THE PATHCARE NEWS

Serum Free Light Chains - an Essential Test in Myeloma

Multiple Myeloma (MM) is the 2nd most common haematological malignancy. Serum free light chain (s-FLC) testing now forms an integral part of the management of MM.[1]

FACTORS INFLUENCING S-FLC LEVELS:

The serum levels of free light chains (s-FLC) may rise during an inflammatory response, renal impairment, or monoclonal proliferation. The kappa:lambda ($\kappa : \lambda$) ratio can differentiate monoclonal proliferation from the other causes, since the involved FLC (iFLC) will be produced in excess to the uninvolved FLC (uFLC). The ratio is therefore used in diagnosis and risk determination.

However, during treatment the ratio may reflect immune suppression of the uFLC more than the tumour burden. The absolute value is therefore more appropriate for monitoring.[2]

A slight increase in the ratio may be seen during renal impairment, due to the decrease in preferential filtering of the smaller κ FLC. A reference interval of 0.37 - 3.1 is recommended for patients with renal impairment.[3]

RISK DETERMINATION:

Virtually all cases of MM are preceded by monoclonal gammopathy of undetermined significance (MGUS) or smouldering MM (SMM).[1] Being one of the risk factors, s-FLC play an important role in determining risk for progression of these pre-malignant conditions to MM. The most significant risk factors are: monoclonal peak (MP) size >15 g/L, non-IgG isotype, and an **abnormal FLC ratio** (>10 or <0.1). In Waldenströms macroglobulinaemia (WM), however,the value of s-FLC has not been established. Only MP size and % bone marrow (BM) Lymphoplasmacytic cells are risk factors for progression of IgM MGUS to WM.[4]

DIAGNOSIS OF MM:

According to the new International Myeloma Working Group criteria, MM is diagnosed if there are >10% clonal BM plasma cells, together with any one or more of the following myeloma defining events:

- Evidence of end-organ damage: hypercalcaemia, renal impairment, anaemia, or bone lesions

  or
- Biomarkers of malignancy: **FLC ratio ≥ 100 or ≤ 0.01#**, >1 focal bone lesion on MRI, or if the clonal BM plasma cells are > 60%.[5]

 # iFLC must be >100 mg/L

MONITORING:

s-FLC form part of the Response Criteria for light chain MM (LCMM), non-secretory and oligosecretory MM, and AL amyloidosis.[6]

In ~10% of MM relapse cases, only the FLC rise, without an increase in the original monoclonal intact immunoglobulin – a phenomenon known as "Light Chain Escape". This can be overlooked if s-FLC are not included in the follow-up of MM patients.[7]

SCREENING:

In MM the clonal plasma cells may produce only intact immunoglobulins (Ig), only FLC, or a combination. It is therefore imperative that a screen for MM should include both the monoclonal intact Ig and monoclonal FLC.

The recommended screening panel for MM is serum protein electrophoresis **(SPE) + s-FLC.**

S-FLC may substitute urine Bence Jones proteins (u-BJP), except when systemic amyloidosis (AL) is suspected, in which case u-BJP must also be done.[6]

WHO SHOULD BE SCREENED FOR MM?

Patients with anaemia, bone pain, renal impairment, weakness, hypercalcaemia, infections, or weight loss, as these are the most frequent presenting symptoms of MM.[1]

RECOMMENDATIONS FOR WORK-UP OF MGUS:

