1 Waldenström Macroglobulinaemia: Pathological Features and Diagnostic Assessment

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1.1 Morphology and Immunophenotype

Waldenström macroglobulinaemia (WM) is a distinct B-cell lymphoproliferative disorder (LPD) characterised by IgM monoclonal gammopathy and bone marrow (BM) infiltration by lymphoplasmacytic lymphoma (Fig. 1.1) LPL) [1]. The latter is defined as a small B-cell neoplasm composed of lymphocytes, plasma cells and plasmacytoid lymphocytes which does not meet the criteria of other small B-cell disorders [2]. Unfortunately LPL was shown to be one of the least reproducible lymphoma categories by the Non-Hodgkin Lymphoma Classification Project [3]. Similarly, an IgM monoclonal (M) protein, regardless of concentration, cannot be considered indicative of a diagnosis of WM as they may be demonstrable in a proportion of patients with all B-cell LPD, with considerable overlap in serum concentrations [4–6].

Detailed morphologic and immunophenotypic assessment of the bone marrow along with close clinical correlation is therefore required if a definitive diagnosis of WM is to be made. It is good practice that a trephine biopsy be examined in addition to bone marrow aspirate cytology as the pattern of infiltration is important to assess, and it will also provide a better overall assessment of the degree of infiltration [7, 8]. LPL is a LPD comprised of small lymphocytes in which there is morphological evidence of plasma cell differentiation (Fig. 1.1) [2]. This phenomenon is most readily appreciated on trephine biopsy sections and can be further accentuated by staining sections with Giemsa as well as haematoxylin and eosin or more definitively by immunohistochemistry using plasma cell-specific antibodies such as CD138, CD319 and IRF4 (Fig. 1.1c, e, f). The pattern of infiltration is typically interstitial, nodular or diffuse, while a purely paratrabecular pattern is unusual and raises the possibility of follicular lymphoma [7]. Additional morphological clues

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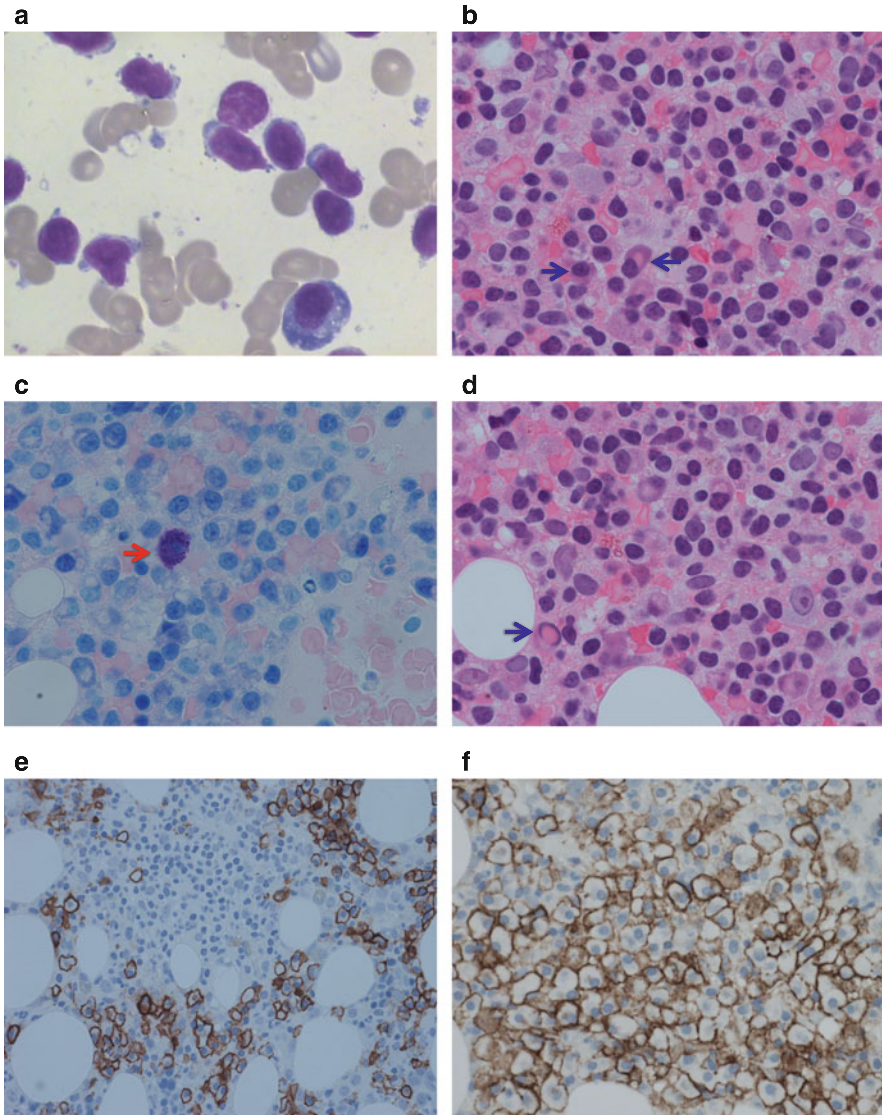

