Chapter 10
Rare B-cell Lymphomas

Primary Mediastinal, Intravascular, and Primary Effusion Lymphoma

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10.1 Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma. This group of diseases is defined pathologically by a diffuse infiltrate of large neoplastic B-cells and clinically by aggressive presentations. Variants and subtypes of DLBCL are recognized in the REAL (Real European-American Lymphoma Classification) and WHO (World Health Classifications) based on unique pathologic features and clinical presentations. Herein are described the three clinical subtypes of DLBCL.

10.2 Primary Mediastinal Large B-Cell Lymphoma

Primary mediastinal large B-cell lymphoma (PMBCL) is recognized as a unique clinical subtype of DLBCL based on distinct clinical and pathologic features and it is believed to arise from thymic medullary B-cells, suggesting a unique histogenesis (1). It accounts for approximately 2% of patients with non-Hodgkin's lymphoma with a propensity to affect young adults. Although morphologically it resembles DLBCL, it has distinct morphologic, immunophenotypic, and genetic features. Further, it has long been appreciated that there is considerable clinical and pathologic overlap with nodular sclerosis Hodgkin's lymphoma and recent microarray studies confirm that PMBCL nasa gene signature with striking similarities to that of classical Hodgkin's lymphoma (CHL)(2).

10.2.1 Pathology

The tumor is composed of diffuse large cells with pale or 'clear' cytoplasm and variable degrees of sclerosis (Figure 10.1). PMBCL is derived from B-cells and the malignant cells express pan-B-cell antigens (CD19, CD20, CD22). However,

S.M. Ansell (ed.), *Rare Hematological Malignancies.*

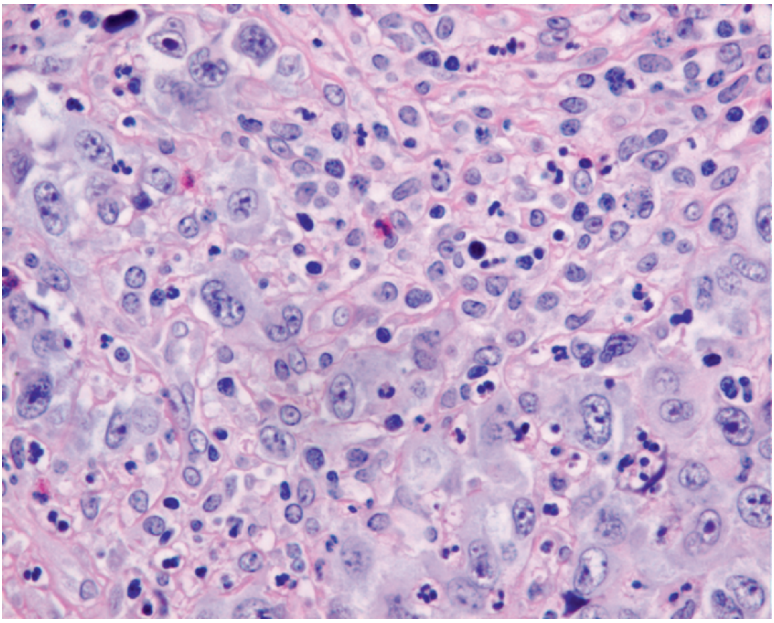

Figure 10.1 PMBCL large malignant cells with clear cytoplasm compartmentalized by fine delicate bands of fibrosis.

unlike other B-cell lymphomas, the malignant cells often lack surface immunoglobulin (sIg) (1), despite expression of the Ig coreceptor CD79a. CD30 expression is often weak and inhomogeneous in contrast to uniform and strong expression seen in classical Hodgkin's lymphoma or anaplastic large-cell lymphoma.

The mediastinal location of PMBCL in addition to the finding of Hassall's corpuscles and thymic lobules in some cases suggest a thymic origin. Although it is primarily a site of T-cell maturation, the thymus does contain a small number of B-cells that are positive for CD19, CD20, CD22, IgM, and lack CD21 (3). Hypermutated VH and BCL6 genes of a similar pattern have been observed in both PMBCL tumor cells and thymic B-cells, supporting derivation from the thymus and suggesting exposure to the germinal center at some point in histogenesis (4).

10.2.2 Molecular Genetics

Primary mediastinal large B-cell lymphoma is characterized by distinctive chromosomal aberrations, including consistent gains in chromosome 9p and 2p corresponding to JAK2 and c-REL, respectively (5, 6). Gains in chromosome 9 are highly specific for PMBCL and occur only sporadically in other B-cell lymphomas.

Aberrations in chromosome X are also observed at a high frequency, but the significance is unknown. Conversely, BCL2 and BCL6 rearrangements found in a subset of DLBCL are notably absent in PMBCL. More recently, a more sensitive technique than standard CGH (comparative genomic hybridization) using a tiling resolution array CGH has also demonstrated a significant number of chromosomal losses, including 1p13.2 and 17p12 (7), but the corresponding genes involved are unknown.

Biallelic mutations of SOCS1 (suppressor in cytokine signaling) in the MedB1, a PMBCL cell line, were recently discovered that result in sustained activity of phospho-JAK2 through delayed protein turnover (8). Mutations in the SOCS1 gene are seen at a relatively high frequency in PMBCL tumors correlating with gains at 9p24, the JAK2 locus (8). Similarly, Karpas 1106, another PMBCL cell line, harbors a homozygous deletion at 16p13.13 and absent expression of SOCS1, providing further evidence that SOCS1 qualifies as a novel tumor suppressor in PMBCL (9).

