Generalized Edema and Telangiectasia: Unusual Presentation of Intravascular Large B-cell Lymphoma

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Intravascular large B-cell lymphoma is characterized by clusters of large neoplastic B cells within small blood vessels, most commonly in the dermis and subcutis. There is no nodal or parenchymal involvement until late in the disease, and its endothelial tropism is responsible for the variable clinical features. We report the case of a 51 year-old man who presented with fever, altered mental status, generalized edema, and profound telangiectasia. The diagnosis was made by a skin biopsy from the right thigh. Histology revealed ectatic vessels in the superficial dermis and large atypical lymphoid cells filling the small blood vessels in the deep dermis. Immunohistochemical staining showed strongly positive results for CD45 and CD79a. This was a rare case of intravascular large B-cell lymphoma with generalized edema and telangiectasia as the only cutaneous manifestation. (Dermatol Sinica 27: 248-253, 2009)

Key words: Intravascular large B-cell lymphoma, Angiotropic lymphoma, Telangiectasia

INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) was first described by Pfleger and Tappeiner in 1959 as “angioendotheliomatosis proliferans systemisata” and was erroneously thought to be a malignant vascular neoplasm called “malignant angioendotheliomatosis” thereafter. However, further immunochemical and ultrastructural studies had shown these cells are actually neoplastic lymphocytes. Therefore, the term “intravascular (angiotropic) lymphoma” was proposed. Most of the cases involved a B-cell lineage, and only rare cases showed a T-cell phenotype.¹ IVLBCL is a rare, aggressive extranodal non-Hodgkin’s lymphoma, and represents a subtype of diffuse large B cell lymphoma. It is characterized by clusters of large neoplastic B cells within small blood vessels, most commonly in the dermis and subcutis.² There is no nodal or parenchymal involvement until late in the disease, and its endothelial tropism is responsible for the variable clinical features.³

We report a rare case of IVLBCL with generalized edema and telangiectasia as the only cutaneous manifestation.

CASE REPORT

A 51-year-old man presented to our
hospital with a 3-month history of progressive dyspnea and facial edema. He had experienced a fainting event while exercising in a park 3 days before the visit, leaving no neurological sequelae. In addition, dizziness and fever had been noted for 2 days.

On physical examination, the patient had fever up to 38.7°C, altered mental status, generalized pitting edema, along with profound telangiectasia on the trunk and proximal extremities (Fig. 1A, 1B). His condition was initially treated as sepsis, and an extensive work-up for underlying infectious etiologies was performed; however, there was no definite infectious focus found.

Despite various antibiotic and antifungal regimens, persistent laboratory abnormalities during the hospitalization included normocytic anemia with hemoglobin ranging from 7.9 to 11.7 gm/dL and mean corpuscular volume ranging from 80.5 to 82.8 /fl, hypoalbuminemia with albumin ranging from 0.7 to 2.5 gm/dL (3.5-5.0), elevated lactate dehydrogenase up to 637 U/L (135-225), increased C-reactive protein up to 22.76 mg/dL, and elevated ferritin ranging from 780.6 to 962 ng/mL (27-300).

A diagnosis of an occult neoplasm, such as lymphoma, had been strongly suggested. Nevertheless, imaging studies including whole-body computed tomography scan and brain magnetic resonance imaging, plus bone marrow biopsy all showed no evidence of malignancy.

Because the cutaneous findings were limited to generalized edema and telangiectasia, a skin biopsy was performed late in the hospitalization, and was taken from the right thigh where telangiectasia was obvious. Histology revealed ectatic vessels in the superficial dermis, and large atypical lymphoid cells filling the small blood vessels in the deep dermis (Fig. 2A, 2B). Immunohistochemical staining showed strongly positive results for CD45 and CD79a (Fig. 3A, 3B), and negative results for CD3, CD56, myeloperoxidase, terminal deoxyribonucleotidyl transferase, and Epstein-Barr virus. These findings were consistent with a diagnosis of IVLBCL. However, the patient passed away because of profound shock before a combination chemotherapy for lymphoma could be started.

DISCUSSION

It is difficult to make a correct diagnosis of intravascular large B-cell lymphoma because of its heterogeneous clinical manifestation, nonspecific laboratory findings, and subtle histologic evidence. Our case is an excellent example of this problem.
The variable clinical presentation is attributed to possible occlusion of the small vessels in nearly every organ. The most common features can be categorized as follows: neurologic symptoms and signs, cutaneous presentation, fever of unknown origin (FUO), and hemophagocytic syndrome. Involvement of other organs, including the heart, lungs, adrenal glands, liver, spleen, gastrointestinal tract, kidneys, and urinary tract, has also been reported.

