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Intravascular Large B-cell Lymphoma Transformed from a Mantle Cell Lymphoma: A Case Report and Literature Review

Long Yang[1], Beth Harrison[1], Mary Ann Perle[1], Mandeep Singh[1,2], Zhiheng Pei[1,2], Jonathan Melamed[1], Peng Lee[1,2], Sherif Ibrahim[1]* & Rosemary Wieczorek[1,2]*

[1] Department of Pathology, New York University School of Medicine, New York, USA

[2] Department of Pathology, VA New York Harbor Healthcare System, New York, USA

*Co-correspondence: Rosemary Wieczorek, Department of Pathology, New York University School of Medicine, 423 E 23rd Street, New York, NY 10010, USA. Tel: 1-212-686-7500. E-mail: rosemary.wieczorek@med.va.gov; Sherif Ibrahim, Department of Pathology, New York University School of Medicine, 560 First Avenue, New York, NY 10016, USA. Tel: 1-212-263-5967. E-mail: sherif.ibrahim@nyumc.org

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Abstract

Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal diffuse large B-cell lymphoma (NHL) characterized by the presence of neoplastic lymphocytes only in the lumina of small vessels and capillaries. Although studies have shown an association of IVLBCL with other lymphomas, its relationship with mantle cell lymphoma has not been reported. Here we report a rare case of a 76 year-old male with intravascular transformation of mantle cell lymphoma in the adrenal glands. Histopathological examination of the adrenal mass biopsy revealed two cell populations within the fibrovascular tissue – a diffuse and infiltrative small lymphoid cell population and an unexpected large neoplastic cell population. Immunohistochemistry (IHC) for the small lymphoid cells are positive for CD5, CD20, and cyclin D1, with the t(11;14)(q13;q32) chromosomal rearrangement on cytogenetic analysis by interphase fluorescence *in situ* hybridization (FISH), characteristic for mantle cell lymphoma. The large cells are positive for CD5, CD20 and CD79a and negative for cyclin D1 on IHC, demonstrating exclusive localization within small capillaries by CD34 staining, evident of IVLBCL. In addition, FISH analysis revealed that the large cells also have the t(11;14)(q13;q32) mantle cell lymphoma rearrangement. To our knowledge, the present study provides the first reported case of IVLBCL transformation from mantle cell lymphoma and supports the hypothesis that IVLBCL may arise by transformation from other lymphomas.

Keywords: intravascular large B-cell lymphoma, mantle cell lymphoma, transformation

1. Introduction

Intravascular large B-cell lymphoma (IVLBCL), a rare subtype of diffuse large B-cell lymphoma, is a fatal disease characterized by preferential proliferation of malignant cells within capillaries, arterioles and venules. Patients with IVLBCLs present with a variety of symptoms due to occlusion of small vessels in different organs. Based on the clinical presentation, two variants of IVLBCLs have been recognized (Swerdlow et al., 2008b). The Western variant is characterized by predominantly neurological or cutaneous involvement. The Asian variant is characterized by multiple organ failure, hepatosplenomegaly, pancytopenia and haemophagocytic syndrome. The etiology of IVLBCL is still under debate. The intravascular pattern is hypothesized to be secondary to defects in homing receptors on the neoplastic cells, such as loss of CD29 and CD54 (Ferry et al., 1988; Ponzoni et al., 2000). However, neoplastic cells of IVLBCL show a tremendous heterogeneity of immunophenotypic and cytogenetic abnormalities among patients. In addition, rare cases of IVLBCL that occurred following a prior lymphoma or coexisting with other lymphomas have been reported. For example, there is a report of a patient with documented follicular lymphoma with subsequent IVLBCL (Carter, Batts, de Groen, & Kurtin, 1996). There are other reports of patients with localized diffuse large B-cell lymphoma (DLBCL) who relapsed with generalized IVLBCL (Glass, Hochberg, & Miller, 1993; Kamath, Gilliam, Nihal, Spiro, & Wood, 2001). These observations led to the hypothesis that IVLBCLs may be transformed from other lymphomas (Yegappan et al., 2001). However, clonality studies to test this hypothesis were lacking in most reported cases. How the transformation occurs in this context remains unknown. In addition, the possible relationship of IVLBCL with

mantle cell lymphoma has not been reported. In the present study, we describe a case of IVLBCL concurrent with mantle cell lymphoma in adrenal glands. We take this rare opportunity to demonstrate, for the first time, that IVLBCL may be transformed from mantle cell lymphoma using Interphase fluorescence *in situ* hybridization (FISH) analysis.

