Clinical, pathological and genetic features of primary mediastinal large B-cell lymphomas and mediastinal gray zone lymphomas in children

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ABSTRACT

Background
Primary mediastinal large B-cell lymphoma is a rare lymphoma accounting for no more than 3% of all B-cell lymphomas in children and adolescents. However, patients in this young age group with this lymphoma have the shortest event-free survival of patients with any B-cell lymphoma under current standard chemotherapy protocols. Lymphomas with features intermediate between primary mediastinal large B-cell lymphoma and classical Hodgkin's lymphoma (mediastinal gray zone lymphomas) have been acknowledged in the latest World Health Organization classification. Recent studies suggest that mediastinal gray zone lymphomas have an aggressive clinical course whereas patients, at least adult ones, with primary mediastinal large B-cell lymphoma might respond very well to chemotherapy in combination with anti-CD20 antibody.

Design and Methods
We aimed to evaluate whether biological differences or so far unrecognized admixed mediastinal gray zone lymphomas might explain the relatively poor outcome of pediatric patients with apparent primary mediastinal large B-cell lymphoma. We, therefore, performed a retrospective histopathological, immunohistochemical and interphase cytogenetic analysis of 52 pediatric lymphomas.

Results
The childhood primary mediastinal large B-cell lymphomas (n=44) showed a similar pattern of histology, immunophenotype and gains at 9p (59%) and 2p (41%) as adult cases, as determined from published data. We identified only four so far unrecognized cases of mediastinal gray zone lymphoma among 52 lymphomas registered in previous trials.

Conclusions
Mediastinal gray zone lymphoma is very rare in children and adolescents. It does, therefore, seem unlikely that these lymphomas account for the unsatisfactory clinical results with current therapy protocols in pediatric patients. These data have major implications for the design of future treatment protocols for mediastinal lymphomas in children and adolescents.

Key words: PMBCL, MGZL, dose-adjusted EPOCH, mediastinal lymphoma, Hodgkin lymphoma, 9p, 2p.

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The online version of this article has a Supplementary Appendix.

Introduction

Primary mediastinal (thymic) large B-cell lymphoma (PMBCL) is an aggressive B-cell lymphoma. PMBCL characteristically presents as a large mediastinal tumor, frequently involving adjacent mediastinal structures and often accompanied by superior vena cava syndrome and obstruction of the upper airways.[1] Patients with PMBCL are predominantly female and often present with pleural and/or pericardial effusions.[2] The most frequent extrathoracic manifestations are tumors in the kidney and more rarely in the liver, spleen and pancreas, while spread to other extranodal organs is rare. The clinical presentation suggests that PMBCL may arise from specific B cells residing in the thymic medulla.[1,3]

PMBCL has a typical histopathological morphology with blastic cytology and compartmentalizing alveolar fibrosis.[3,4] However, the morphology can be very variable. PMBCL tumor cells are usually medium-sized with pale cytoplasm and nuclei of moderate size, but in some tumors the cells are more pleomorphic and may even resemble Reed-Sternberg cells.[1,4] In contrast to patients with classical Hodgkin's lymphomas (cHL), patients with PMBCL have a preserved B-cell program and express most B-lineage markers, including CD20, CD19 and CD79a; furthermore, they are typically positive for CD23. CD30 expression is frequently detected. Gains of chromosome 9p (including *JAK2*, *PDL1*, *PDL2*) are detected in up to 75% of cases of PMBCL and gains of 2p (including *REL*, *BCL11A*) in up to 50%.[5,6] Gains of the same regions are also highly recurrent in cHL.[7,8] These morphological, immunophenotypic and genetic features suggest that there is a close biological relationship between PMBCL and cHL, a hypothesis that is supported by molecular profiling, which has revealed a substantial overlap in the gene expression pattern of these two diseases.[9,10] The biological continuum between PMBCL and cHL is most evident in so-called mediastinal gray zone lymphomas (MGZL), in which features of cHL and PMBCL occur simultaneously in one biopsy specimen or even sequentially in specimens taken at different points in time.[11-13] The existence of MGZL with transitional features between PMBCL and cHL was recently acknowledged by the inclusion of the category in the World Health Organization classification, designated as "B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma".[1] Although the true incidence of MGZL in adults is not known, the disease seems to be rare, since the largest series reported so far included only 21 patients.[13]

