Case Report
Intravascular large B-cell lymphoma secondary to lymphoplasmacytic lymphoma: a case report and review of literature with clonality analysis

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Received December 23, 2014; Accepted February 22, 2015; Epub March 1, 2015; Published March 15, 2015

Abstract: Intravascular large B-cell lymphoma (IVLBCL) can be a fatal malignancy mainly because of difficulty in early detection. Due to the lack of specific clinical manifestations, early detection of IVLBCL remains a challenge, especially in the presence of comorbidities. Lymphoplasmacytic lymphoma (LPL) is an indolent B-cell lymphoma accompanied by monoclonal immunoglobulin M protein in most patients, and known to be associated with high risk of secondary hematological malignancies. Here, we report a patient who developed IVLBCL during treatment for LPL that presented a diagnostic challenge. Rearrangement analysis of the immunoglobulin heavy chain revealed the different clonal origins of two lymphomas, implying a predisposition of LPL to develop unrelated secondary lymphoma. Secondary lymphoma including IVLBCL during the treatment for LPL deserves consideration in order to facilitate early diagnosis and intervention.

Keywords: Intravascular large B-cell lymphoma, lymphoplasmacytic lymphoma, secondary lymphoma, immunoglobulin rearrangement

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare type of B-cell non-Hodgkin lymphoma, characterized by the infiltration of vessels by tumor cells without forming an extravascular mass [1]. Even though successful early detection and treatment with systemic chemotherapy were recently reported [2], the aggressive nature and rarity of clinical manifestations still hamper the antemortem diagnosis in a considerable number of patients.

Lymphoplasmacytic lymphoma (LPL) is a neoplasm of small B lymphocytes often associated with a paraprotein, usually IgM type. In spite of its indolent nature, LPL has been reported to be associated with high risk of developing secondary aggressive lymphoma, mainly diffuse large B-cell lymphoma (DLBCL) [3]. The mechanism of secondary lymphoma development from LPL has yet to be elucidated.

Here, we report a case of IVLBCL that developed after treatment for LPL. IVLBCL has never been reported as a secondary malignancy after LPL. We were able to analyze the clonality by employing an immunoglobulin gene rearrangement study.

Case report

A 69-year-old male presented with deterioration of the mental status and dyspnea. He had been diagnosed with LPL/Waldenström’s macroglobulinemia at the age of 66, when his serum IgM level was 8,000 mg/dL. Bone marrow biopsy and inguinal lymph node biopsy revealed infiltration by CD20-positive, CD5-negative small lymphocytes (Figure 1A, 1B). He achieved partial remission with treatment of melphalan and prednisone. Two months after discontinuation of the treatment, laboratory findings showed a decrease in his hemoglobin and absence of reticulocytes, and bone marrow aspira-
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int showed a marked decrease in erythroblasts without morphological dysplasia in any blood cell lineage, which was compatible with pure red cell aplasia. Oral cyclosporine was started, and his hemoglobin level normalized within 4 months and the immunosuppression was maintained.

Four years after the diagnosis of LPL, he showed deterioration of the mental status and dyspnea. His vital signs were stable with the exception of hypoxia. He showed no neurological deficit. Laboratory tests revealed a decrease in the platelet count to 46,000/μL, hemoglobin to 8.7 g/dL, and an increase in lactate dehydrogenase (LDH) to 1,182 U/L (normal range: 119-229 U/L). His IgM level was stable (754 mg/dL). Diagnostic work-up including blood culture and lumbar puncture showed no abnormality. Imaging studies identified only slight swelling of his adrenal glands. Serum ACTH and cortisol levels were within normal limits. Bone marrow biopsy showed normocellular marrow without infiltration by tumor cells. As he had been in a state of immunosuppression with cyclosporine, we started anti-bacterial, fungal, and viral agents. Subsequently, he suffered from respiratory failure and progressive hypotension. On day 7 after admission, MRI of the head showed a small, scattered, high-intensity area in the white matter without vascular abnormality. Cerebrospinal fluid PCR for viral DNA of HSV, CMV, HHV6, EBV, and JCV was performed, and all tests were negative. On day 14, MRI of the head showed a diffuse expansion of a high-intensity area in the white matter. Because of unstable blood pressure, biopsy was not performed. On day 30, he died from respiratory and circulatory failure.

Autopsy revealed diffuse infiltration by neoplastic cells into blood vessels in multiple organs. Small vessels, sinusoids of the brain, lung, liver, kidney and other organs were involved. (Figure 1.)

Figure 1. A. Inguinal lymph node biopsy sample, HE staining. Plasmacytoid small lymphocytes are shown. B. CD20 staining. C. Postmortem adrenal gland biopsy sample, HE staining. Tumor cells are packed in veins. D. CD20 staining.
In particular, parenchyma of the adrenal gland was mostly substituted by neoplastic cells due to extravasation. Immunohistochemical staining demonstrated that the tumors were positive for CD20 and CD5, and negative for cyclin D1. Microscopic morphology and immunohistochemical features led to a diagnosis of IVLBCL.