2. Case History

The patient is a 76 year-old male with a past medical history significant for melanoma of the back diagnosed 6 years ago. He was brought by his wife to the emergency department of our institution due to altered mental status. An abdominal Magnetic Resonance Imaging (MRI) performed for hematuria 4 days prior to admission revealed bilateral adrenal masses, measuring 3.7 cm on the right and 4.3 cm on the left, and splenomegaly. A Computed Tomography (CT) scan of the chest showed enlarged subcarinal lymph nodes and upper abdominal lymphadenopathy. At admission the patient had a low-grade temperature (100.3° F) and normal vital signs. Complete blood counts showed mild pancytopenia with a hemoglobin of 12.5 g/dl, hematocrit of 36%, white blood cell count of 3.9 x 1012/l, and platelet count of 109 x 109/l. The patient was admitted for work-up for lymphoma, leukemia and other malignancy. A bone marrow biopsy, a core biopsy of the mass in the right adrenal gland and a transbronchial core biopsy of the subcarinal lymph node were performed for pathologic evaluation. Due to the scant nature of the subcarinal lymph node biopsy specimen, studies were focused on the bone marrow biopsy and the right adrenal biopsy. Results are reported in detail below.

3. Results

3.1 Histopathology

Histological examination of the bone marrow revealed a hypercellular bone marrow with 75% cellularity. An atypical small lymphocytic infiltrate was present both para-trabecularly and interstitially (Figure 1A). These small lymphocytes were monomorphic and contained sparse cytoplasm. The nuclei of these small lymphocytes were irregular with frequent cleaves and grooves and contained clumped chromatin and inconspicuous nucleoli (Figure 1B). No large lymphocytic or carcinomatous cells were identified. There was trilineage hematopoiesis with maturation in the remaining marrow. A needle biopsy was performed in the right adrenal mass. Histological examination revealed that the mass was composed of two cell populations within the fibrovascular tissue. A small lymphoid cell population was diffuse and infiltrative through 80% of the tissue. A large lymphoid cell population had a nested distribution pattern throughout 50% of the tissue (Figure 2A). Morphologically the small cells were reminiscent of those small lymphocytic infiltrates found in the bone marrow. The large cells were on average five times bigger than the small cells. They had large, round, granular nuclei and multiple prominent nucleoli (Figure 2B and C).

