Clinical case

Intravascular large B-cell lymphoma with a fulminant clinical course: a case report with definite diagnosis post mortem

M. Fiegl1*, R. Greil1, C. Pechlaner2, J. Krugmann3 & S. Dirnhofer3

1Department of Internal Medicine, Division of Hematology and Oncology; 2Intensive Care Unit; 3Institute of Pathology, University of Innsbruck, Innsbruck, Austria

Received 30 January 2002; accepted 19 February 2002

A patient is described who presented with pancytopenia, splenomegaly and excessively elevated lactate dehydrogenase levels in concurrence with signs of extramedullary hematopoiesis. Although initially considered in the differential diagnostic spectrum, a highly aggressive lymphoma could not be identified before the patient died, 6 weeks after admission. Even an intensive diagnostic work-up including splenectomy and repeated bone marrow biopsies was inconclusive. Finally, the diagnosis of an intravascular large B-cell lymphoma, a highly aggressive clinical subtype of a diffuse large B-cell lymphoma, spreading within vascular structures of multiple organs was established by autopsy. Intravascular large B-cell lymphoma is often not diagnosed before death due to the exclusive intravascular growth pattern of the tumor cells and a fulminant clinical course. The heterogeneous clinical features of this lymphoma subtype are discussed.

Key words: angioendotheliomatosis, angiotropic lymphoma, intravascular lymphoma, splenomegaly

Introduction

Intravascular large B-cell lymphoma is a rare subtype of extranodal diffuse large B-cell lymphoma [1]. It is characterized by the presence of lymphoma cells only in the lumina of small vessels, particularly capillaries. Formerly, the disease was named malignant (systemic) angioendotheliomatosis, and, after the lymphoid origin of the infiltrating cells was recognized, intravascular malignant lymphomatosis [2, 3]. It corresponds to angiotropic large cell lymphoma in the Dukes-Collins classification and to angio-endotheliotropic (intravascular) lymphoma in the Kiel classification. In the recently published WHO classification, it is classified as a distinct clinico-pathological subtype of diffuse large B-cell lymphoma [1]. Herein, we report a patient presenting with splenomegaly, pancytopenia and high lactate dehydrogenase (LDH) levels in the absence of a detectable tumor in vivo.

Case report

A 62-year-old man with a short history of progressive impairment of general condition, intermittent fever and weight loss was admitted with thoracic pain, diarrhea, oliguria and signs of neuropsychological alteration. Fourteen years earlier, he had been treated for locally advanced laryngeal carcinoma by surgery, cisplatinum-based chemotherapy and irradiation. Alcohol abuse was the other remarkable condition in the medical history, and the manifest psychosyndrome was clinically attributed to encephalopathy and/or alcohol withdrawal.

X-ray examinations revealed right-sided pneumonia and both-sided pleural effusions. Sonography demonstrated splenomegaly with a maximum diameter of 22 cm, which, at least partly, was interpreted as a consequence of portal hypertension; the presence of cranial, thoracic or abdominal involvement by tumor or lymphadenopathy, however, was excluded by computed tomography (CT) scan. At admission, pronounced pancytopenia with leukocyte and platelet counts of 1.9 and 73 G/l, respectively, and a hemoglobin level of 10.7 g/dl was measured. In the first differential count, there were 58% segs, 24% lymphocytes, 17% monocytes, 1% eosinophils and 1% basophils; the reticulocyte count was within the upper normal limit (3.3%; 122 G/l). Leukemic blasts were not observed. The most striking laboratory features were massive elevations of LDH (4116 U/l; normal range 120–240 U/l) and of uric acid (12.48 mg/dl; normal range 2.4–7.5 mg/dl), indicating hyperproliferation. Bone marrow examination by both pelvic trephine biopsy and aspiration cytology revealed increased hematopoiesis with reactive atypia. A myelo- or lymphoproliferative disorder or non-medullary (ectopic) infiltration by tumor cells, however, was not detectable. Further differential diagnoses such as an autoimmune disease or a fulminant infection were excluded by clinical, laboratory and microbial examinations.