10.2.3 Relationship of Primary Mediastinal Large B-Cell lymphoma with Nodular Sclerosis Classical Hodgkin's Lymphoma

Although PMBCL is considered a subtype of DLBCL, it has several notable overlapping clinical and pathologic features that are shared with the nodular sclerosis subtype of classical Hodgkin's lymphoma (NScHL) (2). Both occur most often in young adults who present with a prominent mediastinal mass but lack extrathoracic disease. Pathologically, sclerosis is prominent in both tumors and Reed-Sternberg-like cells can be seen in PMBCL. Further, the Hodgkin Reed-Sternberg cells (HRS) are typified by the absence of surface immunoglobulin (sIg) and, similarly, the malignant B-cells of PMBCL lack sIg in up to 70% of cases. Classical Hodgkin's lymphoma also harbors gains in chromosome 2p and 9p and, in addition, SOCS1 mutations have also recently been found in cHL, resulting in accumulation of phospho-STAT5, supporting the hypothesis that this pathway might be critical in both tumors (2). MAL, a lipid raft component, is differentially expressed in PMBCL compared to DLBCL and is found in some cases of NScHL (10–12) and might be associated with a worse prognosis (13). In addition to these striking clinical, immunologic, and molecular similarities, there are rare reported cases of composite or sequential NScHL and PMBCL in addition to "mediastinal gray zone lymphomas" with features between NScHL and PMBCL. (14). In cases of sequential lymphoma, IgH rearrangements of a similar size have been found, confirming a common origin (14).

Despite these similarities, there are still important differences between PMBCL and NScHL. Unlike HRS cells, PMBCL tumor cells retain several B-cell differentiation markers and histologically appear more similar to other DLBCLs. The brisk inflammatory background seen in cHL is not usually seen in PMBCL.

These observations support the notion that PMBCL may be pathogenetically related to NScHL. This hypothesis of an overlapping relationship is further supported

by two recent gene expression profiling studies that demonstrated that the molecular signature of PMBCL had a striking resemblance to the expression profile of HRS cell lines (12, 15) (Figures 10.2A and 10.2B). A prominent cytokine pathway with overexpression of IL13Rα1, JAK2, and STAT1 were present (15) (Figures 10.2A and 10.2B), in addition to chemokines TARC and RANTES, both of which have been identified in HRS cells (16). Further, a prominent tumor necrosis factor (TNF) signature was identified in both cHL and PMBCL, including the adaptor protein TRAF1 (12, 15). Nuclear factor (NF) κB promotes HRS cell survival and, similarly, nuclear localization of c-REL, consistent with activation, was seen in the majority of cases of

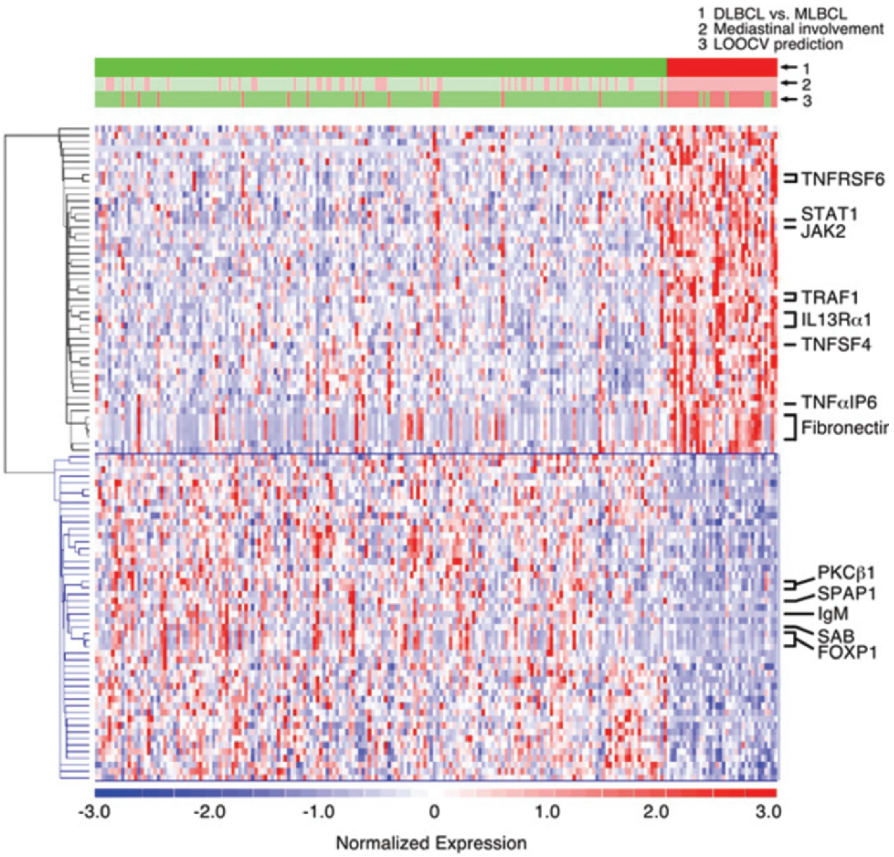

Figure 10.2 **(A)** Comparative gene expression profiles of DLBCL and PMBCL. At the top, the actual clinical/pathologic diagnosis of DLBCL versus PMBCL (green vs. red), presence or absence of mediastinal disease (pink vs. light green), and molecular prediction of DLBCL versus PMBCL (green vs. red) are compared. Genes are clustered using hierarchical clustering. Expression profiles of 176 DLBCLs are on the left; profiles of the 34 PMBCL are on the right. Note: Red = high relative expression, blue = low expression. Column = sample, row = gene. (Copyright American Society of Hematology, adapted and used with permission) (15)

