Primary mediastinal B-cell lymphoma and mediastinal gray zone lymphoma: Do they require a unique therapeutic approach?

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ABSTRACT

Primary mediastinal B-cell lymphoma (PMBL) is a subtype of diffuse large B-cell lymphoma (DLBCL) that is putatively derived from a thymic B-cell. Accounting for up to 10% of cases of DLBCL, this subtype predominantly affects females in the third and fourth decades of life. Its clinical and molecular characteristics are distinct from other subtypes of DLBCL and in fact, closely resemble those of nodular sclerosing Hodgkin lymphoma (NSHL). Recently, mediastinal lymphomas with features intermediate between PMBL and NSHL – called mediastinal grey-zone lymphomas – have been described. The optimal management of PMBL is controversial and most standard approaches include a combination of immunochemotherapy and mediastinal radiation. Recently, the recognition that mediastinal radiation is associated with significant long-term toxicities has led to the development of novel approaches for PMBL that have shown excellent efficacy and challenge the need for routine mediastinal radiation.

INTRODUCTION

Primary mediastinal B-cell lymphoma (PMBL), originally described in the 1980’s, accounts for up to 10% of diffuse large B-cell lymphomas (DLBCL). It is epidemiologically, clinically and biologically distinct from the other subtypes of DLBCL (germinal center B-cell like (GCB) and activated B-cell like (ABC)). Similar to nodular sclerosing Hodgkin lymphoma (NSHL) arising in the mediastinum, it is likely derived from a thymic B-cell and typically presents in adolescents and young adults with an anterior mediastinal mass, which may invade local structures. Studies of gene expression profiling demonstrate a significant overlap between PMBL and NSHL and interestingly,
mediastinal lymphomas, with pathologic features intermediate and transitional between PMBL and NSHL (mediastinal grey zone lymphomas) have been described.

The optimal therapeutic approach to PMBL is controversial with a paucity of prospective studies. Though there are many retrospective studies, one of the challenges in interpreting them is that older studies likely included cases that would not meet the clinicopathologic definition of PMBL today. For the most part, it has been treated in the same way as the other subtypes of DLBCL with R-CHOP. However, the high efficacy of increased dose intensity regimens in this disease suggests that it requires a unique therapeutic approach. The major controversies in PMBL therapeutics are the need for consolidation radiation, the role of FDG-PET scanning and whether or not there are superior chemotherapy platforms to CHOP.

CLINICAL FEATURES

PMBL usually affects adolescents and young adults, with a female propensity, and typically presents in the third and fourth decades of life, which is much earlier than the other subtypes of DLBCL(1). Symptoms at diagnosis are typically caused by an anterior mediastinal mass and complications such as the superior vena cava (SVC) syndrome are common at presentation. PMBL tends to stay confined to the mediastinum and sometimes, may invade local structures such as the anterior chest wall and lungs. Disseminated disease may occur at diagnosis when extranodal sites such as the kidney, liver and adrenal gland may be involved. Nodular sclerosing Hodgkin lymphoma - arising in the mediastinum - shares many clinical characteristics with PMBL and also typically presents in young females. Recently, mediastinal grey zone lymphomas
(MGZL) with clinical and pathologic features intermediate between PMBL and classical Hodgkin lymphoma have been recognized. MGZL predominantly affect males and appear to have an inferior outcome compared to PMBL(1, 2).