In clinical trials involving children and adolescents with PMBCL, the event-free survival rate was about 70%, which is significantly lower than that in other B-cell lymphomas, such as diffuse large B-cell lymphoma or Burkitt's lymphoma, in this age group.[2] Remarkably, in contrast to the situation with all other B-cell lymphomas, the outcome of adults with PMBCL has been reported to be similar or even better than that of pediatric patients with PMBCL. This was particularly the case if an anti-CD20 antibody was included in the treatment, a procedure that is standard for aggressive B-cell lymphomas in adults,[14] but not so far for children and adolescents.[15] Improving the treatment outcome in children suffering from PMBCL is, therefore, a major challenge for pediatric oncologists.[16]

The clinical presentation of patients with PMBCL is comparable in adult and pediatric series.[2] However, the frequency of MGZL in children and adolescents has not been studied in large series. MGZL has attracted considerable attention among pediatric oncologists, because it is possible that the outcomes of patients with PMBCL and MGZL differ. Recently, an excellent progression-free survival rate was reported for patients diagnosed with B-cell lymphomas in the mediastinum treated with DA-EPOCH (dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone) chemotherapy in combination with the anti-CD20 antibody rituximab (DA-EPOCH-R).[17] Interestingly, however, in that study the outcome of patients with PMBCL and MGZL differed dramatically, with progression-free survival rates of 100% (n=35) and 30% (n=11), respectively. The data of Dunleavy *et al.* suggest that PMBCL can be successfully treated with DA-EPOCH-R. However, if current diagnostic criteria are used, MGZL remains a disease with a poor outcome.[17] It is noteworthy that the aforementioned trial was not randomized and did not include any children or adolescents (median age 32 years, range 19 to 52 years). Furthermore, detailed immunohistochemical and genetic studies of pediatric PMBCL are lacking so far. It is, therefore, unclear whether biological differences between PMBCL in children and adults might explain the differences in outcome. Finally, it is not known whether cases of unrecognized MGZL might have been included within the cohorts of the previous trials for pediatric PMBCL. If there had been such an admixture, this too may have been the cause of the relatively poor outcome. We, therefore, identified 52 patients with mediastinal tumors initially diagnosed and treated as PMBCL in the study groups for pediatric non-Hodgkin's lymphoma in Italy (AIEOP) and Germany (NHL-BFM) and then reanalyzed the cases using the same diagnostic criteria as in the new World Health Organization classification. In addition, we characterized these cases by interphase cytogenetics.[1]

Design and Methods

Clinical data

Samples from 43 of 55 patients registered at the German NHL-BFM study group between December 1986 and January 2009 with the diagnosis of PMBCL were available for review. Thus, the cohort appears to be representative of the whole NHL-BFM group. The NHL-BFM group is a population-based clinical cohort for Germany. However, we cannot exclude that patients older than 14 years (70% of all patients in the cohort presented here) in Germany are treated outside of the NHL-BFM trials. Staging was performed according to the St. Jude Staging system and included physical examination, peripheral blood and bone marrow smears, cerebrospinal fluid analyses, measurement of serum lactate dehydrogenase level and adequate imaging techniques. Patients were treated according to the successive protocols NHL-BFM 86, 90, 95 and B-NHL BFM 04, which had a common chemotherapeutic backbone, and had comparable outcomes. Nine Italian patients with available samples were also included in this study. These patients were diagnosed between June 2000 and September 2009 and treated according to the modified AIEOP LNH97 protocol. Seven of the nine patients were additionally treated with rituximab.

The study was carried out in accordance with both local ethical guidelines and the ethical guidelines of the studies in which the patients were treated.

