CLINICOPATHOLOGICAL CRITERIA FOR WM.

RG Owen, R de Tute, AS Jack, AC Rawstron. St James's Institute of Oncology, Leeds, UK.

WM is by definition characterized by bone marrow infiltration by lymphoplasmacytic lymphoma (LPL) in the context of IgM monoclonal gammopathy. From a morphological perspective LPL comprises, in the majority of patients, a dominant small B-cell population showing evidence of plasma cell differentiation. The latter is most readily appreciated on trephine biopsy sections and can be further highlighted by CD138 and/or IRF4 immunostaining as the expression of these antigens is confined to the plasma cell component of the disease. The extent to which plasma cell differentiation varies considerably, and is likely to be the main determinant of IgM concentration rather than overall disease bulk.

B-cell phenotyping, ideally by flow cytometry, is essential in confirming a diagnosis of WM. Historically LPL/WM has been a diagnosis of exclusion but considerable progress has been made in recent years with clarifying the immunophenotypic profile of WM. We have identified a number of broad phenotypic profiles in WM, which appear to be distinct from patients with MZL as well as those with CLL, mantle cell and follicular lymphoma. Knowledge of these presenting immunoprofiles facilitates the development of MRD assays, as it is clear that WM B-cells are distinct from B-progenitors and normal mature B-cells. Specific plasma cell immunophenotyping is not routinely required in WM but may become more relevant if plasma cell specific monoclonal antibodies, such as elotuzumab, are incorporated into treatment regimens.

In a minority of patients plasma cells appear to be the predominant cell type and myeloma becomes part of the differential diagnosis. The rare entity of IgM myeloma has become better characterized over recent years and detailed morphologic, immunophenotypic and genotypic investigations allow for definitive distinction in most cases. IgM myeloma is characterized by the absence of a surface Ig+ CD20+ B-cell component, an aberrant (CD19- CD45-) plasma cell phenotype and a high incidence of *IGH* translocations and the t(11;14) in particular.

Conventional karyotyping has limited applicability in WM, as it is difficult to obtain tumour metaphases. There are no disease defining abnormalities but translocations involving the *IGH* locus at 14q32 are very rare. The prognostic significance of del 6q has not been definitively established. Deletion of *TP53* in common with other B-cell disorders is demonstrable in 5-10% of newly presenting symptomatic patients but it remains to be seen whether this has the same prognostic significance as in CLL and myeloma.

Detailed pathological assessment is needed in patients with suspected histologic transformation. These events have traditionally been considered to occur within the original B-cell clone as a consequence of the acquisition of additional genetic events. Recent data however has demonstrated the diverse nature of transformation events and in particular the role of EBV. These latter events include EBV-positive but clonally unrelated DLBCL as well as spontaneously resolving EBV-positive mucocutaneous ulcer. In addition to these transformation events the occurrence of synchronous occult WM is being increasingly recognized in patients with apparently de novo DLBCL.