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Supplement Article

IV. Masses in the mediastinum: primary mediastinal lymphoma and intermediate types

Peter W. M. Johnson*

Cancer Research UK Centre, University of Southampton, Somers Cancer Research Building, Southampton General Hospital, Southampton SO16 6YD, UK

**Correspondence to: Peter W. M. Johnson, Cancer Research UK Centre, University of Southampton, Somers Cancer Research Building, Southampton General Hospital, Southampton SO16 6YD, UK.*
E-mail: johnsonp@soton.ac.uk

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Introduction

Lymphoma in the mediastinum is the subject of active research and controversy. Patients are usually young and often present with acute compressive symptoms; the pathology can be difficult to interpret; our understanding of the biology is in evolution and the approach to treatment is also changing, in particular the types of induction immunochemotherapy that are preferred and the role of consolidation radiotherapy. Recent data on functional imaging has given useful results, and important prospective trials are underway which will help with future decision making.

Primary mediastinal B-cell lymphoma (PMBL) was recognized clinically as a particular entity 25 years ago and is now known to be distinct from other types of diffuse large B-cell lymphoma (DLBL) in its epidemiology, biology and clinical behaviour [1]. In common with nodular sclerosing Hodgkin lymphoma in the mediastinum, it is thought to originate from thymic B-cells [2], and there is an intermediate entity which lies between these two types, currently termed mediastinal gray-zone lymphoma (MGZL) [3].

PMBL is relatively uncommon, comprising around 3% of all NHL, and up to 10% of DLBL. It is found worldwide, is more common in females and most often presents in young adults, with a median age of 35 [4]. MGZL is even less common, but appears to have similar clinical characteristics. Both may present with local compressive symptoms including cough, dysphagia, hoarseness and oedema from superior vena cava compromise. Because of these, presentation is usually with early stage but bulky disease, and extrathoracic spread is rare at diagnosis. Around two thirds of patients have elevated lactate dehydrogenase levels at diagnosis [5,6].

Pathology

Diagnosis requires a formal tissue biopsy, although in many cases lymph node resection may not be practicable, especially where airway compromise is present. In these cases, a percutaneous needle core biopsy (*not* a fine needle aspirate) is generally sufficient. Although usually straightforward, the interpretation of biopsies from mediastinal lymphomas can sometimes be challenging, and an adequate diagnosis requires at least morphology and immunohistochemistry, and sometimes genetic/molecular data, especially in cases of doubt (Table 1).

PMBL is composed of large polymorphic B-cells with abundant clear cytoplasm which often have lobulated nuclei with eosinophilic nucleoli. There may be strands of alveolar fibrosis separating islands of lymphoid cells, although this is a variable feature, as is the presence of Reed–Sternberg-like cells. PMBL generally lacks surface immunoglobulin but expresses B-cell antigens including CD19, CD20, CD22, CD79a and the leukocyte common antigen (CD45). B-cell transcription factors such as BOB1, PU1, OCT2 and PAX5 are normally expressed, and CD30 is also positive in many cases, albeit at lower levels than on classical HL [7]. CD15 is generally negative, whereas in MGZL it is reported to stain positive in around half of cases, and in classical HL is typically strongly positive. The definition of MGZL is difficult: it frequently bears morphologic features of HL but protein expression (such as CD20) closer to PMBL [3]. PMBL usually expresses MAL and nuclear REL, whereas neither is common in HL or MGZL [8].

