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

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Abstract

This study investigated the clinical and pathological profiles of germinal center (GC)-derived diffuse large B-cell lymphomas (DLBCL) with abnormal MUM1 co-expression, focusing on comparisons between pediatric and adult patients. A total of 32 cases showing aberrant MUM1 expression were analyzed, comprising 12 pediatric and 20 adult patients. The lymphomas showed a wide age distribution, affected various anatomical locations, and presented with complex histological and clinical features. Pediatric cases showed a significantly higher incidence of Waldeyer's ring (WR) involvement (P = 0.008), were more frequently diagnosed at stage II (P = 0.035), and had a lower mortality rate (P = 0.014) compared to adults. The most frequently affected site was the WR, followed by the gastrointestinal tract, lymph nodes, and bone marrow. WR involvement was significantly more prevalent in children than adults (P = 0.008). In adults, lymphomas involving the WR showed clinical staging, outcomes, and pathological patterns similar to pediatric cases. In contrast, while adult cases with gastrointestinal involvement shared clinical characteristics with pediatric presentations, they showed a higher rate of P53 expression. In summary, adult patients with GC-derived DLBCL and aberrant MUM1 expression display more clinical variability than children, although WR involvement in adults parallels pediatric disease features.

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

Introduction

Diffuse large B-cell lymphoma (DLBCL) is recognized as the most prevalent form of non-Hodgkin lymphoma. Based on the expression of markers such as CD10, BCL6, and interferon regulatory factor 4 (IRF4)/multiple myeloma oncogene 1 (MUM1), DLBCL can be divided into germinal center B cell (GCB)-like and activated B cell (ABC)-like subtypes [1]. Nevertheless, approximately 15% of cases remain unclassifiable using this approach [2]. The Hans algorithm identifies IRF4/MUM1 as a marker indicative of non-GC origin, whereas CD10 and BCL6 are considered GC-associated markers. Interestingly, MUM1 and GC markers generally show mutually exclusive expression patterns, hinting at a possible regulatory interplay between them [3].

The GCB and ABC molecular classifications are widely utilized to estimate patient prognosis in DLBCL [4]. Evidence from prior research indicates that the ABC subtype correlates independently with poorer progression-free and overall survival, whereas the GCB subtype lacks consistent prognostic value [5]. Although MUM1 is commonly viewed as a post-GC marker, some IRF4/MUM1-positive B-cells within the light zone of germinal centers—resembling centrocytes or, in certain cases, exhibiting plasmablastic features—demonstrate that expression of this marker is not strictly limited to post-GC stages [6]. One study reported that even when MUM1 coexists with CD10, such cases were still categorized under the GCB subtype, though MUM1

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expression was linked to worse outcomes in CD10-positive DLBCL patients [7]. Despite these findings, it remains uncertain whether all DLBCL cases with simultaneous expression of CD10, BCL6, and MUM1 share similar pathological traits and clinical behavior, particularly in terms of prognosis.

Extranodal involvement is observed in roughly one-third of DLBCL cases [8], with Waldeyer's ring (WR) being among the most frequently affected extranodal sites [9]. WR-associated DLBCL exhibits unique pathological and clinical characteristics compared to nodal DLBCL and often corresponds to a more favorable prognosis [10]. However, comprehensive analyses of DLBCL arising in specific extranodal regions, especially when stratified by age groups, are still scarce.

This study aims to highlight the distinctive clinicopathological features of GC-derived DLBCLs with abnormal MUM1 co-expression and to further investigate the differences in extranodal manifestations, particularly in WR involvement, between adult and pediatric patients.

Materials and Methods

Patient Selection and study design

This retrospective study was approved by the ethics board of Xinhua Hospital, affiliated with the Shanghai Jiaotong University School of Medicine. Over 5 years (September 2014 to January 2020), 643 lymphoma cases were documented at the hospital. From these, 32 individuals were identified with a subtype of diffuse large B-cell lymphoma (DLBCL) characterized by abnormal co-expression of CD10, BCL6, and MUM1/IRF4 in more than half of the malignant cells, based on combined morphological and immunohistochemical analysis [11].