Fig. 1.1 Morphological features of WM. Bone marrow aspirate smears typically show an excess of lymphocytes and plasmacytoid forms with a minority population of plasma cells (image **a**). Trephine biopsy sections show similar appearances with a predominant lymphoid population and variable numbers of plasma cells (highlighted on image **b**). Plasma cell differentiation may be more readily appreciated on Giemsa-stained sections, which also highlight the increase in reactive mast cells typical of WM (image **c**). Immunoglobulin inclusions such as Dutcher bodies are also considered indicative of plasma cell differentiation (image **d**). Plasma cell differentiation may also be highlighted using CD138 immunostaining (image **e**), and this may be particularly prominent in a minority of cases such that IgM myeloma becomes part of the differential diagnosis (image **f**)

can be obtained from the trephine sections, and these include the presence of increased mast cells (readily seen on Giemsa-stained sections or highlighted with CD117 or mast cell tryptase staining) (Fig. 1.1c). These mast cells appear to provide growth and survival signals via CD40-ligand (CD154), APRIL and BLYS, the expression of which is in turn stimulated by soluble CD27 secreted by the LPL cells [9, 10]. Cytoplasmic immunoglobulin inclusions are also characteristically seen in WM and are considered further morphological evidence of plasma cell differentiation. Russell bodies are single or multiple ovoid cytoplasmic inclusions, while Dutcher bodies are also cytoplasmic in nature but occur as single large inclusions, which overlie or invaginate the nucleus (Fig. 1.1d) [11].

WM is a heterogeneous disorder in which there are significant variations in serum IgM levels and BM cellular content. Some studies have failed to demonstrate a correlation between serum IgM levels and overall BM cellular burden [12, 13]. Similarly, prognostic factor analyses have failed to demonstrate a reproducible effect of IgM concentration on overall outcome except in the context of very high levels when additional factors such as cardiovascular and cerebrovascular complications may also contribute to poor survival [14, 15]. However, when flow cytometry is used to quantify bone marrow B-cells and plasma cells, it is noted that while monotypic B-cells are demonstrable in all patients, they do not appear to correlate with IgM concentration. In contrast the percentage of plasma cells, despite representing a minority population in many patients, does correlate with IgM [16]. This is further supported by studies in which the extent of bone marrow B-cell and plasma cell infiltration has been estimated using CD20 and CD138 immunostaining on trephine biopsy sections [17, 18].

Immunophenotypic studies are necessary for a definitive diagnosis of WM, and this may be achieved using either flow cytometry or immunohistochemistry although the former allows for a more extensive assessment of antigenic determinants [1, 7, 19]. In WM it is generally possible to demonstrate both monotypic B-cells and monotypic plasma cells but extended phenotyping is usually only performed on the B-cell component. A recent study has shown that the majority of WM patients have a characteristic immunophenotype. In addition to the almost universal expression of the pan B-cell antigens CD19, CD20 and CD79, approximately 90 % of cases have a $CD22^{weak}$ $CD25^{+}$ $CD27^{+}$ IgM^{+} phenotype but lack expression of CD5, CD10, CD11c, CD23 and CD103 [19]. This provides a robust basis on which to make a diagnosis and in particular allows distinction from marginal zone lymphoma, which frequently has a $CD22^{+}CD25^{-}CD103^{+}$ immunophenotype.