**Pathology**

PMBL is putatively derived from a medullary thymic B-cell. Morphologically, these are medium to large cells having round or lobulated nuclei and abundant cytoplasm. In most cases, compartmentalizing sclerosis is observed and sometimes tumor cells can resemble Hodgkin/Reed Sternberg cells. The nodal architecture is typically diffuse with occasional cases showing focal nodularity and necrosis is sometimes seen(3). PMBL has a B-cell phenotype and expresses CD20 and pan B-cell markers such as CD79a, but tumor cells do not express surface immunoglobulin– therefore, monoclonality can not be established by kappa and lambda staining in contrast to most B-cell neoplasms (4, 5). B-cell transcription factors including PAX5, OCT2 and BOB1 are typically strongly expressed. CD30 is typically expressed but is dim in comparison to classical HL whereas CD15 is usually negative (3-5). The germinal center markers CD10, BCL6 and CD23 are expressed in most cases of PMBL, in keeping with its thymic B-cell origin(6, 7). Distinguishing PMBL from nodular sclerosis Hodgkin lymphoma can sometimes be challenging for the pathologist – NSHL has a nodular pattern of growth and the presence of lacunar variants of HRS cells with a characteristic immunophenotype. In contrast to PMBL, cells are typically CD15 positive and strongly positive for CD30. The expression of B-cell markers like CD20, CD79a and PAX5 is often weak or negative(8, 9).
The morphological and immunohistochemical features of MGZL are intermediate and transitional between PMBL and NSHL(10-12). As in the case of both PMBL and NSHL, surface immunoglobulin is not expressed. B-cell markers such as CD20 and CD79a are typically expressed, CD30 is usually positive and there is variable expression of CD15. PAX5, OCT2 and BOB1 are also typically expressed. In MGZL cases, an asynchrony between morphology and immunophenotype can be seen – cases can have a PMBL-like morphology but with immunophenotypical features of nodular sclerosis Hodgkin lymphoma or vice versa. The factors that transform a thymic B-cell into one or other of these diseases are not well understood but it is likely that there is plasticity in these events given that it is not uncommon to see them recur as one of the other entities (e.g. PMBL recurs as NSHL or NSHL as MGZL etc.)(figure 3A)(11).

**Genetic and Molecular Characteristics of PMBL**

Gene expression profiling studies have demonstrated that the genotype of PMBL has much more in common with that of NSHL than the other subtypes of DLBCL (i.e. germinal center B-cell like (GCB) and activated B-cell like (ABC))(13, 14). In fact, PMBL shares a third of its genes with NSHL(13). Among the most common genetic alterations in PMBL are abnormalities on chromosome 9p (up to 75%) and 2p (approximately 50%) – while these have been described in NSHL, they are typically not found in the other DLBCL subtypes (15). The 9p region encodes janus kinase 2 (JAK2) which then activates the transcription factor STAT 6 through phosphorylation (13, 16). Recent work has demonstrated that phosphorylated STAT 6 can transcriptionally repress BCL6 in PMBL(17). Suppressor of cytokine signaling 1 (SOCS1) suppresses JAK
signaling and is mutated in a high proportion of PMBL and CHL cases(18). Also in the 9p region, programmed death ligands (PDL) 1 and 2 are rearranged at a frequency of 20% while gains or amplifications of c-REL may be seen at 2p(13, 19). Approximately one third of PMBL cases may have gains in chromosome X. Recently, whole-genome and whole-transcriptome sequencing has identified recurrent somatic coding-sequence mutations in the PTPN1 gene – these are also commonly found in Hodgkin lymphoma cases(20). In PMBL, in contrast to other subtypes of DLBCL, rearrangements of BCL2, BCL6 and MYC are typically absent (15). PMBL and CHL both have constitutively activated nuclear factor kappa-B (NFκB) and PMBL cell line survival is dependent on NFκB target genes.

Due to its rarity, the molecular characteristics of GZL have not been well studied. However, a study that looked at chromosomal aberrations in GZL showed gains including amplifications in 2p16.1(REL/BCL11A locus) in 33% of all cases, alterations of the JAK2/PDL2 locus in 9p24.1 in 55%, rearrangement of the CIITA locus at 16p13.13 in 27% and gains of 8q24 (MYC) in 27%(10). A recent large-scale methylation analysis that included PMBL, CHL and MGZL cases, showed that these entities shared many epigenetic characteristics and that MGZL had a distinct epigenetic signature(21).