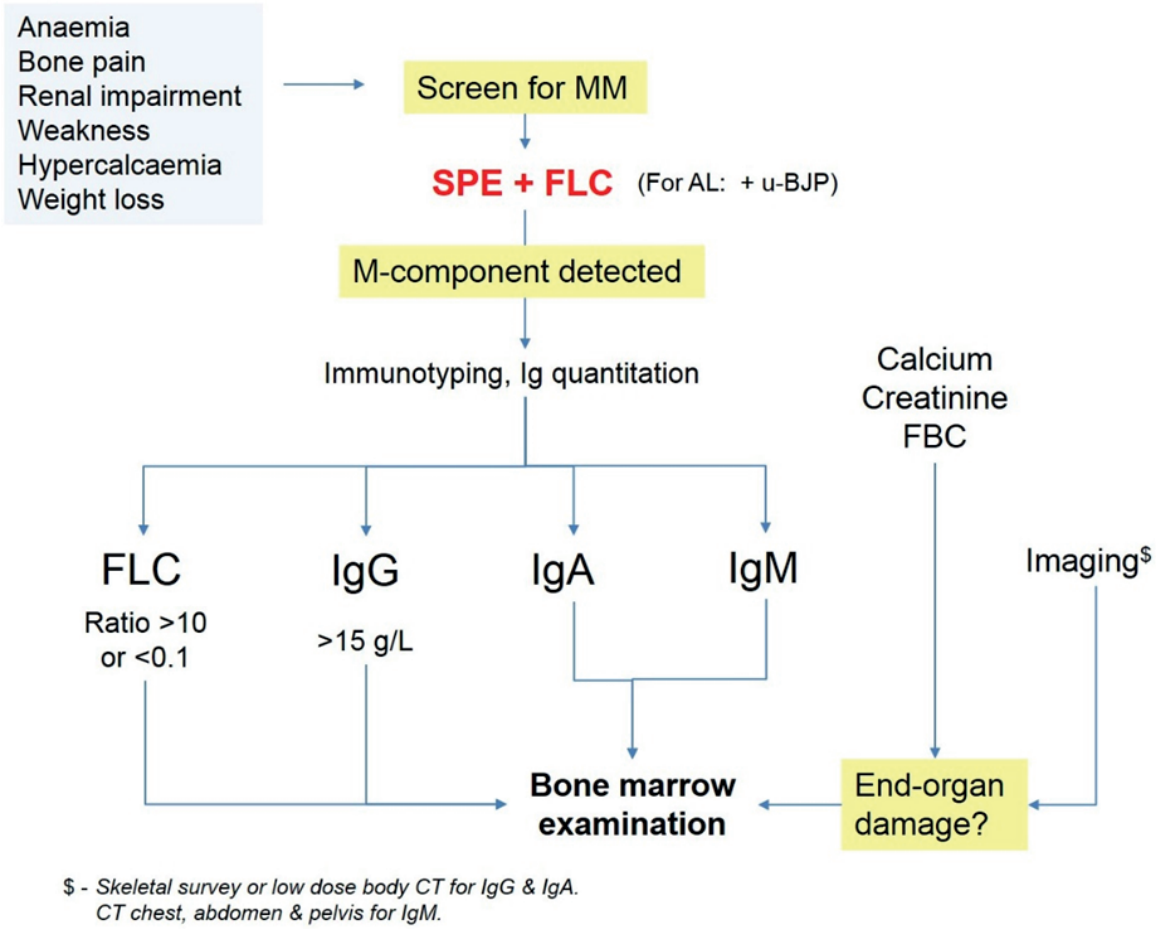
To distinguish MGUS from MM, a BM examination is required. Since MGUS is very common (3 - 4% of population > 50y), a BM would be indicated in the following cases: symptomatic patients, end-organ damage, IgA or IgM MP, IgG MP > 15 g/L, FLC ratio >10 or <0.1.[8]

INTERNATIONAL GUIDELINES FOR S-FLC TESTING:

S-FLC should be used for:

- **Screening** for MM (SPE + s-FLC)
- **Prognosis & risk** for MGUS, SMM, MM, AL amyloidosis, plasmacytoma
- **Monitoring** of oligosecretory MM, LCMM, AL amyloidosis[6]

SYNOPSIS OF BIOCHEMICAL TESTING IN MGUS:



$ - *Skeletal survey or low dose body CT for IgG & IgA. CT chest, abdomen & pelvis for IgM.*

TO SUMMARIZE:

- Screening for MM requires both a SPE and s-FLC.
- U-BJP should be added if AL amyloidosis is suspected.
- Once a M-component is detected, patients at high risk for MM should have a BM examination.
- Risk is determined by Ig isotype, size of MP, FLC ratio, presence of end-organ damage.
- S-FLC should be included in monitoring of MM patients, to detect light chain escape.

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