Pathology review

A total of 52 lymphoma cases from European pediatric lymphoma studies (9 AIEOP, 43 NHL-BFM) diagnosed between 1986 and 2009 were reviewed by expert hematopathologists (EA, ESJ, MLH, WK, PM, IO, and AR) on individual microscopes independently of each other using full slides. Only primary biopsy specimens obtained prior to any treatment were analyzed. For 9/52 (17%) of the cases studied, only a core needle biopsy sample was available. In all other cases an open biopsy sample was available for diagnosis: in 6/52 (12%) cases these samples were less than 0.5 cm in diameter and in 36/52 (69%) they were greater than 0.5 cm in diameter, ensuring sufficient biopsy size, whereas one sample was too small for assessment. The pathologists were asked to assign each lymphoma to the categories PMBCL, MGZL, cHL, diffuse large B-cell lymphoma, or Burkitt's lymphoma, but were free to use other categories if necessary. A final consensus diagnosis was defined if at least six of the seven pathologists came to the same diagnosis independently. For all other lymphomas a final consensus diagnosis was reached by discussing the cases at a multi-head microscope. The consensus diagnoses were used for the correlative studies.

MGZL was diagnosed if: (i) the lymphoma showed morphology resembling cHL in one area and PMBCL in another area (synchronous or composite lymphoma); (ii) morphological features in the whole lymphoma showed an overlap between PMBCL and cHL, such as many Hodgkin-Reed/Sternberg cells admixed in an otherwise typical PMBCL and if additional immunophenotypic features were suggestive of cHL (e.g. positivity for CD15 or Epstein-Barr virus encoded RNA [EBER]), (iii) the morphology was compatible with the diagnosis of PMBCL but the immunophenotype showed features of cHL (e.g. positivity for CD15 or EBER).[1,11,13,18]

Immunohistochemistry

The staining panel included CD20, CD79a, CD30, CD15, CD23, CD5, CD10, Pax5, Oct2, Bob1, BCL6 and MUM1. In addition Epstein-Barr virus was detected using EBER *in situ* hybridization. Due to the retrospective nature of the study, the staining procedures and antibodies varied from patient to patient. Since material obtained from the mediastinum is usually limited, the number of immunohistochemical stainings also varied from case to case.

Table 1. Results of immunohistochemistry. All lymphomas with more than 1% positive tumor cells were assigned as positive.

	PMBCL	MGZL	p*
CD20	98% (43/44)	100% (4/4)	1,0000
CD79a	100% (35/35)	100% (4/4)	1,0000
CD30	77% (30/39)	100% (4/4)	0,5360
CD15	0% (0/36)	25% (1/4)	0,1000
CD23	67% (28/42)	100% (3/3)	0,5412
CD5	0% (0/30)	0% (0/3)	1,0000
CD10	23% (8/35)	25% (1/4)	1,0000
Pax5	100% (30/30)	100% (4/4)	1,0000
Oct2	100% (28/28)	100% (3/3)	1,0000
BOB1	90% (18/20)	67% (1/3)	0,2028
BCL6	97% (28/29)	33% (1/3)	0,0177
MUM1	70% (19/27)	100% (3/3)	0,5448
EBER	0% (0/31)	67% (2/3)	0,0882

*For detailed immunohistochemistry scores, see Online Supplementary Table S2. *Fischers' exact test, PMBCL: primary mediastinal large B-cell lymphoma, MGZL: mediastinal gray zone lymphoma.*

Fluorescence in situ *hybridization*

Interphase fluorescence *in situ* hybridization (FISH) for detection of chromosomal breaks or imbalances involving the *MYC* (8q24), *REL/BCL11A* (2p16) and *JAK2/PDL2* (9p24) loci was performed on available paraffin sections using probes described in *Online Supplementary Table S1* and previously published protocols.[19] Gains were considered to be present when three or four signals per probe were observed in a significant percentage of cells (10%). Amplifications were defined as more than four signals or the presence of a 'signal cloud'.

