Clinical Features and Therapeutic Outcomes Comparing Primary Mediastinal Large B-cell Lymphoma to Mediastinal Hodgkin Disease

Rubén J. Cruz-Chamorro, MD, MS*; Joshua L. Rodríguez-López, MD†; Michael J. González-Soto, MD‡; Raúl Arroyo-Suárez, MD¶; Carmen Ortiz-Sánchez, PhD§; Jarline Encarnación-Medina, MS§; Fernando Cabanillas, MD**

Currently, there is limited data available comparing Primary Mediastinal Large B-cell Lymphoma (PMBL) and mediastinal Hodgkin disease, nodular sclerosis type (HDNS). This is a retrospective cohort study that compares the clinical features, histology through immunohistochemistry (IHC) and treatment outcomes of 19 cases of PMBL and 39 cases of HDNS diagnosed over 13 years at a single institution in San Juan, PR. Superior Vena Cava syndrome (SVCS) and elevated Lactate Dehydrogenase (LDH) levels were more frequently seen in the PMBL cohort. At the median follow-up visit, of 74 months, no significant difference was seen in overall survival or progression free survival between PMBL and HDNS. Almost all of the relapses in the PMBL group occurred within 12 months of diagnosis. Our data suggests that PMBL and HDNS differ in their clinical presentation and have a favorable prognosis.

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It is well known that lymphomas can involve the mediastinum as their primary site. Among them, PMBL and mediastinal Hodgkin Lymphomas originating in the thymus gland have similar clinical features. Both are more common in young women during their second and fourth decades of life (1, 2). PMBL usually presents as a bulky, anterior mediastinal mass and up to 50% of the patients present clinical symptoms of SVCS. Because of this, most of PMBL cases present as early-stage disease (3). PMBL comprises up to 10% of Diffuse Large B-cell Lymphomas (DLBCL), being a unique clinical entity in terms of epidemiology and clinical features when compared to other types of DLBCL (4). Hodgkin disease, nodular sclerosis type (HDNS) is the most common primary mediastinal Hodgkin Lymphoma, representing more than 95% of cases. Almost half of HDNS patients are asymptomatic at presentation and signs of SVCS are rarely seen (5, 6). Currently, most standard approaches in the management of mediastinal lymphomas are generally associated with favorable outcomes, however, treatment of PMBL remains controversial in comparison to other subtypes of Non-Hodgkin Lymphomas. The addition of Rituximab to Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) regimens with or without Radiation Therapy (RT) has shown to be efficacious, with a 5-year overall survival (OS) of approximately 90% (7). Treatment with Dose-Adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide and Rituximab (EPOCH-Rituximab) therapy without mediastinal RT has shown encouraging outcomes in PMBL, with a 5-year OS of 97% (8). Patients with early stage HDNS are typically treated with combined modality therapy (multi-agent chemotherapy followed by consolidative RT). Nonetheless, the current tendency is to minimize the use of RT to avoid potential long-term complications such as coronary artery disease and secondary malignancies. Advance stage HD is treated with a longer course of chemotherapy with or without RT. Population-based analysis have shown that HDNS has a 5-year OS of approximately 90% (9, 10). Even though, several studies have addressed the histopathologic and molecular differences of HDNS and PMBL, there are limited studies identifying methods to successfully distinguish the initial clinical presentation and dissecting the difference in treatment outcomes between these tumors. Therefore, with this retrospective cohort study we aim to compare the clinical features and therapeutic outcomes of patients with HDNS and PMBL.

Methods

Data collection

Study participants were identified using the electronic medical records database at Auxilio Cancer Center (ACC) in San Juan, Puerto Rico. Patients who had a confirmed diagnosis of PMBL (n=28) or HDNS that presented with a mediastinal mass (n=74) who were seen ACC between 2003 and 2016 were retrospectively recruited into this study. After additional revision, 44 of these

*Department of Radiation Oncology, H. Lee Moffitt Cancer Center, Tampa, Fl; †Department of Radiation Oncology, VA Caribbean Healthcare System, San Juan, PR; ‡Department of Radiology, University of Florida, Gainesville, Fl; ¶Department of Radiology, Case Western Reserve University MetroHealth System, Cleveland, OH; §Ponce Health Sciences University School of Medicine, Ponce, PR; **Auxilio Mutuo Cancer Center, San Juan, PR

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Address correspondence to: Rubén J. Cruz-Chamorro, MD, MS. Email: rubencruzeras@gmail.com

cases were excluded since they did not receive treatment at ACC. Demographic and clinical information, including dates of initial diagnosis, relapse and death were obtained from electronic medical records. Data was also collected regarding staging, LDH levels, treatment regimens, clinical findings of SVCS on initial presentation, IHC data and serologic markers.

