Original Article

Germinal Center-Derived Diffuse Large B-cell Lymphomas with Aberrant Co-expression of MUM1 in Adults and Children

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Abstract

The aim of this study is to analyze the clinical and pathological features of germinal center (GC)-derived diffuse large B-cell lymphomas (DLBCL) with aberrant co-expression of MUM1 and to further analyze the differences between adults and pediatric populations. Clinical and pathological data of 32 cases of GC-derived DLBCL with aberrant co-expression of MUM1 were reviewed and analyzed. Thirty-two cases were categorized into pediatric (n=12) and adult (n=20) groups. GC-derived DLBCL with aberrant co-expression of MUM1 was found to manifest a wide age range, extensive involvement sites, different histopathological distribution, and complex clinical presentations. Compared to adults, pediatric patients showed a significantly higher frequency of Waldeyer's ring (WR) involvement (P=0.008), higher frequency of stage II (P=0.035), and lower incidence of fatality (P=0.014). Among the 32 cases, lymphomas were frequently involved in WR, followed by the gastrointestinal tract, lymph nodes, and bone marrow. Pediatric patients showed a significantly higher frequency of WR involvement than adult patients (P=0.008). Lymphomas involving WR in adults showed similar localized clinical stages, excellent outcomes, and pathological features compared to the disease in the pediatric population. Lymphomas involving the gastrointestinal tract in adults shared clinical features with the disease in children but with high P53 positive expression. GC-derived DLBCL with aberrant co-expression of MUM1 in adults is clinically more heterogeneous than children. Tumors involving WR in adults share many similarities to their pediatric counterparts.

Keywords: *GC-derived DLBCL, MUM1, Germinal center, Adults, Children*

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. DLBCL is classified into germinal center B cell (GCB)-like DLBCL, and the activated B cell (ABC)-like DLBCL, according to the immunoreactions of CD10, BCL6, and interferon regulatory factor 4 (IRF4)/multiple myeloma oncogene 1 (MUM1);[1] however, ~15% remains unclassified.[2] Substantially, according to the Hans algorithm, IRF4/MUM1 is considered a non-GC marker, whereas CD10 and BCL6 are considered GC markers. Notably, IRF4/MUM1 and GC markers show mutually exclusive expression patterns in B-cells, suggesting a reciprocal regulation of IRF4/MUM1 and GC markers expression.[3]

GCB and ABC markers have been the most favored algorithms to predict prognosis in DLBCL patients.[4] Previous studies showed that the ABC type was an independent predictor of progression-free survival and overall survival, whereas the GCB type was not a prognostic factor.[5] Although MUM1 is used as a post-GC marker, IRF4/MUM1 positive expression is observed in a small proportion of GC B-cells that reside within the light zone of GCs and displays the morphology of centrocytes, or plasmablastic features in some cases.[6] In a previous study, although MUM1 is used as a post-GC marker, DLBCL with coexpression of CD10 and MUM1 was classified as a GCB subtype. MUM1 expression is associated with worse outcomes in CD10+ DLBCL patients.[7] However, it is still unclear whether all DLBCLs with coexpression of CD10, BCL6, and MUM1 represent clinically and pathologically the same disease with poor prognosis.

About one-third of DLBCLs manifest primarily in extranodal sites.[8] Waldeyer's ring (WR) represents one of the most common extranodal sites.[9] WR DLBCLs display distinct clinicopathologic features compared with conventional DLBCLs and seem to be associated with a better outcome

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than their nodal counterpart.[10] However, published series of DLBCL arising in specific extranodal sites among different age groups are limited.

In this study, we describe the peculiar clinicopathologic characteristics of patients of GC-derived B-cell lymphoma with aberrant co-expression of MUM1. Moreover, we further analyze the differences in specific extranodal sites between adults and pediatric population.

Materials and Methods

Case selection

Our study was approved by the Ethics Committee of Xinhua Hospital, Affiliated with Shanghai Jiaotong University School of Medicine. From September 2014 to January 2020, 643 cases of lymphoma were obtained from a single institution of Shanghai Xinhua Hospital. According to histopathological, and immunohistochemical analyses, 32 cases diagnosed as DLBCL aberrantly co-expressing CD10, BCL6, and MUM1/IRF4 in >50% of tumor cells were included in the study.[11]

Ann Arbor classification and the International pediatric NHL staging system were staged for adult and pediatric patients, respectively. Clinical information was recorded for each patient, including age, gender, date of initial diagnosis, symptoms and signs at presentation, clinical stage, and follow-up information.