**Diagnosis of PMBL and Prognostic Factors**

The diagnostic work up for PMBL should include the same routine tests that are performed for any other DLBCL patient. Most importantly, the tissue biopsy should be evaluated by a pathologist expert in the diagnosis of lymphoma. For the aforementioned reasons, it can sometimes be challenging to distinguish PMBL from NSHL. A thorough
history and physical examination, complete evaluation of hematological and biochemical parameters, computerized tomography of the chest, abdomen and pelvis and a bone marrow aspirate and biopsy should be performed. Though CNS involvement is very rare at initial diagnosis, the CSF should be checked by cytology and flow cytometry in the presence of clinical characteristics that are associated with a higher risk of CNS spread(22). It is common for pleural and pericardial effusions to occur at presentation so it may be useful to perform an echocardiogram. While the international prognostic index (IPI) is useful in DLBCL, its utility in PMBL specifically is limited by the young age distribution of the disease and its typical confinement to the mediastinum(23). Various studies have looked at the role of IPI but it is not clear that it is helpful in predicting outcome (24). Some retrospective studies have suggested that factors like LDH level, male sex, performance status and advanced stage disease may be useful predictors of survival but this is controversial and has not been validated in prospective studies(25, 26).

**Primary Treatment and Outcome**

As PMBL is relatively rare and only recently described, there is a paucity of prospective treatment data and a lack of randomized studies. Therefore controversies abound about what the optimal therapeutic approach should be and which regimen is best. The cure rate for progressive or recurrent disease following primary therapy is low so it is critical to optimize up-front outcomes. Most effective approaches to date have incorporated consolidation radiation – though high cure rates are achieved with combined modality therapy, it is increasingly apparent, especially from follow-up data on long-term
survivors of HL, that mediastinal radiation is associated with significant late sequelae – particularly a high risk of breast tumors in females (27, 28). Though some studies suggest that lower doses of radiation and more focused treatment fields may reduce these complications, this has not been clearly demonstrated and some studies contest this(29). It is therefore important in PMBL to develop platforms that obviate the need for routine radiation and thus eliminate these complications.

**Radiation and Dose Intensity**

Early studies in PMBL suggested that consolidation radiation was a critical component of curative therapy. One of these that led to this widely held acceptance was a study of MACOP-B (methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin) followed by mediastinal radiation therapy in 50 untreated PMBL patients(30). While 66% of patients were gallium scan positive (this study was done in the pre FDG-PET era) at the end of chemotherapy, only 19% were gallium positive after radiation and this supported a combined modality approach, which is taken by most today. Early (albeit retrospective) studies also suggested a benefit to increasing dose intensity, which has been shown to be important in Hodgkin lymphoma, a closely related disease clinically and biologically. One such study retrospectively compared MACOP-B and VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) to CHOP in 138 patients – those who received CHOP had a worse outcome, suggesting a role for dose-intensity(31). The largest study to look at the dose intensity question was conducted by the International Extranodal Lymphoma Study Group (IELSG) and evaluated 426 newly diagnosed PMBL patients who received
MACOP-B, VACOP-B, ProMACECytaBom or CHOP (26). Although response rates were similar among the groups, projected long-term PFS and OS survival rates were higher in patients who received third-generation regimens. Additional retrospective series from the British Columbia Cancer Agency and MSKCC groups also suggested that increased dose-intensity regimens might be superior to CHOP-like approaches in this disease (24, 25). Nonetheless, prospective comparisons of increased dose-intensity versus CHOP-like regimens have not been done in PMBL – though the Southwest Oncology Group (SWOG) prospectively compared second and third generation regimens to CHOP in DLBCL, the outcome of PMBL was not assessed as it was not a recognized disease entity at this time (32).

The Role of Rituximab

While the addition of rituximab to CHOP chemotherapy in DLBCL has been shown to improve survival in several different studies, this has not been well studied or established in PMBL due to the rarity of the disease (33). A subgroup analysis of the prospective, randomized, phase III MabThera International Trial (MiNT) evaluated the role of rituximab in combination with CHOP-like regimens in PMBL patients with an age adjusted IPI of ≤ 1 (34). The rituximab arm was clearly superior in terms of 3-year event-free survival (78% versus 52% in the chemotherapy arm alone), but no statistically significant difference in OS was detected due to small numbers of patients. When the outcome of patients who received DA-EPOCH alone in the pre-rituximab era was compared to those who received DA-EPOCH-R, albeit a non-randomized comparison, there was a significantly better event-free and overall survival in the group who received
rituximab (35). Though an earlier retrospective study from the British Columbia Cancer Agency in the pre and post rituximab period demonstrated no survival advantage in patients when rituximab was added to CHOP, a more recent report from the group showed an improved time to progression and longer overall survival in those receiving rituximab(25, 36).