Statistical analysis

Demographics, immunohistochemical markers, and outcomes were analyzed using contingency tables and chi-square tests. Yates' correction was applied when the number of observations was less than five. The survival curves were performed to evaluate the progression free survival (PFS) along with the overall survival (OS). Non-parametric test (Mantel–Cox test) was used to compare the survival distributions and estimate differences between PMBL and HDNS patients. Significance was achieved at p-value of <0.05.

Results

Our study cohort was composed of 19 PMBL and 39 HDNS cases. The demographics are summarized in Table 1. The median follow-up for the entire cohort was 74 months. The PMBL group had longer follow up (median 91 months, range 10-200 months) compared to the HDNS group (median 68 months, range 3-161 months). Alterations in certain markers were also evaluated in patients with both PMBL and HDNS (Table 2).

In the PMBL cohort, 13 were females and 6 were males, with a female to male ratio of 2.17 with a median age of 35 years. Regarding treatment, 17 patients (89%) with PMBL were treated systemically with the R-CHOP (rituximab, cyclophosphamide, vincristine, and prednisone), 1 patient received EPOCH-R, and 1 patient who presented with advanced-stage disease received GROC. More than half of the patients with PMBL (63%) received RT throughout the course of their illness. Among patients with PBML, five (26%) presented with SVCS at the time of diagnosis, while 14 (74%) did not (Table 1). Eight patients presented with extranodal involvement at the time of diagnosis (42%). Four patients (21%) presented with systemic B symptoms. Twelve patients (63%) had early stage (I-II) disease, while 7 patients had advanced stage (III-IV) disease (37%). LDH levels were elevated at presentation in 17 cases (90%) of patients with PMBL. Four patients suffered relapse (21%), 3 of them (75%) within 1 year of diagnosis and 1 patient (25%) relapsed

Table 1. Clinical and demographic characteristics of the study cohort (N=58).

Variables	PMBL (n=19) n (%)	HDNS (n=39) n (%)	p-value
Age, median (IQR)	35 (30-39)	37 (24-51)	0.631
Sex			0.487
Male	6 (32)	16 (41)	
Female	13 (68)	23 (59)	
Stage			0.905
I-II	12 (63)	24 (61)	
III-IV	7 (37)	15 (39)	
Extranodal sites			0.135
Yes	8 (42)	9 (23)	
No	11 (58)	30 (77)	
SVCS*			0.058
Yes	5 (26)	2 (5)	
No	14 (74)	37 (95)	
Elevated LDH			<0.001
Yes	17 (90)	11 (28)	
No	1 (5)	22 (56)	
Missing	1 (5)	6 (16)	

p-value was obtained from Chi-squared and Yate's correction was applied when required.
Significance for age was obtained using Mann-Whitney U test.
PMBL: primary mediastinal large B-cell lymphoma; HDNS: Hodgkin disease nodular-sclerosis type; SVCS, Superior Vena Cava syndrome at initial diagnosis.

Table 2. Serologic and Immunohistochemical markers evaluated for study participants.

Markers	PMBL (n=19) n (%)	HDNS (n=39) n (%)	p-value
B2MGB*			0.167
Yes	1 (5)	9 (23)	
No	15 (79)	23 (59)	
Missing	3 (16)	7 (18)	
CD20			<0.001
Yes	19 (100)	7 (18)	
No	0 (0)	29 (74)	
Missing	-	3 (8)	
CD15			<0.001
Yes	0 (0)	33 (85)	
No	8 (42)	5 (13)	
Missing	11 (58)	1 (2)	
CD30			0.003
Yes	12 (63)	38 (97)	
No	5 (26)	0 (0)	
Missing	2 (11)	1 (3)	
PAX5			0.582
Yes	12 (63)	33 (85)	
No	0 (0)	1 (2)	
Missing	7 (37)	5 (13)	
CD45			<0.001
Yes	7 (37)	1 (3)	
No	2 (10)	31 (79)	
Missing	10 (53)	7 (18)	
CD10			0.160
Yes	4 (21)	0 (0)	
No	13 (68)	14 (36)	
Missing	2 (11)	25 (64)	
Bcl-2			0.350
Yes	14 (74)	13 (33)	
No	2 (11)	6 (16)	
Missing	3 (16)	20 (51)	
Bcl-6			<0.001
Yes	17 (89)	9 (23)	
No	0 (0)	14 (36)	
Missing	2 (11)	16 (41)	
MUM-1			0.499
Yes	10 (53)	11 (28)	
No	1 (5)	1 (3)	
Missing	8 (42)	27 (69)	

p-value was obtained from Chi-squared and Yate's correction was applied when required. *Yes = Elevated B2MGB over 1.7 mcg/mL.

Table 3. Treatment and relapse data from study participants.

