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LETTER TO THE EDITOR

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Successful treatment of relapse of an intravascular B-cell lymphoma with rituximab-CHOP polychemotherapy

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In intravascular (angiotropic) lymphoma, malignant, mainly B-cell proliferation presumably can be found within the small vessels of the skin or the central nervous system [5]. Obliterations of capillaries, venules, and small arteries are responsible for the clinical signs. Erythematous papules, teleangiectasias, and paresthesias as well as other bizarre neurological signs can be seen [8]. During progression secondary organ involvement could also appear. Most of the cases are diagnosed by postmortem examination.

Our patient, a 79-year-old female, had suffered from hypertension since 1994. She was treated in many outpatient facilities because of hemihypesthesia, short aphasic episodes, lower limb paresthesias, and painful erythematous papules of the skin. She received topical corticosteroid treatment for her skin lesions.

She was admitted to the Dermatological Department of our hospital in 1998 because of generalized teleangiectasias, edema, and "orange-like" skin phenomenon. There was no palpable hepatomegaly, splenomegaly, or lymphadenomegaly. The computed tomography (CT) scan of the whole body was negative. Laboratory tests showed highly elevated lactate dehydrogenase levels (5804 U/l, normal range: 230–460 U/l), elevated serum β_2-microglobulin (5.17 mg/l, normal range: 0.9–2.5 mg/l) levels, and accelerated sedimentation rate (32 mm in 1 h). Blood test showed mild anemia (red blood cell count: 3.69×10^{12}/l, hemoglobin level: 10.5 g/dl, packed cell volume: 0.32). The platelet count was 126×10^{12}/l, and the total protein was 53 g/l with albumin content of 33 g/l. The examination of peripheral blood smear and bone marrow aspiration revealed the existence of a malignancy-associated secondary myelodysplasia. We did not find any cytogenetic aberrations. Serology for *Borrelia burgdorferi* was negative. The histopathological analysis of the skin biopsy specimen from the abdominal skin lesion revealed perivascular lymphoid infiltration. Numerous dilated capillaries were seen in the dermis containing many huge atypical centroblast-like lymphoid cells with nuclei containing one or two nucleoli. Fibrin deposits were seen between the intravascular cell groups. According to the immunohistochemical analysis, intravascular cells were identified as $CD45^+$, $CD20^+$, $CD79a^+$, and $HLA\text{-}DR^+$ B-cells with high proliferation (MIB-1) activity (Table 1).

Right after the proper diagnosis, the patient received systemic treatment with psoralen ultraviolet A-rays (PUVA) and then chlorambucil 2×5 mg weekly. Her edema and teleangiectasias disappeared, laboratory parameters normalized, neurological symptoms ended, and she achieved complete remission.

The patient relapsed with almost the same symptoms described above in 2000. After administration of three cycles of CHOP chemotherapy, complete remission was achieved again. Maintenance therapy with interferon-alpha (3×4.5 MIU/week) was applied successfully.

The patient was admitted to our department because of a 1-week history of left leg swelling in May of 2003. At admission she had aphasia, hemihypesthesia of the left side, and multiple teleangiectasias on the chest, abdomen, and the lower extremity (Fig. 1). Color-coded Doppler ultrasonography showed a deep vein thrombosis in the iliofemoropopliteal region of the left leg combined with

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Table 1 Immunohistochemical findings. *NK* natural killer, *EBV* Epstein-Barr virus

CD	Specificity	Result
CD45	Leukocyte common antigen	+
CD20	B cells, some macrophages	+
CD79a	B cells	+
CD34	Endothelial cells, some lymphoid precursor cells	−
CD3	T cells	−
CD45RO	T cells, some macrophages, granulocytes	−
CD30	Activated T and B cells, some macrophages	−
CD68	Macrophages	−
HLA-DR	Pre-B, B cells, monocytes (T, NK cells)	+
MIB-1 (Ki-67)	Proliferation	+
LMP-1	EBV virus genome	−

femoral arterial involvement. Lymphadenomegaly or splenomegaly was not found. The CT scan revealed multiple lacunar brain infarcts and hepatomegaly, but no abnormality in the lung. Laboratory test results were as follows: blood sedimentation rate 42 mm in 1 h, serum lactate dehydrogenase 2322 U/l, serum β_2-microglobulin 8.7 mg/l, white blood cell count 3.1×10^9/l, hemoglobin level 11.5 g/dl, and platelets 161×10^{12}/l. Histopathology of the skin biopsy specimen revealed relapse of the intravascular B-cell lymphoma.

