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Aggressive Diffuse Intermediate Size B-Cell Lymphoma With P53 Mutation Presented as Primary Bone Marrow Lymphoma

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Abstract

Primary bone marrow lymphoma (PBML) is a disease entity in which lymphoma primarily originates in the bone marrow without signs of involvement of lymph nodes, spleen, liver, or any other organs, and excludes leukemia/lymphoma. PBML has been a rare presentation of malignant lymphoma, and most of the cases have a poor prognosis and require rapid diagnoses and treatments. Among all PBMLs, diffuse large B-cell lymphoma (DLBCL) is the most common pathological subtype. Over 25 years and from 7 institutions, the International Extranodal Lymphoma Study Group retrospectively collected PBML cases and, in 2012, published these 21 cases, including 19 cases of B-cell lymphoma and 2 cases of peripheral T-cell lymphoma. Among the B-cell types, DLBCL accounted for 79% and follicular lymphoma (FL) for 21%. DLBCLs were characterized by the existence of large cells. In this article, we present a rare case of high-grade aggressive type with P53 mutation, intermediate-sized B-cell lymphoma, excluded FL by the absence of FL lymphoma markers, presented as PBML. Our patient had rapid progression and succumbed to the disease shortly after diagnosis. Upon literature review, 62 B-cell lymphoma cases were identified that presented as PBML (51 high-grade and 11 low-grade)—mostly case reports. Among these, only one case was reported as intermediate-sized DLBCL-like lymphoma but not with aggressive features. Our case represents the first case of aggressive intermediate-sized lymphoma, not a FL, with P53 mutation, highly elevated lactate dehydrogenase, and Ki-67 presented as PBML. Such a profile would need to be quickly recognized and aggressive treatment applied, such as CART (chimeric antigen receptor T-cells) therapy or DA-EPOCH-R (dose-adjusted EPOCH [etoposide-prednisone-oncovin-cyclophosphamide-hydroxydaunorubicin] and rituximab) with or without venetoclax.

Keywords

cytopenia, primary bone marrow lymphoma, PBML, P53 mutation

Introduction

Primary bone marrow lymphomas (PBMLs) are lymphomas originating in the bone marrow without evidence of lymph node, spleen, liver, or any other organ involvement.[1] Based on a retrospective study of the International Extranodal Lymphoma Study Group spanning 25 years and 7 countries within 25 years, only 21 PBML cases met the criteria reflecting its infrequency.[1] Most PBMLs are B-cell non-Hodgkin lymphomas, among which the diffuse large B-cell lymphomas (DLBCLs) account for the majority. In the above-cited study, 19 of the 21 cases were B-cell lymphoma, and 79% were DLBCL and 21% were follicular lymphoma (FL). DLBCLs are known for poor prognosis with a 2-year survival rate of 30% and median survival of 14.9 months.[2] Multiple known factors, such as high lactate dehydrogenase (LDH) or high Ki-67 proliferation index, indicate the poor prognosis of primary bone marrow B-cell lymphoma.

In this article, we present a rare case of aggressive high-grade intermediate-sized B-cell lymphoma with P53 mutation presented as PBML, without a typical marker of a large-sized cell as DLBCL and following a rapid clinical course as DLBCL.