Variables	PMBL (n=19) n (%)	HDNS (n=39) n (%)	p-value
Radiation Therapy			0.019
Yes	12 (63)	12 (31)	
No	7 (37)	27 (69)	
Relapse			0.673
≤12 months	3 (16)	4 (10)	
>12 months	1 (5)	2 (5)	
No relapse	15 (79)	33 (85)	

p-value was obtained from Chi-squared and Yate's correction was applied when required.

13 months after diagnosis (Table 3). None of the PMBL patients who relapsed presented with SVCS at diagnosis. One patient had a relapse after 13 months of initial diagnosis (Figure 1). Out of the 19 cases of PMBL, 17 (89%) are currently alive and in remission after therapy (Figure 2).

In the HDNS cohort, 23 were females and 16 were males, with a female to male ratio of 1.44 and a median age of 37 years. All patients (100%) with HDNS received ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). Twelve (12) patients (31%) received consolidative RT, versus 63% of the patients with PMBL throughout the course of their illness (p=0.019) (Table 3). Most of the HDNS patients did not have extranodal involvement (77%) nor presented with SVCS (95%) at the time of diagnosis. Twelve patients (31%) presented with systemic B symptoms at the time of diagnosis, 24 (61%) had early stage (I-II) disease, and 11 (28%) patients had elevated LDH levels at diagnosis. Out of the 6 patients (15%) that suffered relapse, 4 (67%) cases were within 1 year of follow up and 2 cases (33%) relapsed 13 months after diagnosis. One HDNS patient who relapsed presented with SVCS at diagnosis. One of the patients suffered a first relapse after 8 months and a second relapse 46 months after initial diagnosis. Two of the patients with HDNS died.

The PMBL cohort showed CD20 (100%), CD45 (37%), and Bcl-6 (89%) positivity more frequently, whereas CD15 (85%) and CD30 (97%) positivity was more commonly seen in the HDNS cohort (Table 2). Regarding OS and PFS, no significant differences were observed among patients with PBML and HDNS (p>0.05).

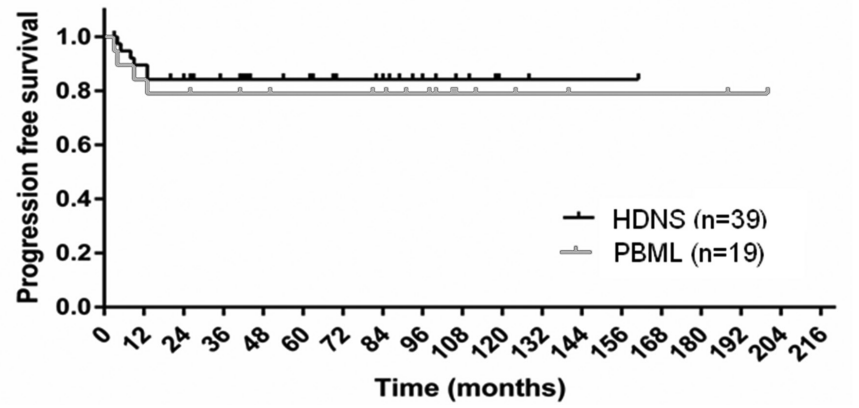
Discussion

In this report, we describe the clinical features and outcomes of PMBL and HDNS patients that were treated with chemotherapy and +/- RT. We found no statistically significant differences in OS and PFS between patients with PMBL and patients with HDNS.

Comparison of clinical features between PMBL and HDNS

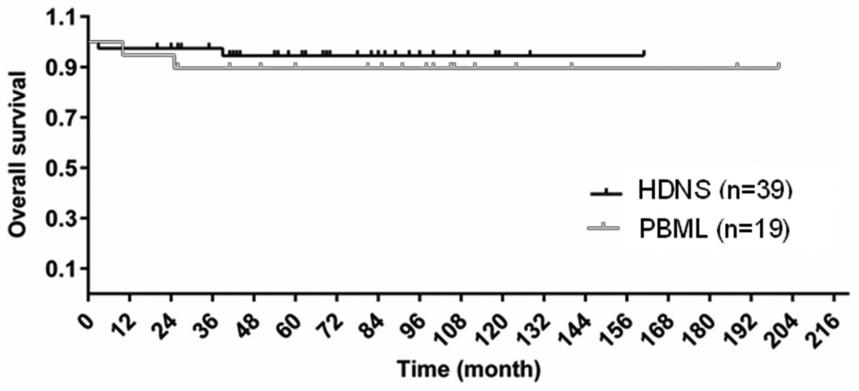
Consistent with prior reports, both groups showed a female predominance (Table 1) (2, 11, 12). Previous studies have shown that SVCS is the most common complication at diagnosis in patients with PMBL, occurring in up to 50% of patients (2, 3). Our study found that SVCS was more prevalent in patients with PMBL (26%) than in patients with HDNS (5%) (p=0.058). None

Figure 1. Progression-Free Survival (PFS) of patients with Primary Mediastinal B-Cell Lymphoma (PMBL) versus Hodgkin disease, nodular sclerosis type (HDNS).