Flow cytometric studies may also provide useful prognostic information. The presence of 100 % light chain restriction within the bone marrow B-cells predicts, in multivariate models, for progression in patients with asymptomatic WM and overall survival in patients with symptomatic disease [19]. This criterion may also be used in conjunction with the International Prognostic Scoring System for WM (IPSSWM). Patients defined as high risk by IPSSWM who also have 100 % light chain restricted B-cells, a combination, which defines 20 % of symptomatic patients, have a particularly poor outcome (median survival 16 months) [14, 19].

It is also recognised that a proportion of patients with LPL have IgG or IgA rather than IgM M proteins. Recent data would suggest that these patients are also characterised by a CD22^{weak} CD25^{+} CD27^{+} immunophenotype as well as the MYD88 L265P mutation [20]. This has clear therapeutic implications in the era of targeted therapies but also suggests that such cases could also be included in WM clinical trials.

1.2 Extramedullary Involvement

Symptomatic extramedullary involvement is uncommon at diagnosis in WM. Lymphadenopathy is present in approximately 15 % of patients at presentation but may be more common at disease progression but is infrequently the primary reason for treatment [13, 14]. Lymph node biopsies in addition to showing a lymphoplasmacytic infiltrate may show extracellular immunoglobulin deposition (both amyloid and non-congophilic) along with a giant cell reaction [21]. In some instances, this histiocytic response is particularly prominent resulting in a so-called pseudo-Gaucher appearance. Splenic involvement is relatively uncommon and splenectomy/splenic biopsy is rarely performed for diagnosis but red pulp infiltration is typical [22].

Examination of the peripheral blood can also be informative in WM. Red cell agglutination and rouleaux formation may be seen although an overt lymphocytosis is rare. Recent studies, using allele-specific PCR for the MYD88 L265P mutation (see below), have demonstrated the presence of low-level peripheral blood involvement in the majority of patients with untreated WM but also a significant proportion of patients with IgM MGUS [23]. Further studies are warranted as non-invasive methods are clearly desirable for both diagnosis and disease response assessment.

In a small minority (<5 %) of patients, involvement of extramedullary sites other than the lymph node and spleen is documented although this does not appear to confer a poor survival outcome. Sites include the lung, central nervous system (CNS), soft tissue, bone and kidney [24]. CNS involvement has been best characterised in WM, the so-called Bing-Neel syndrome. This can be the presenting feature in WM but more commonly occurs as a progression event in patients with an established diagnosis although not necessarily in the context of systemic relapse [24–26]. Diagnosis can be made in the majority of patients through a combination of MRI imaging and CSF examination with flow cytometry showing monotypic B-cells and/or allele-specific PCR demonstrating the MYD88 L265P mutation [27, 28]. In some patients meningeal or parenchymal brain biopsies are however required for definitive diagnosis.

Renal dysfunction is a well-recognised feature of plasma cell myeloma but it is increasingly recognised that a range of renal syndromes can occur in the context monoclonal gammopathies regardless of heavy chain isotype, underlying pathologic diagnosis and disease burden [29, 30]. The concept of monoclonal gammopathy of renal significance (MGRS) has emerged, and a range of pathologies including light chain deposition disease (amyloid and non-amyloid types),

membranoproliferative glomerulonephritis, cast nephropathy, acquired Fanconi syndrome as well as direct tumour infiltration have all been described in WM [31, 32]. Renal biopsy should therefore be considered in WM patients with unexplained renal impairment and/or significant proteinuria.