Pediatric patients received chemotherapy from the China Children's Cancer Group (CCCG)-BNHL protocol. Regimens of R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone), R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and adriamycin) or EPOCH, both R-CHOP and R-EPOCH, R-CHOP and MTX (methotrexate), R-MA (methotrexate and cytarabine), both R-CHOP and ICE (Ifosfamide, carboplatin, and etoposide), and R-COP (rituximab, cyclophosphamide, vincristine, and prednisone), were used for adult patients.

Histopathology and immunohistochemistry

The morphologic and immunophenotypic features were studied on formalin-fixed and paraffin-embedded tissue sections of the diagnostic biopsies. Immunohistochemistry was performed using a panel of monoclonal and polyclonal antibodies, as follows: CD10 (clone 56C6, Leica Biosystems); BCL6 (clone P1F6, DAKO); MUM1 (clone MUM1p, DAKO); Ki-67 (clone MIB-1, DAKO); BCL2 (clone 100/D5, DAKO); MYC (DAKO); P53 (clone DO-7, DAKO). MYC was considered as positive when greater than 40% of tumor cells exhibited staining.[12] A positive threshold was defined at 50% for BCL2 and MUM1, 30% for CD10 and BCL6. GCB phenotype was evaluated by antibodies of C10, BCL6, and MUM1.

Statistical analysis

Contingency tables were analyzed using Pearson Chi-square statistic. Differences with *P*-value <0.05 were defined as statistically significant. The software of SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical calculations.

Results and Discussion

Clinical findings

Table 1. Clinical features of germinal center-derived B-cell lymphomas with IRF4/MUM1 positive expression in 32 cases

Case no.	Age (year)/ Gender	Clinical initial diagnosis	Site of Involvements		LDH (u/L)	Stage	Treatment protocol	Follow-up (months)
			EN	LN				
				Pediatric patients				
1	5/M	Tongue base mass	Tongue base	Cervical LN	233	II R2	CCCG-BNHL	CR (21)
2	5/M	Parotid gland mass	Parotid gland	Cervical LN	220	II R2	CCCG-BNHL	CR (14)
3	6/M	Intussusception	Ileum	Mesenteric LN	243	II R1	CCCG-BNHL	CR (30)
4	7/M	Tonsillitis	Palatine tonsil	None	191	II R2	CCCG-BNHL	CR (58)
5	8/M	Tonsillitis	Palatine tonsil	Cervical LN	280	II R2	CCCG-BNHL	CR (32)
6	8/M	Intussusception	Ileocecum	Mesenteric LN, bone marrow	306	IV R4	CCCG-BNHL	CR (41)
7	10/F	Abdominal mass	Retroperitoneum and pelvis	Mesenteric LN	349	III R3	CCCG-BNHL	CR (52)
8	10/M	Tonsillitis	Nasopharynx and tongue base	Mesenteric LN	242	III R3	CCCG-BNHL	CR (28)
9	11/M	Pharyngeal mass	Palatine tonsil, nasopharynx	None	179	I	CCCG-BNHL	CR (50)
10	11/M	Cervical mass	Palatine tonsil	Cervical LN	213	II	R-CHOP	CR (41)