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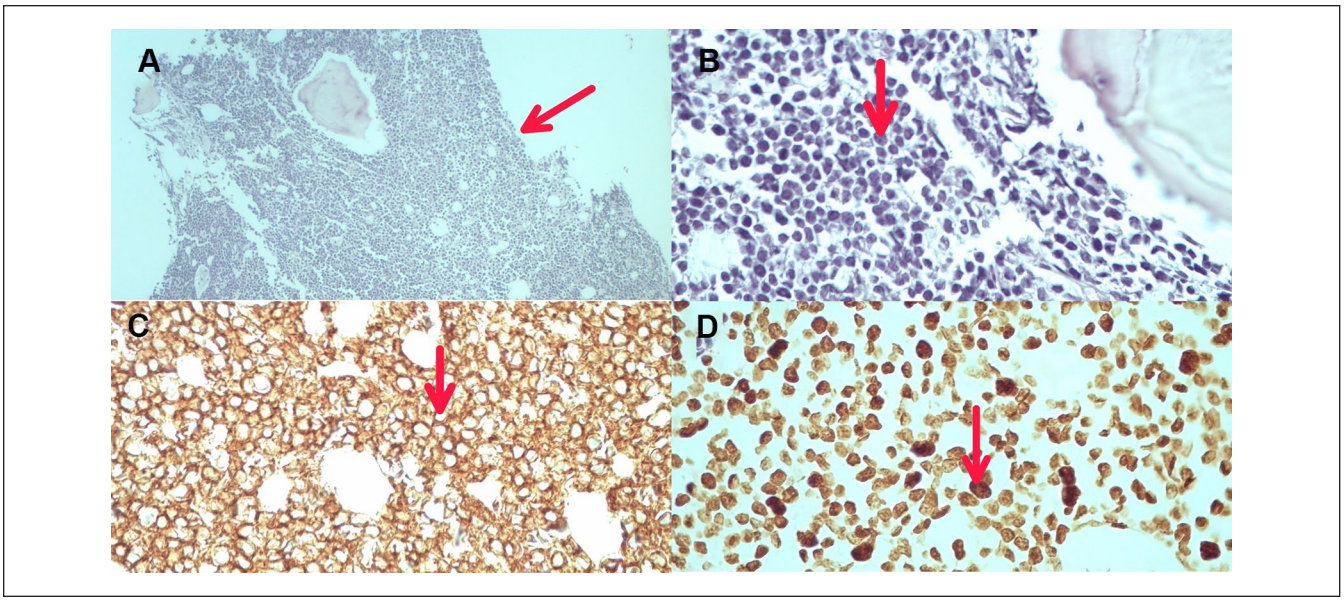

Figure 1. Bone marrow biopsy. (A) Bone marrow core biopsy, hematoxylin and eosin (H&E) stain, 10×. Markedly hypercellular marrow (>90%) with diffuse atypical lymphoid Infiltrate (arrow). (B) Bone marrow biopsy, H&E stain, 50×. Sheets of atypical medium-sized lymphoid cells (arrow). (C) Positive for CD20 immunohistochemical stain showing strong membrane positivity (arrow) 50×. (D) Ki-67 immunohistochemical stain very high (>90%). Arrow indicating strong nuclear staining positivity 50×.

Case Report

A 74-year-old Hispanic male with a past medical history of asthma and chronic obstructive pulmonary disease presented to the hospital with generalized weakness and weight loss. The initial laboratory result was significant for thrombocytopenia with a platelet count of 30×10^9/L and normocytic anemia with hemoglobin of 12.1 g/dL and hematocrit of 35.6. The comprehensive metabolic panel showed increased creatinine of 1.27 (which resolved with IV fluids), normal alanine aminotransferase, slightly elevated aspartate aminotransferase of 99, and a significantly elevated LDH of 4300 IU/L. The patient was also found to have an elevated lactic acid of >12, likely secondary to the rapid turnover of tumor cells. Serum protein electrophoresis showed findings suggestive of acute inflammation pattern with an elevation of acute-phase proteins. The HIV test was negative. Vital signs and physical examination were unremarkable, with no lymphadenopathy or splenomegaly. Peripheral smear showed 1 to 2 lymphoblast-like cells and nucleated red blood cells, with no schistocytes or platelet clumping. Imaging studies, including computed tomography of the chest, abdomen, and pelvis, revealed no significant lymphadenopathy or splenomegaly. Then, bone marrow biopsy was performed, which showed markedly hypercellular marrow with sheets of atypical medium-sized lymphoid cells, and no evidence of hemophagocytosis (Figure 1). Flow cytometry analysis on bone marrow cell showed 54% were abnormal lymphocytes, expressing Lambda, CD19, CD20, CD22, CD10dim, CD11c, CD23, and FMC7 suggests follicular center cell derivation indicated B-cell lymphoma. Immunohistochemistry indicated B-cell lymphoma with CD20+, CD3−, CD5−, CD10+, CD23−, CD43+, Cyclin D1−, BCL-2−, BCL-6+, MUM-1−, and Ki-67+ (>90%). Fluorescence in situ hybridization (FISH) tests showed no evidence of MYC gene rearrangement, no evidence of BCL2-IGH [translocation t(14;18)] gene rearrangement, and no evidence of BCL6 (3q27) breakpoint translocation. Immunochemistry also showed no Myc expressions.