**Can mediastinal radiation be omitted?**

Despite a lack of prospective studies, there does appear to be a benefit to adding rituximab to chemotherapy in PMBL. Therefore, can rituximab abrogate any advantage of dose-intensive platforms over CHOP and obviate the need for routine radiation? While the subset analysis in the MInT study demonstrated improved responses and EFS in patients receiving rituximab, preplanned radiotherapy was still administered to 73% of patients in the immunochemotherapy arm and adding radiation improved remission rates. In addition and importantly, the study was confined to patients with a low IPI score (≤1) who truly represent very favorable subset of patients without the presence of unfavorable characteristics at diagnosis. A recent retrospective analysis of R-CHOP (followed by mediastinal radiation in 77% of responders) in 58 PMBL patients that included all IPI groups showed a high rate of primary induction failures (21%) and an overall PFS of 68% at 5 years(37). Another retrospective analysis from the MSKCC group evaluated R-CHOP followed by ifosfamide, cyclophosphamide and etoposide (ICE) without radiation and reported a PFS of 78% at 3 years(38). A British Columbia study that looked at the outcome of PMBL in the rituximab era reported on a subset of patients in whom an FDG-PET guided RT approach (i.e. FDG-PET negative cases were not radiated) was used.
Despite this, a sizeable proportion of PET negative cases subsequently relapsed (36). Due to the observation that dose intensity has been important in PMBL, an NCI study evaluated dose adjusted EPOCH-R without radiation in PMBL and included all clinical risk groups (39-41). In 51 patients, at a median follow-up of 5 years, EFS and OS were 93% and 97% respectively and just 2 patients required consolidation radiation (35). In an additional 16 PMBL patients who received the regimen at Stanford, both EFS and OS were 100% without radiation. This approach is now being tested in multicenter studies and an early report from a pediatric/adolescent study suggested high efficacy without the need for radiation in this population (42).

**FDG-PET evaluation following therapy**

At the completion of treatment for PMBL, a residual mediastinal mass is commonly present, particularly in cases where there had been a large mass at initial diagnosis or a large fibrotic component to the mass. It is not uncommon for these masses to persist for several months after the completion of therapy and this is an important consideration in interpretation of follow-up imaging. Hence, computed tomography (CT) alone is limited in its scope to assess for the presence of residual disease. Gallium scanning was used as an adjunct imaging test in the past for this purpose but it is now regarded as a cumbersome test and is infrequently used today. While studies looking at the role of end of treatment FDG-PET and its ability to guide the use/need for consolidation radiation are limited, the technique has been found to have a very high negative predictive value in this disease (35). However, the positive predictive value of FDG-PET in PMBL is poor in contrast to the high clinical accuracy of FDG-PET in other
aggressive lymphomas(35, 42). Following DA-EPOCH-R, 18 of 36 patients who underwent an FDG-PET scan, had a maximum standardized value (SUV) above the mediastinal blood pool but only 3 of these were found to have residual lymphoma. One retrospective study that looked at interim PET in PMBL patients receiving R-VACOP-B also reported a low positive predictive value(43). This is likely due to ongoing inflammatory activity in residual mediastinal masses that may be FDG-PET avid. Therefore, it is not a very accurate technique for determining the presence of residual disease at the end of treatment and alternative, more specific imaging modalities should be investigated.

**Therapeutic Decision Making**

In making decisions about the initial treatment of PMBL, one must consider the long-term complications of mediastinal radiation in this population who are predominantly young females(27). While R-CHOP followed by radiation has been effective in low-risk patients, it appears to be insufficient therapy for patients with high-risk disease and is associated with a high rate of primary refractory disease(44). Based on its promising efficacy in an NCI study, we recommend DA-EPOCH-R without radiation while confirmatory studies are in progress. Following this regimen without radiation, end of therapy FDG-PET has an excellent negative predictive value but low positive predictive value so end of therapy positive FDG-PETs need to be interpreted cautiously with regard to decisions about consolidation radiation. A prospective study of FDG-PET directed therapy by the IELSG is currently underway.
Treatment of Mediastinal grey-zone lymphomas