Participants were grouped as pediatric or adult cases. Pediatric patients were staged according to the international pediatric non-Hodgkin lymphoma (NHL) system, while adults were evaluated using the Ann Arbor classification. Clinical data—including demographic information, diagnosis date, presenting features, disease stage, and follow-up outcomes—were obtained through medical records.

Children received chemotherapy under the CCCG-BNHL protocol. Adult patients were treated with various regimens, such as R-CHOP, R-EPOCH, and other combinations like R-CHOP with methotrexate (MTX), R-MA (methotrexate and cytarabine), or ICE (ifosfamide, carboplatin, etoposide). Some also received EPOCH alone or in alternation with other regimens depending on clinical indication.

Tissue Processing and immunomarker evaluation

Formalin-fixed, paraffin-embedded biopsy tissues were used for histological examination and immunohistochemistry. A set of monoclonal and polyclonal antibodies was applied, targeting key proteins: CD10 (clone 56C6), BCL6 (clone P1F6), MUM1 (clone MUM1p), Ki-67 (clone MIB-1), BCL2 (clone 100/D5), MYC, and P53 (clone DO-7)—with all antibodies sourced from either Leica Biosystems or DAKO.

Expression thresholds for positivity were set at: > 40% for MYC [12]; > 50% for BCL2 and MUM1; and > 30% for both CD10 and BCL6. GC phenotype classification was based on the combined expression pattern of CD10, BCL6, and MUM1.

Data handling and statistical approach

Statistical analysis was performed using SPSS software (version 17.0, SPSS Inc., Chicago, IL, USA). Categorical variables were compared using Pearson's Chi-square test. A result was considered statistically significant when the P-value was < 0.05.

Results and Discussion

Table 1. Clinical characteristics of 32 Germinal center-origin B-cell lymphoma cases with positive IRF4/MUM1 expression

Case	Age (yrs) / gender	Initial clinical manifestation	Site(s) involved	LDH (u/L)	Stage	Treatment plan	Follow-up (months)
			EN/LN				
Pediatric cases							
1	5 / M	Tongue base mass	Tongue base/cervical LN	233	II R2	CCCG-BNHL	CR (21)

2	5 / M	Parotid swelling	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	Tonsillar inflammation	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	Intestinal obstruction	Ileocecum/mesenteric LN, bone marrow	306	IV R4	CCCG-BNHL	CR (41)
7	10 / F	Abdominal tumor	Retroperitoneum and pelvis/mesenteric LN	349	III R3	CCCG-BNHL	CR (52)
8	10 / M	Throat infection	nasopharynx and tongue base/mesenteric LN	242	III R3	CCCG-BNHL	CR (28)
9	11 / M	Pharyngeal tumor	palatine tonsil, nasopharynx/none	179	I	CCCG-BNHL	CR (50)
10	11 / M	Neck swelling	Palatine tonsil / cervical LN	213	II	R-CHOP	CR (41)
11	13 / M	Intussusception	Ileocecum/none	167	II	NA	NA
12	17 / M	Parotid mass	Parotid and nasopharynx/cervical LN	204	II	R-CHOP	CR (25)
Adult cases							
13	33 / M	Cervical mass	Spleen/cervical LN	320	III	R-CHOP	CR (22)
14	38 / M	Abdominal growth	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 with a neck mass	Palatine tonsil/cervical LN	258	II	R-EPOCH	CR (30)
17	56 / M	Abdominal swelling	Stomach, liver, pancreas, bone marrow/none	1135	IV	R-CHOP + HD-MTX	CR (24)
18	56 / M	Cervical lump	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	Tumor in pancreas	Pancreas and duodenum/multiple LN	851	IV	R-EPOCH	DOD (1)
21	60 / F	Cervical swelling	Palatine tonsil, nasopharynx, uterus/multiple LN	284	IV	R-EPOCH	CR (24)
22	65 / M	Inguinal lump	None/inguinal LN	NA	I	Resection	CR (47)
23	66 / M	Vertebral tumor	Lumbar spine, kidney, bone marrow/none	343	IV	R-EPOCH	CR (26)
24	67 / F	Pancreatic mass	Pancreas and gallbladder/none	NA	III	R-CHOP	DOD (4)
25	67 / M	Gastric growth	Stomach/mesenteric LN	817	II	R-CHOP	CR (44)
26	67 / M	Bowel blockage	Colon/retroperitoneal LN	NA	II	NA	NA
27	68 / F	None reported	Temporal lobe/none	184	I	R-MA	CR (15)
28	72 / M	Brain tumor	Multiple intracranial areas, bone marrow/none	223	IV	Biopsy	DOD (6)
29	75 / F	Gastric lesion	Stomach/NA	NA	NA	NA	NA
30	84 / M	Tonsillitis + lymph node swelling	Palatine tonsil/cervical and axillary LN	314	II	R-CHOP	DOD (6)
31	85 / F	Neck lump	None/cervical LN	NA	NA	NA	NA
32	86 / M	Abdominal tumor & bladder cancer	Ileocecum/retroperitoneal and mediastinal LN	164	IV	R-CHOP + R-EPOCH	DOD (24)