Molecular analyses have yielded more information about the different mediastinal lymphomas. Gene expression profiling first demonstrated the resemblance of PMBL and HL, which share the expression of around 30% of genes [9,10]. Deregulation of the JAK–STAT pathway, promoting B-cell growth and survival, is a common theme of many abnormalities in PMBL, including copy number gains in REL, JAK2 and JMJD2C; chromosomal rearrangement of CIITA; mutations of *SOCS1* and *PTPN1 or* STAT6; or promotor hypermethylation of p16/INK. These are also seen in HL and MGZL, although the methylation

Table 1. Pathologic and immunophenotypic features of the common mediastinal lymphomas (reproduced from Dreyling et al., Springer-Verlag Berlin Heidelberg, 2014)

Features	PMBCL	DLBCL	NScHL	MGZL
Morphology	Sheets of large cells; clear cells; no inflammatory	Sheets of large cells with variable aspects	Lacunar Hodgkins Reed–Stenberg cells; inflammatory polymorphous infiltrate	Sheets of pleomorphic large cells; lacunar Hogkins Reed–Stenberg cells; sparse inflammatory infiltrate
Sclerosis	70–100% (alveolar, fine bands)	Absent	100% (large bands)	Focal fibrous bands
CD45	Positive	Positive	Negative	Positive
CD30	Positive weak (70–80%)	Rare (anaplastic variant)	Positive	Positive
CD15	Negative	Negative	Positive	Positive
CD20	Positive	Positive	Negative	Positive
CD79a	Positive	Positive	Usually negative	Positive
PAX-5	Positive	Positive	Weak positive	Positive frequently
Immunoglobulin	Negative	Positive	Negative	Negative
BOB-1	Positive	Positive	Negative	Positive frequently
OCT-2	Positive	Positive	Negative	Positive frequently
MAL expression	60–70%	<10%	20%	30–40%

profile of the latter may be distinct [11]. Copy number gains on chromosome 9p not only affect JAK2 but also the PD-L1 and PD-L2 genes [12,13], which may result in impaired T-cell recognition.

Primary treatment: chemotherapy

Historically PMBL was treated with CHOP, in keeping with other types of DLBL, but the results were unsatisfactory and appeared to be better with more dose-dense third generation regimens such as MACOP-B and VACOP-B, at least in retrospective and non-randomized comparisons [6]. The introduction of rituximab with chemotherapy seems to have eliminated such differences, and overall results after rituximab-containing regimens appear better. There is relatively little randomized trial evidence, but a subset analysis of 87 patients with PMBL in the phase III MiNT study showed that addition of rituximab to CHOP increased the complete response (CR) rate from 54 to 80%, and 3-year event-free survival (EFS) from 52 to 78% ($p = 0.012$) [14]. The small numbers prevented the difference in overall survival (OS) reaching statistical significance (3-year OS 78 vs 89%, $p = 0.16$), but it was similar to that seen for the rest of the study (85 vs 93%, $p < 0.001$). The prospective single arm IELSG 26 study of rituximab-chemotherapy in 125 patients gave a 5-year PFS of 86% and OS 92%, which appears better than previous results [15]. Similarly the addition of rituximab to the infusional DA-EPOCH regimen seems to have improved results in a non-randomized cohort comparison with better EFS ($P = 0.036$) and OS ($P = 0.023$) [16].

It is not clear whether any particular chemotherapy regimen is superior, although it is interesting that DA-R-EPOCH appeared to elicit a high proportion of cures without consolidation radiotherapy in a series of 65 patients, whereas R-CHOP is generally felt to require subsequent radiotherapy to the mediastinum in most cases. The recently completed randomized comparison of R-CHOP versus DA-R-EPOCH being conducted by the CALGB (NCT00118209) will give important information on this.

The results with MGZL are generally less favourable than those of PMBL, with either R-CHOP or DA-R-EPOCH. A prospective study of 24 patients treated with DA-R-EPOCH compared the results to those for the NCI cohort of PMBL treated with the same regimen, and showed 5-year EFS and OS results which were significantly less good: 62% versus 93% ($P = .0005$) and 74% versus 97% ($P = .0012$) respectively [17].