1.3 Cytogenetics and Molecular Genetics

Conventional karyotyping has limited applicability in WM as it is difficult to obtain tumour metaphases because of the low rate of cell proliferation. There are no disease defining cytogenetic abnormalities but translocations involving the immunoglobulin heavy chain (*IGH*) locus at 14q32 are characteristically rare, and this can be helpful in distinguishing WM from IgM myeloma which is characterised by a high incidence of *IGH* translocations and the t(11;14) in particular (see below) [33–37]. Further data has been obtained with the use of high-resolution methodologies such as array-based comparative genomic hybridisation and single nucleotide polymorphism arrays. These studies have shown a wide range of copy number abnormalities in up to 80 % of patients with a median of three abnormalities per patient. Deletion of chromosome 6q appears to be the commonest cytogenetic abnormality occurring in up to 50 % but other recurrent abnormalities include losses at 11q, 13q and 17p as well as partial or whole gains of chromosomes 3, 4, 18 and X [38–40]. These abnormalities have limited applicability in the diagnostic context but del 6q, del 11q and trisomy 4 appear to be associated with adverse clinical and laboratory parameters, while deletion of *TP53* appears to predict for a short progression-free interval and duration of response [41, 42].

In 2012 whole genome sequencing (WGS) demonstrated the presence of a single T-to-C point mutation in the myeloid differentiation factor 88 (*MYD88*) gene at chromosome 3p22.2. This results in a leucine-to-proline amino acid change at position 265 and has been confirmed to be present in approximately 90 % of patients with WM and results in activation of both interleukin-1 receptor-associated kinase (IRAK) and Bruton tyrosine kinase (BTK) which ultimately results in downstream translocation of nuclear factor kappa B (NFkB) and malignant cell growth (43, 44]. Further studies have confirmed the very high incidence of the MYD88 L265P mutation in WM and its relative rarity in other B-cell LPD and myeloma [45–48]. This has obvious diagnostic utility, and allele-specific PCR strategies have been developed and are in routine use in many laboratories [45, 46, 48, 49]. Allele-specific PCR strategies have reported sensitivities of 0.1–0.25 % but it is recommended that each laboratory determines their own sensitivity thresholds through dilution experiments. There is a clear rationale for the use of allele-specific PCR in the routine assessment of patients with suspected WM but a small minority of patients would be missed with this approach. These patients may have alternative MYD88 mutations such as the S243N or an L265P occurring as a consequence TG-to-CT substitution rather than the single T-to-C point mutation [50]. WGS studies have also demonstrated a number of additional recurrent mutations occurring in >5 % of patients. These involve in decreasing

frequency, the following genes: CXCR4, ARID1A, CD79b, TP53 and MYBBP1A [51].

CXCR4 mutations occur in approximately 30 % of patients and involve the carboxyl terminal of the gene which is responsible for regulating signalling following ligation with SDF-1a (CXCL12). A number of truncating nonsense and frameshift mutations have been described, and these are similar to those described in a known immunodeficiency disorder the warts, hypogammaglobulinaemia, infection and myelokathexis (WHIM) syndrome [51]. These mutations were initially evaluated by Sanger sequencing but recent studies with sensitive allele-specific PCR have suggested a higher incidence of mutation [52]. In addition these studies have demonstrated that CXCR4 mutations are almost exclusively seen in patients with the MYD88 L265P and appear to be subclonal in nature and that multiple mutations may occur in some patients [51, 52]. CXCR4 mutations are also demonstrable in approximately one third of IgM MGUS [52].

Recent studies have also demonstrated that tumour genotype has a profound influence on clinical phenotype, response to targeted therapy and overall survival. Patients who are wild type for MYD88 L265P are characterised by lower levels of IgM and marrow involvement, poor quality categorical responses to ibrutinib and an inferior overall survival outcome [53, 54]. Patients with CXCR4 mutations have a lower incidence of lymphadenopathy, and in particular those with nonsense mutations have higher levels of BM involvement and serum IgM and as a consequence more frequent hyperviscosity syndrome [53].

