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Extranodal T-cell/Histiocyte-rich Large B-cell Lymphoma Presenting Primarily on the Skin

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T-cell/histiocyte-rich Large B-cell lymphoma (THRLBCL) presenting primarily on the skin is an extremely rare entity (1). THRLBCL is considered a subtype of diffuse large B-cell lymphoma, and is characterized by a limited number of scattered, large, atypical B cells embedded in a background of abundant T cells and histiocytes (1). In general, THRLBCL mainly affects the lymph nodes and often presents as stage IV disease. Several reports have suggested that stage I extranodal THRLBCL has a good prognosis, while nodal THRLBCL is considered an aggressive lymphoma.

Granulysin is a cationic molecule present in the granules of cytotoxic T lymphocytes (CTL) and natural killer (NK) cells. Granulysin has homology with other cytotoxic molecules of the saponin-like protein family (2). Indeed, several reports have suggested that granulysin lyses a variety of microbes and tumours in conjunction with perforin. Moreover, in addition to eliminating pathogens and tumour cells, granulysin acts as a chemoattractant for monocytes, $CD4^+$ and $CD8^+$ memory T cells, NK cells, and mature monocyte-derived dendritic cells (MoDC) (3). In summary, granulysin has even been reported as a potential therapeutic factor in cancer.

CASE REPORT

A 40-year-old Japanese man presented with a 1-year history of a developing nodule on his leg. On his first visit to our hospital, physical examination disclosed an elastic, hard, 50 × 30 mm, reddish nodule on his right leg, clinically similar to leg-type large B cell lymphoma (Fig. 1). We surgically excised the tumour with a 5 mm margin. Histological findings revealed that atypical large cells densely infiltrated through the upper dermis to the subcutaneous tissue with minimal involvement of the overlying epidermis (Fig. 2A). In addition, numerous small-sized lymphocytes surrounded atypical large cells (Fig. 2B). Immunohistochemical staining revealed that these large cells were positive for CD20 (Fig. 2C), CD79a (Fig. 2D), bcl-2, bcl-6, and MUM-1, and negative for CD3, CD10, CD15, ALK and EBER. Small T cells diffusely positive for CD3 (Fig. 2E) surrounded large atypical cells. Interestingly, these T cells were mainly positive for CD8 (Fig. 2F), and partially positive for granulysin (Fig. 2G) and granzyme B. Atypical large cells were positive for Ki67 (Fig. 2H). Few $Foxp3^{high+}$ cells were scattered in the $CD3^+$ area (data not shown). Southern blot analysis from a skin biopsy revealed monoclonal rearrangement of the immunoglobulin heavy chain gene. A full blood count and biochemical profile revealed normal levels of serum IL-2R (245 U/ml). Serological tests for human immunodeficiency virus (HIV) and human T-cell leukaemia virus type 1 (HTLV-1) were negative. From the above data, we diagnosed this patient as having primary THRLBCL. We screened for possible metastatic lesions with positron emission tomography (PET) and found no evidence of metastasis. After surgical treatment, we administered radiation therapy, 28 Gy in 14 fractions, to his right leg and there has been no sign of local recurrence or systemic lesions for one year.

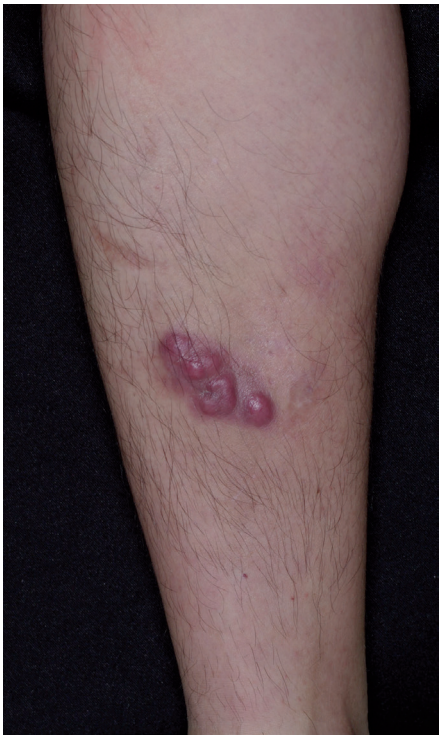

Fig. 1. An elastic, hard, reddish nodule on the right leg, clinically similar to leg-type large B cell lymphoma.

DISCUSSION

THRLBCL presenting primarily on the skin is extremely rare; only 18 cases have been reported previously in the English literature (1). In the World Health Organization/European Organization for Research and Treatment of Cancer (WHO/EORTC) classification of cutaneous lymphomas, diffuse large B-cell lymphomas (DLBCLs) are divided into 2 groups: DLBCLs, leg-type (-LT) and DLBCL, others (-O) (4). In addition, Kodama et al. reported previously that LBCL-O showed a better prognosis compared with other subtypes of LBCLs. THRLBCL is categorized as a variant of LBCL-O, and is known to have a relatively good prognosis (1, 4). Cutaneous Hodgkin's lymphoma, which ir required for a diagnosis of THRLBL, was excluded based on a negative result for CD15 immunostaining. In this report, we shed light on the profiles of T cells infiltrating around the tumour cells of THRLBCL, focusing especially on cytotoxic molecules and immunosuppressive T cells.

