Haemophagocytosis-related Intravascular Large B-cell Lymphoma Associated with Skin Eruption

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The World Health Organization (WHO) classification of haematopoietic tumours defines intravascular large B-cell lymphoma (IVLBCL) as an extranodal, diffuse, large B-cell lymphoma characterized by the presence of neoplastic lymphocytes only in the lumina of small vessels, particularly capillaries (1). IVLBCL has two clinical subtypes: Western variant (classic type) and Asian variant (haemophagocytosis-related type) (2). Classic type IVLBCL, which occurs mostly in patients diagnosed in Western countries, displays a relatively high frequency of central nervous system and skin involvement (3). In contrast, Asian variant patients preferentially show haemophagocytotic syndrome (HPS), bone marrow involvement, fever, hepatosplenomegaly, and thrombocytopaenia (4). This difference may stem from ethnic differences associated with the production of inflammatory cytokines: soluble interleukin-2 receptor (sIL-2R) levels are significantly higher in patients with haemophagocytosis-related IVLBCL than in patients with classic IVLBCL (5). In a recent analysis of patients with IVLBCL in Asian countries, all cases of CD10-negative IVLBCL were categorized as non-germinal centre types (6). By comparison, 20% of classic IVLBCL cases were classified as germinal centre B type in an immunophenotypic analysis of cases. In Japan, CD5-positive IVLBCL was associated with a higher prevalence of marrow/blood involvement and thrombocytopaenia and a lower frequency of neurological abnormalities among CD10-negative patients (6, 7). Haemophagocytosis-related IVLBCL patients have not only been reported in Asian countries; a few cases have been described in Western countries (8). Cutaneous involvement is rare in IVLBCL in Asian countries; only a few cases of cutaneous variant have been reported in Japan (9). We describe here a rare case of a Japanese patient with IVLBCL with associated HPS and erythema.

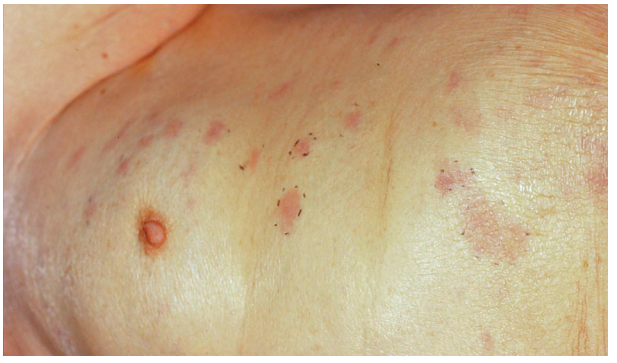

Fig. 1. Multiple, scattered erythema patches on the chest and back, not associated with pain, tenderness or telangiectasias.

CASE REPORT

A 79-year-old Japanese woman was referred to us from another hospital with a fever of unknown origin that had begun one month previously. The multiple, scattered erythema patches appeared on her trunk and thighs at the first examination (Fig. 1). A skin biopsy specimen demonstrated the presence of atypical, large lymphoma cells in thin-walled and ectatic vessels of the dermis and subcutaneous tissues (Fig. 2a). Immunohistochemical staining with antibodies to CD20 and CD79a was positive (Fig. 2b). CD3 and CD5 were negative. These results led us to a diagnosis of IVLBCL. Laboratory studies revealed mild anaemia (haemoglobin 10.5 g/dl), thrombocytopenia (platelets 73×10^6/ml), and high serum lactate dehydrogenase (1296 IU/l), ferritin (1540 ng/ml; normal <138 ng/ml), sIL-2R (6779 U/ml; normal <587 U/ml), and C-reactive protein (17.2 mg/dl; normal <0.3 mg/dl). A bone marrow biopsy specimen showed mild haemophagocytosis (Fig. 3) and clustering of tumour cells without chromosome abnormalities. Whole-body computerized tomography revealed hepatosplenomegaly, but no mass formation in any other organs. The fever of unknown origin, anaemia, thrombocytopenia, high serum lactate dehydrogenase, ferritin, and sIL-R2 levels, as well as the presence of mild haemophagocytosis and hepatosplenomegaly and lack of masses in other organs, are specifically associated with HPS (10). These results fulfilled the diagnostic criteria of haemophagocytosis-related IVLBCL (2, 4). The patient was given