Black line represents patients with HDNS. Gray line represents patients with PMBL.

Figure 2. Overall Survival (OS) of patients with Primary Mediastinal B-Cell Lymphoma (PMBL) versus Hodgkin disease, nodular sclerosis type (HDNS).



Black line represents patients with HDNS. Gray line represents patients with PMBL.

of the PMBL patients that presented with SVCS relapsed. This may suggest that SVCS is a good prognostic factor in patients with PMBL by allowing early detection and prompt management. One retrospective study of 153 patients showed that 77% of patients with PMBL presented with elevated LDH levels and 47% of the patients presented with systemic B symptoms (i.e., fever, night sweats, weight loss) at the time of diagnosis (5). In our PMBL group, we found that most of the patients (90%) presented with elevated LDH levels ($p<0.001$). This highlights the clinical value of LDH in the initial workup of a mediastinal mass, especially when trying to differentiate between PMBL and HDNS. Furthermore, 4 patients (21%) with PMBL presented with systemic B symptoms. Twenty-seven patients (69%) in the HDNS cohort did not present systemic B symptoms at the initial visit. Reports of HDNS patients have shown that 30% of patients develop systemic B symptoms (6). In our study, 42% of PMBL cases presented with extranodal disease, 16% of them involving two or more sites. All patients with PMBL who relapsed presented with extranodal disease. Which is similar to previously reported data by the National Cancer Institute (NCI) that described a series of 27 patients with PMBL where extranodal disease was found more commonly in cases with disease recurrence (13). In our study, 23% of HDNS patients presented with extranodal disease, with the majority (78%) involving only one site. Two (33%) of the HDNS patients who relapsed presented with extranodal disease.

Results of therapy

Reported studies on management and outcome of patients with PMBL have been variable, showing Failure-Free Survival (FFS) rates ranging between 39-88% (2). Prospective trials in the Rituximab era have demonstrated an improvement in FFS rates up to 93% (8, 14, 15). Our study showed a 5-year PFS rate of 80% and a 5-year OS rate of 90% for patients with PMBL, suggesting that their prognosis is superior to that of the non-mediastinal large cell lymphomas, with a 5-year PFS and OS rate of approximately 57% and 55%, respectively (16, 17).

Previous studies have shown that 95% of patients with HDNS will be alive and disease-free at 10 years after chemoradiation (6). This cohort demonstrated a 5-year PFS rate of 85% and a 5-year OS rate of 95%, consistent with the results reported in the literature (Figures1 and 2). PFS and OS difference between patients with PMBL and HDNS was not statistically significant ($p=0.59$ and $p=0.47$, respectively), suggesting that current treatment regimens for both diseases show favorable outcomes. A phase 2, prospective study of NCI showed encouraging outcomes in 51 patients with PMBL treated with infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) and filgrastim without RT. After follow-up, 94% of the patients were in complete remission with an event free survival rate and an overall survival rate of 93% and 97%, respectively. Two of the three patients who had persistent disease after DA-EPOCH-R treatment received RT (8).

Several limitations are associated with our study, including its retrospective nature as well as the small number of patients. In addition, this study only included patients treated at a single institution. The variability in treatment regimens in our study may also impact our results.

Conclusion

In conclusion, PMBL and HDNS share several features such as their initial location and excellent prognosis. Nonetheless, they differ in their initial clinical presentation, biological characteristics, and treatment regimens. SVCS presentation and elevated levels of LDH are key findings in patients with PMBL. Most of the relapses in patients with PMBL occur within 12 months of initial diagnosis. Future studies should focus on treatment de-intensification to minimize toxicity.

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Resumen

Actualmente, la data disponible comparando el Linfoma Primario de mediastino de célula B grande (PMBL) y Hodgkin linfoma del mediastino (HDNS) es limitada. Realizamos un estudio retrospectivo para comparar la presentación clínica, histología y los resultados del tratamiento de 19 casos de PMBL y 39 casos de HDNS que fueron tratados en una sola institución en San Juan, PR. El Síndrome de la Vena Cava Superior (SVCS) fue visto más frecuentemente en pacientes con PMBL, al igual que niveles elevados de Lactato Deshidrogenasa (LDH). En una mediana de tiempo de seguimiento de 74 meses, no hubo diferencia significativa en sobrevivencia promedio (OS) ni en supervivencia libre-de progresión. La mayoria de los casos de PMBL que sufrieron recaídas ocurrieron dentro de los primeros 12 meses del diagnóstico. Nuestra data sugiere que PMBL y HDNS se diferencian en su presentación clínica y se asimilan en su prognosis favorable.

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