*Correspondence to: Dr M. Fiegl, Department of Internal Medicine, Division of Clinical Hematology and Oncology, University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria. Tel: +43-512-504-4003; Fax: +43-512-504-4006; E-mail: Michael.fiegl@uibk.ac.at

© 2002 European Society for Medical Oncology
Four days after admission, the patient was transferred to the intensive care unit because of progressive respiratory insufficiency, necessitating ventilation support. Additionally, pancytopenia was aggravated, requiring frequent substitution of erythrocytes and thrombocytes. The appearance of numerous erythroblasts (leukoerythroblastic picture) pointed to a severe disturbance of the bone marrow–blood barrier and/or extramedullary hematopoiesis. A hemato-oncologist was consulted, and, due to the differential diagnoses considered (Table 1), splenectomy and an additional bone marrow biopsy (day 31 after admission) were carried out. Pathohistological evaluation of the spleen, including immunohistochemistry, was diagnostic neither for lymphoma nor a chronic myeloproliferative disorder. The bone marrow showed reactive changes in a hyperproliferative hematopoiesis. Furthermore, there was a scattered infiltration of single atypical, CD20+ lymphoid cells, which, however, did not allow for a definitive diagnosis of lymphoma.

In the period that followed, rapid deterioration with progressive encephalopathy (as determined by electroencephalography and evoked potentials) and multiorgan failure developed, and the patient died on day 35 after primary admission.

In the post mortem evaluation, the following pathological features were noted. Macroscopically, there was excentric cardiac hypertrophy, terminal lung edema and slight hepato-megaly without cirrhosis; there was neither gross lymphadenopathy nor signs of a mass lesion or recurrence of the former larynx carcinoma. Microscopically, the predominant finding was atypical blastoid cells with multiple mitoses, which exclusively proliferated within vascular and sinusoidal structures of lymph nodes, liver, lung or bone marrow (Figure 1A and B). Immunohistochemical staining revealed positivity for the B-cell markers CD20 and CD79a in the absence of staining for T-cell markers. Cytochemistry for myeloperoxidase and hemoglobin A1 was negative. Thus, the definitive diagnosis of a diffuse large cell B-cell lymphoma of the intravascular subtype was made. In a retrospective re-evaluation of the splenectomy and previous bone marrow specimens, a definitive lymphoma diagnosis at that time would not have been possible. At death, the proportion of lymphoma cells infiltrating the bone marrow sinusoids was 20% of all nucleated cells, indicating massive lymphoma expansion terminally (Figure 1C and D).

Discussion

The most remarkable feature of our case is the fact that, despite intense efforts, the definitive histopathological diagnosis of aggressive B-cell lymphoma could not be established before the patient died. Splenomegaly, pancytopenia, erythroblastosis and massive elevation of LDH levels urgently suggested the presence of a hematological neoplasia, in particular a myeloproliferative syndrome or aggressive lymphoma.

---

Table 1. Differential diagnosis and discussion of the combined presentation of pancytopenia, erythroblastosis, splenomegaly and excessively elevated LDH

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Reasons why inapplicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hemolytic anemia</td>
<td>Coombs tests negative; hemolysis parameters other than LDH normal</td>
</tr>
<tr>
<td>2. Low-grade malignancy</td>
<td>Excessively high LDH, therefore improbable</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>CT scans negative for lymphadenopathy</td>
</tr>
<tr>
<td>Splenic lymphoma</td>
<td>Excluded by splenectomy</td>
</tr>
<tr>
<td>Myeloproliferative disease</td>
<td>Bone marrow fibrosis lacking, no pathological megakaryocytes</td>
</tr>
<tr>
<td>Idiopathic myelofibrosis</td>
<td>No lymphadenopathy</td>
</tr>
<tr>
<td>3. High-grade malignancy</td>
<td>Pancytopenia unexplained, CT scans negative</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>Leukemic blasts not detectable</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>No bone marrow fibrosis</td>
</tr>
<tr>
<td>Acute myelofibrosis</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Nodal</td>
<td></td>
</tr>
<tr>
<td>Extramedullary</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Endoscopy negative</td>
</tr>
<tr>
<td>Bronchial</td>
<td>Bronchoscopy negative</td>
</tr>
<tr>
<td>CNS</td>
<td>Liquor, CT scans negative</td>
</tr>
<tr>
<td>Skin</td>
<td>No infiltrative skin lesions</td>
</tr>
<tr>
<td>Pleura</td>
<td>Effusion cytology not suspect</td>
</tr>
<tr>
<td>Intravascular</td>
<td>Applicable: excessive LDH elevation; no circumspect lymphoma detectable</td>
</tr>
</tbody>
</table>
Only autopsy revealed the presence of an intravascular large B-cell lymphoma, which obviously progressed rapidly in the final days.

