Asian Variant of CD5+ Intravascular Large B-cell Lymphoma with Splenic Infarction

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Abstract

A 57-year-old man was admitted with fever and epigastralgia, and presented with splenomegaly and pancytopenia. A CT scan revealed splenic infarctions. There were no lymphadenopathies, skin lesions, or neurological abnormalities. A splenectomy was performed. Bone marrow involvement with hemophagocytosis was noted. The diagnosis of Asian variant of intravascular diffuse large B-cell lymphoma was based on intravascular and sinusoidal distribution of large CD5+ B cells. The patient died of the disease 11 months after onset. To our knowledge, this is the first report of AIVL that presented with splenic infarction. This distinct lymphoma should be included in the differential diagnosis of splenic infarction.

Internal Medicine 42: 105-109, 2003

Key words: hemophagocytic syndrome, intravascular lymphoma, splenic infarction, Asian variant, splenectomy

Introduction

Intravascular large B-cell lymphoma (IVL) is an uncommon lymphoma characterized by the systemic proliferation of neoplastic B-cells within the lumina of small to medium-sized vessels (1). It is well known that IVL often involves the nervous system and/or the skin, but rarely the bone marrow, lymph nodes, liver, or spleen. Non-specific clinical features such as fever, malaise, or respiratory symptoms, and the absence of lymphadenopathy and mass formation, often cause ante-mortem diagnostic difficulties (2).

A new variant of IVL, termed the Asian Variant of IVL (AIVL), is proposed by the authors. This variant is characterized by hemophagocytic syndrome (HPS), usually associated with bone marrow and hepatosplenic invasion, but rarely with neurological abnormalities and skin lesions (3). This distinct subgroup of IVL seems to be prevalent in eastern Asia and may merit separate consideration because of the problems posed in initial diagnosis and subsequent therapeutic approaches. Here, we report an interesting case of AIVL presenting with splenic infarction, which has not been previously documented in the literature.

Case Report

A 57-year-old Japanese man was admitted to Nishio Municipal Hospital in January 2001 due to spiking fevers and left epigastralgia of three weeks duration. A dynamic computed tomography (CT) scan revealed mild splenomegaly and splenic infarctions. In addition to mild anemia (Hb 11.1 g/dl), the CRP and serum lactate dehydrogenase (LDH) were elevated to 189 mg/l and 443 IU/l (normal: 103–238), respectively. Symptomatic therapy including intravenous antibiotics improved his complaints, and the levels of CRP returned to normal; he was discharged on the ninth day after admission. Four months later, a high fever and left epigastralgia recurred. The patient was readmitted with a worsened general condition. Physical examination revealed splenomegaly palpable 5 cm below the costal margin, but no neurological abnormality, skin lesion, lymphadenopathy, or hepatomegaly. His hematological profile was as follows: WBC, 6.8x10^7/ with 59% of neutrophils, 10% of monocytes and 31% of lymphocytes; RBC, 3.64x10^12/; Hb, 10.8 g/dl; platelets 83x10^9/; and fibrin/fibrinogen degradation products (FDP), 12.7 mg/l. Blood chemistry analysis revealed markedly elevated levels of LDH (1,462 IU/l), CRP (127 mg/l), ferritin (>3,000 mg/l) and soluble form of IL-2 receptor α.
chain (33,900 U/ml). The other abnormal laboratory findings were as follows: total protein 52 g/l, serum albumin 29 g/l, alkaline phosphatase (ALP) 1,176 IU/l, gamma-glutamyl transpeptidase (γ GTP) 213 IU/l, aspartate aminotransferase (AST) 49 IU/l, total bilirubin 12 mg/l, sodium 127 mEq/l and chloride 96 mEq/l. Monoclonal-protein was not detected by immunoelectrophoresis. Hepatitis B surface antigen, anti-hepatitis C virus and anti-human T-cell leukemia virus-1 antibodies were undetectable. Re-examination of the abdominal CT scan disclosed enlargement of the spleen and multiple splenic infarctions. A tumor of 4 cm in diameter was also suspected in the liver (Fig. 1). Splenectomy and a liver wedge biopsy were performed to confirm the diagnosis. The spleen weighed 1,130 g. Histologic examination of the spleen showed diffuse infiltration of neoplastic large B cells, mainly in the red pulp (Fig. 2). Interestingly, some of the lymphoma cells were gigantic and convoluted. The diagnosis of IVL was based on the sinusoidal and intravascular distribution of neoplastic large B cells in the liver (Fig. 3). Bone marrow involvement was also noted, with hemophagocytosis of the reactive macrophages (Fig. 4). Immunohistochemically, the lymphoma cells were positive for CD5, CD20 (L-26), CD45 (leukocyte common antigen, LCA) and CD79a, and negative for CD10, CD23, CD30 (Ki-1), and CD45 RO (UCHL-1). Over-expression of cyclin D1 protein was not detected. For the chromosome analysis of the bone marrow cells, hypotetraploidy with complex abnormalities was observed in a chimeric fashion with normal chromosomes (three versus 14, respectively) (Fig. 5). Since the patient’s condition deteriorated rapidly with progression to jaundice, he received systemic chemotherapy consisting of dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC). The high fever disappeared, and LDH returned to normal. However, the level of LDH began to rise again after the
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Figure 5. Chromosome analysis of the bone marrow cells shows hypotetraploidy with complex abnormalities: 81, XXY, +X, −1, −1, −2, −2, add (3) (q11), add (3) q27, −4, −4, −5, del (5) (q2?), −6, add (6) (p21), der (6) add (6) (p21) del (6) (q2?), add (8) (p11) ×2, add (8) (p21), −11, −11, add (12) (q24), −13, −13, add (14) (q32), −16, add 16 (q24), add (19) (p13), add (19) (q13), −20, −22, −22, add (22) (q11), +mar 1, +mar 2×2, +mar 3.

