Intravascular large B-cell lymphoma: four case reports from a single centre and review of literature

S. Drieghe, B. Cauwelier, T. Lodewyck, D. Selleslag, J. Van Droogenbroeck, A. Van Hoof, J. Van Huysse, J. Billiet

Intravascular lymphoma is a rare haematological malignancy characterised by neoplastic proliferation of lymphoid cells particularly within the lumina of capillaries, heterogeneity in clinical presentation, disseminated disease with aggressive behaviour and often fatal course. In the present case report, we describe four cases of intravascular lymphoma diagnosed in a single centre over a period of ten years.
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Introduction

The WHO classification of tumours of haematopoietic and lymphoid tissues defines intravascular large B-cell lymphoma (IVLBCL) as a rare subtype of extranodal diffuse large B-cell lymphoma (DLBCL) characterised by the selective growth of lymphoma cells within the lumina of vessels, particularly capillaries, with the exception of larger arteries and veins.[1] Few cases of intravascular lymphoma exhibiting a T-cell or Natural Killer-cell phenotype have been described.[2] The heterogeneity of clinical presentation and lack of detectable tumour mass or lymphadenopathy often hampers timely and accurate diagnosis. This is partly reflected in the fact that an IVLBCL usually presents as a widely disseminated lymphoma with an aggressive and rapid progressive clinical course. In recent years, the increased awareness of IVLBCL has resulted in more patients being diagnosed during life, whereas in the past diagnosis was made postmortem. We diagnosed four cases of this rare lymphoma entity in our hospital over a period of ten years. In this paper we give a description of these four cases as well as a review of the literature.

Case reports

Case 1

A seventy-year old woman presented with a two week history of high fever, rigors, anorexia and abdominal pain. A laparoscopic cholecystectomy was performed as cholecystitis was suspected. However, after surgery she developed dyspnoea, kidney failure, elevated LDH levels and haemolytic anemia (positive direct and indirect Coombs). Peripheral blood analysis revealed a low haemoglobin (9,7 g/dL), normal white blood cell count (9,9.10^9/L) with a slight lymphopenia, severe thrombocytopenia (27.10^9/L) and elevated transaminases. As her serum LDH level rapidly raised to 11.955 U/L, a haematological disorder was suspected and a bone marrow trephine biopsy and aspirate were performed. Cytomorphologic

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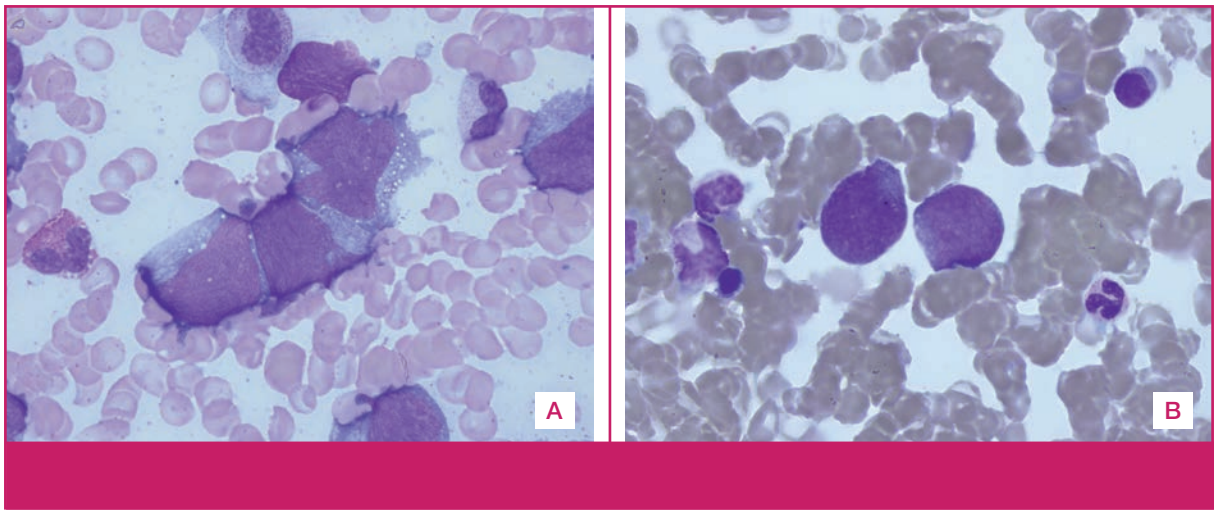