Immunoglobulin heavy chain variable region (*IGHV*) sequence analysis has been performed by a number of investigators, and this shows evidence of somatic hypermutation without intraclonal diversity in virtually all patients which is consistent with an origin in a post-germinal centre B-cell. Furthermore these studies have also demonstrated preferential use of *VH3* segments and the *VH3-23* in particular with no evidence of canonical motifs indicative of antigen selection [55–59]. This is in contrast to splenic marginal zone lymphoma which is characterised by both mutated and unmutated *IGHV* with a significant proportion of cases showing preferential use of *VH1-2* with canonical motifs [59].

1.4 IgM MGUS

It is important that IgG and IgA MGUS be distinguished from IgM MGUS as the former is a precursor of myeloma and the latter a precursor of WM or other B-cell LPD. IgM MGUS is defined by IgM monoclonal gammopathy without morphological evidence of BM infiltration or other features indicative of an underlying LPD such as lymphadenopathy [1]. It is however recognised that clonal B-cells are demonstrable in a significant proportion of patients without morphological evidence of BM disease. It has been demonstrated that B-cells comprise approximately 2 % of total BM cells in IgM MGUS and that a median of 75 % are monotypic, while only a small minority (~1 %) of patients show complete light chain restriction and >10 % B-cells [19]. This latter observation may provide a more meaningful

and reproducible definition of IgM MGUS. Similarly the MYD88 L265P mutation is demonstrable in approximately 50 % of cases, while CXCR4 mutations and specific copy number abnormalities (+4, del 6q, +12 and +18q) are demonstrable in a significant minority of patients [40, 45, 46, 48, 52, 60].

The role of marrow assessment in asymptomatic individuals is not established but an arbitrary cut-off of 10 g/l has been proposed in some guidelines [61]. Bone marrow examination should however be considered at lower IgM concentrations particularly if the patient is suspected of having an IgM-related syndrome (see below). If marrow examination is performed, it is important that a trephine biopsy be obtained in addition to a marrow aspirate and that flow cytometry and molecular studies for MYD88 L265P be performed as they provide prognostic information. Some asymptomatic patients will be reclassified as asymptomatic WM following marrow examination and by definition have a greater risk of progression to symptomatic disease requiring therapy [62]. Similarly IgM MGUS patients with the MYD88 L265P mutation show a greater rate of progression to symptomatic disease [63]. It is unclear whether this prognostic impact relates to the presence or absence of the mutation per se or reflects disease burden above and below the sensitivity threshold of allele-specific PCR.

1.5 IgM-Related Syndromes

In a proportion of patients with IgM monoclonal gammopathy, clinical features may occur as a consequence of the physico-chemical and immunological properties of the M protein rather than disease burden. A number of syndromes are recognised, and these include anti-myelin-associated-glycoprotein (MAG) peripheral neuropathy, cold agglutinin disease (CAD), cryoglobulinaemia, Schnitzler syndrome and acquired von Willebrand disease [13]. There is limited specific pathological data in these disorders but overall marrow burdens are typically low, and many patients would be formally classified as IgM MGUS.

In CAD the monoclonal IgM (typically kappa) has binding specificity for I/i red cell antigens causing complement activation and phagocytosis by the reticuloendothelial system. The pathological features underlying CAD have been recently described [64]. Morphological evidence of marrow infiltration is demonstrable in the majority of patients but the level of infiltration is low (median 10 %) and a nodular pattern is typical. Monotypic plasma cells are seen but these surround the lymphoid nodules but also show a dispersed interstitial pattern. Monoclonal B-cells are usually demonstrable by flow cytometry in those patients lacking morphological evidence of disease [64, 65]. There is some evidence to suggest that there may be significant immunophenotypic and genotypic differences between WM and CAD. Flow cytometry has shown that CAD B-cells show higher levels of expression of CD5, CD11c, CD23, CD39 and CD200 along with lower levels of CD19, CD79 and IgM compared to WM B-cells [65]. Similarly, *IGHV* sequencing has demonstrated almost universal usage of the *IGHV4-34* in CAD while *IGHV3* genes predominate in WM. The *IGHV4-34* framework region 1 (FR1) is mainly responsible for

I-antigen binding [55–59, 66]. Two studies have also suggested a lower incidence of the MYD88 L265P mutation in CAD [64, 65].