11	13/M	Intussusception	Ileocecum	None	167	II	NA	NA
12	17/M	Parotid gland mass	Nasopharynx and parotid gland	Cervical LN	204	II	R-CHOP	CR (25)
				Adult patients				
13	33/M	Cervical mass	Spleen	Cervical LN	320	III	R-CHOP	CR (22)
14	38/M	Abdominal mass	None	Multiple LN	915	III	Resection	DOD (0)
15	49/F	Intussusception	Ascending colon, bone marrow	Mesenteric LN	NA	IV	Resection	DOD (2)
16	54/M	Tonsillitis and cervical mass	palatine tonsil	Cervical LN	258	II	R-EPOCH	CR (30)
17	56/M	Abdominal mass	Stomach, liver, pancreas, bone marrow	None	1135	IV	R-CHOP+HD-MTX	CR (24)
18	56/M	Cervical mass	Palatine tonsil	Cervical LN	126	II	R-CHOP	CR (52)
19	58/M	Axillary mass	None	Multiple LN	246	III	R-EPOCH	CR (57)
20	59/M	Pancreatic mass	Pancreas, duodenum	Multiple LN	851	IV	R-EPOCH	DOD (1)
21	60/F	Cervical mass	Palatine tonsil, nasopharynx, uterus	Multiple LN	284	IV	R-EPOCH	CR (24)
22	65/M	Inguinal mass	None	Inguinal LN	NA	I	Resection	CR (47)
23	66/M	Lumbar vertebra mass	Lumbar vertebra, kidney, bone marrow	No	343	IV	R-EPOCH	CR (26)
24	67/F	Pancreatic mass	Pancreas, gallbladder	No	NA	III	R-CHOP	DOD (4)
25	67/M	Gastric mass	Stomach	Mesenteric LN	817	II	R-CHOP	CR (44)
26	67/M	Bowel obstruction	Colon	Retroperitoneal LN	NA	II	NA	NA
27	68/F	None	Temporal lobe	None	184	I	R-MA	CR (15)
28	72/M	Brain mass	Multiple intracranial masses, bone marrow	None	223	IV	Biopsy	DOD (6)
29	75/F	Gastric mass	Stomach	NA	NA	NA	NA	NA
30	84/M	Tonsillitis and cervical lymphadenopathy	Palatine tonsil	Cervical and axillary LN	314	II	R-CHOP	DOD (6)
31	85/F	Cervical mass	No	Cervical LN	NA	NA	NA	NA
32	86/M	Abdominal mass Bladder cancer	Ileocecum	Retroperitoneal and mediastinal LN	164	IV	R-CHOP+ R-EPOCH	DOD (24)

CR, complete remission; DLBCL, diffuse large B-cell lymphoma; DOD, died of disease; F, female; LN, lymph node; Lt., left; M, male; NA, not available; R-CHOP, (R, Rituximab; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone); R-EPOCH regimen (R, Rituximab; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and adriamycin).

Clinical information is summarized in **Table 1**. A total of 32 cases were included in the study, ranging from 5 to 86 years, with a median of 55 years. There were 12 pediatric patients with a median age of 9 years (range, 5–17 years), and 20 adult patients with with a median age of 65.5 years (range, 33–86 years). The pediatric group included 6 cases of (< 10 years) and 6 cases within the (10–< 20 years) groups of age, while adults had 0, 2, 1, 5, 7, and 5 cases from the groups of (20–< 30 year), (30–< 40 year), (40–< 50 year), (50–< 60 year), (60–< 70 year), and (≥70 years) of age, respectively, of the 32 cases, 25 were males, and 7 were females.

Four patients (13%) had a nodal presentation, whereas 28 patients (87%) showed an extra-nodal presentation. Twelve cases involved the Waldeyer's ring, 10 cases involved the gastrointestinal tract, 4 cases involved bone marrow, 1 case involved the central neural system, and 1 case involved the retroperitoneum and pelvis. The 12 pediatric patients were exclusively involved in extra-nodal sites (12/12, 100%), including WR, gastrointestinal tract (GIT), and retroperitoneum and pelvis in 8, 3, and 1 case, respectively. Adult patients' tumor involvements were distributed differently in lymph nodes (4/20, 20%) and extra-nodal sites (16/20, 80%). Pediatric patients showed a significantly higher frequency of Waldeyer's ring involvement than adult patients (8/12, 67% vs. 4/20, 20%, P=0.008), and a lower frequency of nodal and bone marrow than adult patients **(Table 2)**.