Figure 1. A-B (May-Grünwald-Giemsa stain x 1000) Cytomorphologic aspects of the neoplastic cells in a bone marrow smear from two different patients: large, atypical lymphoid cells, often with one or multiple prominent nucleoli, strongly basophilic cytoplasm and an intermediate to high nuclear-cytoplasmic ratio.

evaluation of the bone marrow smear revealed 40% atypical large sized lymphoid cells *(Figure 1A)*. Histopathologic evaluation of the bone marrow biopsy confirmed the presence of neoplastic lymphoid B-cells (CD20+/CD79a+), showing expression of BCL2 and absence of CD10/CD3/BCL6 on immunohistochemical staining; CD31 confirmed the intravascular localisation of the lymphoma cells *(Figure 2A-C)*. Flowcytometric analysis demonstrated a CD5 and CD10 negative B-cell population (CD19+/CD20+) with restriction for kappa light chain surface immunoglobulin. Heteroduplex PCR analysis confirmed clonal IgH and IgK rearrangements. Conventional karyotyping methods revealed a pseudotetraploid karyotype with complex deviations of chromosome 17. A laparoscopic biopsy of a retroperitoneal lymph node also showed the presence of a DLBCL. The patient was treated with chemotherapy using the R-CHOP regimen (Rituximab, Adriamycin, Endoxan, Oncovin and Prednison), followed by high dose chemotherapy (BEAM) supported with autologous stem cells. She is currently surviving and has been disease free for nine months.

Case 2

A 48-year old woman was referred because of massive hepatosplenomegaly. She had a one year history of flu-like symptoms, headache, dizziness and fever, followed by episodes of malaise and myalgia. An abdominal echography showed hepatosplenomegaly, ascites and a hypodense nodule in the spleen. Peripheral blood analysis revealed pancytopenia (haemoglobin 7,9 g/dL, platelet count 123.10^9/L and white blood cell count $2,4.10^9$/L with a slight monocytosis), elevated liver enzymes (LDH, AST, ALT and GGT), CRP (7,2 mg/dL) and ferritin (737,7 μg/L). Cytomorphological evaluation of the bone marrow aspirate demonstrated 8% atypical large sized lymphoid cells. There were no morphological features of haemophagocytic syndrome. Histopathologic evaluation of the bone marrow biopsy revealed the presence of neoplastic lymphoid B-cells (CD20+), with positive immunohistochemical staining for BCL2 and absence of CD10/BCL6/MUM1. Additional staining for CD31, CD34 and factor VIII confirmed the intravascular localisation of the lymphoma cells *(Figure 2D)*. Flowcytometric analysis revealed the presence of a B-cell population without restriction for kappa or lambda light chain immunoglobulin. Heteroduplex PCR analysis confirmed clonal IgH and IgK rearrangements. Conventional karyotyping methods showed a normal karyotype (46,XX in 7 mitoses). Cytomorphology and heteroduplex PCR analysis also revealed the presence of the lymphoma cells in bronchoalveolar lavage specimen. She was treated with R-CHOP but died due to a rapidly progressive invasive pulmonary aspergillosis following the first treatment cycle.

Case 3

A 44-year old woman was referred with a history of sustained complaints of mesogastric abdominal pain since several months. CT scan of the abdomen

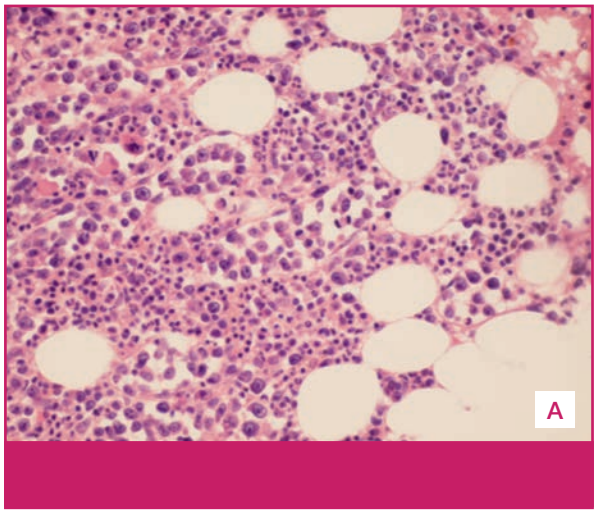

Figure 2A. Bone marrow biopsy revealed the presence of large, atypical lymphoma cells with vesicular nuclei and prominent nucleoli, infiltrating sinusoidal vessels (haematoxylin and eosin stain x 200).