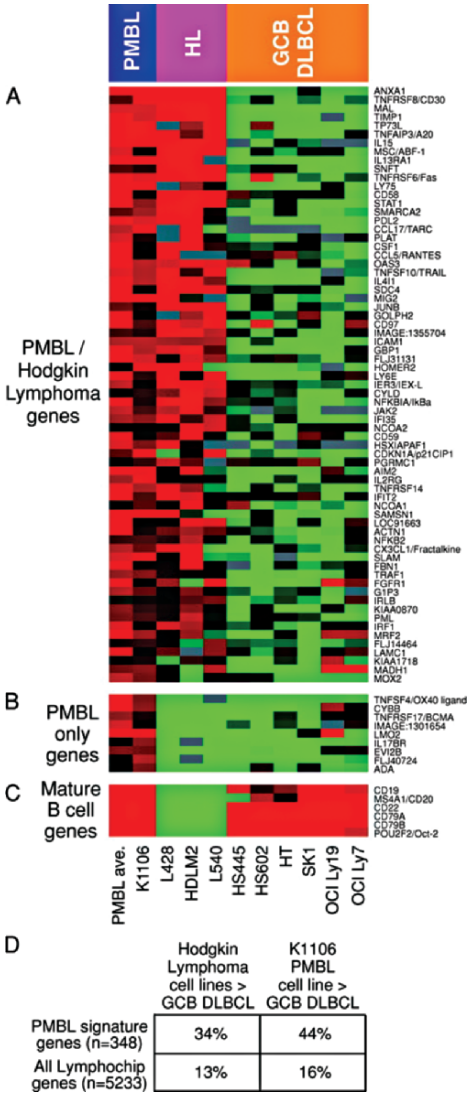

Figure 10.2 **(B)** Relationship of PMBCL to Hodgkin lymphoma. Relative gene expression is shown in primary PMBCLs (average of all biopsy samples), the PMBCL cell line K1106, three Hodgkin's lymphoma (HL) cell lines, and six GCB DLBCL cell lines, according to the color scale shown in (A) PMBCL signature genes that are also expressed at high levels in Hodgkin's lymphoma cell lines compared with GCB DLBCL cell lines. (B) PMBCL signature genes not expressed in Hodgkin lymphoma cell lines. (C) Mature B-cell markers expressed in PMBCL and GCB DLBCL but not in Hodgkin's lymphoma. (D) Enrichment within the set of PMBCL signature genes of genes highly expressed in Hodgkin's lymphoma cell lines or in the K1106 PMBCL cell line relative to GCB DLBCL cell lines. (Adapted from the *Journal of Experimental Medicine*, by copyright permission of The Rockefeller University Press)

PMBCL (15). Further, increased expression of downstream targets of NFKB is also seen in PMBCL, supporting that this pathway might also be critical in disease pathogenesis (15, 17).

The expression of TRAF1 and nuclear c-REL together may also aid in differentiating PMBCL from the morphologically similar DLBCL (18). These and other markers that can reliably and reproducibly differentiate PMBCL will also facilitate future study comparisons.

10.2.4 Clinical Features

Patients with PMBCL are typically females in their third to fourth decade who present with large, often bulky, anterior mediastinal masses with associated respiratory symptoms (Figures 10.3A and 10.3B). Superior vena caval syndrome can occur with facial swelling, dyspnea, headache, neck vein distention, and, occasionally, thrombosis. Most patients have bulky, stage I or II disease at diagnosis, often

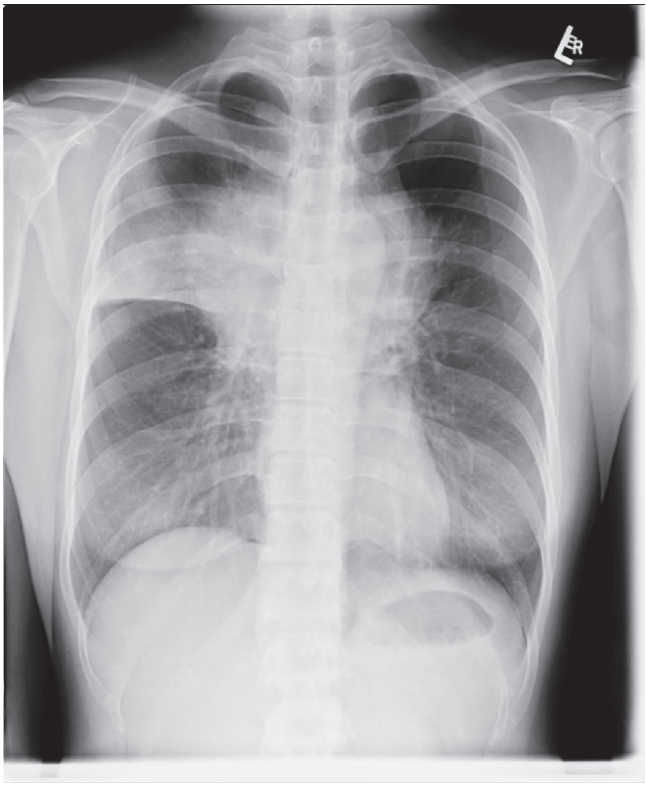

Figure. 10.3 **(A)** Chest X-ray of a patient with a bulky anterior mediastinal mass; **(B)** CT scan of a patient with a bulky anterior mediastinal mass.

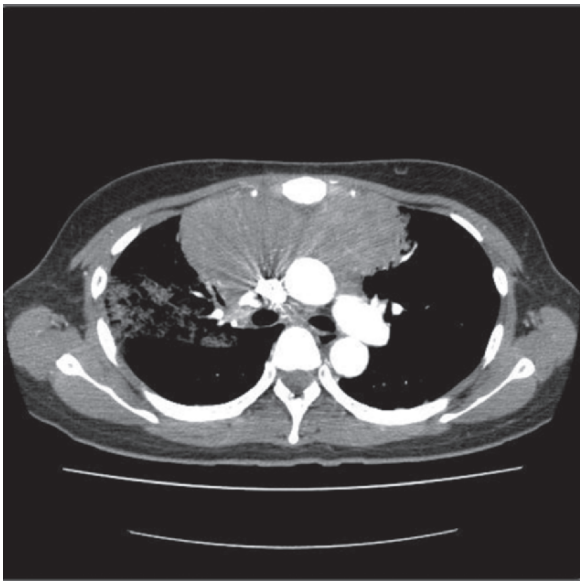

Figure. 10.3 (B) (continued)

accompanied by intrathoracic extension into the lung, chest wall, and pericardial and pleural effusions can occur. Extrathoracic disease, including bone marrow involvement, at presentation is rare. However, at relapse, disease in unusual extranodal sites such as the liver, kidneys and central nervous system (CNS) can occur (2).