second course of DeVIC, and bone marrow invasion was still suspected. The ensuing chemotherapy, which consisted of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), was temporarily effective. The patient died of the disease 11 months after onset. Neither skin lesions nor neurological abnormalities were seen throughout his clinical course. At autopsy, no enlarged lymph nodes or soft tissue mass lesions were detected. Virtually all organs, including the lung, liver, heart, kidney, gastrointestinal tract, pancreas, adrenal gland, prostate (Fig. 6), testis and epididymis, showed centroblastic lymphoma cells, mainly located within small to medium sized vessels or sinusoids. The central nervous system was not examined.

Discussion

In 1959, Pfleger and Tappeiner described the first case with intravascular lymphoma as an endothelial neoplasm

Figure 6. At necropsy, vessels in the prostate are filled with lymphoma cells (HE stain, ×50).
under the name of “angioendotheliomatosis proliferans systemisata” (4). Later studies, however, unequivocally established the lymphoid nature of this unique disease (2, 5), which predominantly affects small vessels in the skin and/or central nervous system of middle-aged or elderly persons and produces a variable clinical picture (1, 2). Although rare cases of T-lineage intravascular lymphoma have been described (6, 7), most cases with intravascular lymphoma are classified as a subtype of diffuse large B-cell lymphoma (DLBCL), i.e., IVL, according to the revised WHO classification (1). Over 300 cases with IVL have been reported in the world. However, ante-mortem diagnosis of IVL is still difficult, especially when skin lesions or neurological abnormalities are absent, as in the present case (3). On the other hand, it is also suggested that this form of lymphoma is potentially curable when chemotherapy is initiated early (8). Thus, IVL cases associated with unique clinical presentations are worth describing. To our knowledge, this is the first report of IVL that presented with splenic infarctions, although two clinically similar cases were reported from Korea under the diagnosis of DLBL without referring to the presence of the intravascular pattern (9, 10). In the present case, a number of patchy necroses were grossly observed in the resected spleen. These multiple splenic infarctions were speculated to be due to the occlusion or disruption of the sinus and small vessels by the lymphoma cells, although such a phenomenon was not evidently detected in the lesions because of their massive hemorrhagic necrosis. The chief complaints of the present case were fever of unknown origin and left epigastralgia, both of which are probably related to splenic infarction. Interestingly, these initial symptoms temporarily improved. However, they relapsed four months later, when his condition deteriorated drastically. Similar patterns are relatively common in patients with IVL (11).