1.6 IgM Plasma Cell Myeloma

In a proportion of patients with WM (up to 20 % in some series), the degree plasma cell differentiation may be such that plasma cells are the predominant cell type and IgM myeloma becomes part of the differential diagnosis (Fig. 1.1f) [67]. This phenomenon may also be seen at disease progression and may be promoted by rituximab-based therapies [68–70] (see below). Although this is a rare scenario, it is essential that a correct diagnosis be made given the availability of targeted therapies in WM and the poor clinical outcome in IgM myeloma [54, 71]. For a diagnosis of WM to be made, a $CD20^{+}$ IgM^{+} B-cell component needs to be demonstrated, and this is most readily done by flow cytometry, which may also demonstrate the WM-specific immunophenotype [19]. Similarly WM plasma cells lack the phenotypic characteristics of myeloma plasma cells such as the absence of CD19 and the expression of CD56 and cyclin D1 [19, 33, 67].

IgM myeloma is characterised by translocations involving the *IGH* locus at 14q32 and the *CCND1-IGH* translocation in particular, and while only limited numbers of cases have been assessed, the MYD88 L265P appears to be lacking [33, 37, 72].

1.7 Assessment of Bone Marrow Response

Criteria for the assessment of post-treatment response were first proposed in 2003 and have been further revised in 2006 and 2013 [73–75]. These have been developed to promote uniform reporting of clinical trial data, and the response categories are predominantly based upon percentage reduction in IgM as this appears to predict progression-free survival in patients treated with rituximab-containing regimens [76, 77]. It has however become clear that there may be discrepancies between serum IgM and bone marrow responses. IgM responses are typically slow with purine analogue and monoclonal antibody-based therapy as these agents selectively deplete the $CD20^{+}$ B-cell component while sparing the $CD138^{+}$ plasma cell component of the disease [68, 69]. In this context it is possible to demonstrate significant B-cell depletion in the marrow but suboptimal IgM responses. Satisfactory IgM responses may subsequently be documented at a median of 6 months following the completion of therapy in fludarabine-treated patients for instance [68]. Conversely bortezomib-containing regimens may demonstrate excellent IgM responses but suboptimal BM responses [78, 79].

Previous studies in myeloma and CLL have shown the value of quantitative assessment of residual BM disease as there are demonstrable improvements in outcome with each log depletion [80–83]. Furthermore, it is noted that conventional complete response (CR; immunofixation-negative CR in myeloma and iWCLL

defined CR in CLL) fails to retain prognostic significance in multivariate models for both progression and overall survival when considered along with quantitative residual BM disease assessment by flow cytometry [82, 83]. Accurate and reproducible quantitative methods are clearly desirable in WM, and planned sequential BM assessments are encouraged in clinical trials. The most appropriate methodologies have not been established in WM. Flow cytometry can be used to quantitate residual B-cells and is applicable to most patients on the basis of the WM-specific CD22^{weak} CD25^{+} immunophenotype [19]. In this setting a single study has demonstrated that a residual B-cell burden of $>5\,\%$ is associated with an inferior outcome [84]. Given the heterogeneity of cellular responses in the BM, it is important to assess residual plasma cells as well as B-cells and to correlate this with quantitative changes in IgM. It is also possible to quantitatively assess residual disease with molecular methods based either on the presence of the disease defining MYD88 L265P mutation or unique immunoglobulin sequence. Molecular methods are likely to offer greater sensitivity compared to flow cytometry but they will not be able to demonstrate any heterogeneity within B-cell and plasma cell responses [81]. Ideally studies should evaluate the peripheral blood in parallel with the BM as non-invasive methods are clearly desirable.

Repeat BM assessments can provide significant value in the management of individual patients particularly if there are uncertainties surrounding IgM responses or persisting cytopenia. In order to make a detailed assessment of residual infiltrates, it is recognised that both BM aspirate and trephine biopsies should be obtained and that these should be routinely supplemented by flow cytometric and immunohistochemistry studies. Attempts should be made to characterise residual infiltrates with respect to their B-cell and plasma cell content, and immunohistochemical assessment of trephine biopsy sections provides the optimal method at present. CD138 and/or IRF4 may be used to demonstrate residual plasma cells, while CD20 may be used to define residual B-cell infiltration although additional markers such as PAX5 may be necessary in rituximab-treated patients due to the loss of CD20 expression which can be seen in post-treatment specimens.