10.2.5 Prognostic Features

There have been varied reports regarding survival in PMBCL that might, in part, be due to diagnostic imprecision and the difficulty in separating PMBCL from DLBCL with secondary mediastinal involvement because there are no definitive biological markers of PMBCL. This diagnostic uncertainty can influence reports on biological characteristics and survival analyses, complicating comparisons between studies. This problem is highlighted in earlier studies in which a more aggressive course was observed (19–21), with cure rates in some cases worse than DLBCL despite the younger age of presentation. In contrast, more recent analyses have demonstrated outcome patterns at least equivalent to or superior than DLBCL (22–26) (Table 10.1 and Figure 10,4A and 10.4B). Further, using a refined molecular signature to diagnose PMBCL, a more favorable survival is observed, supporting the notion that PMBCL might have a different natural history than DLBCL (12). This is further highlighted by the clear plateau seen in the progression-free survival (PFS) curve of PMBCL with rare relapses seen beyond 2 years (26) in distinct comparison to DLBCL (Figure 10.4A).

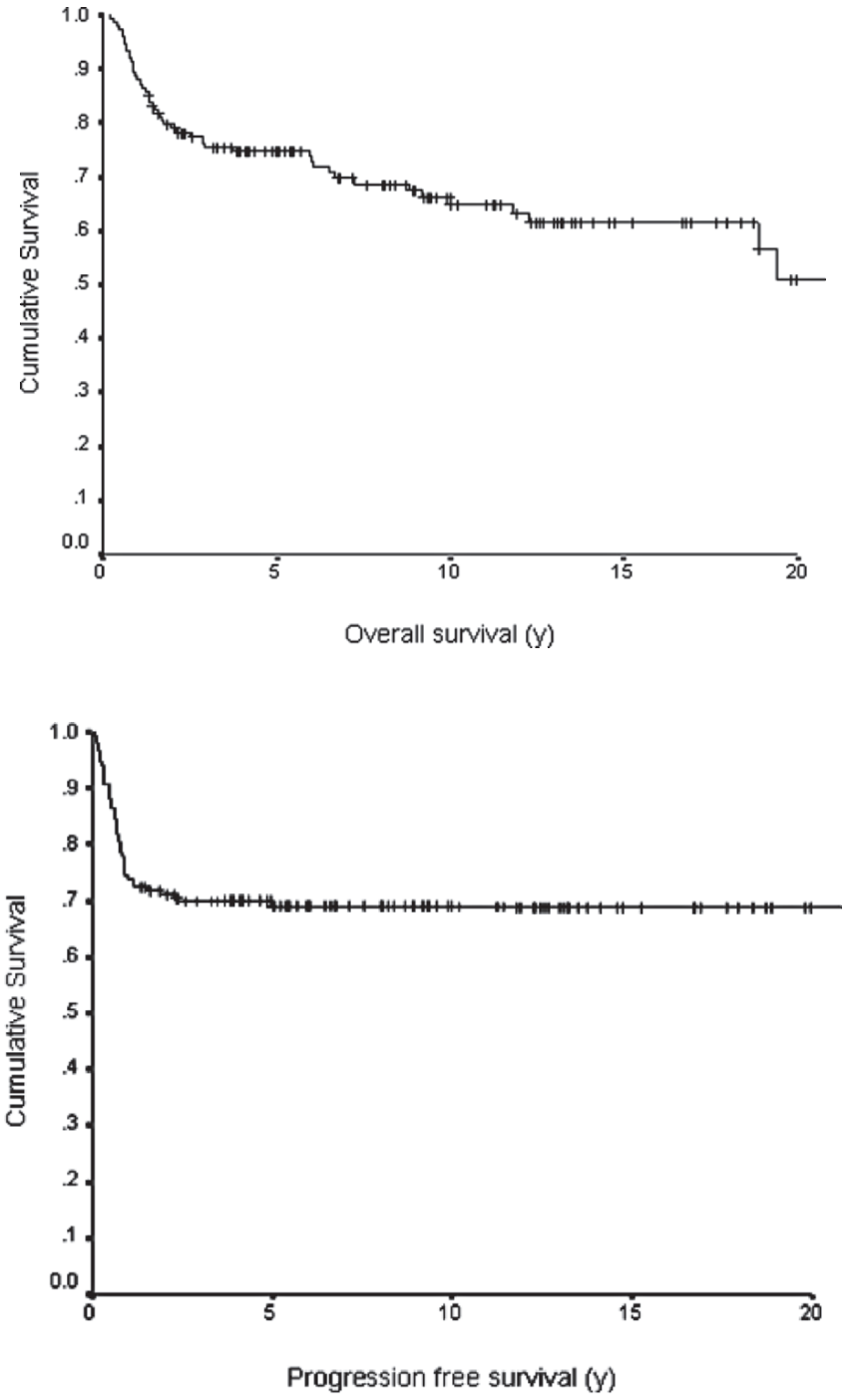

Figure 10.4 **(A)** Overall survival of PMBCL; **(B)** Progression-free survival of PMBCL (26)

The International Prognostic Index (IPI) was originally developed in diffuse large-cell lymphoma prior to the recognition of PMBCL. Subsequent studies evaluating the IPI or the aaIPI (age-adjusted) have been discrepant in PMBCL (23, 25–27). This may reflect differences between studies assigning patient as stage IV or stage IIE if multiple but contiguous extranodal sites are involved. In the few studies that have found the index useful, it has been the IPI that was applied, suggesting that it is primarily age that drives the poor prognosis. Even if the aaIPI is used, which eliminates the number of extranodal sites as a risk factor, most patients will have an elevated lactate dehydrogenase (LDH), again reducing the usefulness of its discrimatory power (27). Other factors that in individual studies have been found to prognosticate also include pleural or pericardial involvement and poor performance status (26, 28).