Abbreviations: CR: complete remission, DOD: died of disease, EN: extranodal, LN: lymph node, NA: not available, BM: bone marrow; treatment details: R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, R-EPOCH: rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, R-MA: rituximab, methotrexate, cytarabine, CCCG-BNHL: China children's cancer group protocol for B-NHL, HD-MTX: high-dose methotrexate.

Clinical characteristics overview

Table 1 outlines the clinical data of all 32 cases enrolled in the study. Patient ages ranged from 5 to 86 years, with

the overall median age being 55 years. Among them, 12 were pediatric patients, whose ages spanned from 5 to 17 years (median: 9 years), while the remaining 20 were adults, with a median age of 65.5 years (range: 33–86 years). In the pediatric subset, six patients were younger than 10 years, and the other six were between 10 and under 20 years. In contrast, the adult group included patients distributed across the following age brackets: 0 in 20 – < 30 years, 2 in 30 – < 40 years, 1 in 40 – < 50 years, 5 in 50 – < 60 years, 7 in 60 – < 70 years, and 5 aged 70 years or above. Overall, 25 of the 32 patients were male, and the remaining 7 were female.

Regarding tumor localization, 4 patients (13%) exhibited disease limited to lymph nodes, while the majority, 28 patients (87%), had tumors arising in extranodal regions. Among these, the Waldeyer's ring was affected in 12 cases, the gastrointestinal tract in 10, bone marrow in 4, the central nervous system in 1, and the retroperitoneum/pelvis in 1 case. All 12 pediatric cases presented with exclusively extranodal disease (100%), including involvement of the Waldeyer's ring in 8, the GI tract in 3, and the retroperitoneum/pelvis in 1. In comparison, adult cases showed a mix of nodal (4/20, 20%) and extranodal (16/20, 80%) involvement. Waldeyer's ring was significantly more frequently involved in children than in adults (67% vs. 20%, P = 0.008), while lymph node and bone marrow involvements were more prevalent among adults (see **Table 2**).