1.8 Disease Progression and Histologic Transformation

Histologic transformation, primarily to diffuse large B-cell (DLBCL), is a well-recognised phenomenon in all forms of indolent B-cell LPD. It has been reported to occur in 5–10 % of patients with WM which is similar to the incidence reported in CLL [7, 85–92]. Histologic transformation events have been thought traditionally to occur within a single B-cell clone through the sequential acquisition of additional genetic events. Analysis of paired samples has demonstrated this linear pattern of disease evolution in CLL. It is estimated that approximately 20 additional/novel events are acquired within the predominant CLL clone [93]. A more complex pattern has been demonstrated in follicular lymphoma with transformed and non-transformed clones appearing to arise by divergent evolution from a common precursor through the acquisition of distinct genetic events [94]. This so-called

branching pattern of disease progression and transformation is clearly more complex than the traditional linear model of evolution. It is unclear whether disease transformation and progression in WM occurs through branching or linear patterns and detailed assessment of sequential biopsies will be required to clarify.

It is also noted that Epstein-Barr virus (EBV) may have a role in the aetiology of some transformation and progression events in patients with B-cell LPD. These may occur within EBV-infected but clonally unrelated B-cell populations as a consequence of both disease-related and treatment-induced immunosuppression. EBV-associated DLBCL is well recognised in CLL typically occurring in the context of highly immunosuppressive therapy such as purine analogues and alemtuzumab. Immunoglobulin sequencing has shown independent B-cell clones and a poor clinical outcome is typical [95–98]. EBV-associated DLBCL has been reported in WM [99].

EBV-associated mucocutaneous ulcer is also a well-recognised consequence of immunosuppression and is characterised by ulcerative lesions affecting the skin, oropharynx and GI tract. Histologically these lesions consist of a population of large "Hodgkin-like" mononuclear cells, which show expression of CD30 and IRF4 within a polymorphous inflammatory background. The large mononuclear cells, similar to Hodgkin Reed-Sternberg cells, show variable expression of B-cell antigens (CD20, CD79 and PAX5) and the transcription factors OCT2 and BOB1 [100, 101]. EBV-associated mucocutaneous ulcer has been described in WM in the context of fludarabine-based therapy and spontaneous regression can occur [102]. Rare cases of peripheral T cell lymphoma have also been described in WM, and these may also be associated with minority populations of $CD30^+$ B-cells showing EBV incorporation [102].

Progression events in which plasma cells dominate have also been described [70, 102]. These can occur in the previously asymptomatic patients but also in heavily pretreated patients and may mimic plasmacytoma/myeloma. Rituximab-based conventional chemotherapy regimens may have a role in this pattern of disease progression given that they have been shown to selectively deplete B-cells in the post-treatment setting [68, 69].

Oncogenic MYD88 mutations, predominantly the L265P, are well described in de novo DLBCL and were originally described in approximately one third of patients with an activated B-cell (ABC) gene expression profile [103]. Subsequent studies have shown a particularly high incidence of the mutation in primary extranodal DLBCL at immune-privileged sites such as the brain, testis and breast [104–114]. It is unclear at this stage whether there is a unifying etiological link between these lymphomas and WM but it is intriguing to note that a recent study has demonstrated the MYD88 mutation in the peripheral blood of patients with primary CNS lymphoma [112].

The complex and diverse nature of disease progression events highlights the importance of detailed pathological evaluation that should include the assessment of EBV by immunohistochemistry and/or in situ hybridisation. The assessment of sequential samples using next-generation sequencing approaches is likely to provide insights into the nature of transformation and disease progression. Ideally

surgical biopsy specimen should be obtained if histologic transformation is suspected and PET imaging can guide biopsy procedures [115, 116].

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