Intravascular Large B-Cell Lymphoma Associated with t(14;19)(q32;q13) Translocation

Taishi Kobayashi and Hitoshi Ohno

Abstract

We report a 59-year-old man with intravascular large B-cell lymphoma (IVLBCL) associated with hemophagocytic syndrome, disseminated intravascular coagulopathy, and lung involvement. G-banding analysis of the metaphase spreads obtained from the bone marrow showed that the lymphoma cells were near-tetraploid and included two homologues of the 14q+ chromosome. Spectral karyotyping revealed that complex translocations occurred among chromosomes 3, 12, 14, and 19, and additional materials of 14q+ were from chromosome 19 with the breakpoint at 14q32 and 19q13. To the best of our knowledge, this is the first report describing t(14;19)(q32;q13) in IVLBCL.

Key words: intravascular large B-cell lymphoma, spectral karyotyping, t(14;19)(q32;q13)

(DOI: 10.2169/internalmedicine.50.5706)

Introduction

The WHO 2008 classification scheme of hematolymphoid tumors differentiates intravascular large B-cell lymphoma (IVLBCL) from diffuse large B-cell lymphoma (DLBCL), and lists IVLBCL as a unique subtype within mature B-cell neoplasms (1). IVLBCL is characterized by the selective growth of lymphoma cells within the lumina of vessels, particularly capillaries, causing the failure of virtually any vital organs (1). Patients with the Asian variant of IVLBCL often present with multiple organ failure, hepatosplenomegaly, pancytopenia, and hemophagocytic syndrome (HPS) (1-3); nevertheless, the disease responds well to chemoimmunotherapy including rituximab (3). In contrast to the establishment of clinical features as well as the response to treatment, the cytogenetic abnormalities of IVLBCL have not fully been described (1, 3). Here, we report a case of IVLBCL, in which lymphoma cells carried t(14;19)(q32;q13).

Case Report

The patient was a 59-year-old man, who had a four-month history of anorexia, weight loss, and fatigue. When the patient was transferred to our hospital by ambulance, he was febrile and hypotensive. On examination, he was somnolent but responded to questions correctly. There was no unequivocal superficial lymphadenopathy. The liver and spleen were not noted on palpation. Oxygen saturation was 94%. The hemoglobin level was 11.6 g/dL, the white cell count was 3,200/μL with a normal differential, and the platelet count was 102×10^3/μL. The aspartate aminotransferase value was 199 IU/L and lactate dehydrogenase was 1,306 IU/L. Hematologic parameters indicative of disseminated intravascular coagulation (DIC) included: activated partial thromboplastin time, 47.4 seconds (reference range, 23.0-36.0); fibrinogen, 151 mg/dL (reference, 200-400); D-dimer, 34.3 μg/mL (reference, ≤1.0); activity of antithrombin III, 30% (reference, 75-150); thrombin-antithrombin complex, >60 ng/mL (reference, ≤3); and plasmin α2-plasmin inhibitor complex, 7.6 mg/mL (reference, ≤0.8). Ferritin was 3,730 ng/mL and soluble interleukin 2 receptor was 3,546 U/mL.

A computed tomographic (CT) scan of the brain was normal. CT of the body revealed minimal lymphadenopathy of the neck, mediastinum, and the para-aortic region within the abdomen; the sizes of each detectable lymph node were <10 mm in diameter. CT of the chest with the lung window setting revealed the diffuse interstitial infiltration of both lungs,
Figure 1. Bone marrow appearance, showing (A) lymphoma cells (May-Giemsa staining, ×100 objective), (B) hemophagocytosis (May-Giemsa staining, ×100 objective), (C) intravascular infiltration of lymphoma cells (Hematoxylin and Eosin staining, ×40 objective), and (D) positive expression of CD20 of lymphoma cells (anti-CD20 immunostaining, ×40).

showing a ground-glass appearance.

Examination of the bone marrow smear slides revealed aggregates of large lymphoma cells with basophilic cytoplasm, cytoplasmic vacuoles, and fine nuclear chromatin (Fig. 1A). There were macrophages ingesting blood cells (Fig. 1B). Pathological sections prepared from the bone marrow revealed the sinusoidal infiltration of lymphoma cells expressing CD20 (Fig. 1C, D). Flow cytometry showed that the lymphoma cells were positive for CD5, CD10, CD19, and CD20 antigens, and expressed the immunoglobulin λ-light chain on their cell surface. The patient was diagnosed with IVLBCL associated with HPS, DIC, and lung involvement, and then treated with a regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisolone in combination with rituximab (R-CHOP). As a response to the treatment, the patient’s condition markedly improved, and DIC and pulmonary infiltration were resolved.