Table 2. Comparisons of clinical, histological subtypes, and immunohistochemical features between pediatric and adult patients

	Pediatric patients n = 12	Adult patients n = 20	Total patients n = 32	*P*-value (P vs. A)
Clinical features				
Median age, year (range)	9 (5-17)	65.5 (33-86)	55 (5-86)	
M: F	11:1	14:6	25:7	0.151
Involvement sites				
Lymph nodes	0/12	4/20	4/32	0.098
WR	8/12	4/20	12/32	**0.008**
GIT	3/12	7/20	10/32	0.555
Multiple sites and bone marrow	0/12	4/20	4/32	0.098
Elevated serum LDH level	6/12	11/14	17/26	0.127
Clinical stage				
Stage I	1/12	2/18	3/30	0.804
Stage II	8/12	5/18	13/30	**0.035**
Stage III	2/12	4/18	6/30	0.709
Stage IV	1/12	7/18	8/30	0.064
Outcome				
CR/NR	11/11	10/17	21/28	**0.014**
DOD	0/11	7/17	7/28	
Immunohistochemical features				
BCL2+ expression	8/12	13/20	21/32	0.923
P53+ expression	4/12	10/20	14/32	0.358
MYC+ expression	3/12	6/20	9/32	0.761

Symptoms were closely related to the location and size of the masses. The 12 cases involving WR frequently presented with mass pharyngeal discomfort and tonsillitis. The 10 cases involving the gastrointestinal tract mostly presented with abdominal pain, in which 4 cases were initially diagnosed with intussusception. Serum LDH level was elevated in 17 patients.

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Of the 30 patients with available clinical information, clinical stages of I, II, III, and IV were shown in 3, 13, 6, and 8 cases. Clinical stages of I, II, III, and IV were identified in 1, 8, 1, and 1 case among children, respectively, and in 2, 5, 4, and 7 cases, respectively, among the adults. Pediatric patients showed a significantly higher frequency of stage II than adult patients (8/12, 67% vs. 5/18, 28%, *P*=0.035).

Treatment data was available in 28 cases, including 4 patients with surgical resection/biopsy, and 24 with surgical resection/biopsy and post-chemotherapy. Twenty-one patients were alive at follow-up, with a median follow-up of 41 months (range 14-58 months). Seven adults passed away due to multiple organ failure after resection in 3 cases and 4 during chemotherapy. Compared to pediatric cases, adult cases showed a higher incidence of fatality (0/11, 0% vs. 7/17, 41.2%, *P*=0.014).

All cases showed expression of CD10, BCL6, and MUM1/IRF4 in more than 50% of tumor cells. Among the 32 cases, MYC was positive in 11 cases. BCL2 was positive in 21 cases. P53 showed positive expression in 14 cases.

Characteristics of different involvements in GC-derived DLBCL with aberrant co-expression of IRF4/MUM1 in adults and children

Table 3. Clinicopathological features among the Waldeyer's ring, gastrointestinal, and lymph node involvements of GC-derived B-cell lymphomas with MUM1 positive expression

Variable	WR (n=12)		GIT (n=10)	
	P (n=8)	A (n=4)	P (n=3)	A (n=7)
Median age, y (range)	11 (5-17)	60 (54-84)	13 (6-13)	67 (34-86)

Clinical features				
M: F	8: 0	3:1	3:0	4:3
Clinical stage				
Localized stage of I/II	7/8	3/4	2/3	2/7
Advanced stage of III/ IV	1/8	1/4	1/3	5/7
Immunohistochemical features				
BCL2+ expression	5/8	2/4	2/3	6/7
P53+ expression	3/8	3/4	**0/3**	**5/7**
MYC+ expression	2/8	1/4	1/3	1/7
Outcome				
CR/NR	12/12	3/4	3/3	3/7
DOD	0/12	1/4	0/3	4/7

CR, complete remission; DOD, died of disease; F, female; M, male; WR, Waldeyer's ring; GIT, gastrointestinal tract.

As shown in **Table 3**, 12 cases involving WR were identified, with a median age of 56 years age (range 5-84 years). They predominantly occurred in males (M: F =11: 1). Tumors commonly involved in palatine tonsil, palatine tonsil with nasopharynx, tongue base, and nasopharynx and tongue base. Ten cases involving WR exhibited localized clinical stage I/II, including 7 children and 3 adult patients, while two cases presented with advanced stage III/ IV. Only 1 case passed away, and the other 11 cases achieved complete remission without relapse.

