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Intravascular Large B-Cell Lymphoma; Our Experience with the Disease at Two Medical Centers

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Abstract

Background: Intravascular Large B-cell Lymphoma (IVLBCL) is a rare lymphoma.

Methods: We retrospectively analyzed six patients with IVLBCL in Japan.

Results: Hemophagocytic syndrome was seen in 4/6 patients, splenomegaly in 5/6 patients, and all patients had B symptoms. The diagnostic site was the bone marrow in 5/6 patients, and patients were found to have a complex karyotype. Four patients had a chromosome 1 abnormality and three had chromosome 11 and 21 abnormalities. Median survival was 11.9 months.

Conclusion: A bone marrow exam might be more useful in detecting IVLBCL than a random skin biopsy in Asian variants.

Keywords: Chromosome abnormalities; Intravascular Large B-cell Lymphoma; Hemophagocytic

Introduction

Intravascular large B-cell Lymphoma (IVLBCL) is a rare lymphoma characterized by selective growth of lymphoma cells in the lumen of small vessels without marked lymphadenopathy. Clinically, there are three variants: classical, cutaneous, and hemophagocytic. Classical and hemophagocytic variants are seen in both Western and Asian countries, whereas the cutaneous variant is seen mostly in western countries [1]. However, aspects concerning IVLBCL remain unclear. We describe our experience with IVLBCL patients and identify cytogenetic features of the disease.

Patients and Methods

In this retrospective study, transplant-ineligible patients with IVLBCL were treated in two hematology centers, Kansai Medical University Hospital and Kansai Medical University Medical Center, between January 2006 and December 2017. This study was conducted in accordance with the Declaration of Helsinki and the requirements of the institution's review board.

Statistical Analysis

Overall Survival (OS) was calculated from the time of diagnosis until the time of death or the last clinical follow-up. Survival curves were generated using the Kaplan-Meier method, and differences were evaluated using the log-rank test. All statistical tests were two-sided. Statistical significance was defined as $p<0.05$ and 95% Confidence Intervals (CI) were calculated. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 2.13.0 (The R Foundation). Specifically, EZR is a modified version of R Commander (version 1.6 to 3), which adds statistical functions frequently used in biostatistics [2].

Results

Clinical characteristics of patients (n=6; median age, 77 years, range, 63 years to 84 years; 50% were male) included in this study are shown in Table 1. A Performance Status (PS) of 1 was seen in two of six patients. According to the International Prognostic Index (IPI), two patients were classified as being high-intermediate risk and four as high risk. Hemophagocytic Syndrome (HPS) was seen in four patients, splenomegaly in five patients, and disseminated intravascular coagulation in two patients. All patients showed B symptoms and three patients were CD5-positive. Bone Marrow (BM) was the diagnostic site in 5 patients and spinal fluid in one patient. 18F-Fluoro-

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Table 1: Patients characteristics.

Case	Age	Sex	PS	IPI	HPS	Splenomegary	DIC	B Symptoms	PET	B Mothers (%)	Cytogenetic anlysis (BM)	CD 5	CNS	Detected site	Chemo Tx	Outcome
1	78	M	0	HI	-	+	-	+	Not inspected	62.1	45, X, -Y, der(8;17)(q10;q10), +r1*2, +mar1[6]/45,X, -Y, add(3)(p21), i(8)(q10)[4]	-	-	BM	R+CPA	Dead
2	77	M	0	High	+	+	+	+	Liver(3.4)/ spleen(6.2)bone(5.7)	52	46, XY, -11, +mar1[2]/46, XY, add(6)(p21), del(6)(q?), -7, -8, add(9)(p11), add(12)(p11.2), -17,-22, +4mar[1]/46, XY[16]	-	-	BM	R-CHOP	Unknown
3	74	F	0	HI	+	-	-	+	Not inspected	5.7	86<3n>, -X, -X, add(X)(p11.2), add(1)(p11), +add(1)(p11), +add(2)(q21),+3,+5, -6, del(6) (q?), +8,-9, -9, -10, add(10)(q22), +der(11)t(1;11)(q12;q23), +12,+13, add (14)((q32), +16, +add(17)(p11.2), +18, -19, -19, add(19)(p11), -20, -22, +r, +16mar[1]/46, XX[15]	-	-	BM	PSL	Dead
4	84	F	1	High	-	+	-	+	Not inspected	25.2	48, X, add(X)(p11.2), add(3)(q27), +5, del(6)(q?), add(7)(q32), add(8)(p11.2), +add(11)(p11.2), del(11)(q?), add(13)(q14), add(19)(q13.1)[2]/48, idem, add(1)(q11), der(1;11)(q10;q10), -add(11), +13, -add(13), del(14)(q?)[2]/46, XX[12]	+	-	BM	R-CHOP	Alive
5	63	M	0	High	+	+	+	+	Liver(1.9)/ spleen(2.7)bone(5.0)	82.6		+	-	BM/skin	R-CHOP	Dead
6	77	F	1	High	+	+	-	+	Not inspected	0.6	46,XX[20]	+	+	BM/CNS	R-CHOP	Alive