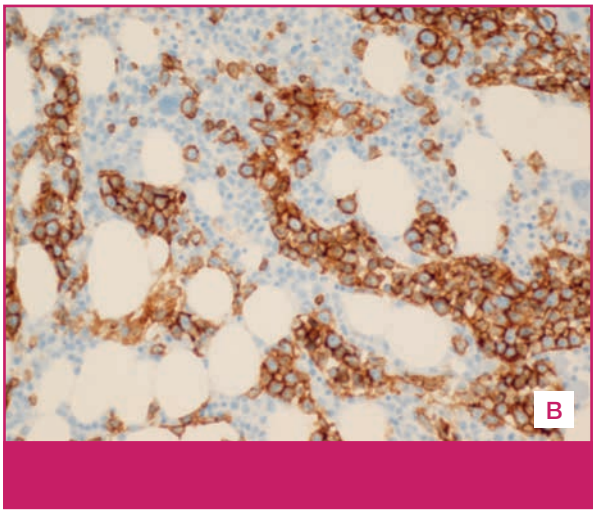

Figure 2B. Immunohistochemical staining for CD20 showed that the lymphoma cells were CD20 positive (haematoxylin and eosin stain x 200).

was suggestive for lymphoma. Her complaints of abdominal pain worsened during the last weeks, and she developed additional symptoms lower back pain, slight weight loss, dyspnoea and night sweats. Physical examination revealed a palpable spleen, no palpable hepatomegaly or lymphadenopathy. A repeat CT scan of the abdomen showed multiple hypodense spleen nodules, variable in size and progressive in comparison with previous images, mesenteric adenopathies in the left hypochrondrium and invagination of the small intestine. Peripheral blood examination showed a normal haemoglobin (13,5 g/dL) and white blood cell count (5,4.10^9/L) with a slight left shift and monocytosis, a marked thrombocytopenia (77.10^9/L) and abnormal liver function tests (AST, ALT and GGT) with a serum LDH of 2794 U/L. Cytomorphologic evaluation of the bone marrow aspirate demonstrated 16% atypical large sized lymphoid cells (*Figure 1B*). Bone marrow biopsy and aspirate revealed a DLBCL (stage IVB) with the presence of a predominant interstitial infiltrate of neoplastic lymphocytes and a concomittant minimal intravascular localisation. Immunohistochemical staining revealed the presence of CD20/BCL2 and the absence of CD3/CD5/CD10/CD34; the proliferation marker MIB-1 was strongly positive (+/- 90% of the neoplastic cells). Flowcytometric analysis did not identify the atypical cells on the scatter plots. Heteroduplex PCR analysis showed clonal IgH and IgK rearrangements. Conventional karyotyping methods showed a normal karyotype (46,XX in 15 mitoses). She was treated with combination chemotherapy with the ACVBP regimen (Adriamycin, Cyclophosphamide, Vindesine, Bleomycin and Prednison), Rituximab and central nervous system prophylaxis (Methotrexate). Until today she is surviving and has been disease free for fifteen months.

Case 4

A 62-year old woman was referred because of fatigue, weight loss and fever. At presentation she showed mental disorientation and loss of decorum. She had been treated for seven weeks with corticosteroids for a posterior scleritis of the right eye. Physical examination only revealed a small nodule at the angle of the left mandible. Laboratory investigations demonstrated LDH elevation of 895 U/L. The titre of ANA (Antinuclear Antibodies) was 1:10240 with a homogenous pattern and the titre of anti-DNA antibodies was 1:160. C3 en C4 were normal and rheumatoid factor was absent. A CT scan showed bleeding in the frontal region of the brain together with multiple small infarcts. Cerebrospinal fluid contained 150 white blood cells per μL with 70% lymphocytes and no atypical cells. Biopsy of the nodulus at the mandible angle revealed two concordant tumours: a myoepithelioma of the parotis together with an IVLBCL. Lymphoma cells were also found on a buffy coat preparation of the peripheral blood and a bone marrow smear. CT scan of the chest and abdomen demonstrated small lymphadenopathies. Fifteen days after admission the patient died from massive pulmonary embolism.