Table 2. Comparison of clinical profiles, histopathological subtypes, and immunohistochemical markers between pediatric and adult patients

Feature	Pediatric patients (n = 12)	Adult patients (n = 20)	All patients (n = 32)	P-value (P vs. A)
Median age, years (range)	9 (5–17)	65.5 (33–86)	55 (5–86)	–
Male: female ratio	11:1	14:6	25:7	0.151
Tumor involvement sites				
Lymph nodes only	0/12	4/20	4/32	0.098
Waldeyer's ring (WR)	8/12	4/20	12/32	0.008
Gastrointestinal tract (GIT)	3/12	7/20	10/32	0.555
Multiple sites/bone marrow	0/12	4/20	4/32	0.098
Elevated LDH levels	6/12	11/14	17/26	0.127
Clinical staging				
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
Treatment outcomes				
Complete remission / not reached	11/11	10/17	21/28	0.014
Died of disease (DOD)	0/11	7/17	7/28	–
Immunohistochemical Findings				
BCL2 positive	8/12	13/20	21/32	0.923
P53 positive	4/12	10/20	14/32	0.358
MYC positive	3/12	6/20	9/32	0.761

Symptoms were generally influenced by the tumor's anatomical location and volume. Among the 12 cases with Waldeyer's ring involvement, most presented with pharyngeal mass effects or symptoms resembling tonsillitis. Patients with gastrointestinal tract involvement, accounting for 10 cases, typically experienced abdominal discomfort; notably, 4 of these were initially misdiagnosed with intussusception. Elevated lactate dehydrogenase (LDH) levels were observed in 17 patients across the cohort.

The symptoms observed were directly associated with the location and size of the tumors. In the 12 cases involving the Waldeyer's ring (WR), patients primarily complained of pharyngeal discomfort and tonsil-related inflammation. The 10 cases related to the gastrointestinal (GI) system typically presented with abdominal pain, with 4 of these initially diagnosed with conditions like intussusception. Additionally, elevated serum LDH levels were noted in 17 individuals.

Out of the 30 patients whose clinical data was available, 3 were classified as stage I, 13 as stage II, 6 as stage III,

and 8 as stage IV. For children, there was 1 patient each in stages I, III, and IV, while 8 were in stage II. In adults, the distribution was 2 in stage I, 5 in stage II, 4 in stage III, and 7 in stage IV. A notable observation was that pediatric patients had a significantly higher incidence of stage II (67%) compared to adults (28%, P = 0.035).

Treatment details were available for 28 patients, with 4 undergoing surgical resection or biopsy alone, while 24 received both surgery and subsequent chemotherapy. At the follow-up stage, 21 patients were still alive, with a median follow-up period of 41 months (ranging from 14 to 58 months). Seven adults died, with 3 passing away due to organ failure after surgery and 4 during chemotherapy. The mortality rate among adults was significantly higher than that in children (41.2% vs. 0%, P = 0.014).

Immunohistochemical analysis revealed that all tumors expressed CD10, BCL6, and MUM1/IRF4 in more than 50% of the cells. In the group of 32 patients, MYC expression was positive in 11 cases, BCL2 in 21, and P53 in 14.

Table 3. Clinicopathological features of GC-derived DLBCL with MUM1 co-expression across different involvements

Parameter	WR (n = 12)	GIT (n = 10)	P (n = 8)	A (n = 4)	P (n = 3)	A (n = 7)
Median age (range)	11 (5-17)	60 (54-84)	13 (6-13)	67 (34-86)		
Sex distribution (M:F)	8:0	3:1	3:0	4:3		
Clinical stage I/II	7/8	3/4	2/3	2/7		
Clinical stage III/IV	1/8	1/4	1/3	5/7		
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		
Outcome (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**, the 12 cases involving WR had a median age of 56 years (range 5-84 years), with a predominance of male patients (11 males, 1 female). The tumors were mostly located in the palatine tonsils, nasopharynx, or tongue base. Most of the WR cases were diagnosed in early clinical stages (I/II), including 7 children and 3 adults, with just 2 patients presenting at advanced stages (III/IV). Only one case ended in death, with the rest achieving complete remission without recurrence.