Results

Pathology review

The retrospective review of 52 lymphoma cases by the international panel of pathologists led to the diagnosis of PMBCL in 44 cases (85%), MGZL in four cases (8%) and diffuse large B-cell lymphoma in two cases (4%). It was not possible to classify two lymphomas (4%) because of the limited amount of material available for review and these cases were, therefore, labeled as B-cell lymphoma, not otherwise specified. Two lymphomas were classified as MGZL due to histological features of PMBCL in one

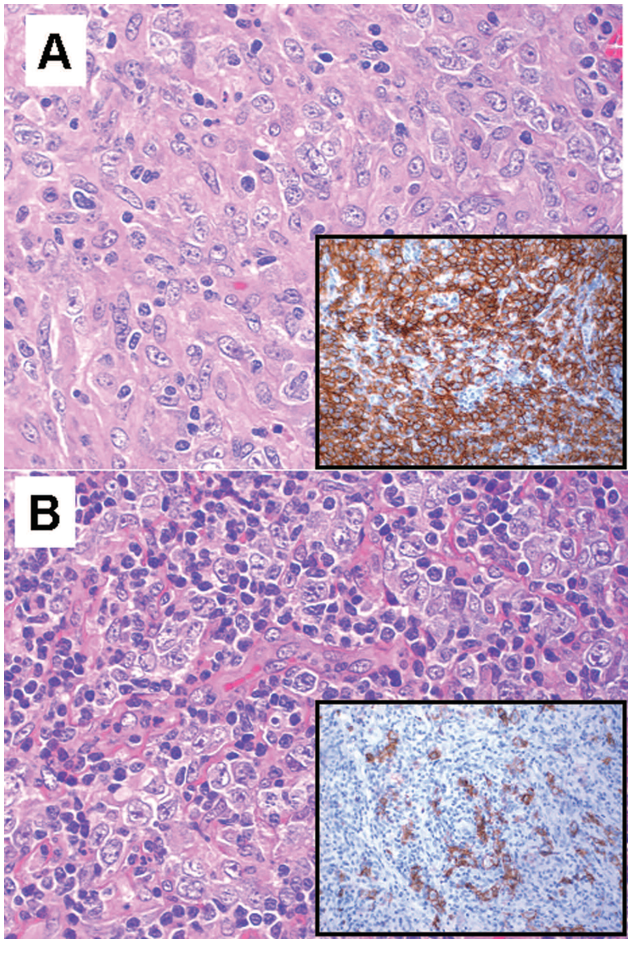

Figure 1. Representative example of MGZL (corresponding to case 34 in *Online Supplementary Table S2*) displaying areas with typical PMBCL morphology with sheets of medium to large blasts (A) and areas with a morphology reminiscent of cHL with single blasts in a T-cell-rich background in the same tumor specimen (B) (H&E, inserts CD20).

area of the tumor and of cHL in another (composite lymphoma) of which one additionally expressed CD15 (Figure 1 and cases 30 and 34 in *Online Supplementary Table S2*). The other two lymphomas had the typical morphology of PMBCL but were ascribed to the category of MGZL because of positivity for Epstein-Barr virus as detected by EBER (cases 47 and 49 in *Online Supplementary Table S2*).

The inter-observer concordance was very good. In 42 of 52 cases (81%) at least six of the seven pathologists reached the same diagnosis after the individual microscope analysis. However, since the study was not designed to test inter-observer reproducibility and because a very large group of observers (n=7) analyzed the specimen the Kappa value was relatively poor ($\kappa = 0.35$).[20] Ten cases were discussed at the multi-headed microscope. The final consensus diagnosis was PMBCL in four cases, MGZL in another four cases and B-cell lymphoma, not otherwise specified in two cases (*Online Supplementary Table 2*).

