

Intravascular Large B-cell Lymphoma: Successful Therapy with Bendamustine and Rituximab

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Sir,

Intravascular large B-cell lymphoma (IVLBCL), also termed “angiotropic lymphoma” (1) is a rare aggressive disease characterized by a malignant proliferation of large neoplastic B lymphocytes within the lumina of small-to-medium-sized vessels, causing vascular occlusion of venules, capillaries and arterioles. IVLBCL was originally believed to represent a vascular neoplasm. Later studies confirmed the lymphomatous nature of IVLBCL by immunohistochemical markers of the malignant cells as well as the presence of immunoglobulin gene rearrangement (2). Due to the initial classification as a vascular neoplasm, a number of historical terms have been used to describe this form of B-cell lymphoma, including “neoplastic angioendotheliosis”, “malignant angioendotheliomatosis” and “angiotropic large cell lymphoma” (2). In the WHO-EORTC (2005) classification, IVLBCL is a rare subtype of primary cutaneous diffuse large B-cell lymphoma representing less than 1% of all cutaneous lymphomas. Only 6 cases of IVLBCL were registered at the Dutch and Austrian Cutaneous Lymphoma Group (3). Between 1985 and 2003 the International Extranodal Lymphoma Study Group (IELSG) had provided data for 38 haematological patients with IVLBCL. Among the 30 patients diagnosed pre-mortem, only 12 were classified as having the cutaneous variant of this disease (4). Isolated skin involvement is rare and appear invariably in females with a normal platelet count. The primary involvement of the skin has been suggested to have a significantly better prognosis overall (for review see (5)). More often, IVLBCL is disseminated at primary diagnosis, predominantly affecting elderly patients and involves the central nervous system, lungs, bone marrow and kidneys (4, 6).

CASE REPORT

A 79-year-old woman presented with a painful indurated, violaceous, haemorrhagic and partially teleangiectatic plaque on the left medial thigh for several months (Fig. 1A). Three months prior to presentation, the patient had noticed a small bluish patch on her left thigh that rapidly increased in size. Lymph node enlargement was subsequently observed by the patient 3 months later. On examination the patient's neurological status was normal, and anaemia, leucopaenia, thrombocytopaenia, or hepatosplenomegaly were absent. However, increased serum lactate dehydrogenase (LDH: 6.14 $\mu\text{mol/l}$ (normal 2.25–3.55 $\mu\text{mol/l}$) and C-reactive protein (CRP: 20.2 (normal <5)) were noted. Lymphoma staging procedures comprising abdominal and thoracic computerized tomography (CT scans) and magnetic resonance tomography (MRT) of the brain excluded involvement of any other organ. Except for the involvement of the skin, the inguinal lymph node enlargement was the only extracutaneous manifestation of IVL-

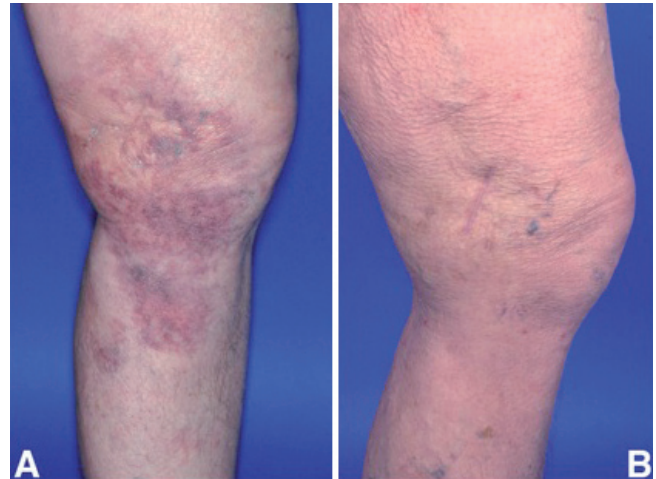


Fig. 1. (A) Intravascular large B-cell lymphoma of the skin. A painful indurated, violaceous, hemorrhagic and partially teleangiectatic plaque is visible on the left medial thigh. (B) Complete remission of IVLBCL after 6 cycles of a combination therapy of bendamustine and rituximab.

BCL. The Ann Arbor disease stage was IV_{AX} and in the International Prognosis Index (IPI) of our patient was 3, indicating an intermediate to high risk with respect to 5-year survival (5).

Dermatohistopathology revealed a proliferation of large atypical lymphocytes that were restricted to dilated blood vessels within the dermis and subcutaneous tissue (Fig. 2A). Neoplastic cells were positive for CD20 (Fig. 2B), CD31 (Fig. 2C), CD79 α , Bcl-2, CD11a, and leukocyte common antigen (LCA), but were negative for CD5, Bcl-6 and CD10. Ki67 positivity was > 80%, indicative of a high proliferative potential. Histology of the extirpated left inguinal lymph node revealed an infiltrate of large immunoblasts, which were positive for CD20, CD79 α and Bcl-2, whereas these cells were negative for CD23, cyclin-D1, CD30 and CD138, indicative of an infiltrate of a large B-cell lymphoma.

We diagnosed IVLBCL, primarily involving the skin and, secondarily, the inguinal lymph nodes. Because of the advanced age of our patient as well as the co-morbidities that precluded multi-agent chemotherapy, a combination therapy consisting of 90 mg/m² of bendamustine at day 1 and day 2 and rituximab 375 mg/m² at day 1 was initiated. This therapeutic regimen was repeated every 28 days for 6 cycles. At that time, a complete remission of skin infiltrates (Fig. 1B), as well as of the inguinal lymph nodes, was detected. LDH and CRP decreased to 3.37 and 6.7, respectively. Moreover, chest X-rays and abdominal and lymph node ultrasound were normal. The patient is in complete remission 13 months after the initial diagnosis of IVBCL.