10.2.6 Primary Treatment of PMBCL

The optimal type of chemotherapy and role of consolidative radiotherapy in the management of PMBCL is unknown. Treatments at various study centers have been extremely heterogeneous with respect to the choice of chemotherapy regimen and whether radiotherapy was utilized in the primary therapy (Table 10.1). In several retrospective analyses, there is emerging evidence that dose-intensified therapy using Methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin (MACOPB) or Etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin (VACOPB) may be superior to cyclophosphamide doxorubicin, vincristine, prednisone (CHOP) chemotherapy (23, 25) (Table 10.1). Survival using CHOP ranges from 40% to 71%, and for MACOPB/VACOPB, it ranges from 71% to 93% (Table 10.1). The large retrospective SWOG study comparing CHOP to second- and third-generation regimens, including MACOPB, in the treatment of diffuse large-cell lymphoma was performed prior to the recognition of PMBCL as a distinct entity; thus, information regarding the superiority of these intensified regimens over CHOP from a randomized trial are not available (29). The group at Memorial Sloan-Kettering recently reported a retrospective series comparing “CHOP-like” chemotherapy, which included second and third-generation regimens, to an intensified regimen, NHL-15 (dose dense sequential induction with doxorubicin followed by cyclophosphamide with GCSF support) (Table 10.1). NHL-15 was associated with a more favorable outcome in multivariate analysis (Table 10.1). However, the number of patients receiving specific regimens was too small for individual comparisons. Further, in general there is an inherent selection bias of patients chosen to be treated with more intensive regimens.

Some researchers support using autologous stem cell transplant in the primary treatment of PMBCL with one small report of 15 patients with high–intermediate- or high-risk disease achieving a disease-free survival (DFS) of 93% after a median follow-up of 35 months with transplant (30). However, all but two patients were in a complete remission (CR) or partial remission (PR) prior to transplant with induction

Table 10.1 Recent studies in the last 10 years of the treatment and survival in PMBCL

Reference	No. of patients	Mediastinal radiation planned	Chemotherapy (n)	PFS/EFS (%)	OS (%)	Comment
Zinzani et al. (1996) (40)	22	Yes (100 %)	MACOPB F-MACHOP	86 (2 years)		
Cazals-Hatem et al. (1996)(24)	141	No	Intensive regimens[a]	61 (2 years)	66	Similar oucome vs. "nonmediastinal"
			Group 1 (14)	—	100	Only 1 patient received RT
			Group 2 (104)	59	60	Treatment regimens were not formally compared
			Group 3 (23)	58	69	
Lazzarino et al. (1997) (19)	106	Yes (77%)	CHOP (36)[b] MACOPB/VACOPB (29) CHOP-like Intensive(41)	N/A	52 (3 years)	
Martelli et al. (1998) (54)	37	Yes (89%)	MACOPB	91 (2 years)	93	
		No	F-MACHOP	60 (2 years)	70	
				$p < 0.02$	p = ns	
Abou-Ellela et al. (1998) (55)	43	Not reported	CHOP-like regimens[c]	38 (5 years)	46 (5 years)	Similar outcome vs. "nonmediastinal" Heterogeneous tx; some with non-anthracycline regimens
Zinzani et al. (1999) (22)	50	Yes (94%)	MACOPB	82 (8 years)	93 (8y)	
Bieri et al. (1999) (39)	27	No (41%)	CHOP (11)[d]	44 (5 years)	55 (5 years)	Type of chemotherapy ("Intensive") improved PFS in MVA
			CHOP-like (intensified) (12)			RT improved PFS in MVA but no XRT group also includes induction failures
			CVP (4 elderly)			
Nguyen et al. (2000) (56)	40	Yes (85%)	CHOP (12)[e]	67 (5 years)	72 (5 years)	
			CHOP-like (intensified) (13)			
			Doxorubicin/salvage-type (14)			

Zinzani et al. (2002) (25)	426	Yes (80%)	All	62 (10 years)	65 (10 years)	Type of chemotherapy (CHOP vs. intensive) improved OS but not PFS in MVA
			CHOP (105)	35	44	
			MACOPB (204) / VACOPB (34) or ProMACE CytaBOM (39)	67	71	
			High-dose sequential (27) or ASCT (17)	78 $p = .0003$	77 $p = .0001$	
Todeschini et al. (2004) (23)	138	Yes Yes If CR or Cru 75%	CHOP (43)	39.5		Type of chemo (MACOPB/VACOPB) improved OS in MVA RT improved EFS in pts in CR
			MACOPB/VACOPB (95)	76 $p<.001$		
Hamlin et al. (2005) (27)	141	Variable (23%)	All	50	66	Type of chemo NHL-15/ASCT improved EFS/OS in MVA
			CHOP/CHOP-like (intensive)[f]	34	51	
					84 $p < .001$	
			NHL-15	60		
			ASCT	60 $p < .001$	78	
Savage et al. (2006) (26)	153	Before 1998 variable After 1998 routine	All	69	75	Type of treatment not significant in MVA
			MACOPB/VACOPB (47)[g]		87	
			CHOP/CHOP-like (intensive) (63)		71	Addition of radiation did not improve PFS or OS
			CHOPR (18)		82 $p = 0.048$	Improved PFS and OS compared to DLBCL

RT = radiation therapy; MVA = multivariate analysis; OS = overall survival; PFS progression-free survival; EFS = event-free survival

[a] Three treatment groups (24)
No poor prognostic factors and < 70
1. ACVBP v mBACOD
Adverse prognostic factors and <55
2. ACVBP vs, NCVBP (N = mitoxatrone)—pts achieving CR randomized condolidation chemotherapy

(continued)

Table 10.1 (continued)

LNH-84 vs. intensive consolidation with CBV + autologous stem cell transplant
Adverse prognostic factors and >55
Adverse prognostic factor = bulky disease ≥ 10 cm, bone marrow or CNS involvement, 2 extranodal sites, PS ≥ 2
3. LNH-84 vs. VIM3

[b]Three treatment groups (19)
1. CHOP
2. MACOPB or VACOPB
3. CHOP-like Intensive (CH2OP (11) (doxorubicin repeated day 2); CHOEP (10); hCHOP (high-dose cyclophosphamide)/IVEP (ifosfamide, vindesine, etoposide, prednisone) or CHOP/VIM (etoposide, ifosfamide, methotrexate, prednisone) (13)