Cytogenetic analysis revealed a normal karyotype: 46, XY [20]. A next-generation sequencing study showed TP53 (pTP53 p.Tyr220His) and unknown clinical significance of NRAS (p.Ser65Asn) mutation. The patient was found to have elevated transaminases and bilirubin prior to initiation of chemotherapy. Subsequent liver biopsy showed the same histology as bone marrow. The patient's essential clinical features are summarized in Table 1. The NCCN-IPI score of 6 (age >60 to ≤75, LDH >3-times upper limit of the normal range, Ann Arbor stage IV, extranodal disease, ECOG [Eastern Cooperative Oncology Group] Performance Status = 1) gave a poor prognosis. The patient was empirically started on the R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen. Unfortunately, 1 hour after the infusion of rituximab, the patient had a cardiac arrest. The patient eventually expired despite supportive measures.

Discussion

Primary bone marrow lymphomas are lymphomas that primarily arise in the bone marrow without lymphadenopathy and hepatosplenomegaly. Current criteria for the diagnosis

Table 1. Summary of Patient's Pertinent Laboratory Findings.

CBC	Hb = 12 g/dL; WBC = 4.2 × 10^9/L; platelets = 30000/μL[a]
PB smear	Erythroblast (+), immature lymphocytes (+)
Chemistry	LDH = 4300 IU/L[b]; AST = 99 μ/L
CT scan	Hepatosplenomegaly, minimal lymphadenopathy
Bone marrow	Full of atypical medium sized lymphoid cells
Flow cytometry	CD19+, CD20+, CD10dim, CD22+, CD23+, CD11c+, FMC7+
Immunochemistry	CD20+, CD3−, CD5−,CD10+, CD23−,CD43+, CyclinD1−, BCL2−, BCL6+, MUM-1−, Ki-67 (90%)
FISH test	No MYC gene rearrangements, No BCL-2-IGH, or BCL6 breakpoint translocations
Cytogenetic studies	46XY
NG sequence	TP53 (p.Tyr220His) mutation, NRAS (p.Ser65Asn) mutation

Abbreviations: CBC, complete blood count; Hb, hemoglobin; WBC, white blood cells; PB, peripheral blood; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; CT, computed tomography; FISH, fluorescence in situ hybridization; NG, next generation.
[a]Per milliliter.
[b]Normal values (140-280 IU/L).

of PBML are as follows: (1) isolated bone marrow infiltration (regardless of peripheral blood involvement); (2) no evidence of lymph node, spleen, liver, or other extra bone marrow involvement on physical examination or imaging studies (thoracic, abdominal, and pelvic computed tomography scan or ^{18}F-fluorodeoxyglucose positron emission tomography scan); (3) absence of localized bone tumors; (4) absence of bone trabeculae destruction in the bone marrow biopsy; and (5) exclusion of leukemia/lymphoma, such as chronic lymphocytic leukemia/small lymphocytic lymphoma, prolymphocytic leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma, splenic marginal zone lymphoma, hairy-cell leukemia, Burkitt lymphoma (BL), and acute lymphoblastic leukemia.[1] The most common type of PBML is DLBCL. There are also other types, including Hodgkin's lymphoma, peripheral T-cell lymphoma, ALK-negative anaplastic large cell lymphoma, and FL.[3]