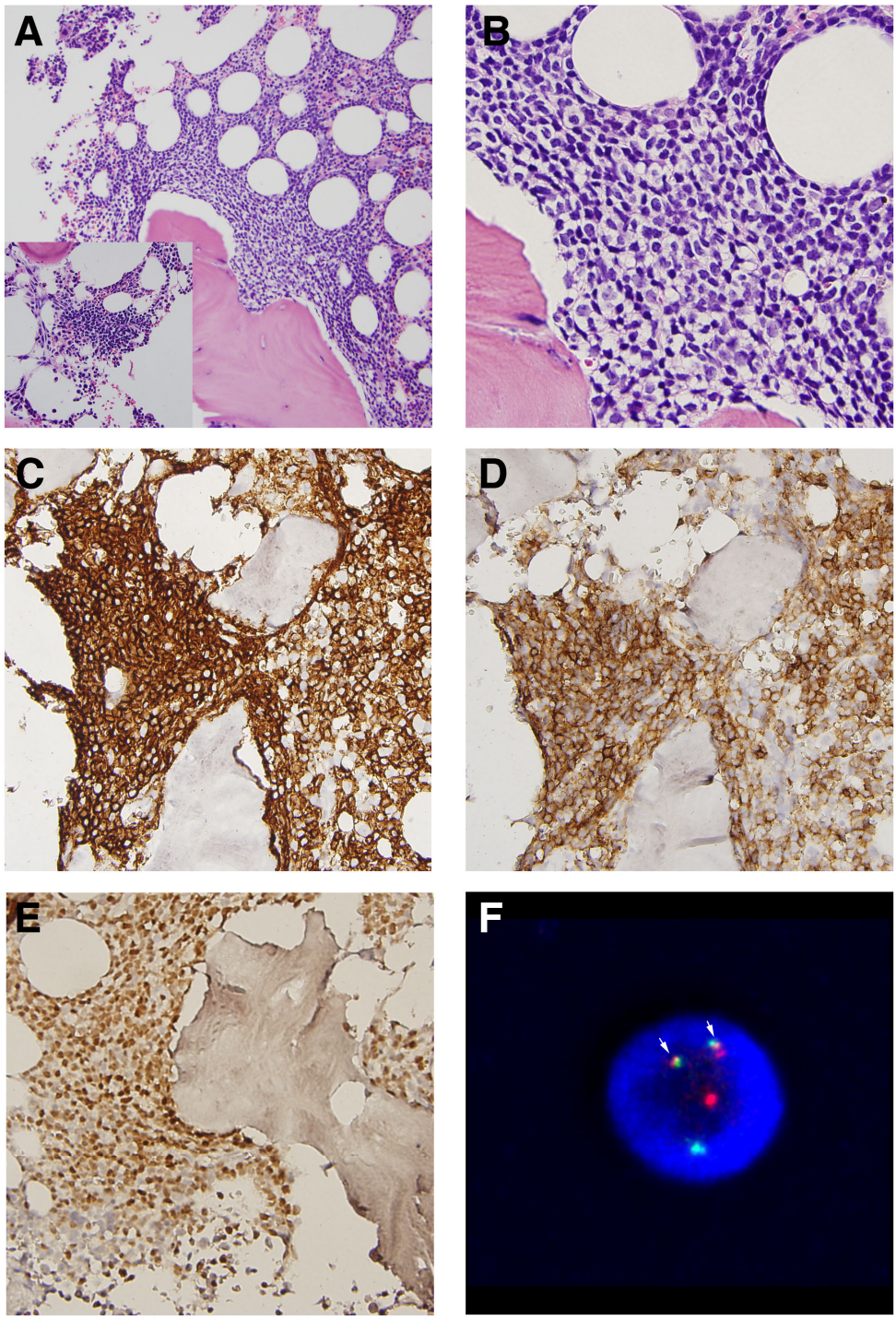

Figure 1. Bone marrow

A small atypical para-trabecular lymphocytic infiltrate and interstitial lymphocytic infiltrate (insert) at low (A, 200X) and high (B, 600X) magnification. Immunohistochemical stains at high (400X) magnification: C- CD20, D- CD5 and E- Cyclin D1. Interphase FISH of the bone marrow with arrows pointing to the two fusion signals demonstrating a t(11;14)-IGH/CCND1 rearrangement (F). The red and green signals denote the normal chromosomes 11 and 14.