Immunohistochemistry and EBER in situ *hybridization*

The immunohistochemical profile of PMBCL and MGZL revealed only minor differences. Both entities were positive for B-cell markers such as CD20, CD79a and Pax5, and frequently expressed CD30 and CD23 (Table 2). The only statistically significant difference was that BCL6 expression turned out to be more frequent in PMBCL (28/29) than in MGZL (1/3, P=0.0177, Fisher's exact test). The data from the immunohistochemical analysis are summarized in Table 1 and *Online Supplementary Table S2*.

Within this large cohort the panel of pathologists observed some unusual features of PMBCL and MGZL. One lymphoma was negative for CD20 but otherwise showed the typical morphology and immunophenotype of PMBCL (case 36, *Online Supplementary Table S2*). The panel agreed that this lymphoma represented a rare example of a primary CD20-negative PMBCL. It is worth noting that two cases classified as MGZL were positive for EBER, as detected by EBER *in situ* hybridization. Nevertheless, the panel agreed that the morphological features of these lymphomas, which included sheets of blasts, and the immunophenotype, with a preserved B-cell phenotype (positive for CD20, and CD79a), did not favor the diagnosis of cHL and the lymphomas were classified as MGZL (Figure 2).

Interphase cytogenetics

Unfortunately, genetic studies could be performed for only one of the four cases of MGZL, which did not show gains of 2p or 9p or a *MYC* break (*Online Supplementary Table S2*). The pediatric PMBCL showed signal patterns indicating gains or amplifications of 2p16 (*REL/BCL11A*) and 9p24 (*JAK2/PDL2*) in 7/17 (41%) and 10/17 (59%) cases, respectively (Table 2). Interestingly, one case showed an atypical hybridization signal with the 9p24 probe, suggesting the presence of a chromosomal breakpoint (*data not shown*). It is noteworthy that a signal pattern indicating a break in the *MYC* gene locus was observed in a significant number of interphase nuclei in one lymphoma that was classified independently as PMBCL by all pathologists, blind to the clinical and genetic results, when using individual microscopes (Figure 3).

Clinical correlations

Table 3 outlines the clinical characteristics of the patients with PMBCL and MGZL. Although statistical comparisons of these characteristics between PMBCL and MGZL cases were not feasible because of the small number of MGZL cases in our cohort, there were no obvious

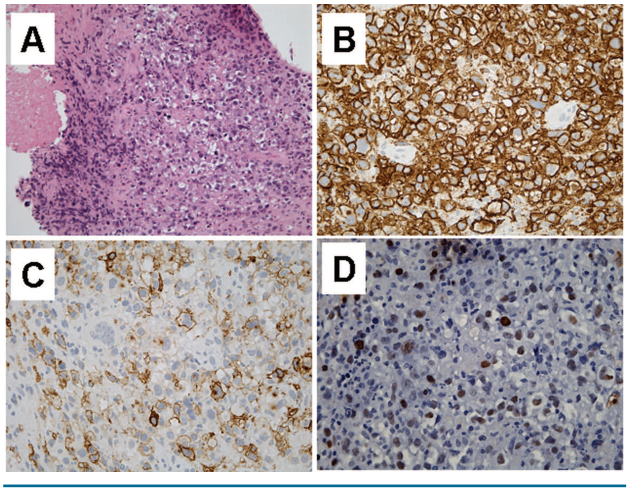

Figure 2. MGZL positive for EBV-encoded RNA (EBER) corresponding to case 49 in *Online Supplementary Table S2* (A) = H&E, (B) = CD20, (C) = CD30, (D) = EBER.