In the group of 10 cases involving the GI tract, the ages ranged from 6 to 86 years. The tumors were located in various regions, including the ileocecum, stomach, colon, and pancreas. Of these, 4 were in the early stages, and 6 were in the advanced stages. Adult patients showed a notably higher rate of P53 positivity (5/7 vs. 0/3, P = 0.038), and their mortality rate was slightly higher than in children.

In the 4 cases involving multiple sites and bone marrow, all patients were adults, ranging in age from 49 to 72 years, and all were diagnosed with stage IV disease. Two of these patients succumbed to multiple organ failure.

The study highlights the clinical and pathological characteristics of 32 cases of GC-derived DLBCL with aberrant MUM1 co-expression. These cases demonstrated a bimodal age distribution, male dominance, diverse clinical stages, and a high incidence of BCL2 expression, with moderate levels of MYC and P53 expression.

Age remains a critical prognostic factor, with children generally showing better outcomes than adults. This study indicates that although pediatric and adult cases of GC-derived DLBCL with MUM1 co-expression share several features, adults tend to have more complex tumor locations and a higher mortality rate, suggesting significant genetic and phenotypic differences. Recent research also suggests that DLBCL in adults with co-expression of CD10, BCL6, and MUM1 is genetically more complex, often showing higher mutation rates, especially in MYD88 and KMT2D genes.

The primary site of lymphoma, including both extra-nodal and nodal regions, has been suggested as a key factor for differentiating groups. Although adult DLBCLs are categorized within the same group, they display clinical alterations based on the site of involvement. DLBCL affecting the Waldeyer's ring (WR) presents unique clinicopathologic features compared to nodal counterparts, including typically localized stage disease, a lower frequency of BCL2 rearrangements, and better overall outcomes [10, 13, 14].

In line with this, our study found that the WR group predominantly consisted of patients at localized stages who had an excellent response to conventional chemotherapy. In contrast, the adult cases within the study showed clinicopathologic features similar to pediatric cases, which may suggest that these cases share comparable molecular characteristics.

The gastrointestinal (GI) tract remains the most frequent extranodal site for lymphoma, with no significant differences between GC and ABC groups in terms of involvement [15, 16]. In our research, the GI group included both localized and advanced stages. Adult patients demonstrated a slightly higher proportion of advanced-stage disease and a higher incidence of fatality compared to pediatric cases. A high expression of P53 was noted in adult cases involving the GI tract, indicating the possibility of distinct molecular features that could influence treatment strategies.

Previous studies have indicated that bone marrow (BM) infiltration negatively affects prognosis, with lower progression-free survival and overall survival rates [12]. BM involvement generally signals a poorer prognosis, especially when it is concordant with lymphoma involvement. In our study, cases involving multiple sites and the bone marrow were predominantly observed in adults over the age of 40, and these patients mostly presented with advanced-stage disease and poor prognosis. These cases showed molecular features more aligned with ABC cases, contrasting with other DLBCL types involving WR and the GI tract.

IRF4 translocation is found in a small subset of GC-derived B-cell lymphomas, such as GCB-type DLBCL [17]. We have previously proposed that IRF4/MUM1 positive lymphoma be recognized as a new entity—large B-cell lymphoma with IRF4 rearrangement (LBCL-IRF4) [18]. This entity has been added to the WHO classification and typically exhibits a GCB phenotype, though it also demonstrates strong expression of MUM1 and IRF4. Upon comparing DLBCL-IRF4 in adults and children, we identified molecular differences, highlighting the significant role of MUM1/IRF4 in shaping the phenotypic features of DLBCL in different age groups [14, 19].

Conclusion

In conclusion, we found that IRF4/MUM1 positive expression is linked to broad age distribution, diverse site involvement, and a variety of clinicopathological subtypes within GC-derived B-cell lymphomas. DLBCL-IRF4 in adults shares similarities with its pediatric counterpart, particularly in patients with WR involvement. However, important molecular distinctions exist within the adult IRF4-rearranged subgroup when compared to the pediatric form, suggesting that these differences have a significant impact on the disease's molecular landscape.

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