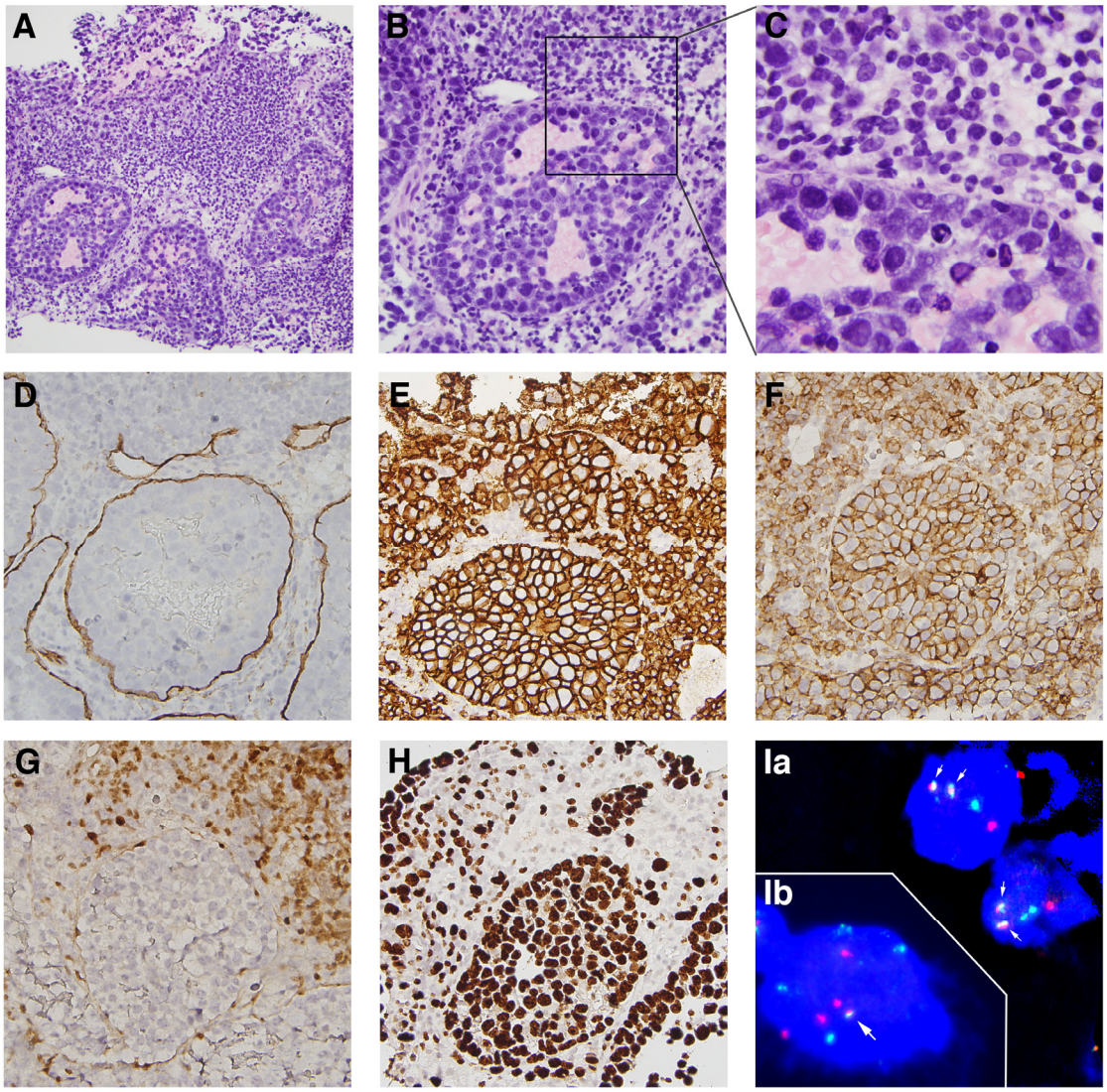

Figure 2. Right adrenal mass at low (A- 200X) and high (B- 400X and C- 1000X) magnification

Immunohistochemical stains at high (400X) magnification: D- CD34, E- CD20, F- CD5, G- Cyclin D1 (CCND1) and H- Ki-67. Interphase FISH of the right adrenal mass showing two small cells (Ia, arrows point to the two fusion signals in each cell demonstrating a t(11;14)-IGH/CCND1 rearrangement) and one large cell (Ib, the arrow points to the single fusion demonstrating an IGH/CCND1 rearrangement). The red and green signals denote the normal chromosomes 11 and 14. Small cells are enlarged 3 times for better visualization.

3.2 Immunohistochemistry

Immunohistochemical studies revealed that the atypical small lymphocytic infiltrates in the bone marrow were diffusely positive for CD20 (Figure 1C), CD5 (Figure 1D) and negative for CD23, CD30, and BCL-6 (data not shown). Cyclin D1 (CCND1) staining demonstrated specific nuclear staining in almost all small atypical lymphocytes (Figure 1E). In the right adrenal mass, both small cells and large cells were diffusely positive for CD20 (Figure 2E), CD5 (Figure 2F) and CD45 and CD79A (data not shown), and negative for CD3, inhibin, chromogranin and melanA (data not shown). Cyclin D1 staining was positive in almost all nuclei of the small cells but not in those of the large cells (Figure 2G). Ki-67 was seen in up to 40% of the small cells and greater than 90% of the large cells, indicating a much higher mitotic rate of the large cells than that of the small cells (Figure 2H). In addition, CD34 staining showed that the large cell population was confined within small capillaries (Figure 2D). These findings are suggestive of a mantle cell lymphoma with both bone marrow and

adrenal involvement. The immunophenotype and exclusively intravascular distribution pattern of large cells were consistent with an IVLBL within the adrenal capillaries.