PS: Performance Status; IPI: International Prognostic Index; HPS: Hemophagocytic Syndrome; DIC: Disseminated Intravascular Coagulation; PET/CT: Positron Emission Tomography/Computed Tomography; FDG: Fluoro-2-Deoxy Glucose; BM: Bone Marrow; CNS: Central Nervous System; Chemo Tx: Chemotherapy; M: Male; F: Female; HI: High-Intermediate; R+CPA: Rituximab Combined with Cyclophosphamide; R-CHOP: Rituximab plus Cyclophosphamide, doxorubicin, vincristine, and prednisone; PSL: Prednisolone

2-Deoxy-D-Glucose (FDG) -Positron Emission Tomography/ Computed Tomography (PET/CT) was performed in two patients. Both patients revealed hot spots in the spleen, liver, and bone. Cytogenetic analysis revealed a complex karyotype in four patients. The median follow-up period was 9.7 months (range, 2.5 months to 29.6 months). Four patients received R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. One patient received rituximab combined with cyclophosphamide, and one patient was treated with only prednisolone. Three patients died and two patients were still alive; one is unknown. Median overall survival was 11.9 months (range, 2.5 not reached months) (Figure 1).

Discussion

Treatment of IVLBCL had been improved in the rituximab era. Shimada et al. reported on 106 patients with IVLBCL in Japan [3]. They compared treatment with/without rituximab and concluded that rituximab improved IVLBCL patient outcomes (2-years OS: 66% *vs.* 46%). In our study, 5/6 patients were treated with rituximab. One patient could not be treated with the drug because of that patient's condition and older age. In the rituximab era, all patients should be considered for treatment with the agent. In the Shimada et al. study [3], detailed clinical information was obtained, and most patients showed B symptoms (82% to 86%), splenomegaly (63% to 67%), and HPS (59% to 60%). Those features were compatible with our patients: HPS was seen in four patients, splenomegaly in five patients, and all patients had B symptoms. Ferreri et al. reported on 30 patients with IVLBCL in Italy [4]. They also underscored the utility of rituximab, in which they compared treatment with and without rituximab (3-years OS: 89% *vs.* 38%). They described that skin involvement occurred in 43% of patients, whereas it was 9% to 27% in Japanese reports. In contrast, splenomegaly occurred more often in Japanese patients (63% to 67%) than in Italian patients (37%). Comparing the two reports above, typical Japanese variants can most likely explain the differences observed between two patient populations.

IVLBCL patients present with many non-specific symptoms, such as fever, HPS, and involvement of the Central Nervous System (CNS). The diagnosis of IVLBCL requires identifying lymphoma cells confined within vessels and a lack of nodal involvement or tumor mass formation [5]. IVLBCL was so difficult to diagnose, in fact, that the majority of patients were diagnosed at autopsy [6]. Thus, we think that the detected sites are important in making a diagnosis. Experience and clinical presentation provide hints to physicians, allowing them

to consider IVLBCL. Traditionally, when physicians suspect IVLBCL, a random skin biopsy has been recommended. However, in our cohort, a Bone Marrow Exam (BME) was used to diagnose IVLBCL in 5/6 patients. In our study, random skin biopsies were performed but failed to diagnose the disease. Different from the Western variant, the Asian variant shows more HPS. This means that more lymphoma cells are found in the BM. We assumed that in Japan, a BME might be more useful in detecting IVLBCL than a random skin biopsy.

The most important aspect of our report is that we performed cytogenetic analysis. To date, no large report has shown the karyotype of IVLBCL in detail. A few case reports described that chromosome 14 [7,8], 11 [9], and 6 [10-12] abnormalities were seen in each patient. Klairmont et al. [5] collected 29 cases with IVL reported chromosome abnormalities. They said chromosome 1,6 and 18 were present in more than 50% of the patients [12]. Our patients revealed complex karyotypes. Four patients had a chromosome 1 abnormality, and three patients had chromosome 11 and 21 abnormalities. Even in few cases, this information might offer important features of cytogenetic abnormalities in IVLBCL. However, correlation between chromosome abnormalities and clinical features remains unknown. It was reported that CD5 is seen in 30% to 40% of IVLBCL [13]. In our cases, 3/6 patients were CD5-positive. However, the clinical meaning of CD5-positive in IVLBCL is not clear.

IVLBCL is a rare but aggressive lymphoma that would benefit from a greater understanding of the disease. Although rituximab improved outcomes, current treatment results are not enough. We have to develop better treatment strategies for IVLBCL and gain a more thorough understanding of the genetic features of this devastating disease.

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