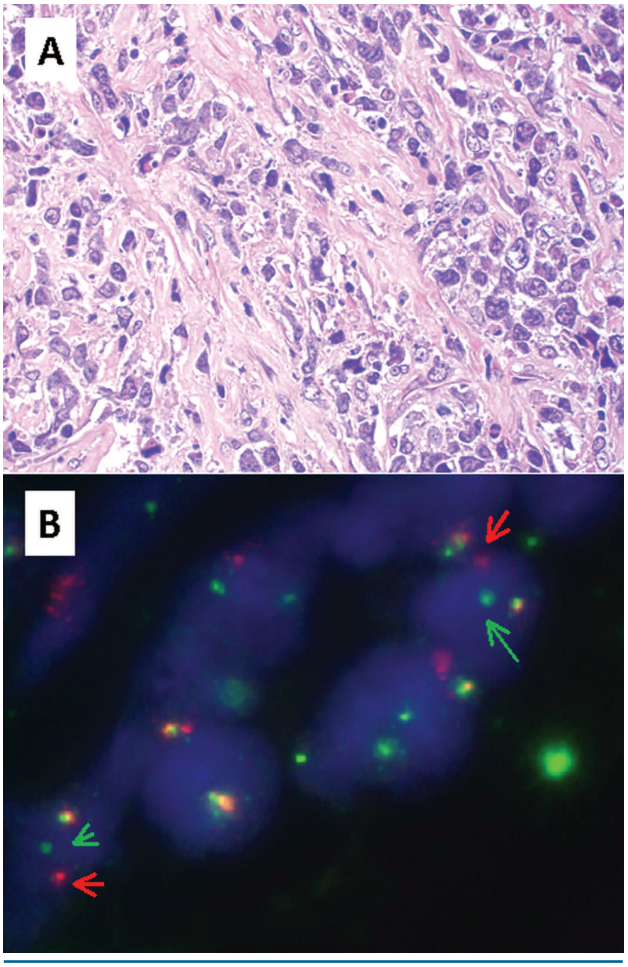

Figure 3. H&E morphology (A) and FISH for breaks in the *MYC* gene (B) in a case of a PMBCL (case 26 from *Online Supplementary Table S2*). Split signals are indicated by red and green arrows.

differences between the two entities with respect to gender distribution, median age, lactate dehydrogenase concentration, or pleural effusions (Table 3). The female to male sex ratio in PMBCL was 21:23 whereas it was 1:3 in MGZL (Table 3).

The two patients with lymphomas that were re-classified by the panel of pathologists as diffuse large B-cell lymphoma had mediastinal masses, but the panel felt that the morphology and immunophenotype of these cases were not typical of PMBCL. The reclassification by the panel was done without knowledge of the clinical data. Interestingly, one of these two patients had extensive lymphomatous involvement including multiple bone lesions and bone marrow infiltration and a complex aberrant karyotype (*data not shown*). The second patient had a large mediastinal tumor, pleural and pericardial effusions as well as enlarged abdominal lymph nodes.

The patient with the break in the *MYC* gene whose lymphoma was diagnosed by the panel as PMBCL had a mediastinal mass, pericardial effusion, enlarged cervical and abdominal lymph nodes as well as a lactate dehydrogenase concentration of 680 U/L. Interestingly, almost half of the patients of the NHL-BFM group with morphologically and immunophenotypically classical PMBCL showed lymphoma manifestations on both sides of the diaphragm, according to the Ann Arbor re-evaluation.

Discussion

This study is based on the largest series of cases of PMBCL and MGZL in children and adolescents analyzed so far for pathological, clinical and genetic features. In fact, no systematic series of genetic analyses of pediatric PMBCL have been published yet. The review process involving internationally recognized experts in the field of hematopathology who reviewed all cases on individual microscopes independently of each other revealed a high inter-observer concordance. Most of the pediatric lymphomas were morphologically prototypic cases of PMBCL, and discussions of discordant cases (for which fewer than six of the seven pathologists constituting the panel independently reached the same diagnosis) were primarily required for MGZL and other diagnoses. Only four cases of PMBCL, accounting for 9% of all PMBCL in the cohort, required additional discussion.