3.3 Cytogenetics

FISH studies were performed on both bone marrow cells and formalin-fixed paraffin-embedded tissue from the right adrenal mass biopsy, using the commercially available IGH(14q32) and CCND1(11q13) dual color dual fusion translocation probe (Abbott Molecular, Des Plaines, IL) according to the manufacturer's instructions. Additionally, FISH was performed on bone marrow cells with a commercial set of DNA probes, including TP53(17p13.1), D13S19(13q14.3), LAMP1(13q34), ATM(11q22.3), and D12Z3(12p11.1-q11) (Abbott Molecular, Des Plaines, IL). A population of bone marrow cells was detected with a dual fusion pattern positive for an IGH/CCND1 rearrangement (20.5%, n=200, Figure 1F) and with deletion of ATM (11q22.3) (9.3%, n=200). Normal signal patterns were seen with all other probes. The t(11;14)(q13;q32) confirmed the diagnosis of mantle cell lymphoma involving the bone marrow. A minimum of 20 interphase small cells and large cells were analyzed in the paraffin-embedded tissue from the right adrenal mass biopsy. Both cell types demonstrated fusion signal patterns consistent with a t(11;14)(q13;q32). In small cells, a classic dual fusion pattern (two fusions, one red, one green signal) was seen similar to that in bone marrow cells (Figure 2Ia). In large cells, the most consistent signal pattern showed one fusion (with likely loss of the non-oncogenic derivative), three to four red, and three to four green signals (Figure 2Ib). The multiple red and green signals likely represent a hyperdiploid karyotype with additional copies of chromosomes 11 and 14, as reported before (Rashid, Johnson, Morris, et al., 2006). The IGH rearrangement in both small cells and large cells was also confirmed by interphase FISH study using an IGH dual-color, break-apart probe (data not shown) (Abbott Molecular, Des Plaines, IL).

3.4 Final Diagnosis and Follow-Up

A diagnosis of mantle cell lymphoma with intravascular large cell transformation was made. At six months follow-up, the patient is alive in remission status post r-CHOP chemotherapy (cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone, with rituximab).

4. Discussion

The initial diagnosis of bilateral adrenal masses in this patient with mantle cell lymphoma involving lymph nodes, peripheral blood and bone marrow was adrenal infiltration of mantle cell lymphoma. Consistent with the diagnosis, the small lymphoid cell population in the adrenal mass has characteristics of mantle cell lymphoma. These small neoplastic cells are immunohistochemistry (IHC) positive for CD20, CD5 and negative for CD3. In addition, cyclin D1 staining shows specific nuclear reactivity in small cells and cytogenetic analysis demonstrates the classic t(11;14) chromosomal rearrangement. However, unexpectedly, there is the presence of a population of large neoplastic cells in the adrenal mass. The morphological features of these large cells raise the possibility of several different diagnoses including adrenal cortical carcinoma, pheochromocytoma and neuroblastoma. However, these diagnoses were excluded by the negative IHC reactivities for inhibin, chromogranin and melanA. The expression of CD45, CD20, CD79a and CD5 in these large cells is consistent with a CD5 positive B-cell lymphoproliferative disorder. Furthermore, these large cells are shown to be exclusively localized within small capillaries by CD34 staining. These results are characteristic of an IVLBCL involving the adrenal glands.

In this case, the adrenal mass either represents a composite lymphoma of mantle cell lymphoma and IVLBCL or a mantle cell lymphoma with intravascular transformation. Although cases in which mantle cell lymphoma occurring as a major pathologic component of composite lymphoma have been reported (Papathomas et al., 2012), we conclude that this specific case represents the latter based on the following evidence. First, IVLBCL has been proposed to be transformed from other low-grade lymphomas because many IVLBCL cases have other coexisting or preceding lymphomas, and there is a great heterogeneity of the immunophenotype of IVLBCL (except its consistent expression of B-cell markers) (Carter et al., 1996; Rashid, Johnson, Morris, et al., 2006; Vieites et al., 2005; Yegappan et al., 2001). Second, in contrast to the lack of clonal relationship between individual lymphomas in most cases of composite lymphoma with a mantle cell component (Papathomas et al., 2012), both the mantle cell lymphoma component and intravascular lymphoma component in this patient's case had a CD5+CD10-Bcl2+Bcl6- expression pattern (data for CD10, Bcl2 and Bcl6 stains not shown) and the t(11;14)(q13;q32). The t(11;14)(q13;q32) chromosomal rearrangement between the cyclin D1 and IGH genes is present in almost all mantle cell lymphoma cases and considered to be the primary genetic event for oncogenic transformation (Swerdlow et al., 2008a). This cytogenetic abnormality has been reported in a few IVLBCL cases and was proposed to be the evidence for an IVLBCL transformation from an occult mantle cell lymphoma (Khoury et al., 2003; Rashid et al., 2006). The lack of cyclin D1 nuclear reactivity in the IVLBCL cells is also