DISCUSSION

Rare primary cutaneous lymphomas, such as IVLBCL, often have a distinct clinical behaviour and prognosis compared with similar systemic lymphomas, which may

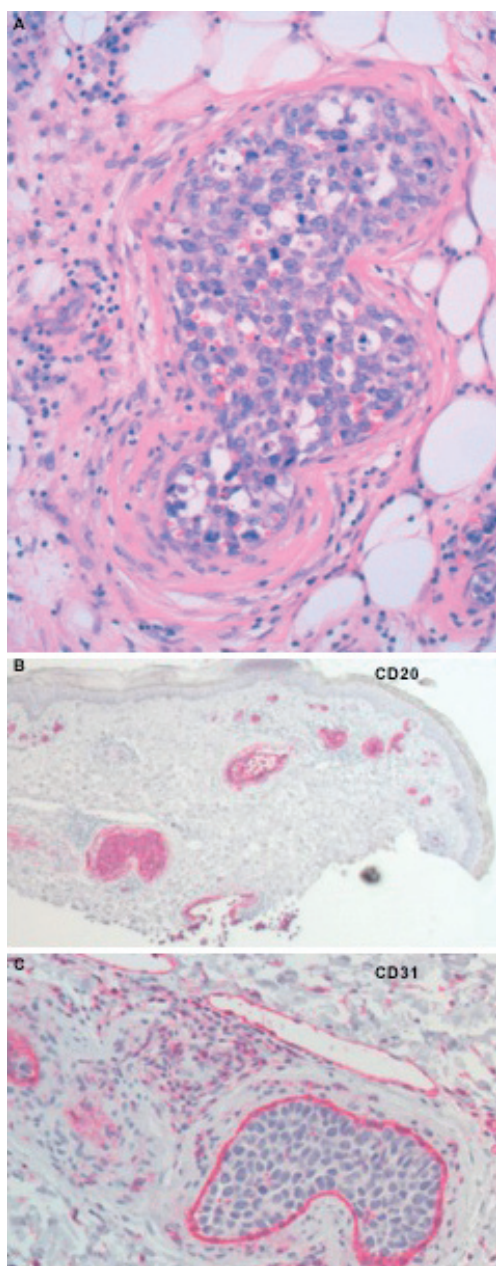


Fig. 2. (A) Dermatohistopathology (haematoxylin and eosin (H&E) $\times 100$). Cytomorphological analysis demonstrates the complete occlusion of the vessels with large atypical cells with high mitotic index and large nuclei. Immunohistological analysis at scanning ($\times 10$; B) or higher magnification ($\times 40$; C). (B) CD20-positive neoplastic cells are located strictly within (C) CD31-positive vessels.

secondarily involve the skin (3). It has been suggested that these lymphomas may require differential treatment (3). For example, IVLBCL patients with isolated skin lesions have a significantly better survival than those with primary systemic involvement (3-year overall survival rate: 56% vs. 22%) (7). The skin and the central nervous system are by far the most common sites of involvement for IVLBCL and may be clinically invisible to the eye (8), or manifest with extremely atypical skin symptoms,

such as generalized teleangiectasias (9). However, any other organ may be involved, making the primary diagnosis of IVLBCL a challenge. The distinction between primary cutaneous and a primary systemic lymphoma may be difficult at times, as in our case. Interestingly, colonization of cutaneous cherry haemangiomas by neoplastic cells as the only presenting sign of IVLBCL has been reported (8). IVLBCL was originally thought to represent a malignant proliferation of endothelial cells. However, the reported factor VIII-related antigen expression in IVLBCL was clouded by the difficulty of distinction of a positive staining of tumour cells from entrapped or adjacent vascular endothelial cells (2). Additionally, electron microscopic studies of Wick et al. (10) in IVLBCL excluded Weibel-Palade bodies, pinocytotic vessels, or microfilaments to further support its vascular endothelial origin. With the advance of immunohistochemical characterization, however, the cell of origin of IVLBCL has been convincingly demonstrated to be of B-cell lineage, including in our case. The detection of CD20-positive blasts only within arterioles and venules (Fig. 2) clearly argues for the diagnosis of primary cutaneous IVLBCL. The reason why the neoplastic B-cells of IVLBCL are confined within the vessels remains unclear. The absence of molecules crucial for adhesion of lymphocytes to endothelial cells and transmigration out of the vessels (CD29, CD54) has been observed in some cases, leading to the hypothesis that neoplastic lymphocytes in IVLBCL are unable to transmigrate the vessel wall (11). More recently, a concept of "homeless" neoplastic B-cells has been proposed (12). Our own immunohistochemical analysis could clearly demonstrate that neoplastic B-cells are strictly confined to CD31-positive vessels, whereas cells did not home within lymphatic vessels (data not shown). Future studies are required to elucidate the exact mechanisms for the lack of evasion of these neoplastic B-cells from the vessels. Potentially, innovative modalities, such as multiple epitope ligand topography (MELK), might further our understanding in this respect even with minute amounts of material (13).

If tolerable, multi-agent chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) is recommended also in patients presenting with skin-limited disease, as in our case (4). Because of the advanced age of our patient and significant comorbidities, CHOP was not considered. More recent retrospective analysis in IVLBCL has suggested that rituximab might prove valuable in this B-cell lymphoma entity (14). The alkylating chemotherapeutic agent bendamustine has recently been advocated as a well-tolerated and synergistically efficient treatment for refractory CD20-positive B cell neoplasms (15). Thus we performed combined immunochemotherapy with bendamustine and rituximab every 28 days, achieving complete remission after 6 cycles.

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