PMBCL in children expressed a 'complete' B-cell immunophenotype, including CD20 in all but one case. The expression of CD30 and CD23 in childhood PMBCL (77% and 67%, respectively) is comparable to that reported for adults (>80% and 70%, respectively).[1] Furthermore, the frequency of gains/amplifications in 2p16 (*REL/BCL11A*, 41%) and 9p24 (*JAK2/PDL2*, 59%) was similar to that reported for adult PMBCL.[1] We, therefore, conclude that the morphology, genetics and immunophenotype of PMBCL are similar between children and adolescents on the one hand and between these young patients and adults on the other hand. This study did not find any indication of biological differences between childhood and adult PMBCL, as had been speculated in previous publications discussing therapeutic aspects of pediatric PMBCL.[16] However, more comprehensive molecular genetic profiling will be needed in future studies to determine conclusively whether or not there are molecular differences between the two age groups. Interestingly, lymphomas morphologically and immunophenotypically resembling PMBCL can harbor chromosomal translocations involving the *MYC* locus, as we found in one case in our series.

The term MGZL is reserved for lymphomas that share histological and immunophenotypic features of PMBCL and cHL and that cannot be assigned to either of the two categories. According to previous detailed descriptions,[13,18] several conditions may lead to the diagnosis of MGZL. In the first case the lymphoma may show variable morphology resembling cHL in one area and PMBCL in another area (synchronous or composite lymphoma). In the second case, morphological features in the whole lymphoma

Table 2. Summary of results from FISH of PMBCL (the sum of all percentages does not correspond to 100% since some cases carried more than one aberration).

	MYC	2p (*REL/BCL11A*)	9p (*JAK2/PDL2*)
Wild-type	73% (11/15)	59% (10/17)	41% (7/17)
Gain	20% (3/15)	29% (5/17)	35% (6/17)
Amplification	7% (1/15)	12% (2/17)	24% (4/17)
Break	7% (1/15)	0% (0/17)	6% (1/17)

Table 3. Clinical characteristics of patients with PMLBL and MGZL.

	PMLBL (n=44)		MGZL (n=4)	
Gender female : male	21 : 23	48% : 52%	1 : 3	25% : 75%
Age at diagnosis				
median age (range)	15.2 y	(3.2 - 18.7y)	13.7 y	(10.7 - 17.9y)
<10 years	2	5%	0	0%
10-14 years	11	25%	2	50%
>14 years	31	70%	2	50%
St. Jude stage of disease				
≤II	0	0%	0	0%
III	43	98%	4	100%
IV	1	2%	0	0%
Lymphoma manifestations				
pleural+pericardial effusion (+ascites)	8	18%	1	25%
pleural effusion only	4	9%	0	0%
pericardial effusion only	13	30%	0	0%
no malignant effusions	19	43%	3	75%
mediastinal involvement	44	100%	4	100%
lung	10	23%	0	0%
kidney	10	23%	0	0%
central nervous system	1	2%	0	0%
bone marrow	0	0%	0	0%
Initial serum LDH level				
LDH < UNL	8	19%	1	25%
LDH > UNL but < 2x UNL	24	56%	2	50%
LDH > 2x UNL	11	26%	1	25%
no data	1	-	-	-
B symptoms at diagnosis				
B symptoms	20	48%	2	50%
no data	2	-	2	50%
Events				
non-response/ progression/relapse	15	34%	2	50%[1]
toxic death in CR	1	2%	-	-

LDH: lactate dehydrogenase; UNL: upper normal limit (LDH UNL=300 U/L in BFM, UNL=460 U/L in AIEOP), CR: complete remission. [1]One EBER-positive and one EBER-negative MGZL relapsed.