consistent with previously reported results. In all reported IVLBCL cases, there is only one case that has aberrant cyclin D1 expression together with the t(11,14) (Rashid et al., 2006). It is likely that during the intravascular transformation, malignant cells may lose cyclin D1 overexpression due to another unknown genetic event.

IVLBCL remains a rare and poorly characterized disease due to the limited number of cases and a myriad of clinical presentations. Cases of IVLBVL associated with other lymphoma are even more rare. To the best of our knowledge, nineteen cases have been reported since 1993 (Asagoe et al., 2003; Carter et al., 1996; Ferreri et al., 2004; Glass et al., 1993; Kamath et al., 2001; Kasuya, Hashizume, & Takigawa, 2011; Katz, Miller, & Gregory, 2010; Matsue et al., 2008; McKelvie, Wools, Roberts, & Cook, 2013; Ponzoni et al., 2000; Rashid et al., 2006; Yamada et al., 2012; Yegappan et al., 2001; Zhao et al., 2005; Zlotnick et al., 2008), with clonality studies performed in five of them (Asagoe et al., 2003; McKelvie et al., 2013; Yegappan et al., 2001; Zhao et al., 2005; Zlotnick et al., 2008). IGH rearrangement studies showed clonal relationship in four out of five cases: three cases were IVLBCLs with concurrent DLBCLs, and the fourth case was an IVLBCL following a CD5- low grade lymphoma (Table 1). The present study provides the first reported case of IVLBCL transformed from a mantle cell lymphoma with the characteristic t(11;14)(q13;q32) rearrangement. Our study, together with other reported cases, supports the hypothesis that IVLBCL may arise from the transformation of other lymphomas. How the transformation occurred in this case is still unclear. Determining the expression pattern of the surface adhesion molecules such as CD29 and CD54 may provide additional insights. Although rare, the possibility that an IVLBCL could be transformed from an otherwise typical diffuse mantle cell lymphoma should now be taken into consideration.

Table 1. Comparison of present case with cases of IVLBCL transformed from other lymphomas reported in the English-language literature (from 1993 to April 2013)

Reference	Patient age/Sex	Diagnosis	Immunophenotype of both lympomas	Clonality studies	Treatment and follow up
Yegappan et al., 2001	62/M (patient #16)	CD5 negative low grade lymphoma; IVLBCL at autopsy 10 months later	CD20, CD10	identical IGH gene rearrangement by PCR and sequencing	not responsive to adriamycin-based chemotherapy; DOD
Asagoe et al., 2003	44/F	ureteral DLBCL ; nodal and cutaneous IVLBCL 18 months later	CD20, CD79a	IGH gene rearrangement of identical size by PCR	high dose chemotherapy and autologous peripheral blood stem cell transplantation and in remission; die of PCP 2 years later
Zhao et al., 2005	59/M	nodal DLBCL with minor intravascular component followed by IVLBCL 2 years later	CD20, CD79a, Bcl-2	IGH gene rearrangement of identical size by PCR	CHOP chemotherapy; in remission until the development of aggressive IVLBCL; DOD
Zlotnick et al., 2008	69/M	testicular DLBCL; IVLBCL at autopsy 16 years later	CD20, Pax5	IGH gene rearrangement of identical size by PCR	no corresponding treatment; DOD
Present case	76/M	mantle cell lymphoma in BM, lymph nodes adrenal glands; IVLBCL in adrenal glands	CD20, CD79a, Bcl-2, CD5	same t(11;14)(q13;q32) chromosomal rearrangement between the cyclin D1 and IGH genes by FISH	r-CHOP chemotherapy and in remission

BM- bone marrow; CHOP- cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone; r-CHOP- cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone, with rituximab; DLBCL- diffuse large B-cell lymphoma; DOD- die of disease; FISH- fluorescence *in situ* hybridization; IGH- Immunoglobulin heavy chain; PCR- polymerase chain reaction; PCP- pneumocystic pneumonia.

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