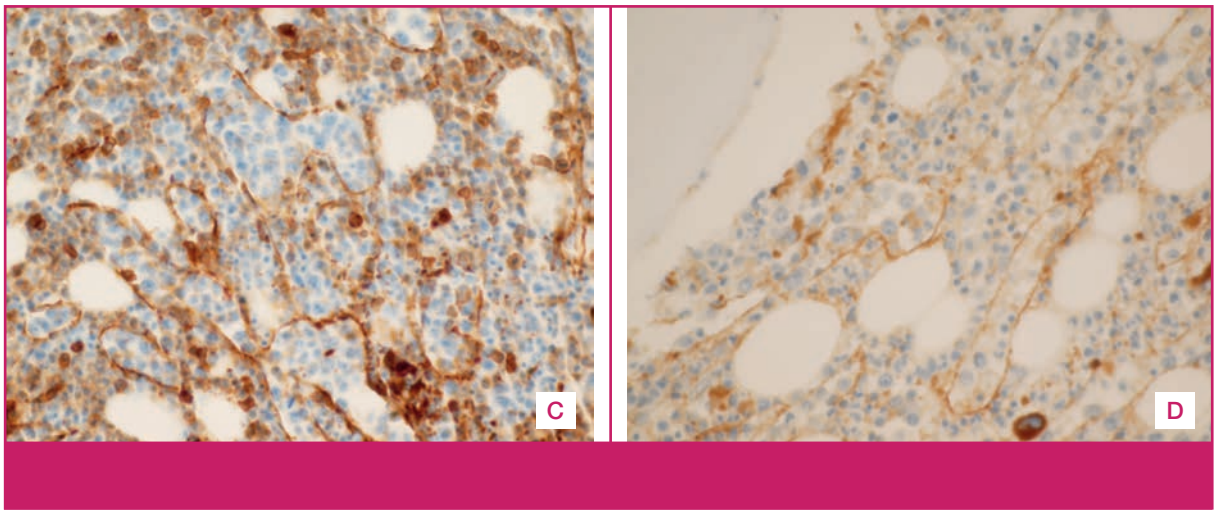

Figure 2. The CD31 (C) and Factor VIII (D) endothelial staining showed that the neoplastic large B-cells were restricted to the sinusoidal vessels in the bone marrow (haematoxylin and eosin stain x 200).

Discussion

The clinical presentation of an intravascular lymphoma is extremely variable and caused by occlusion of small vessels. Two different modes of clinical presentation have been recognized: a Western variant (classic-type) and an Asian variant, each having its own pattern of organ infiltration. Cases diagnosed in Western countries display a relatively high frequency of central nervous system (CNS) and skin involvement, while patients from Asian countries preferentially present with haemophagocytic syndrome, bone marrow involvement, fever, hepatosplenomegaly and thrombocytopenia. A third type of clinical presentation has been described, where lymphoma infiltration is strictly limited to the skin. Almost all patients with this cutaneous variant are females with a good performance status, this in contrast with the other presentation forms without male or female predominance.[5-12] Peripheral blood involvement is rarely observed (5 to 9%).[3] Laboratory findings are usually non specific. Anemia (65%), increased serum LDH and β2-microglobulin concentrations (80 to 90%) are the most frequent observed abnormalities.[5-8,11] Our patients presented mainly with B-symptoms and hepatosplenomegaly. Only one patient showed lymphadenopathy. Despite the fact that all the presented cases were from European-Western origin and thus can be considered as classic-type, they all showed bone marrow infiltration and no skin or CNS involvement. Peripheral blood involvement was only seen in one case in a buffy coat preparation. Infiltration of the pulmonary vascular bed, characterised by hypoxia, dyspnoea and abnormal chest findings was probably the mean reason for decease of two of our four cases.