In addition to the splenic infarction, the present case showed the characteristic features of HPS, such as fever, anemia, thrombocytopenia and splenomegaly. HPS has been reported in association with various malignant conditions, especially with peripheral T-cell lymphoma, nasal NK/T cell lymphoma, anaplastic large cell lymphoma and DLBL including AIVL (12–14). The pathologic diagnosis of IVL was based on the intravascular and sinusoidal involvement of neoplastic large B-cells in the liver wedge biopsy, making the diagnosis of AIVL strongly indicated from the clinical viewpoint. We have recently proposed diagnostic criteria for AIVL for the purpose of early diagnosis and prospective studies of this disease (Table 1) (14). The present case, on the second admission, did not match for “criterion 1.c.”, since a tumor in the liver was observed when he was readmitted. However, this case did meet two (1.a: anemia and thrombocytopenia and 1.b: splenomegaly) out of the three clinical and laboratory criteria and all three histopathologic criteria (2.a: hemophagocytosis, 2.b: neoplastic large B-cells, 2.c: intravascular and/or sinusoidal involvement). Thus the diagnosis of AIVL was confirmed.

Interestingly, the lymphoma cells were positive for CD5.

### Table 1. Improved Diagnostic Criteria for the Asian Variant of Intravascular Lymphoma (AIVL)(14)

<table>
<thead>
<tr>
<th>Criteria 1 and 2 are required for the diagnosis of AIVL (definite AIVL). However, if a case meets with Clinical and Laboratory Criteria (Criteria 1), the diagnosis of AIVL is suspected solely by Criterion 2.b (probable AIVL).</th>
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<tr>
<td>1. Clinical and Laboratory Criteria (at least 2 out of 3 are required)</td>
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<td>a. Cytopenia (not caused by hypoplastic or dysplastic marrow), affecting at least one of the two lineages, i.e., erythrocytes and platelets. Leucocytes are not included. It is prescribed by: Hemoglobin (&lt;11g/dl) or RBC (&lt;3.5x10⁷/l), and/or Platelet count (&lt;100x10⁷/l)</td>
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<tr>
<td>b. Hepatomegaly and/or splenomegaly, identified by computed tomography, ultrasound, sonography or physical examination</td>
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<td>c. Absence of overt lymphadenopathy and tumor formation</td>
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<td>2. Histopathologic Criteria (all 3 terms are required)</td>
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<tr>
<td>a. Erythrocyte-hemophagocytosis; usually seen mildly or moderately in hemopoietic system</td>
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<tr>
<td>b. Immunophenotypic evidence of proliferating neoplastic B cells with large cell morphology</td>
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<tr>
<td>c. Pathologic findings of intravascular proliferation and/or sinusoidal involvement of lymphoma cells</td>
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CD5 antigen is usually regarded as a T-cell associated marker, which is also expressed in subsets of cases with mature B-cell neoplasms, including B-cell chronic lymphocytic leukemia, mantle cell lymphoma, and, less frequently, DLBL. Yamaguchi et al recently reported that de novo CD5+ DLBL has many aggressive clinical features or parameters as compared to CD5− DLBL. Of 109 cases with CD5+ DLBL, they reported that an intravascular or intrasinusoidal infiltration pattern was observed in 19% (15). On the other hand, not all cases with IVL are positive for CD5; its reported frequency in IVL varies considerably by author (18%−75%) (14, 16, 17). However, no clinical differences between the CD5+ and CD5− IVL cases have been found to date (14).

Chromosome analysis of the bone marrow cells in the present case showed extremely complex abnormalities mixed with a normal karyotype (Fig 6). The hypotetraploidy might suggest gains involving chromosome 18, which has been reported as a candidate for common chromosome abnormalities in the AIVL (14). In addition, 8p21 and 19q13, both of which Shimazaki et al reported as characteristic chromosome abnormalities in their cases of DLBL with HPS, are also involved in the present case (18).

In reviewing the literature from Japan, we recently reported that the median survival for AIVL is 12.5 months from onset, while it is 16 months for classical IVL, given the administration of systemic chemotherapy (19). The present patient survived only 11 months from the onset of the disease, although systemic chemotherapies were administered...
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just after the diagnosis. This relatively poor outcome might be partially explained by the advanced stage of the disease, exacerbated by the difficulty in making the initial diagnosis of the splenic infarction, followed by a temporary relief from the symptoms, while the disease continued to progress latently.

In summary, we have reported an interesting case of AIVL presenting with splenic infarction. The AIVL frequently poses diagnostic and therapeutic problems for clinicians, especially those in eastern Asia, because it usually lacks identifying peripheral lesions, such as lymphadenopathy or skin eruption. It is suggested that this distinct lymphoma should be included in the differential diagnosis of splenic infarction. Application of the criteria for this variant as proposed by authors, plus biopsy of the appropriate sites, might allow a prompter diagnosis. To improve the prognosis of patients with the AIVL further, the optimal strategy for treatment should urgently be established.

References