Based on the CD20 positivity of the intravascular lymphoma cells [3], we decided to use rituximab-CHOP combination therapy (rituximab 600 mg, doxorubicin 80 mg, vincristine 2 mg, cyclophosphamide 1200 mg, and methylprednisone 100 mg for 5 days). After three cycles of treatment, the patient's complaints ceased including the neurological and dermatological symptoms and she achieved complete remission again (Fig. 2). Molecular analysis of the bone marrow and peripheral blood did not reveal clonal immunoglobulin gene rearrangement. The laboratory parameters were also normalized.

Intravascular lymphoma is a rare extranodal subtype of large cell lymphoma resulting in multifocal vascular occlusion and concomitant diffuse thrombosis. Many organs can be affected by intravascular lymphoma, but skin and brain vasculatures are especially susceptible causing a high incidence of neurological and cutaneous involvement. The organ specificity and intravascular localization of this lymphoma is an unexplained issue and the lack of homing receptors and adhesion molecules (CD29, CD54) from lymphoma cells and specific binding affinities of affected vessels hypothesized [2, 9].

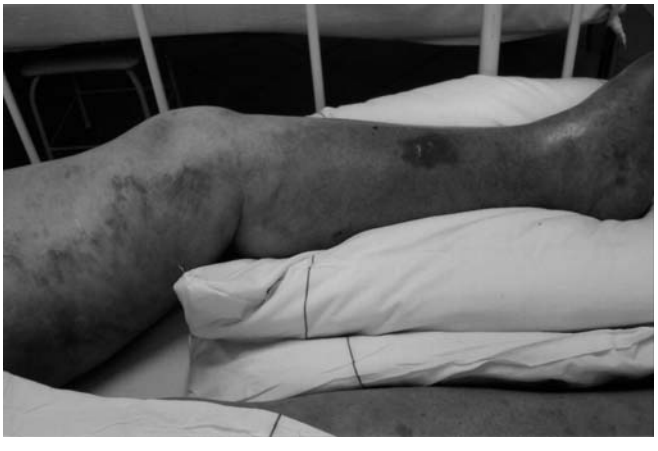

Fig. 1 Generalized teleangiectasia and a hemorrhagic bulla formation on the edematous left lower extremity

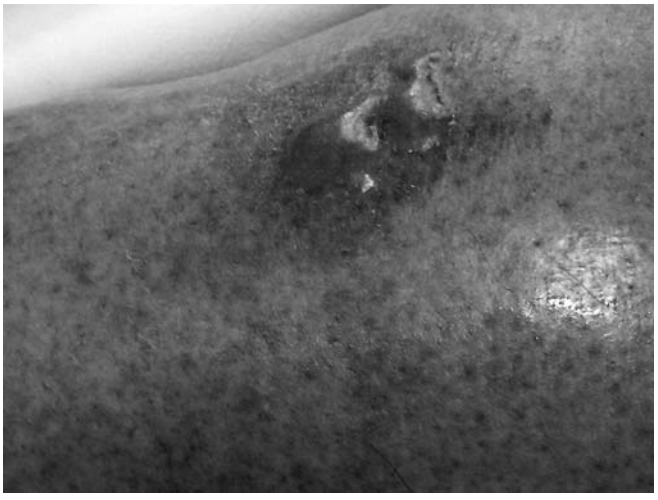

Fig. 2 Disappearance of teleangiectasias and partial resolution of the bulla of the left leg

The literature shows that therapy of intravascular lymphoma is composed of irradiation, corticosteroid, PUVA treatment, and chemotherapy. The CHOP protocol seems to be the best choice [1] and autologous peripheral stem cell transplantation had also been performed [7]. Unfortunately, due to the poor response to the aforementioned treatments, the usual clinical course of intravascular lymphoma is extremely aggressive and new treatment options are desperately needed. Successful treatment of our reported patient suggests that rituximab could be used as a valuable treatment option in the salvage therapy of CD20-positive angiotropic lymphoma. This proposal offered in our report is in accordance with new findings about the efficacy of rituximab-containing regimens in the (re)treatment of this clinical entity that were published independently during the preparation and revision of this manuscript [4, 6, 10].

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