Diagnosis of intravascular lymphoma is mainly based on cytologic recognition of large atypical lymphoid cells on bone marrow smears. Additional histopathology and immunohistochemistry are necessary to confirm the selective growth of neoplastic lymphoid cells in the lumina of small blood vessels which is demonstrated using endothelial staining such as CD31, CD34 or FVIII. However, a concomitant minimal extravascular localisation of neoplastic cells, usually surrounding involved vessels, may occasionally be observed.[4] Intravascular neoplastic lymphocytes can also be found in other lymphoproliferative disorders (such as rare cases of splenic marginal zone lymphoma), either as a predominant feature or in association with a predominant extravascular component. The small tumoural cell size allows an easy distinction between these lymphomas and IVLBCL.[3] Our third case revealed some diagnostic difficulties as there was limited intrasinusoidal infiltration of large sized neoplastic cells associated with a predominant interstitial marrow infiltrate. Ponzoni et al (2007) propose to consider these cases as highly suggestive for IVLBCL, especially if diagnosis is made through core biopsy. In clinical practice treatment strategy is similar for DLBCL and IVLBCL, bearing in mind the less favourable prognosis when IVLBCL is suspected. However, for the cutaneous variant local therapy (and radiotherapy) could be considered.[3]

In contrast to the well described spectrum of cytologic characteristics of IVLBCL cells on haematoxylin and eosin stained smears (large cells with vesicular nuclei, prominent nucleoli, frequent mitotic figures, or coarse nuclear chromatin, or irregular and indented nuclei), only limited information is available about the cytomorphologic aspects of these neoplastic cells in May-Grünwald-Giemsa stained bone marrow smears.[1,4] In all four cases presented, the bone marrow aspirate revealed the presence of atypical large sized lymphoid cells (range: 8-40%, *Figure 1A-B*). The lymphoma cells often present with one or multiple prominent nucleoli, strongly basophilic cytoplasm with a strongly basophilic border and an intermediate to high nuclear-cytoplasmic ratio. The cytoplasm may contain small vacuoles.

Tumour cells typically express B-cell antigens such as CD19, CD20, CD22 and CD79a. The reported frequency of CD5 positivity varies considerably (22-75%). A subset of IVLBCL cases also expresses CD10. In most cases the neoplastic cells are reactive for BCL2 with at least 25% of cells being positive for BCL6. Molecular studies have been performed only in a limited number of cases, and most have shown clonal immunoglobulin heavy chain gene rearrangements supporting a B-cell origin.[3,5,6,9] Clonality can also be determined by flow cytometric analysis for light chain surface immunoglobulin distribution. However, flow cytometry is often hampered by the low number of neoplastic lymphoid cells present. In our cases clonality (restriction for kappa light chain surface immunoglobulin) was diagnosed with flow-cytometric analysis in the bone marrow aspirate in only one case where the proportion of infiltrating lymphoma cells was high (40% lymphoma cells). Only limited information is available about chromosomal abnormalities in IVLBCL. Gains or losses involving chromosome 18 and abnormalities of 8p21 and 19q13 have been reported in several case reports.[11, 14]

Conclusion

Clinicians should be aware that intravascular lymphomas may present with atypical clinical symptoms and high serum LDH levels but without obvious lymphadenopathy or without detectable tumour mass. In patients presenting with these findings it is important to perform a bone marrow biopsy. Indeed, in all our patients diagnosis of IVLBCL was made or confirmed by bone marrow biopsy.

These case reports illustrate that the presence of (even few) atypical large lymphoid cells on a bone marrow smear may be the first clue pointing to a diagnosis of intravascular B-cell lymphoma, before histopathologic data are available. The recognition of these cells may lead to a more rapid diagnosis of a lymphoma entity frequently missed by clinicians. Earlier diagnosis and treatment of this aggressive lymphoma may have a favourable impact on outcome. The final diagnosis however should still be based on histopathology and immunohistochemistry.

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Key messages:

1. **Keep a possible diagnosis of intravascular lymphoma always in mind despite its rare occurrence. Unexplained fever, elevated LDH, thrombocytopenia, haemophagocytic syndrome, dyspnoea, central nervous system symptoms or skin infiltration are common presenting findings.**
2. **When suspecting an intravascular lymphoma always perform a bone marrow aspirate and bone marrow biopsy.**
3. **Even a few atypical large lymphoid cells on a bone marrow smear may be the first clue pointing to an early diagnosis of intravascular large B-cell lymphoma, before histopathology is available.**
4. **Therapeutic management should be similar to DLBCL with high-risk features. Local therapy (including radiotherapy) could be considered for the cutaneous variant.**

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