32.1. Introduction

Summary:
- Waldenström’s macroglobulinaemia is a rare lymphoplasmacytic lymphoma associated with the production of monoclonal IgM.
- sFLC analysis is informative in the majority of patients at diagnosis.
- Elevated concentrations of FLCs at baseline are associated with shorter time to treatment and reduced overall survival.
- The involved FLC concentration is a useful marker of response to treatment and may show responses and disease progression earlier than IgM.
- Quantification by IgM Hevylite® may be useful in cases where the monoclonal protein concentration is low, forms multimers or co-migrates with other serum protein peaks.
- IgM Hevylite may be useful for monitoring responses to treatment and identifying patients with inferior survival.

Waldenström’s macroglobulinaemia (WM) is a rare, low-grade, lymphoplasmacytic lymphoma characterised by the production of monoclonal IgM. The incidence rate of WM is approximately 5 cases per million persons per year, about 5 - 10% that of multiple myeloma (MM). The median age at diagnosis is 65 years, and up to 70% of patients are male. Median survival for younger patients exceeds 10 years, but for older patients this is shorter. However, many patients die from unrelated causes, and approximately 10% of patients are still alive after 15 years. The majority of patients diagnosed with WM do not require immediate therapy as they are detected before symptoms occur, and the median time to symptom development is 5 - 10 years. In a recent review, Buske et al. followed 454 WM patients across Europe for a median of 87 months and identified anaemia and constitutional symptoms as the most common reasons for initiation of a front-line therapy. In these patients, the median overall survival was not reached and the estimated 5- and 10-year overall survival was 87 and 69%, respectively.

Infiltration of bone marrow and extramedullary sites by malignant B-cells, and elevated serum IgM concentrations are responsible for the majority of symptoms associated with WM. Whilst the most common presenting symptom is fatigue related to anaemia, symptoms vary considerably among patients and may include night sweats, weight loss, bleeding tendency, polyneuropathy, lymphadenopathy, hepatosplenomegaly and symptoms relating to hyperviscosity (i.e. headaches, blurred vision, confusional episodes, epistaxis).

Cryoglobulinaemia (where monoclonal IgM reversibly precipitates at temperatures below 37 °C) affects up to 20% of patients, although <5% have symptoms (Section 34.2). The presence of cryoglobulins makes serum collection and laboratory quantification of IgM difficult, as they need to be performed at elevated temperatures.

The diagnosis of WM requires demonstration of a lymphoplasmacytic lymphoma with bone marrow involvement, and the detection of an IgM M-protein of any concentration. Widely used consensus panel recommendations were published following the Second International Workshop on Waldenström’s Macroglobulinaemia, and are summarised in Table 32.1. These form the basis of European and American guidelines.
Diagnostic criteria for WM:

- IgM monoclonal gammopathy of any concentration.
- Bone marrow infiltration by small lymphocytes showing plasmacytoid or plasma cell differentiation.
- Intertrabecular pattern of bone marrow infiltration.

Table 32.1. Diagnostic criteria for WM: consensus panel recommendations [9].

Accurate diagnosis of WM is difficult in some cases, due to the ill-defined overlap of clinical features between WM and two related conditions: IgM monoclonal gammopathy of undetermined significance (IgM MGUS), and smouldering WM (SWM; also known as asymptomatic WM) [10].

SWM is similar to IgM MGUS in that they both are asymptomatic conditions, but SWM patients have a higher risk of progression to WM within the first 5 years (12% vs 2% per year) [11][12]. At diagnosis, up to one third of WM patients have SWM [11][13][14], which is defined by the presence of an IgM M-protein ≥30g/L and/or ≥10% bone marrow lymphoplasmacytic infiltration and no end organ damage. Due to the lack of symptoms, treatment is not required but regular monitoring is recommended [15].

References