In this patient, the morphology of lymphoma cells is characterized by diffuse pattern atypical medium-sized lymphoid cells. The surface markers CD10+, BCL2−, BCL6+, and the highly expressed Ki67 indicated highly aggressive B lineage lymphoma, and pointed to the possibility of BL. However, the lack of MYC/IGH gene or Myc-kappa chain or Myc-lambda chain rearrangement makes BL unlikely, and the absence of large lymphoid cells usually does not fit the diagnosis of DLBCL, but more like FL type. FL was characterized by t(14;18) by FISH or cytogenetic studies, so the FISH and cytogenetic studies showed he apparently was not a case of FL. The lack of BCL-2 and BCL-6 translocation also ruled out the diagnosis of double-hit lymphoma. Using the 2008 classification, this case is categorized as "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL" (BCLU) for the subset of very aggressive tumors, which are hard to distinguish between DLBCL and BL. In the 2016 World Health Organization classification, these cases are included under the category of high-grade B-cell lymphoma, not otherwise specified (HGBL, NOS).[4]

On literature review from 2000 to August 2020, we identified 62 primary bone marrow B-cell lymphoma (PBMBCL) cases presented in the English literature, including our case (Table 2). There were 51 high-grade BCL cases, and among these 77% (48/62) were DLBCL and 5% (3/62) were left unclassifiable.[1,3,5-33] Meanwhile, there were 11 cases of low-grade BCL, and 11% (7/62) were FLs.[1,34,35] According to the character of our case, we focused more on the analysis of HGBL. HGBLs were characterized as rapidly progressive and had high mortality, even with treatment. In our review, 40% (16/40) of cases died within 2 years (Figure 1). DLBCL is the most common pathological type in HGBL. Most DLBCLs presented diffuse large lymphoid cells or the existence of large lymphoid cells mixed with medium/small lymphoid cells in bone marrow smear. Kosugi et al[6] reported a case with monomorphic medium-sized atypical lymphocytes on bone marrow smear, and they diagnosed the case as DLBCL based on the immunophenotype result. However, the LDH is not highly elevated, and the progression of this case is relatively benign, likely was a case of FL with a good prognosis. Our case is the first reported case of aggressive type with medium size-like FL type PBMBCL.

Leucoerythroblastic reaction, defined as the presence of immature erythroid cells and immature myeloid cell in the peripheral blood, is associated with metastatic cancer or hematologic neoplasia. Leucoerythroblastic reaction is common in solid tumors such as prostate, lung, breast, and gastric cancer. Leucoerythroblastic reaction is usually considered as a sign of bone marrow infiltration or disseminated metastatic disease and is viewed as a poor prognosis factor.[36] These signs are among the characteristics of the peripheral findings of PBMBCL.

For the past 20 years, R-CHOP have been used as the first-line standard treatment to an aggressive form of non-Hodgkin's lymphoma, such as DLBCL. In cases of PBMBCL, the same regimen has been applied due to the similar immunophenotypic category. However, the prognosis of patients varies extremely. In our review of the high-grade PBMBCL

Table 2. Clinical Features of Reported Cases of Primary Bone Marrow Lymphoma.

