In smouldering multiple myeloma:

- sFLCs are abnormal in approximately 80% of patients.
- Abnormal κ/λ sFLC ratios are associated with an increased risk of progression.
- Asymptomatic patients with an involved/uninvolved sFLC ratio ≥100 and 10% clonal bone marrow plasma cells or biopsy-proven plasmacytoma have been reclassified as multiple myeloma requiring treatment.

14.1. Introduction

Smouldering multiple myeloma (SMM) is an asymptomatic plasma cell disorder. In 2014, the International Myeloma Working Group (IMWG) revised their definition of SMM and a definitive diagnosis now requires two criteria to be met: 1) the presence of a serum monoclonal protein (IgG or IgA) at a concentration of ≥30 g/L or a urinary monoclonal protein ≥500 mg/24 hours and/or 10 - 60% clonal bone marrow plasma cells (BMPCs), and 2) the absence of myeloma defining events or amyloidosis (Section 25.2). This revised definition excludes asymptomatic patients with clonal BMPCs ≥60%, an involved/uninvolved sFLC ratio of ≥100, or those with two or more focal lesions revealed by MRI, which in conjunction with a minimum of 10% clonal BMPC or biopsy-proven plasmacytoma are consistent with a diagnosis of multiple myeloma (MM, Section 25.2). In a retrospective audit of 216 SMM patients by Kastritis et al., 13% of SMM patients were re-classified as MM using this definition. Similar findings were reported by Kyrtsonis et al.

Prior to the 2014 revised diagnostic criteria, Dispenzieri et al. noted that unlike MGUS, in which the rate of progression remains constant over time (Chapter 13), the overall risk of progression in SMM was greatly influenced by the length of time from diagnosis, with the highest rates of progression occurring in the first few years. Presumably this reflected the fact that prior to the updated criteria, patients classified as SMM were a very heterogeneous population, comprising some patients that would now be reclassified as MM, and others that were biologically more similar to MGUS. With increasing follow-up the cohort would have become enriched with low-risk patients, resulting in progressively lower rates of progression.

Risk stratification is valuable for SMM patient management. Patients identified as high-risk require close follow-up and, if possible, inclusion into clinical trials as initial studies suggest these patients benefit from therapy. Early studies identified a variety of risk factors for progression, including a high percentage of BMPCs, a monoclonal protein concentration ≥30 g/L, an IgA isotype and Bence Jones proteinuria. Subsequently, monoclonal serum free light chains (sFLCs) were identified as a significant, independent risk factor, as discussed below. Preliminary evidence suggests that immunoglobulin heavy/light chain (Hevylite®, HLC) assays may also have a role in SMM prognosis (Section 14.4).

14.2. Monoclonal sFLCs and SMM progression

IMWG guidelines recommend that sFLCs are measured at baseline for all SMM patients to allow risk stratification (Section 25.3.2). A number of studies that demonstrate the prognostic utility of sFLC measurements in SMM are described below, but it should be noted that many predate the 2014 revisions to diagnostic criteria, which reclassify high risk SMM patients as MM patients requiring treatment (Section 25.2).

The largest study to assess risk factors for SMM in the context of the 2014 diagnostic criteria was reported by Lakshman et al., and included 421 SMM patients followed up for a median of 74.8 months. At diagnosis, a number of variables were assessed as potential prognostic markers to predict malignant progression, and ROC analysis was performed to identify the optimal cut-offs. The variables included M-protein size and type, the proportion of BMPCs, involved/uninvolved sFLC ratio and
the presence of immunoparesis. On univariate analysis, only the M-protein size (>20 g/L), proportion of bone marrow plasma cells (BMPC >20%) and the involved/uninvolved FLC ratio (>20) were significantly associated with progression, and the same three variables remained prognostic on multivariate analysis. Combining these risk factors, Lakshman et al.\textsuperscript{[12]} developed a risk stratification model that divided patients into three groups: low-risk (no risk factors), intermediate risk (1 risk factor) and high risk (2 or 3 risk factors). The estimated median time to progression for the low-, intermediate- and high-risk groups were 110, 68 and 29 months respectively (p<0.0001). The authors conclude that high-risk patients may benefit from clinical trials of early intervention to prevent/delay progression to MM or AL amyloidosis. Similar risk factors were reported by Akhlaghi et al.\textsuperscript{[13]}, although the design of this study was not identical to the one described above, as the definition of SMM was based on the IMWG criteria at the time of diagnosis, which ranged between the year 2000 and 2017.