Cytogenetic Studies

Metaphase spreads obtained from the bone marrow specimen were subjected to cytogenetic studies. By conventional G-banding, the lymphoma cells were near-tetraploid and included two homologues of the 14q+ chromosome (Fig. 2A). Spectral karyotyping (SKY) revealed that complex translocations occurred among chromosomes 3, 12, 14, and 19, and additional materials of 14q+ were from chromosome 19 with the breakpoint at 14q32 and 19q13 (Fig. 2B). The other copies of der(14) consisted of a part of chromosome 12. The complete karyotype determined by the combination of G-banding and SKY was: 90, YY, der(X)t(X;3)(p22.1;?)×2, +der(1)t(1;14)(q21;?), del(1)(p11)x2, t(3;12)(q21;p13)x2, -4, der(6)t(6;18)(q15;q21)x2, -7, der(7), -12, -12, der(13)t(13;18)(p11.2;q11.2)x2, der(14)t(12;14)(?;q22)x2, der(14)t(14;19)(q32;q13)x2, i(19)(q10), der(19)t(12;19)(q15;q13)x2, +20, der(22)t(7;22)(?;p11.2), +mar (Fig. 2A).

Discussion

IVLBCL, by definition, lacks lymphadenopathy. In the present case, as lymph nodes in the cervical, mediastinal, and para-aortic regions were detectable on CT scans, the lymphoma could be included in CD5-positive DLBCL (4), which is currently not listed independently but included in the DLBCL, not otherwise specified category of the WHO 2008 classification (5). Japanese investigators have shown that intravascular/sinusoidal infiltration of lymphoma cells is also observed in a significant proportion of CD5-positive DLBCL, and suggested that fractions of IVLBCL and CD5-positive DLBCL overlap (4). Nevertheless, because the lymphadenopathy was not considered to reach the significant level, we conclude that IVLBCL is preferable to CD5-
positive DLBCL for the clinical diagnosis of this particular case.

Cytogenetic and/or molecular evidence of translocations involving the 14q32 chromosomal band and/or immunoglobulin heavy chain gene (IgH) have been reported in IVLBCL (Table 1) (2, 6-10). To the best of our knowledge, this is the first report describing t(14;19)(q32;q13) in IVLBCL. Of the 9 cases listed in Table 1, two were confirmed to involve previously known oncogenes, BCL2 (10) and CCND1 (7); in the latter case, nuclear expression of cyclin D1 was demonstrated by immunohistochemistry (7). To date, however, no recurring 14q32/IgH translocation has been identified in IVLBCL.

The t(14;19)(q32;q13) translocation, which was initially found in B-cell chronic lymphocytic leukemia, results in the juxtaposition of BCL3 on 19q13 with IgH on 14q32, leading to an increased expression of BCL3 at both mRNA and protein levels (11, 12). To elucidate whether BCL3 is involved in t(14;19)(q32;q13) in the present case, we performed immunohistochemistry of the bone marrow specimen using an anti-Bcl-3 antibody (#sc-185, Santa Cruz Biotechnology, Santa Cruz, CA, USA); however, the lymphoma cells were negative for the expression (data not shown). Thus, it is unlikely that t(14;19)(q32;q13) in the present case targeted BCL3, even though the breakpoint was 19q13 at the cytogenetic level.
A literature review showed two cases of B-cell lymphoma that had t(14;19)(q32;q13) by cytogenetic analysis but lacked rearrangement of BCL3 by Southern blot using probes for the gene; i.e., an aggressive small non-cleaved cell lymphoma (13) and a CD5-positive DLBCL (14). As the latter case was associated with hepatosplenomegaly, pan- cytopenia, bone marrow infiltration of large lymphoma cells, and HPS, but no superficial lymphadenopathy, the lymphoma may actually have been an IVLBCL, raising the possibility that t(14;19)(q32;q13) is a recurring translocation of IVLBCL. As suggested by Yamamoto et al (14), another oncogene, independent of BCL3, could be localized on 19q13 and deregulated by juxtaposition to IgH, playing a role in the pathogenesis of a fraction of this particular type of lymphoma.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
The authors wish to thank Dr. A. Takasu, Department of Pathology, Hyogo Prefectural Amagasaki Hospital, for pathological examination.

References