

PATHOLOGICAL DIAGNOSIS OF WM.

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The laboratory diagnosis of haematological cancers relies upon the recognition that each disorder comprises a distinct clinico-pathological entity. This is the principal that underlies the World Health Organization classification of haematopoietic tumours. Distinct clinico-pathological entities are defined using the following parameters

- **Morphology** – the microscopic appearance of tumour cells
- **Immunophenotype** – the pattern of specific molecules (termed as antigens) expressed by the tumour cells. These antigens are typically denoted by CD numbers such as CD20, the target for rituximab
- **Genotype** – the genetic changes seen in the tumour cells
- **Clinical features**

WM is a bone marrow disorder and hence bone marrow aspiration and trephine biopsy are essential for diagnosis. Utilising the WHO principles WM is characterised by the following –

- **Morphology** – a so-called lymphoplasmacytic infiltrate in the bone marrow. Essentially this means that WM has two main cellular components. The dominant component is comprised of B-cells which are considered to be the proliferative fraction and will express CD20. The second cellular component comprises plasma cells which are responsible for the production of IgM. These develop or differentiate from the B-cells and the extent to which this occurs varies from patient to patient and explains the variability seen in IgM levels. This fraction will express CD138 but lack CD20. The demonstration of both a B-cell and plasma cell component is central to the diagnosis of WM and allows distinction with those rare cases of IgM myeloma. The infiltrate in WM may also be associated with an increase in mast cells which are readily identified on giemsa stained marrow sections.
- **Immunophenotype** – WM B-cells express CD20 but usually lack CD5, CD10 and CD23. These are not disease defining features but typically allow the exclusion of other lymphomas. Progress is being made towards identifying the “WM phenotype”. This will hopefully allow further refinement of diagnostic criteria and the development of minimal residual assays that will become more applicable as the incidence of complete responses increase with new therapeutic combinations.

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- **Genotype** – as yet there are no disease defining genetic abnormalities in WM. Deletions involving chromosome 6 are the commonest abnormality but routine assessment for this abnormality is not currently required as it does not affect patient management. Deletions of the tumour suppressor gene *TP53* is increasingly recognised in other B cell lymphoproliferative disorders and myeloma and appears to confer a particularly poor outcome. Initial data from France suggest that this may also be the case in WM.
- **Clinical features** – clearly a diagnosis of WM cannot be made in the absence of an IgM monoclonal protein!

The diagnostic criteria also recognise the following groups of patients -

- **Symptomatic WM** - IgM monoclonal gammopathy, bone marrow infiltration and symptoms such as anaemia requiring therapy.
- **Asymptomatic WM** - IgM monoclonal gammopathy, bone marrow infiltration but no symptoms.
- **IgM MGUS** - IgM monoclonal gammopathy but no evidence of bone marrow infiltration and no symptoms.
- **IgM related disorders** – these are the patients who have symptoms attributable to the properties of the monoclonal IgM e.g. neuropathy and cold agglutinin disease. Typically such patients have no or a minimal degree of bone marrow infiltration.