The use of sFLCs as prognostic markers in SMM spans over a decade. The initial observations were reported by Augustson et al.\textsuperscript{[14]} who studied SMM patients recruited to UK MRC MM trials, and their findings were subsequently confirmed by others.\textsuperscript{[15]}, including two notable large studies reported by Dispenzieri et al.\textsuperscript{[4]} and Larsen et al.\textsuperscript{[6]}. Dispenzieri et al.\textsuperscript{[4]} studied the prognostic value of sFLCs in 273 SMM patients attending the Mayo clinic, Rochester, USA. After a median follow-up of 12.4 years, transformation to active disease had occurred in 59% of patients. The authors noted that patients with more extreme sFLC ratios had a higher risk of progression to active MM than patients with normal or near normal values (Figure 14.1), and the prognostic value of the sFLC ratio persisted after adjusting for competing causes of death.

The study by Larsen et al.\textsuperscript{[6]}, baseline sFLC results were analysed retrospectively in 586 patients with newly diagnosed SMM. The κ/λ sFLC ratio was abnormal in 74% of patients. Receiver Operating Characteristic (ROC) analysis identified the optimal diagnostic cut-off for the sFLC ratio to identify patients at highest risk of progression to symptomatic disease within 2 years of diagnosis. A serum involved/uninvolved sFLC ratio ≥100 was used to define high-risk SMM (now considered one of the diagnostic criteria for MM; Section 25.2.1), and included 15% of the total cohort. This resulted in a specificity of 97% and a sensitivity of 16%. The risk of progression to MM within 2 years of diagnosis was 72% for SMM patients with an involved/uninvolved sFLC ratio ≥100 (Figure 14.2). This risk increased to 79% when progression to AL amyloidosis was included as an endpoint in addition to MM. In univariate analysis, BMPC content, serum monoclonal protein concentration and involved/uninvolved sFLC ratio ≥100 were all significant prognostic factors, and all remained significant on multivariate analysis. The prognostic value of extreme sFLC ratios (≥100) for progression from SMM was confirmed by two subsequent studies.\textsuperscript{[6][7]} Kastritis et al.\textsuperscript{[6]} also identified extensive bone marrow infiltration (BMPCs ≥60%) as an additional risk factor. Both risk factors (extreme sFLC ratios, and BMPCs ≥60%) are now included in the revised definition of MM (Section 25.2.1).\textsuperscript{[1]} Why abnormal κ/λ sFLC ratios should predict a worse outcome in SMM is still unclear, but the authors speculated that these patients might have immunoglobulin heavy chain translocations or other genetic disruptions associated with disease progression.\textsuperscript{[68]}

Moreau et al.\textsuperscript{[7]} compared the performance of Freelite polyclonal antisera-based assays and N Latex FLC monoclonal antibody-based assays. The authors concluded that the two assays are not interchangeable, and that cut-offs based on Freelite assays for SMM risk stratification cannot be applied to N Latex FLC assays. This is further discussed in Section 8.6.