The cutaneous presentation can take the form of erythematous maculopapules, indurated noduloplques, hyperpigmented patches, tumors, ulcers, purpura, telangiectasia, or “peau d’orange”-like changes on the trunk and proximal extremities. The most common etiologies of FUO in adults include infections, connective tissue diseases, malignancies, and drugs. Furthermore, lymphoma is the most common in the subset of malignancies. FUO appears approximately in 45% of patients with IVL-BCL. It often arouses an exhaustive search for an infectious etiology, contributing to a delay in diagnosis. Our patient had consistent clinical features including FUO, altered mental status, telangiectasia, and generalized edema. Although telangiectasia and generalized edema had been observed previously in several cases, they were mostly accompanied by other cutaneous features, such as indu-
rated noduloplaques, or “peau d’orange”-like changes. Unlike these cases, the cuta-
neous findings of our patient were not striking enough to prompt the diagnosis of IVLBCL before the pathology report from the skin biopsy. Furthermore, we also spent a great deal of time in searching for an underlying infectious focus that would account for the FUO in our patient. This was the primary reason why the correct diagnosis was made late in the course.

Hemophagocytic syndrome occurs almost exclusively in Asian patients, and is reported especially in the Japanese literature. In contrast to cases of IVLBCL in western patients, involvement of the reticuloendothelial system and the bone marrow are often observed with resultant anemia, thrombocytopenia, and hepatosplenomegaly. Neoplastic lymphocytes and hemophagocytosis can usually be found in a specimen of bone marrow biopsy. However, neither hemophagocytic syndrome nor involvement of the bone marrow was observed in our patient.

Laboratory findings are not specific for but indicative of IVLBCL. Elevated serum LDH, β2-microglobulin, anemia, and elevated erythrocyte sedimentation rate rank among the most common abnormalities. Thrombocytopenia, leukopenia, and hypoalbuminemia occur less often. Generally, lymphoma cells are reported to be absent in peripheral blood. In our patient, associated laboratory abnormalities including anemia, hypoalbuminemia, elevated LDH, and increased CRP (supposedly parallel to elevated erythrocyte sedimentation rate) were found. Although a diagnosis of lymphoma was suspected on the basis of the clinical data described above, it had been supported neither by imaging studies (whole body CT scan and brain MRI) nor by the bone marrow study. This was the second reason for the delay in diagnosis.

The histologic finding comprises intravascular occlusion of small vessels in the deep dermis and subcutis by large, atypical, hyperchromatic cells, and possible fibrin thrombi. Immunophenotype mostly shows a proliferation of B cell with positive staining for CD45, CD20, CD79a, HLA-DR, and Ki-67. Although our case was histologically consistent with IVLBCL, the microscopic findings were so minor that they might be easily have got unnoticed. This was the third reason for the difficulty in reaching the correct diagnosis.

A lower threshold for ordering a skin biopsy has been suggested because the definitive diagnosis is made by histology and immunohistochemical staining. A random or blind skin biopsy is advocated by some authors when IVLBCL is suspected even in the absence of cutaneous findings. Because microscopic findings are subtle and can easily be overlooked, multiple skin biopsies may be needed.

Anthracycline-based combination chemotherapy is recommended for IVLBCL with an 60% overall response rate, and a 3-year survival rate of more than 30%. The most popular and well accepted regimen is a combination of cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (oncovan), and prednisolone, denoted as CHOP. Recently, more and more authors have asserted that adding newer biological agents, such as the CD20 monoclonal antibody, Rituximab, to traditional CHOP (R-CHOP), may improve patients’ survival.

In summary, IVLBCL is indeed a great imitator in the field of oncology. As we found in our patient, who had nonspecific neurological abnormalities, nonspecific cutaneous findings, fever of unknown origin, along with negative evidence of lymphoma in imaging studies and bone marrow biopsy, it is a challenging task to promptly establish a correct diagnosis in time. Therefore, a skin
biopsy or even multiple skin biopsies should be performed. An early diagnosis and timely treatment with newer regimens of chemotherapy (e.g. R-CHOP) may produce a better outcome.

REFERENCES

以全身水腫及血管擴張為皮膚表現的罕見血管內大型B細胞淋巴瘤

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血管內B型大淋巴球淋巴瘤是一種在小血管內充滿大型腫瘤性B細胞的淋巴瘤。最常表現在真皮層及皮下組織的小血管。除非進展到疾病後期，否則一般不會有淋巴結或其他器官實質的侵犯。臨床表現非常多樣化，是由于腫瘤細胞容易侵犯各器官內小血管的內皮細胞所致。我們報告一個五十一歲的男性，其臨床表現為發燒、意識改變、全身性水腫、以及顯著的微血管擴張。我們在其右側大腿的病灶施行皮膚切片。病理下可見表淺真皮層有擴張的血管以及深部真皮層的小血管內充滿大型的腫瘤性淋巴球。免疫化學染色呈現CD45及CD79a陽性反應，進一步證實其為B淋巴球。這是血管內B型大淋巴球淋巴瘤一個罕見的病例，在皮膚上的表現只有全身性水腫及血管擴張。（中華皮誌: 27: 248-253, 2009）