These very rare tumors have histological and immunophenotypic features that are transitional between PMBL and nodular sclerosing Hodgkin lymphoma. Due to their rarity and recent identification, they have been poorly studied. In the past, these tumors were likely called “anaplastic large-cell lymphoma Hodgkin-like” and that entity was reported to have a poor prognosis with short median survivals(45). Their indeterminate pathobiology has led to uncertainty about what the optimal therapeutic strategy should be. One retrospective study reported that the 5-year event-free survival for this entity was worse than that for classical Hodgkin lymphoma (International Database on Hodgkin’s Disease), suggesting adverse biology and a high rate of treatment resistance (45). Recently, a prospective study looked at the clinical characteristics and outcome of MGZL following treatment with DA-EPOCH-R and reported a worse outcome compared to that of PMBL, despite a patient population with similar clinical characteristics (EFS and OS of 62% and 74% versus 93% and 97% for PMBL) (46, 47). Studies investigating the molecular characteristics and biological basis for this inferior outcome are ongoing.

Treatment of relapsed or refractory disease

In PMBL, relapses tend to occur relatively early following the completion of treatment and most are observed in the first year or 18 months after therapy. Relapsed disease may stay confined to the mediastinum or spread to extra-nodal sites such as the liver, kidneys or central nervous system. Optimal therapy for relapsed disease has not been well defined and should be decided based on the pattern of relapse and prior treatments received. For relapses that are localized to the mediastinum, chemotherapy
with radiation treatment (with or without autologous stem cell transplantation) may be a curative option, especially in patients who did not receive mediastinal radiation initially. For non-localized relapses, salvage chemotherapy followed by high dose therapy may be considered(48). Allogeneic transplantation is another experimental option that can be considered. The outcome for patients with MGZL is inferior to that of PMBL and relapses should be approached similarly to PMBL.

Novel Agents

The antibody drug conjugate directed against CD30 – brentuximab vedotin - has shown activity in patients with relapsed Hodgkin lymphoma and is currently being studied in PMBL, where CD30 is variably expressed(49). Novel strategies in PMBL and other mediastinal lymphomas should focus on combining targeted agents with effective immunochemotherapy platforms. As the NF-kappa B signaling pathway is one of the most important deregulated pathways in PMBL, inhibitors of this pathway are rational strategies in PMBL. A region on chromosome 9p24 is amplified in 70% of cases of PMBL that constitutes critical targets including janus kinase 2 (JAK2) and the PD1 ligands programmed cell death ligand 1 (PD-L1) and PD-L2 (50-52). Selective JAK2 inhibition has been shown to specifically decrease mediastinal large B-cell lymphoma growth in vitro and in vivo (53). Agents such as JAK-STAT pathway inhibitors or neutralizing antibodies to PD-1, like pidilizumab, are worthwhile investigating in PMBL.(54)

Conclusions
Controversies abound as to what the optimal regimen is for PMBL but evidence from several studies suggests a benefit to regimens with increased dose-intensity. Recent data demonstrates that DA-EPOCH-R can obviate the need for routine mediastinal radiation. These results are now being validated in multicenter settings in distinct patient groups. Though FDG-PET is routinely used for end of treatment assessment in PMBL, it has a low positive predictive value that limits its usefulness in the assessment of residual masses.

**Authorship**

KD and WHW contributed to the writing of the manuscript and approved the final version. KD and WHW have no relevant conflicts of interest.