14.3. The prognostic value of HLC analysis at baseline
Hevylite assays allow the measurement of isotype-specific suppression of the uninvolved HLC-pair (i.e. suppression of IgG in an IgGκ patient) (Section 11.2). As HLC-pair suppression has been identified as an adverse prognostic marker in MM and MGUS patients (Chapters 13 and 20), it may also have prognostic significance in SMM. In the largest prospective study of HLC and SMM published to date, HLC-pair suppression was observed in 39/50 (78%) patients at diagnosis, compared with 32/50 (64%) patients who had conventional immunoparesis, i.e. suppression of uninvolved polyclonal immunoglobulins [19]. Of the 18 patients without immunoparesis, HLC-pair suppression was present in 8/18 cases and was associated with adverse biological features such as more skewed κ/λ sFLC ratios and a more pronounced distribution of abnormal/normal plasma cells. Isola et al. [20] prospectively monitored 18 patients with SMM. Highly abnormal HLC ratios (<0.02 or >45) and severe HLC suppression (>50% below lower level of normal) were found in 44% (8/18) and 55% (10/18) patients at diagnosis, and both features were present in all three patients who progressed to symptomatic disease during follow-up.

In an initial investigation by Maisnar et al. [21], HLC-pair suppression was associated with increased risk of progression in IgG (n=51, p=0.006) but not IgA (n=20) SMM, although patient numbers were small. Further studies are now required to confirm the prognostic significance of HLC-pair suppression in SMM.

14.4. The prognostic value of changes in monoclonal protein concentration

Several studies have evaluated the prognostic impact of an increasing monoclonal protein concentration during follow-up on risk of SMM progression. Many [20][22][23][24], but not all studies [25], have reported a higher risk in patients who demonstrate a progressive rise in serum monoclonal protein. For example, Fernandez de Larrea et al. [22] studied 206 SMM patients, and defined an “evolving” monoclonal protein type as either a 10% increase within the first year after diagnosis (for patients with an initial monoclonal protein ≥30 g/L) or a progressive increase in consecutive annual measurements during a period of 3 years (for patients with an initial monoclonal protein <30 g/L). A quarter of patients displayed an evolving type, and once recognised, patients had a median time to MM progression of only 1 year, and a five-fold increased risk of progression compared to non-evolving patients. On multivariate analysis, an evolving pattern was the strongest risk factor for progression, and for these patients the other known risk factors (such as the monoclonal protein size or percentage of BMPCs) failed to provide additional prognostic information. The authors concluded that SMM should be routinely monitored for an evolving type during follow-up.

International guidelines recommend that serum protein electrophoresis and 24-hour urine electrophoresis are performed at SMM diagnosis and at 2 - 3 months. If the results are stable, the patient should be followed every 4-6 months for 1 year and, if stable, every 6 - 12 months (Section 25.3.2). Whilst there are no recommendations for the frequency of sFLC analysis during follow-up, in a recent review article, Rajkumar [25] suggested that sFLCs should be evaluated every 3 - 4 months. This information can then be used to identify SMM patients at the highest risk of disease evolution [20].

In a recent study, Wu et al. [15] compared evolving biomarkers as risk factors to identify ultra-high-risk SMM in a cohort of 273 SMM patients. Baseline immunoparesis and evolving concentrations of M-protein (64% increase), haemoglobin (1.57g/dL decrease) and dFLC (169% increase) within one year from diagnosis were identified as predictors of ultra-high-risk progression to MM. The median time to progression in patients with ≥3 risk factors was 13 months.

An initial prospective study of the value of HLC measurements during SMM follow-up was reported by Fernandez de Larrea et al. [27]. Of the 12/30 patients who demonstrated a progressive increase in involved HLC (iHLC) levels during follow up, 5 patients progressed to symptomatic MM. In one patient, the increase in iHLC preceded the increase in the M-protein measured by SPE by several months. Further study of the role of HLC analysis to monitor SMM is now warranted.
Figure 14.1. Effect of increasing abnormal sFLC ratios on the relative risk of progression of SMM to MM or related disorders.

BMPC: bone marrow plasma cells. (This research was originally published in Blood© the American Society of Hematology).

Figure 14.2. Extreme involved/uninvolved sFLC ratios identify SMM patients at risk of imminent progression to MM.

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References