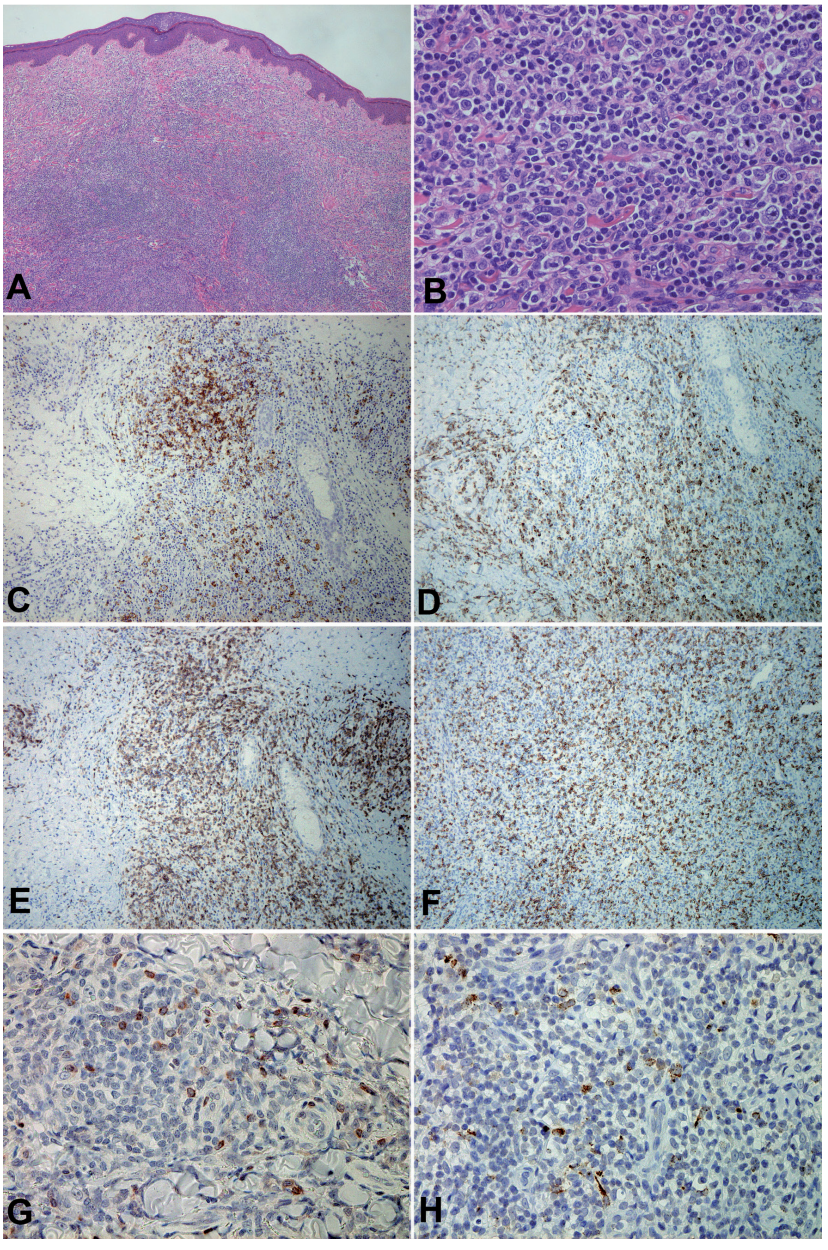

Fig. 2. Atypical large cells densely infiltrated the upper dermis and the subcutaneous tissue with minimal involvement of the overlying epidermis. Numerous small-sized lymphocytes surrounded by atypical large cells (haematoxylin and eosin (H&E) staining, original magnification: (A) ×50 (B) ×400). Paraffin-embedded tissue samples were stained as follows. (C) CD20, (D) CD79a, (E) CD3, (F) CD8, (G) with new fuchsin for granulysin (original magnification (C, D, E, F) ×100, (G, H) ×400) and (H) Ki67. The sections were developed with 3,3-diaminobenzidine tetrahydrochloride.

The expression of granulysin has been reported to correlate with the prognosis of cancer patients. Pagès et al. (5) reported the correlation of granulysin with early metastasis and survival in colorectal cancer. In haematological fields, Kitamura et al. (6) reported the expression of granulysin in systemic anaplastic large cell lymphoma (ALCL), which has a relatively good prognosis. They concluded that the high expression of granulysin might correlate with the biological features of ALCL (6). In the present case, tumour-infiltrating T cells were mainly composed of $CD8^+$ cells, and were positive for granulysin. These data support the hypothesis that the better prognosis of THRLBCL presenting primarily on the skin might be due to the tumour-infiltrating cytotoxic T cells.

Not only cytotoxic T cells, but also immunosuppressive cells, such as regulatory T cells (Tregs), myeloid derived suppressor cells (MDSC), and M2 macrophages play a role in maintaining the tumour environment (7, 8). The role of Tregs is currently an area of interest in the field of human disease pathogenesis. The high frequency of Tregs in patients with carcinomas reportedly contributes to lymphocyte dysfunction, leading to the suppression of anti-tumour immune responses (9). More recently, Felcht et al. (10) reported the induction of $Foxp3^+$ Tregs in DLBCL-LT, and the expression of Foxp3 even on the tumour cells of DLBCL-LT. Although the correlation of expression levels of Foxp3 with the prognosis of lymphoma is still controversial, Tregs may be connected with immune-tolerance and suppressed recognition of tumour antigens in tumour progression and recurrence together with immunosuppressive macrophages. In the present case, few $Foxp3^{high+}$ cells were scattered in the $CD3^+$ area, which might also suggest that this represents a good prognostic factor in THRLBCL.

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