[c]Four treatment groups (55)
1. Cyclophosphamide, doxorubicin, vincristine, procarbazine, prednisone, bleomycin
2. Cyclophosphamide, doxorubicin, vincristine, procarbazine, dexamethasone, bleomycin
3. Cyclophosphamide, mitoxantrone, vincristine, procarbazine, prednisone
4. M mitoxantrone, vincristine, prednisone

[d]Three treatment groups (39)
1. CHOP
2. "Third-generation" CHOP-like intensive (doxorubicin D1/8, cyclophosphamide D1/D8, vincristine D1/D8, methotrexate alternating Q 22 days with etoposide, AraC, bleomycin, procarbazine
3. CVP (elderly)

[e]Three treatment groups (56)
1. CHOP
2. CHOP-like Intensive (CHOP-Bleo; CHOP-Bleo/OPEN (vincristine, prednisone, etoposide, mitroxantrone)
3. ASHAP (doxorubicin, methylprednisone, AraC, cisplatin)/MBACOS (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, methylprednisolone) and MINE (Mesna, ifosfamide, mitroxantrone, etoposide)

[f]Three treatment groups (27)
a. Includes CHOP and CHOP-like (CHOP-bleomycin, ProMACE-CytaBom, MACOPB)
b. Dose –dense sequential chemotherapy with GCSF support
c. TBI and upfront transplant— this patient group were from a trial comparing ASCT to MACOPB for patients with bulky disease or LDH > 2.5 times ULN

[g]Three treatment groups (26)
1. CHOP or CHOP-like [ACOP12, ECV (CHOP ×4 then high dose etoposide, cyclophosphamide, vincristine)]
2. MACOPB/VACOPB
3. CHOPR

therapy consisting of VACOPB, and due to the high frequency of residual masses in this disease, many of the PR patients by imaging might be in a pathological CR; thus, the true impact of consolidative autologous stem cell transplant (ASCT) is unknown.

Further complicating the evaluation of the effectiveness of dose-dense and dose-intensive regimens is that these studies were undertaken in the "pre-rituximab" era. The addition of rituximab to CHOP chemotherapy has been shown in multiple studies to improve cure rates in DLBCL over CHOP alone (31–33). The value of adding rituximab to CHOP (R-CHOP) in PMBCL is unknown; however, it is likely that the same magnitude of benefit will be observed. Dose-adjusted Etoposide, vincristine, doxorubicin, bolus cyclophosphamide, prednisone (EPOCH) (DA-EPOCH) was recently evaluated in 36 patients with PMBCL, 22 of whom received DA-EPOCH in combination with rituximab (DA-EPOCH-R). This regimen administers the natural product chemotherapy agents by continuous infusion (etoposide, doxorubicin, vincristine) in addition to bolus cyclophosphamide and oral prednisone with dose adjustments based on the neutrophil nadir (34). With a median follow-up of 8.6 years, patients treated with DA-EPOCH-R had a 2-year event-free survival (EFS) that was superior to DA-EPOCH alone (94% vs. 64%, respectively, $p = 0.036$) (35). However, the utility of more intensive chemotherapy regimens in the treatment of PMBCL can only be evaluated in a well-designed randomized clinical trial that includes the addition of rituximab to each regimen. Until such studies are available, it is reasonable to consider R-CHOP chemotherapy as the standard treatment in PMBCL.

10.2.7 Consolidative Radiotherapy in the Treatment of PMBCL

A major challenge in the management of PMBCL is the evaluation of a residual mass postchemotherapy. There is poor correlation between the size of a residual mass on computerized tomography (CT) and risk of relapse (36, 37). In many instances, the residual density represents fibrotic tissue rather than active lymphoma, similar to the problem encountered in bulky mediastinal NScHL (36). Many patients are given mediastinal radiotherapy as consolidative treatment for this reason; however, it is unclear whether this impacts relapse or cure rates. There is also an inherent concern regarding the long-term toxicities of mediastinal radiotherapy, including an increased risk of cardiovascular disease and secondary malignancies, particularly given the young population at risk (38), akin to treatment considerations in NScHL. Although some studies have suggested that radiotherapy improves EFS (23, 25, 39) (Table 10.1), other analyses have demonstrated that chemotherapy alone is effective in many cases (24, 26, 27, 35), suggesting that radiotherapy is not mandatory in all patients. An improvement in EFS was reported in one study when radiotherapy is given to patients achieving a CR (23). However, a recent analysis evaluating the impact on PFS with a policy recommending routine radiotherapy following primary chemotherapy failed to demonstrate a benefit (26). The retrospective nature of such analyses, including definitions of response rates, is problematic and randomized studies addressing this question are lacking. Improved identification of patients who might benefit from the addition of radiotherapy is needed.

^{67}Ga scintigraphy has been used to detect persistent viable tumor in patients with a residual mass after therapy (40). However, Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is superior to ^{67}Ga for the detection of residual disease (41). Therefore, future studies are needed to that evaluate the utility of ^{18}F-FDG PET to select patients with PMBCL who might benefit from radiotherapy and, alternatively, identify those cases where it can be safely withheld without compromising cure rates, with the goal of reducing secondary long-term complications.

10.2.8 Salvage Therapy

Treatment failures in PMBCL tend to occur within the first 6–12 months after treatment completion, with recurrences rare beyond 2 years (25, 26). Like DLBCL, chemosensitivity to the salvage regimen is predictive of a more favorable outcome to ASCT (42). Limited data suggest that PMBCL patients might be less likely to respond to salvage chemotherapy and proceed to ASCT than DLBCL; however, in those patients who could be transplanted, outcomes appear to be similar (43). It is unclear what the outcome of patients with refractory disease is. Some studies have suggested that survival is comparable to relapsed patients (42); however, other studies have found that they might be less likely to respond to salvage chemotherapy (19, 26), with a lower likelihood of survival compared to those with relapsed disease (27).

10.3 Intravascular Lymphoma

Intravascular or "angiotropic" lymphoma (IVL) is a rare clinical subtype of diffuse large B-cell lymphoma characterized by the presence of neoplastic B-cell lymphocytes within the microvasculature (44). It has only recently been included as a clinical subtype of DLBCL in the WHO classification. It typically is widely disseminated at presentation involving multiple, often subclinical, extranodal sites including the **CNS**, skin, lung, kidney, and adrenals.