Intravascular large B-cell lymphoma, a subtype of diffuse large B-cell lymphoma in the WHO classification, is a very rare non-Hodgkin’s lymphoma with an estimated frequency of <1% of all lymphomas. Single cases of aggressive lymphoma of T-cell or histiocytic origin with an angiotropic growth pattern have also been reported [2, 4]. Intravascular lymphoma is characterized by nearly exclusive intravascular neoplastic proliferation of B lymphocytes, usually without involvement of lymphoid tissues and peripheral blood. A variant may be primary large cell lymphoma of the splenic sinuses [5]. Intravascular lymphoma usually shows rapid progression and short survival, with at best transient remissions. The very poor prognosis in these patients reflects in part frequent delays in diagnosis and initiation of therapy due to their extraordinary presentation. Exceptions are rare cases diagnosed in an early stage of disease [6–8]. Common symptoms derive from skin or CNS involvement, of which at least one is observed in two-thirds of cases [6]. Treatment-resistant fever of unknown origin and pain syndromes are recurrent findings leading to diagnostic procedures [7, 9]. Since vessels of all organs may be affected, many different signs can be observed [5, 8]. For example, ‘catastrophic’ cases of intravascular lymphoma have been reported, manifesting as adrenal insufficiency, thrombotic microangiopathy, progressive dementia, interstitial pneumonia or multiple organ failure [10–15].

Little is known about the etiology and pathophysiology of intravascular lymphoma. In the case presented here, radiochemotherapy 14 years before lymphoma manifestation may have had an initiating or promoting effect. Interestingly, a similar case of intravascular lymphoma, treated by radiation for carcinoma of the cervix uteri 14 years earlier, was reported recently [15]. Furthermore, intravascular lymphoma is observed repeatedly in patients with transplantation- or HIV-associated immunosuppression [16, 17], and a relationship with Epstein–Barr virus infection was suggested [18]. Low-grade follicular lymphoma with intravascular growth has also been described [19]. Intravascular lymphoma is characterized by an acquired affinity to vascular structures. This may occur by: (i) a specific interaction of adhesion molecules of lymphoma and endothelial cells favoring intravascular proliferation [20]; and (ii) a lack of homing receptors on the neoplastic cells normally trafficking transvascular lymphocyte migration [21].

Figure 1. Post mortem histopathological work-up by which the definitive diagnosis could be established. (A) Hematoxylin–eosin (H&E) stain of soft tissue intravascular lymphoma infiltration. (B) CD20 immunostain of the neoplastic intravascular B lymphocytes. (C) H&E stain of the bone marrow. Note the presence of some interspersed atypical blasts, leading to suspicion of lymphoma infiltration. (D) CD20 immunostain highlights the neoplastic B lymphocytes in the bone marrow.
In conclusion, a highly elevated LDH and pancytopenia without lymphadenopathy, associated with a leukoerythroblastic picture in peripheral blood should prompt the clinician to consider intravascular lymphoma as a possible differential diagnosis (Table 1). The initiation of an intensive diagnostic work-up in that direction is of paramount importance since a potentially curative therapeutic option is available, but only at an early stage of the disease [7, 22].

Acknowledgements

The publication of this work was kindly supported by Novartis Pharma GmbH, Vienna, Austria.

References