Case	Diagnosis	Age (years)	Sex	B symptoms	LDH	LER	Ki-67	Double hit	TP-53 mutation	Treatment	Initial response	Outcome	OS (month)	Reference
1	DLBCL and HLH	62	Male	+	H					RSHE	NA	Dead	1	3
2	DLBCL and HLH	72	Male	+	H					EDC	CR	Dead/relapse	9	3
3	DLBCL and HLH	57	Male	+	H 309		90%			RCHOP	CR	Alive	10+	5
4	DLBCL and HLH	73	Female	+						RCHOP	PR	Alive	3+	19
5	DLBCL and HLH	70	Female	+	H 882					RCHOP	PR			29
6	DLBCL and CAD	70	Female	−	H 802	−		−		RCHOP	CR	Alive	22+	6
7	DLBCL and CAD	75	Female	−						RCHOP	CR	Alive	6+	6
8	DLBCL and CAD	76	Male	+	H 558					R-THP-COP	CR	Dead/relapse	19	8
9	DLBCL and CAD	69	Male	−	H 728			−		RCHOP	CR	Alive	4.2	7
10	DLBCL	62	Male	+	H					REPOCH	CR	Alive	25+	3
11	DLBCL	50	Female	+	H					RCHOP	PR	Dead/relapse	7	3
12	DLBCL	58	Male	+	H 4703		70%			RCHOP	CR	Dead/relapse	19	9
13	DLBCL	41	Male	+	H 1191	−	+			CHOEP	PR	Lost	10+	10
14	DLBCL	56	Male	−	H 372		+			RCHOP	PR	Alive	43+	11
15	DLBCL (THRLBCL)	52	Female	−	N					RCHOP	PR	Dead		14
16	DLBCL	52	Female	−						RCHOP	NA	Dead		12
17	DLBCL	64	Male	−						ChlP	CR	Alive	180+	12
18	DLBCL	51	Female	−						RCHOP	CR	Alive/relapse		12
19	DLBCL	76	Female	−	H	−				RCHOP	CR	Alive	24+	13
20	DLBCL	39	Female	−	N					RCHOP+ASCT	CR	Alive	84+	15
21	DLBCL	44	Male	+	H 666					CHOP	NA	Dead	8	16
22	DLBCL	65	Male	+	N					RCHOP	CR	Alive	20.4+	1
23	DLBCL	63	Female	−	H					HD-CHOP	PR	Dead	54	1
24	DLBCL	29	Male	−	H					CHOP	F	Dead	7.2	1
25	DLBCL	63	Female	−	H					COP	PR	Dead	21.6	1
26	DLBCL	71	Female	−	H					RCHOP	CR	Dead	18	1
27	DLBCL	45	Male	−						RCHOP	F	Dead	7.2	1
28	DLBCL	72	Male	−	H					RCHOP	F	Alive	4.8+	1

(continued)

Table 2. (continued)

Case	Diagnosis	Age (years)	Sex	B symptoms	LDH	LER	Ki-67	Double hit	TP-53 mutation	Treatment	Initial response	Outcome	OS (month)	Reference
29	DLBCL	67	Male	−	H					ALL	F	Dead	28.8	1
30	DLBCL	32	Male	−	H					VACOPB	CR	Alive	105.6	1
31	DLBCL	78	Female	+	H 45000			−		RCHOP	CR	Dead/relapse	4	17
32	DLBCL	73	Female	+	H 6372			−		CHOP	CR	Dead/relapse	15.6	17
33	DLBCL	42	Male	+	H 647			−		RCHOP	PR	Alive	0.12	17
34	DLBCL	51	Male	−	H					CHOP	F	Dead	12	1
35	DLBCL	79	Male	−	H					RCHOP	CR	Alive	18+	1
36	DLBCL	70	Male	+	N					CHOEP	PR	Dead	9	1
37	DLBCL	67	Male	+										18
38	DLBCL	31	Male	+						RCHOP+ASCT	CR	Alive	12+	20
39	DLBCL	66	Female	+	H 735					RCHOP	CR	Alive	96+	21
40	DLBCL	77	Male	−	H 444			−		RCHOP	CR			22
41	DLBCL	41	Male	+		+				RCHOP	F			23
42	DLBCL (EBV+)	57	Male	−	H 510	−				RCHOP	CR			32
43	DLBCL	18	Female	−	H 496		65%			R-Hyper CVAD	CR	Alive	12+	24
44	DLBCL	64	Male	−	H>1200	−	30%	−	−	RCHOP	CR	Alive	18+	25
45	DLBCL (HIV+)	55	Male	+	H 2400					R		Dead (infection)	0.5	26
46	DLBCL	58	Female	+		−				RCHOP		Lost		27
47	DLBCL	74	Male	−	N 258	−								28
48	DLBCL	40	Male	−	H 3767	−				Hyper CAVD	CR	Alive	23+	31
49	BCLU	73	Male	−	H 1141	−		+ (MYC/ BCL6)		RCHOP	CR	Alive	10+	33
50	PBNHL	55	Female	+	H 456	−				RCHOP	CR	Alive		30
51	High grade BCL	74	Male	−	H 4300	+	>90%	−	+	R		Dead (cardiac arrest)	0.5	Our case