10.3.1 Pathology

A tissue biopsy is essential for the diagnosis to highlight the intravascular growth pattern. Clinically uninvolved organs such as the spleen and bone marrow can demonstrate IVL, and in some instances, a random skin biopsy might yield a diagnosis (44, 45). The "classic variant" of IVL is typified by large neoplastic cells with prominent nucleoli and frequent mitotic figures that are found in the

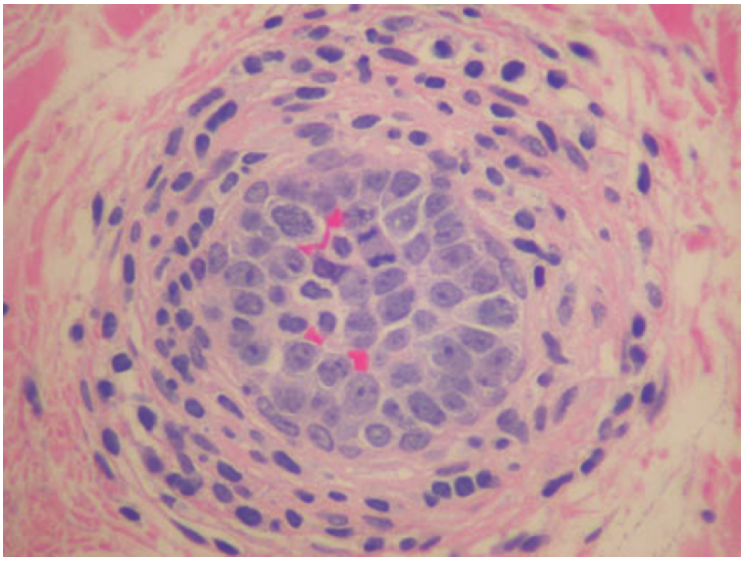

Figure 10.5 H&E stain of intravascular lymphoma with large neoplastic cells detected in a blood vessel lumen.

lumina of small vessels (Figure 10.5). In the bone marrow, sinusoidal involvement occurs. A so-called "Asian variant" has also been described that often has, in addition, a rich infiltrate of non-neoplastic cells, predominantly hemophagocytic histiocytes.

The most distinctive property of IVL malignant cells is their propensity to grow within the lumina of blood vessels. It is hypothesized that the intraluminal growth pattern is secondary to a defect in homing receptors of the neoplastic cells. In support of this, the malignant cells appear to lack CD29 (beta 1 integrin) and CD54 (ICAM-1) adhesion molecules (44).

The majority of IVL display a B-cell phenotype expressing CD20 and/or CD79a. In the Western series, approximately 20% of cases display a germinal center (GC) phenotype (CD10+ or BCL6+), and CD5+ cells can also be seen (46). A recent Japanese series also described CD5 expression in 38% of cases, however, there was no immunophenotypic or clinical differences between the CD5− and CD5+ subgroups. Similar to the classic variant, almost all Asian cases display a non-GCB phenotype (CD10-,BCL6−/+, MUM1) (47).

Rare cases with a T-cell immunophenotype have been reported, occasionally in the setting of HIV infection (48). Anecdotal cases of Natural killer (NK) IVL have also been seen (44).

10.3.2 Molecular Genetics

Due to disease rarity, there have been no large-scale studies evaluating cytogenetic abnormalities in IVL. Aberrations in chromosomes 1, 6, and 18, including 1p and trisomy 6, were frequently observed in one small series. Somatic hypermutation of the Ig heavy chain is apparent in most cases, supporting that exposure to the GC occurred at some point in pathogenesis, but BCL-2 rearrangements are typically absent.

10.3.3 Clinical Features

The median age at diagnosis is approximately 70 years with equal prevalence in both sexes. The clinical presentation can be heterogeneous because virtually any organ might be involved; however, nodal involvement is rare. Fever is common and IVL should always be considered in cases of fever of unknown origin. Patients might also have other B symptoms in addition to a rapid decline in performance status Patients usually present with high or high–intermediate IPI scores (Table 10.2). Even those cases with apparent limited stage disease can often be found at autopsy to have disseminated disease, highlighting some of the limitations of standard staging techniques for the diagnosis of IVL. In more recent series, more patients were diagnosed "in vivo" (versus at autopsy) compared to older reports, consistent with a growing recognition of IVL in recent times.

Interestingly, IVL cases in Western populations display distinct differences compared to those reported in Japanese series (Table 10.2). In Japanese patients, IVL is more often associated with bone marrow involvement with evidence of hematophagocytosis as well as hepato-splenomegaly with thrombocytopenia and anemia, whereas CNS and cutaneous involvement is uncommon, supporting the notion that the "Asian variant" might be a distinct clinical entity (47). Whether other non-Japanese Asian patients have a similar clinical presentation is unknown.

The "cutaneous variant" refers to cases that are exclusively found in the skin after extensive staging procedures and appears to be confined to Western populations. Patients are predominantly female have a good performance status (PS), lack B symptoms, and present at a younger age. In addition, they are less likely to have cytopenias than patients with more widespread disease.

Patients with neurologic involvement can have very heterogeneous symptoms at presentation from sensory and motor neuropathies to seizures and altered consciousness. There are no pathognomonic neuroradiologic findings. Ischemic foci are the most common and it can often be confused with vasculitis.

Additional laboratory findings in both the classic and the Asian variant include an elevated LDH and B2 microglobulin in over 80%. A monoclonal protein is seen in 15% and altered hepatic and renal function can be observed in some cases.