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**References**


**Table 1:** Selected published studies of chemotherapy/immunochemotherapy regimens with and without radiation treatment in PMBL.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Study type</th>
<th>Patient Characteristics</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinzani et al. 10</td>
<td>MACOP-B, VACOP-B or CHOP</td>
<td>Yes</td>
<td>All IPI groups</td>
<td>At 39mos, 93% who achieved CR were relapse-free. At 8 years, OS was 82%</td>
</tr>
<tr>
<td>Todeschini et al. 12</td>
<td>MACOP-B, VACOP-B or CHOP</td>
<td>Yes</td>
<td>All IPI groups</td>
<td>At 66 mos, EFS was 39% for CHOP and 76% for MACOP-B/VACOP-B</td>
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<tr>
<td>Zinzani et al. 16</td>
<td>MACOP-B, VACOP-B, proMACCytAbom, CHOP or HDS/ABMT</td>
<td>Yes</td>
<td>All IPI groups</td>
<td>At 10 years, PFS was 35% for CHOP/CHOP-like, 67% for MACOP-B/VACOP-B and 78% for HDS/ABMT</td>
</tr>
<tr>
<td>Hamlin et al. 24</td>
<td>CHOP/CHOP like, NHL-15, ASCT</td>
<td>No</td>
<td>All IPI groups</td>
<td>At 11 years, EFS was 34% for CHOP/CHOP-like, 60% for NHL-15 and 60% for ASCT</td>
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<tr>
<td>Savage et al. 15</td>
<td>CHOP/R-CHOP/MACOP-B/VACOP-B</td>
<td>Variable</td>
<td>All IPI groups</td>
<td>At 5 years, overall PFS was 69%. Only MACOP-B/VACOP-B versus CHOP-like regimens were significantly different</td>
</tr>
<tr>
<td>Rieger et al. 14</td>
<td>CHOP/R-CHOP</td>
<td>Variable – RT intended in 87%</td>
<td>Retrospective analysis N=87</td>
<td>Confined to AA-IPI of 0-1 At 3 years, EFS was 78% for R-CHOP and 52% for CHOP</td>
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<tr>
<td>Soumerai et al. 14</td>
<td>R-CHOP</td>
<td>Yes – 77% of responding patients</td>
<td>Retrospective study N=63</td>
<td>At 5 years, PFS was 68%</td>
</tr>
<tr>
<td>Dunleavy et al. 22</td>
<td>DA-EPOCH-R</td>
<td>No</td>
<td>All IPI groups</td>
<td>At 5 years, EFS was 93%</td>
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<tr>
<td>Woessmann et al. 44</td>
<td>DA-EPOCH-R</td>
<td>No</td>
<td>All IPI groups</td>
<td>Age &lt; 18 At 19 months, EFS was 92%</td>
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<td>Martelli et al. 27</td>
<td>R-MACOP-B, R-VACOP-B, R-CHOP</td>
<td>Yes</td>
<td>All IPI</td>
<td>Estimated 5 year PFS is 86%</td>
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**Figure Legends**

**Figure 1:** Primary mediastinal B-cell lymphoma. H&E is shown and CD20 and MUM1 staining are positive. MIB-1 scoring is high (Courtesy Stefania Pittlauja).

**Figure 2:** Figure 2. Relationship of PMBL to Hodgkin lymphoma. Relative gene expression is shown in primary PMBLs (average of all biopsy samples), the PMBL cell line K1106, three Hodgkin lymphoma (HL) cell lines, and six GCB DLBCL cell lines. Red represents high gene expression and green low expression. PMBL signature genes that are also expressed at high levels in Hodgkin lymphoma cell lines compared with GCB DLBCL cell lines. (Courtesy Louis Staudt).

**Figure 3:** A. Both PMBL and HL are putatively derived from a thymic B-cell. The events that transform a thymic B-cell into PMBL or HL are poorly understood but there appears to be plasticity in these events as HL can recur as PMBL and vice versa. B. While NSHL is CD15 and CD30 positive and PMBL is CD20 positive, there are mediastinal lymphomas in between these 2 entities with histologic and immunohistochemical features intermediate and transitional between NSHL and PMBL. These disease are called mediastinal grey zone lymphomas (MGZLs).

**Figure 4:** FDG-PET imaging after completion of therapy in PMBL. These are sequential FDG-PET scans of a patient with PMBL who received 6 cycles of DA-EPOCH-R. (a) 3 weeks after the completion of therapy, there was an FDG-PET avid lesion in the anterior mediastinum with an SUV of 6. (b) The patient was followed and approximately 6 weeks later had another FDG-PET (b). The lesion now had an SUV of 2. A subsequent FDG-PET scan 6 weeks later was entirely normal and the patient remains in complete remission several years later.
Figure 3A

Thymic B-cell

HL

PMBL
Figure 4

(a) End of therapy

(b) 6 weeks later
Primary mediastinal B-cell lymphoma and mediastinal gray zone lymphoma: do they require a unique therapeutic approach?

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