We further performed rearrangement analysis of the immunoglobulin heavy chain gene in order to determine whether or not IVLBCL and LPL are different clones. Consensus PCR oligomers of VH and JH regions were used to amplify DNA extracted from the tissue [4]. Gene analysis showed a difference in the length of the products between those of LPL and IVLBCL. The LPL's main peak was detected at 114, while the IVLBCL's main peak was detected at 125 (Figure 2A). Further DNA sequencing of those fragments revealed that the LPL clone utilizes the J4 segment of the immunoglobulin heavy chain gene while the IVLBCL clone utilizes the J6 segment, and different clone-specific sequences were identified (data not shown). Additionally, we designed internal primers from the DNA sequences. Two pairs of specific primers were used; LPL_F-1 (5'-TGTCTATTACTGTGAGAGATTGGGAT-3') and JH_R, IVL_F-1 (5'-CATACTGTGCGAAGCATCAGACG-3') and JH_R.

We confirmed the absence of the IVLBCL clone in the original LPL samples, and the absence of the LPL clone in the IVLBCL samples by 3% agarose gel electrophoresis. A product was amplified only in the LPL sample when the LPL_F-1 and JH primer pair was used, and only in the IVLBCL sample when the IVL_F-1 and JH primer pair was used (Figure 2B).

Discussion

The diagnostic dilemma in IVLBCL is primarily attributed to difficulty in suspecting the disease. While small vessels of a myriad of organs are infiltrated by tumor cells, most patients with IVLBCL show only non-specific manifestations including fever, fatigue, or neurological symptoms, and non-specific laboratory findings such as anemia (65%), increased serum lactate dehydrogenase (80-90%), or an elevated erythrocyte sedimentation rate (43%) [5]. Imaging studies often fail to identify the tumor because of the lack of apparent mass formation, thus the biopsy remains the gold standard for diagnosis. Bone marrow biopsy is generally useful in diagnosing IVLBCL, and random skin biopsy is reported to be another less invasive procedure in diagnosing IVLBCL.

LPL is a substantial risk factor for secondary aggressive B-cell lymphoma. The incidence of DLBCL in patients with LPL is reported to be 1-9% [3]. The pathogenesis of secondary lymphoma from LPL is currently attributed to chemotherapy such as alkylating agents and nucleoside analogues, innate immunologic impairment, or background genetic predisposition.
Little has been known about whether secondary lymphomas are transformed from LPL, or whether they are de novo lymphomas. An immunophenotyping with immunohistochemical staining and flow cytometry is frequently used for clonality analysis in the reports of secondary lymphomas that are regarded to be transformed from LPL [6]. Although an analysis of the rearranged VDJ sequence can provide more accurate results, reports are scarce, partly because of difficulty in acquiring sufficient materials for a molecular study. Among the reports with an immunoglobulin gene analysis, the results are conflicting so far; four case reports showed the same clonal origins in LPL and secondary aggressive B-cell lymphomas [7-10], while the other four case reports supported the different clonal origins [11-14] (Table 1). Furthermore, it is conceivable that several cases of unrelated secondary lymphomas might be regarded as transformed lymphomas in the past reports due to a coincidental match of immunoglobulin phenotypes. In our case, different clonal patterns were shown in LPL and IVLBC, showing independent development of IVLBC from LPL, which might have been influenced by chemotherapy or immunosuppression. Unexpectedly, more than half the cases including ours support unrelated secondary lymphomas. We speculate that among the various mechanisms of developing secondary lymphoma from LPL, the pathway to cause independent de novo lymphomas is robust, unlike chronic lymphocytic leukemia where the clonal evolution with additional genetic events is the dominant mechanism of developing DLBCL [15]. To date, the pathogenesis of clonally unrelated secondary lymphoma from LPL is not known in detail, and it is partly attributed to the attenuated immune function. Together with the increased incidence of various types of secondary malignancies including non-hematological cancer, a disruption of antitumor immunoreaction in LPL is implied [3]. Further elucidation of the mechanism is expected.

In summary, we report a secondary IVLBC arising independently from LPL, which was confirmed by gene sequencing. Our case is the first such case report, as far as we know. IVLBC is a diagnostic challenge, and additional conditions can mask the diagnosis. Secondary lymphoma including IVLBC should be considered when treating LPL, and diagnostic work up for the latent malignancies is warranted.

**Acknowledgements**

This work was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan (Clinical Cancer Research 22-014, 22-031, and 23-004) and the National Cancer Center Research and Development Fund (21-6-3, 20-1, 23-A-17, 23-A-23, 26-A-4, 26-A-24, and 23-C-7).

**Disclosure of conflict of interest**

None.

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**References**


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