Table 10.2 Comparison of presenting clinical features in the Western or "classic variant" and the "Asian variant"

Clinical or laboratory feature	Western "classic variant" *n* (%) Total *n* = 38 (49)	Japanese "Asian variant" *n* (%) Total *n* = 96 (47)
Median age	70	67
Sex (M:F)	.9	~1.1
PS > 1	95% (> 1)	79 (82)
High LDH	25 (86) Total *n*= 29	89 (93)
EN > 1	N/A	65 (68)
IPI		
Low 0, 1	6 (16)	2 (2)
Low-int 2	16 (2 and 3) (42)	6 (6)
High-int 3		17 (17)
High 4, 5	16 (42)	75 (75)
B symptoms	21 (55)	73 (76)
Liver involved	10 (26)	53 (55)
Spleen involved	10 (26)	64 (67)
Neurologic signs/symptoms	13 (34)	26 (27)
CNS	15 (39)	26 (27)
Cutaneous lesions	15 (39)	14 (15)
"Cutaneous variant"	10	0
Advanced stage	5	14 (15)
Bone marrow	12 (32)	67 (75) *n* = 89
Hemophagocytosis		54 (61)
Peripheral Blood	2 (5)	23 (24)
Anemia < 12 g/dL	24 (63)	63 (66)
Thrombocytopenia <150	11 (29)	56 (58)
Leukopenia	9 (24)	26 (27)
Hypoalbuminemia < 36 g/L	81(96)	7 (18)
Event-free survival 3 years	27% (*n* = 30)[a]	27%[a] (*n* = 81)
Overall survival	32%[a]	—

[a]Outcome of patients with in vivo diagnosis. For whole series, 3 years overall survival as 25% for all patients.

Approximately 15% of patients with IVL have a prior history or concomitant malignancy, most often a prior non-Hodgkin's lymphoma. Among solid tumors, renal cell carcinoma has been observed and, occasionally, IVL cells can be seen within the tumor associated vasculature (44).

10.3.4 Primary Treatment of IVL

Typically, IVL has an aggressive course and the median survival is approximately 6 months, with no significant differences observed between Western and Japanese reports. Regimens without anthracyclines appear to be associated with an inferior prognosis (44). It is unknown whether rituximab improves survival rates, given

the rarity of this condition however, CNS penetration is poor. Over half of the patients will ultimately relapse, usually within the first year of diagnosis. Relapses typically involve extranodal sites, and CNS disease can occur in approximately one-third of patients.

Several small series report improved outcome using high dose chemotherapy (HDC) and ASCT as consolidation therapy, however, it remains experimental in this setting. Anecdotal reports using methotrexate-containing chemotherapy (MACOP-B) followed by HDC and ASCT in a patient with initial CNS involvement has resulted in long-term remission (44).

10.3.5 Prognostic Factors

Regardless of the country of origin, the survival of patients with intravascular lymphoma is uniformly poor with a 3-year EFS of 30%, with similar approximations for overall survival (OS), suggesting that salvage therapy is usually ineffective in this population (47, 49). In the Western series, patients with the cutaneous variant, low IPI, and limited stage disease and who are able to receive multiagent anthracyline-based chemotherapy have a more favorable prognosis in multivariate analysis (49). In the Japanese series, older age, thrombocytopenia, and lack of anthracycline-based chemotherapy was associated with a worse outcome (47). In this analysis, there was no difference in outcome regardless of their immunophenotype (i.e., CD5+ vs. CD5− or GC vs. non-GCB) (47).

10.4 Primary Effusion Lymphoma

Primary effusion lymphoma (PEL) is also a recently recognized clinical subtype of DLBCL presenting as a serous effusion composed of large B-cells. It is universally associated with HHV-8/KSHV (human herpes virus 8/Kaposi sarcoma herpes virus) and usually occurs in the setting of HIV (50), but rare cases have been reported in the absence of HIV infection.

10.4.1 Pathology

Malignant B-cells are isolated from the serous effusion and show a range of appearances from large immunoblastic or plasmablastic cells to those with a more anaplastic morphology. The neoplastic cells are positive for HHV8/KSHV in all cases and many are coinfected with Epstein-Barr virus (EBV). The cells usually express leukocyte common antigen (CD45) but are negative for B-cell markers CD19, CD20, and CD79a; however, immunoglobulin rearrangements present, confirming a clonal B-cell origin. Activation (CD30, CD38, EMA) and plasma cell markers (CD138, MUM-1/IRF4) are typically present (50).

Recently, gene expression profiling has been performed on PEL cells and expression patterns have similarities to both plasma cells and EBV-transformed immunoblasts, suggesting that PEL might represent a variant of plasmablastic lymphoma (51). Supervised analysis revealed that PEL has a unique gene expression compared to other B-cell NHL and AIDS-related lymphomas with underexpression of many genes that are B-cell or lymphoid specific.

10.4.2 Clinical Features

Primary effusion lymphoma accounts for approximately 3% of all HIV-related NHL. The majority of patients are homosexual white men with a median age of approximately 40 years. Cases in HIV-negative individuals typically occur in elderly patients from endemic areas of high prevalence of HHV8 or in allograft recipients. Effusions are seen most commonly in the pleural, pericardial, or peritoneal cavities, usually without nodal disease. A recent series of 28 patients reported simultaneous involvement of all serous cavities in 25%, and 43% had extracavitary disease localization, including occasional involvement of lymph nodes, bone marrow, CNS, pancreas, and sinus (52). Some cases might occur in association with Castleman's disease.

10.4.3 Primary Treatment of PEL

Since the widespread use of HAART (highly active antiretroviral therapy), the overall outcome of HIV-associated NHLs has improved; however, it remains poor in PEL. Some exceptional cases have been shown to respond to antiretroviral therapy alone. Most patients are treated with CHOP-like regimens and HAART in the setting of HIV. In most published series, the clinical course is usually aggressive, with a median survival of 6 months. Given that CD20 is negative in these tumors, rituximab will not impact the prognosis and should not be utilized in this disease.

10.4.4 Prognostic Factors

A recent study of clinical factors associated with prognosis PEL demonstrated that poor performance status (>2) and the absence of HAART before the PEL diagnosis were associated with a poor outcome (52) in multivariate analysis. Other researchers have found that a high HHV-8 viral load correlates inversely with CD4 count and is associated with a shorter survival time; however, this requires validation in a larger analysis (53).

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