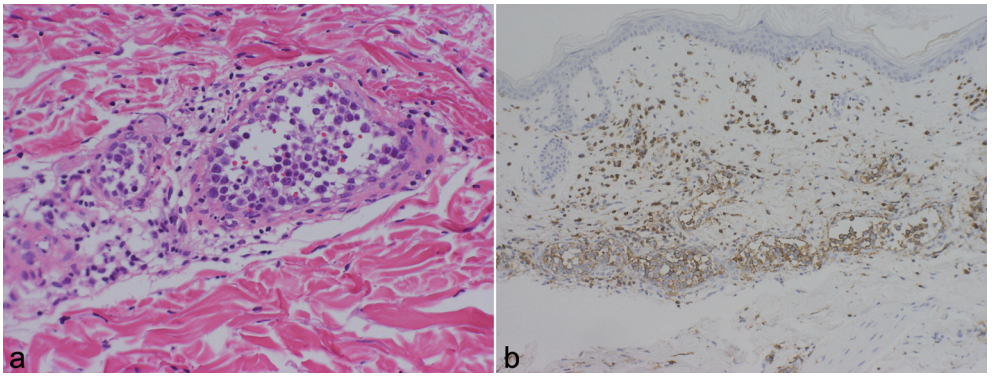

Fig. 2. (a) Atypical, large lymphoma cells infiltrating vessels in the skin (haematoxylin and eosin stain; original magnification, ×200). (b) Lymphoma cells positive for CD20 (original magnification, ×100).

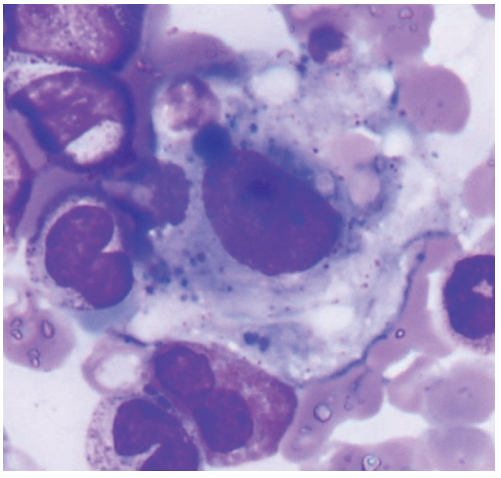

Fig. 3. Bone marrow smear showing a large haemophagocytic histiocyte with cytoplasmic vacuoles (Giemsa stain × 300).

several courses of a combined rituximab and cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (R-CHOP) regimen. The erythema began to disappear within 2 weeks of the administration of chemotherapy. The patient achieved a complete response and showed no recurrence one year after chemotherapy, due to prompt diagnosis and initiation of chemotherapy.

DISCUSSION

Classic IVLBCL frequently presents with dermatological involvement. In an International Extranodal Lymphoma Study Group (IELSG) study, 10 (26%) of 38 IVLBCL patients were diagnosed with the cutaneous variant. Although the cutaneous manifestations of IVLBCL are non-specific, the skin lesions formed are caused by malignant lymphocytes distributed heterogeneously throughout the papillary and reticular dermal vascular plexuses (11). In contrast, haemophagocytosis-related IVLBCL rarely produces skin eruptions (8). HPS, clinically manifested as fever, splenomegaly, and pancytopaenia, includes both primary and secondary disorders. Primary HPS is familial haemophagocytotic lymphohistiocytosis. Secondary HPS can occur in patients with viral, bacterial and fungal infections, autoimmune diseases, and various malignant haematological and non-haematological disorders, or who are being treated with phenytoin (10). Radiological and clinical examinations did not reveal the presence of bacterial or fungal infection in our patient. Moreover, she did not have T-cell lymphoma, and serological studies for Epstein-Barr virus, cytomegalovirus, herpes virus, and varicella-zoster virus did not show active viral infections. She had not been treated with agents linked to HPS. These findings indicated that she had haemophagocytosis-related IVLBCL. This disorder sometimes takes an aggressive clinical course, with a median survival of 2–8 months without skin or central nervous system involvement (6). However, the presence of HPS does not correlate with IVLBCL patient survival. Central nervous system dissemination or relapse and multi-organ failure are associated with poor prognosis in patients with this lymphoma. The combination of rituximab and anthracyline-based chemotherapy could have a positive impact on survival in patients with IVLBCL (5). It has been suggested that chemotherapy plus autologous stem cell transplantation may improve patient outcome (2). Organ biopsies are mandatory for the accurate diagnosis of IVLBCL. Timely and accurate diagnosis is extremely important for patients with this disease, because appropriate treatment can improve clinical outcomes. However, no standard procedure for the accurate diagnosis of IVLBCL has been established (9). We consider that observation of skin eruptions and analysis of skin biopsy samples can be useful for making a diagnosis at an early stage in both classic and haemophagocytosis-related IVLBCL. This paper is the first case report of a skin eruption with haemophagocytosis-related IVLBCL.

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