The role of functional imaging

One of the major difficulties in managing bulky mediastinal lymphomas is to determine whether or not the residual masses which are almost invariably visible on CT scans at the completion of initial chemotherapy represent viable lymphoma or merely fibrotic scar tissue. Functional imaging offers one way to make this distinction, and ^{18}Fluoro-Deoxy-Glucose Positron Emission Tomography (FDG-PET) scanning is established as a key component of response assessment for these illnesses, despite uncertainty about its positive predictive value in particular. A systematic review examined the results of post-chemotherapy FDG-PET scanning in aggressive lymphoma, and found that the sensitivity of PET ranged from 33% to 87% and the specificity from 75% to 100% [18]. It is likely that the specificity in PMBL is lower than this, given results from Memorial Sloan-Kettering in 14 patients with PMBL and interim positive PET scans after four cycles of accelerated R-CHOP, none of whom had viable lymphoma present on biopsy, and all of whom remained in remission

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after completing consolidation R-ICE chemotherapy [19]. Similarly in the IELSG 26 series there was a relatively low rate of negative scans (under 50%) despite excellent clinical outcomes, although consolidation radiotherapy was given in 119 of 125 cases [15]. In the series of MGZL treated at the NCI, the rate of post-chemotherapy PET-positivity was 5/21 patients, with specificity of 100% but sensitivity only 63% [17].

Despite these limitations, the negative predictive value of post-treatment FDG-PET imaging appears to be high for PMBL at least, and this may provide the basis for modulating the use of consolidation radiotherapy.

Primary treatment: radiotherapy

The use of consolidation radiotherapy for PMBL has been an historical standard of care, based upon poor results following chemotherapy alone prior to rituximab, and the excellent results in series such as IELSG 26 where almost all patients underwent irradiation. This is reinforced by the very poor outcomes for patients who develop recurrent disease, highlighting the need to maximize cures at the first attempt [5,20,21]. Set against this, the long-term toxicities of mediastinal radiotherapy are well documented, in particular second malignancies of the breast and lung [22], and accelerated coronary or valvular heart disease [23], in a patient group dominated by young adults.

For this reason, some investigators have elected to omit consolidation radiotherapy. In the NCI, the use of DA-R-EPOCH seems to permit the omission of radiotherapy without compromising cure rates in a small series [16], and the British Columbia Cancer Agency have elected to omit radiotherapy for those FDG-PET negative at the completion of R-CHOP, reducing the use of radiotherapy from 80% to 38% of patients, apparently with good outcomes [24]. There is however no prospective randomized trial in which this question has been addressed to date, and the ongoing IELSG 37 study aims to correct this by offering randomization to standard radiotherapy versus no further treatment for those found FDG-PET negative at the end of initial rituximab-chemotherapy regimens (NCT01599559).

Refractory or recurrent disease

Recurrences of PMBL may show unusual localisations such as the kidneys, pancreas, adrenals, liver and ovaries. Unfortunately in many cases progression occurs soon after initial therapy and most are within 1 year, reflecting a high rate of acquired resistance. Standard salvage regimens with non-cross resistant agents are generally employed, with the intent to proceed with high dose consolidation in the second remission, but this is not often achieved. Among one study of 138 patients with recurrent PMBL all who relapsed died of lymphoma [21], although in another series from the MD Anderson hospital there were 42% long-term survivors [25].

The rarity of PMBL and MGZL, coupled with generally high remission rates from initial therapy, has limited the investigation of novel agents in these illnesses. The expression of CD30 on PMBL has led to the exploration of brentuximab vedotin, an antibody–drug conjugate, for recurrent disease [26], and the possible role of PD-L1 expression in evading immune surveillance may be a target to test with antibodies to PD-L1, which have proven successful in the treatment of Hodgkin lymphoma as well as a range of epithelial cancers. The central role of JAK–STAT signaling in the biology of these lymphomas also suggests that pathway inhibitors may have a role to play in the future.

Disclosures

Professor Johnson has received honoraria for advisory board attendance and speaking engagements from Bristol-Myers Squibb, Takeda and Janssen-Cilag.

Conflict of interest

The authors have no competing interest.

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