The 10 cases involving GIT were included, with ages ranging from 6 to 86 years. Tumors are commonly localized in the ileocecum, stomach, colon, ileum, pancreas, duodenum, stomach, and colon. Patients presented with localized clinical and advanced stages in 4 and 6 cases, respectively. Compared to pediatric patients, adult patients presented with a significantly higher frequency of P53 positive expression (5/7 vs. 0/3, P=0.038) and a slightly higher fatality rate.

The 4 four cases involving multiple sites and bone marrow predominantly occurred in adults aged 49, 56, 66, and 72 years old. Patients presented with clinical stage IV; two died of multiple organ failure.

In the present study, we characterized the clinical and pathological features of 32 cases of GC-derived DLBCL with aberrant co-expression of MUM1. These cases present with a bimodal age distribution, male predominance, various clinical stages, high frequency of BCL2 positive expression, and moderate expression of MYC and P53.

Age is a well-established prognostic impact of lymphoma and children have a more favorable outcome than adults.[13] In our study, patients of GC-derived DLBCL with aberrant co-expression of MUM1 mostly occurred in children and adults > 50 years of age. An important question is whether adults represent the same disease as children. The comparison result demonstrated that although pediatric and adult cases shared the similar clinical and pathological features, adult cases showed higher tumor location complexity and higher incidence of fatality, highlighting the genetic and phenotypic heterogeneity in adults. Recent studies have shown that DLBCL with aberrant coexpression of $CD10^{+}BCL6^{+}MUM1^{+}$ in adult cases showed higher genetic complexity and higher mutational load with frequent MYD88 and KMT2D mutations.[14]

The primary site of lymphoma, including extra-nodal and nodal territories, was proposed as a criterion for separating groups. Adult DLBCLs, although belonging to the same group, showed clinical alterations associated with involving sites. DLBCL involving WR displayed peculiar clinicopathologic features compared to nodal counterpart, with usually localized stage disease, low rate of BCL2 rearrangements, and better outcome.[10] Accordingly, in this study, the WR group predominantly presented with localized stage with excellent response to conventional chemotherapy. Nevertheless, within the adult group, clinicopathologic features were similar to the pediatric counterpart, indicating that these cases might have similar molecular characteristics.

The gastrointestinal tract is the most common extranodal site of lymphoma, and there is no significant difference between GC and ABC groups.[15] In our study, the GIT group showed both localized and advanced stages. Adult patients showed a slightly higher rate of advanced stage and incidence of fatality than children. High positive expression of P53 was shown in adult cases involving GIT. Therefore, it was predicted to be different molecular features that may impact therapeutic strategies.

Previous work has shown the unfavorable prognosis determined by a concordant marrow infiltration, with lower progression-free survival and overall survival.[12] BM infiltration represents a subset with a poor prognosis, whereas the prognostic impact of discordant BM infiltration could be limited to ABC cases.[16] In our study, a disease involving multiple sites and bone marrow occurred in patients older than 40, predominantly presents with advanced stage and poor prognosis, indicating that these cases had molecular features similar to ABC cases and different from other DLBCL involving WR and GIT.

IRF4 translocation is identified in a small subset of GC-

derived B-cell lymphomas, including GCB-type DLBCL.[17] We reported as *IRF4/MUM1* positive lymphoma to be referred to as the new entity of large B-cell lymphoma with *IRF4* rearrangement (LBCL-IRF4).[18] LBCL-IRF4 is newly named in WHO classification and shows mostly a GCB phenotype but with strong MUM1/IRF4 expression.[19] DLBCL-IRF4 in adults showed a different molecular profile when compared with LBCL-IRF4 in the pediatric population, suggesting that MUM1/IRF4 plays an important role in the different phenotypes of DLBCL.[14]

Conclusion

In conclusion, we have demonstrated that IRF4/MUM1 positive expression was related to wide age distribution, extensive involvement sites, and different clinicopathological subtypes in germinal center-derived B-cell lymphomas. Furthermore, DLBCL-IRF4 in adults is similar to its pediatric counterpart, especially in patients involving WR. Our data suggests that within the group of IRF4-rearranged cases in adults, there are important differences from its pediatric counterpart.

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None.

Conflict of interest
None.

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Ethics statement
This study was approved by the ethics committee of Xin Hua Hospital, Affiliated with Shanghai Jiao Tong University School of Medicine.
All patients enrolled provided written informed consent.

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