Abbreviations: ALL, prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide, cytarabine, bleomycin, 6-mercaptopurine; ASCT, autologous stem-cell transplantation; B, B symptoms; BCL, B-cell lymphoma; BCLU, B-cell lymphoma, unclassifiable; C, cyclophosphamide; CAD, cold agglutinin disease; ChlP, chlorambucil, prednisolone; CHOEP, cyclophosphamide, doxorubicin, vincristine, prednisolone, etoposide; CHOP, cyclophosphamide, epirubicin, vincristine, prednisone; COP, cyclophosphamide, vincristine, prednisone; CR, complete response; DLBCL, diffuse large B-cell lymphoma; EDC, etoposide, dexamethasone, cyclosporine; F, failure; FL, follicular lymphoma; H, high; HD, high dose; HLH, hemophagocytic lymphohistiocytosis; HyperCAVD, cyclophosphamide, vincristine, dexamethasone, adriamycin/methotrexate, cytarabine; N, normal; NA, not available; PBNHL, primary B-cell non-Hodgkin's lymphoma; PR, partial response; R, rituximab; RCHOP, rituximab,cyclophosphamide, epirubicin, vincristine, prednisone; REPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; RSHE, rituximab, methylpredinisolone, etoposide; THP-COP, pirarubicin, cyclophosphamide, vincristine, prednisolone; THRLBCL, T-cell/histiocyte-rich large B-cell lymphoma; VACOPB, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin.

cases, some patients remained in remission for several years,[15,21] while other patients relapsed early or responded poorly to therapy that presented an inferior prognosis under standard R-CHOP therapy. The poor response observed in our patient, especially with P53 mutation, might prompt us to use CART (chimeric antigen receptor T-cells) therapy as the initial treatment. Greater experience with such cases might help answer these questions.

Ki-67, a nuclear antigen that was synthesized at the beginning of cell proliferation, is associated with the progression of non-Hodgkin's lymphomas and prognostic significance in DLBCL patients treated with R-CHOP. It is suggested in a study that high expression of Ki-67 in bone marrow, especially more than 90%, would predicate a poor outcome.[37] Thus, Ki-67 works as an independent prognostic factor in the rituximab era. There were only 7 cases reporting Ki-67 on the bone marrow smear, including our case. Two cases reported >90% Ki-67 expression.[5] One had achieved overall survival for more than 10 months, and the other one is our case.

Many studies have shown that P53 mutation is an independent indicator of poor prognosis in DLBCL. Recent studies have suggested that viewing the P53 mutation as another hit predicts a poor prognosis similar to double-hit lymphoma.[38] The P53 protein encoded by the P53 gene is a vital tumor suppressor. P53 mediates cell cycle arrest, DNA repair, apoptosis, senescence, and autophagy in the nucleus and cytoplasm under cell stress. P53 dysfunction is related to the occurrence of lymphoma and the progression of the disease.[39] Therefore, P53 gene mutation or deletion will have a significant impact on the prognosis of lymphoma. The negative impact of P53 mutation on the patient's outcome is associated with R-CHOP failure. Two cases in our review carried the P53 mutation (cases 44 and 51). Our case is the only one we are aware of that has tested positive for the P53 mutation. A couple of cases mentioned the possibility of P53 mutation being the factor of R-CHOP therapy failure or early relapse of lymphoma.

Conclusion

In conclusion, our PBML case represents a rare intermediate-sized B-cell, not typically recognized as DLBCL, with marked elevated LDH, more than 90% Ki-67 index, with P53 mutation, and showed no response to R-CHOP. Aggressive treatment such as CART therapy or DA-EPOCH-R [dose-adjusted EPOCH (etoposide-prednisone-oncovin-cyclophosphamide-hydroxydaunorubicin) and rituximab] with or without venetoclax should be considered in patients with similar characteristics.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Informed consent for patient information to be published in this article was not obtained.

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