cells and benign macrophages that infiltrate to subcutaneous tissue, mimicking lobular panniculitis [3]. It is characterized by cutaneous plaques and nodules which are slowly progressive and have a tendency to ulcerate.

SPLTCL is divided into two subtypes: α/β and γ/δ. In 2005, the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) classification of primary cutaneous lymphomas has restricted the category of SPLTCL to tumors expressing the TCR α/β, CD4-, CD8+, CD56-. Cutaneous γδ T-cell lymphoma was restricted that expressing the TCR γ/δ, CD4-, CD8- [1]. This categorization was based on the differences in prognoses between these two, with SPLTCL showing much favorable clinical outcomes [5].

Gayden et al [6] reported in their, recent studies on the cases showing familial predisposition by gene mutation as one of

the causes of SPLTCL and HLH. TIM-3, a gene likely related to SPLTCL, is a transmembrane protein expressed by CD8+ T cells and natural killer cells, and a negative immune checkpoint through interactions with cognate ligands included galectin-9 [6,7]. Tyr82Cys and Ile97Met at TIM-3 are the most commonly found mutations in SPLTCL. These two variants induce protein misfolding and membrane expression failure in T cells and monocytes, leading to persistent immune activation and increased production of inflammatory cytokines, promoting SPTCL and HLH [6]. Thus, these authors insisted to consider that immunosuppression and more novel agents targeting IL-1 and IFN-γ when the TIM-3 mutation is identified in children with SPLTCL and HLH [6].

The prognosis is poor in malignany-related HLH [8]. Probably the treatment intensity could have been too intensive for induction period. When HLH and malignancy are accompanied, the delay in the diagnosis of HLH due to clinical similarity may also be a contributing factor [9].

Standard therapeutic options for SPLTCL have not been established, and protocols as various as CHOP (cyclophosphamide-vincristine-doxorubicin-prednisolone), SMILE (steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide), NHL-BFM-90, and stem-cell transplantation have been tried [2,4]. CHOP has recently been reported to have little effect. SPLTCL with HLH is a rare disease in children. NHL-BFM-90 was demonstrated to result in relatively good long-term responses with acceptable toxicity in combined SPLTCL and HLH [3,4].

We suspected the present case of SPTCL accompanying HLH. We reviewed the literature of SPLTCL with HLH in children to determine the treatment options for the patient (Table. 1).

Among 11 reported cases, 5 cases were treated with NHL-BFM-90 protocol, 2 cases with CsA and steroid, 2 cases with CHOP and 1 case each with SMILE or CEOP (cyclophosphamide, epirubicin, vincristine, and prednisone). All of NHL-BFM-90 based protocol induced remission. Among 2 cases of patients treated with CHOP, 1 case was induced in remission and another case was expired.

We selected the combination of the NHL-BFM-90 and HLH-2004 protocols. However, when we analyzed the causes of failed cases, most of them expired during initial induction period, indicating that the intensity of the initial treatment might have been too intensive [8].

In addition, treatment of malignant diseases with HLH are known to show no universal conclusions due to lack of large samples or prospective clinical trials [9]. We started dexamethasone and etoposide as these two drugs are included in NHL-BFM-90 and HLH-2004 protocols. We expected these two drugs would work for HLH as well as SPLTCL and not aggravate stormy cytokine reaction. After induction period, when HLH features were improving and subcutaneous masses were decreasing in size, we used anticancer drugs in the NHL-BFM-90 protocol fully.

After complete resolution of the subcutaneous lesions as well as the most features of the HLH were resolved, hyperferritinemia persisted. We had suspicion of incompleted control of HLH related hyperferritinemia [10]. Thus, we tried etaner-

Table 1. Characteristics of pediatric patients with subcutaneous panniculitis-like T-cell lymphoma accompanied by HLH described in the literature

	Age (y), Sex	Country (reference)	Treatment	Outcome
1	14, F	Japan (Sakurai E. et al [3])	NHL-BFM & ALL-90, auto-PBSCT	In remission at 2y
2	11, M	India (Singh S. et al [4])	NHL-BFM-90	In remission at 6m
3	11, M	Republic of Korea (Kim SJ. et al [13])	Modifying NHL-BFM-90 & HLH-2004	In remission at 5y
4	11, M	India (Medhi K. et al [14])	NHL-BFM-90	In remission at 2y
5	5, F	India (Gupta V. et al [15])	NHL-BFM-90	In remission at 2y
6	13, F	U.S.A (Merritt BY. et al [16])	Bexarotene+prednisolone, SMILE	In remission at 2y
7	7m, F	Singapore (Koh MJ. et al [17])	CHOP x 7, Allo-SCT	In remission at 1y 10m
8	12, M	Singapore (Koh MJ. et al [17])	CHOP x 2, fludarabine x 4	Died of sepsis at 15m after diagnosis
9	19, M	India (Babu V. et al [18])	CEOP	in remission at 9m
10	19, F	China (Zhou JC. et al [19])	CsA, Prednisone	Alive at 66m
11	17, F	Saudi Arabia (Al Zolibani AA. et al [20])	CsA, Prednisolone	Alive at 12m

HLH, hemophagocytic lymphohistiocytosis; NHL, non-Hodgkin lymphoma; BFM, Berlin-Frankfurt-Münster; PBSCT, peripheral blood stem cell transplantation; SMILE, steroid methotrexate ifosfamide L-asparaginase etoposide; CHOP, cyclophosphamide doxorubicin vincristine prednisone; SCT, stem cell transplantation; CEOP, cyclophosphamide epirubicin vincristine prednisone; CsA, cyclosporine A.

cept which is known to inhibit the activity of TNF-α by competitively binding with its cell-surface receptors for further control of HLH [11]. Etanercept has been reported to be useful for controlling inflammatory cytokines in therapy-resistant macrophage activation syndrome [11]. The pathophysiology in secondary HLH and macrophage activation syndrome seems to be similar, with excessive immune activation and hemophagocytosis [11]. Takahashi et al [12] successfully treated lupus-associated HLH with etanercept. Thus, we administered etanercept as an immune system mediator to regulate TNF-α. Administration of etanercept led to moderately decreased serum ferritin, but it did not produce a response as dramatic as we had expected.

In summary, we report a case in which the modified NHL-BFM-90 and HLH-2004 protocols were applied in a child of SPLTCL with HLH, and successfully treated. We tried etanercept to reduce high serum ferritin, with some effect. Thus, further studies are needed for unresolved hyperferritinemia. In children with diagnosis of SPLTCL with HLH, initiation of immediate treatment affects prognosis. Prompt initiation of agents such as dexamethasone and etoposide that can simultaneously control underlying disease as well as secondary HLH could lead to successful results.

Ethics approval

This study was exempted from review by the Institutional Review Board (IRB) of Daegu Fatima Hospital (IRB No. 2022-11-002-007). Requirement for informed consent was waived after review of IRB because it was practically impossible and this study was retrospective design.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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