may show an overlap between PMBCL and cHL, such as Hodgkin-Reed/Sternberg cells admixed in an otherwise typical PMBCL. These lymphomas were only classified as MGZL if additional immunophenotypic features were suggestive of cHL (e.g. positivity for CD15 or EBER). Thirdly, lymphomas might be classified as MGZL if the morphology is unequivocally compatible with the diagnosis of PMBCL but the immunophenotype shows features of cHL, such as positivity for CD15 or EBER.[1] The morphology and immunophenotype of MGZL have been described for adults, with the median age of patients with MGZL in the published series being about 30 years.[13] Reports on childhood MGZL are, however, rare and mostly restricted to single cases. Our literature review revealed that only two cases of MGZL in a child have been published so far.[13,21] The results of our study confirm that MGZL is rare in children. Even though more than 95% of newly diagnosed pediatric patients (≤14 years of age) with non-Hodgkin's lymphoma are registered in the NHL-BFM study center, the exact incidence of MGZL cannot be estimated for several reasons: (i) the current study was performed retrospectively on all cases with available samples, but not on the whole cohort of PMBCL patients in the NHL-BFM and AIEOP trials; (ii) patients in the adolescent age group are underrepresented in the pediatric NHL-BFM trials, because in earlier years adolescent patients were treated in adult oncology departments; and (iii) additional cases of MGZL may be registered in the respective Hodgkin's lymphoma trials and may not be included in the current review. Thus the true incidence of MGZL in children can only be assessed if all mediastinal lymphomas in children, including those with Hodgkin's lymphoma, are reviewed. However, the fact that our study identified four cases of MGZL among 52 PMBCL cases analyzed strongly suggests the absolute and relative rarity of MGZL in children.

In recent treatment trials of children and adolescents with PMBCL, the event-free survival rate was approximately 70%.[14] Thus the prognosis of PMBCL is poorer than that of other aggressive B-cell lymphomas in children.[2,16] Compared to pediatric treatment regimens, adult protocols include higher cumulative doses of doxorubicin, etoposide, alkylating agents and bleomycin, but little or no methotrexate.[15,16,22] Furthermore, radiation therapy has been administered in addition to chemotherapy in most adult series, although the role of radiation remains a matter of debate.[14] Data from the National Cancer Institute study using DA-EPOCH-R suggest that patients with PMBCL benefit dramatically from the addition of rituximab to chemotherapy protocols for PMBCL.[17] After addition of rituximab to DA-EPOCH chemotherapy, the progression-free survival increased from 67% to 91% in subsequently treated patients.[17] Although these are the best clinical results that have been reported so far, the study had several limitations, in particular that of having been performed in a single institution. Data on pediatric PMBCL patients treated with DA-EPOCH-R are lacking so far, and other chemotherapy protocols have also proven to be effective.[14] However, our study might be helpful for designing future therapeutic approaches for PMBCL in children. Our data show that the morphological, immunohistochemical and genetic features of PMBCL are similar in children and adults, although we cannot rule out biological differences that might only be detectable by molecular techniques such as gene expression or genetic profiling. The only clinically relevant difference between childhood and adult PMBCL seems to be the gender distribution, with a female predominance in adulthood, while male and female patients are affected equally in childhood. However, lacking any proof of biological differences, we suggest that the differences in therapeutic outcome between the two age groups can most likely be attributed to differences in the treatment protocols.

It should be noted that within the cohort of patients treated with DA-EPOCH-R, the progression-free survival rate at a median follow-up of 4 years was 33% in patients with MGZL compared to 100% in those with PMBCL.[17] Thus even under multi-agent chemotherapy including rituximab, MGZL remains a disease with a very unfavorable diagnosis. However, since MGZL is a rare disease in both adults and children, clinical data on the outcome of MGZL are scarce. Nevertheless, we identified only a very small number of cases of MGZL in past trials of pediatric PMBCL. Indeed, the results of the reclassification and confirmation of diagnosis by the international panel of pathologists using current diagnostic criteria indicate that the unsatisfying therapeutic results in pediatric PMBCL are unlikely to be due to a 'contamination' of the past cohorts by cases of MGZL.

In summary, this large retrospective study did not reveal any morphological, immunophenotypic, or genetic differences between PMBCL in children and adult patients in previous studies. Furthermore, we found that MGZL exists in children but was rare in the cohorts of previous trials on PMBCL. The lack of evidence of biological differences between adult and pediatric PMBCL and the rarity of MGZL in childhood suggest that differences in outcome between children and adults suffering from PMBCL are most likely attributable to differences in therapeutic protocols used for patients in the two age groups. These findings might help in the design of new therapeutic strategies for PMBCL in children.

Authorship and Disclosures

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