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by Friederike Bachmann and Stefan Knop

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What about (MG)US? Towards tailored testing in monoclonal gammopathies

Friederike Bachmann1 and Stefan Knop2

1 Division of Nephrology and Medical Intensive Care, Charité University Medicine, 10117 Berlin, Germany;
2 Nuremberg General Hospital, Dept. of Hematology and Oncology and Paracelsus Medical School, Nuremberg; Germany

Corresponding author: Stefan Knop - stefan.knop@klinikum-nuernberg.de

In this issue of the Journal, Chen and coworkers examine the multitude of challenges around monoclonal gammopathies with their numerous clinical facets.1 Amongst them are malignant diseases such as multiple myeloma as well as exceedingly rare conditions, for instance POEMS syndrome, glomerulopathies, or skin disorders.2 Most likely, the fate of a given individual diagnosed with MGUS (where „U“ stands for „undetermined“) is in fact determined by an array of variables. The challenge for the responsible physician, when encountering an M spike on an electropherogram, is to anticipate whether the underlying clone will remain stable (“true” or “benign” MGUS), develop towards a disease with malignant phenotype or towards one of these rare disorders with devastating end-organ damage. There is significant impact of genetic alterations as well as the differential usage of immunoglobulin variable genes on the phenotype and the longitudinal behaviour of plasma cell diseases.3-5 Much work went into the analysis of genomic and transcriptional changes occurring during the evolution from early to advanced and symptomatic stages of plasma cell diseases.3, 4, 6 Very recently, a group from the US published their insights into how different genetic subtypes of smoldering multiple myeloma (SMM) predispose to specific progression dynamics and clinical outcomes.6 The authors identified six subgroups that rely on different gene enrichments. They were able to identify three SMM groups at high risk for progression to active multiple myeloma. These findings may guide future directions for early interception (particularly in the three high-risk categories) with differential approaches depending on dysregulated molecular and oncogenic networks.6

Given the enormous expense required for sequencing technologies and bioinformatics, such comprehensive analyses are not yet ready for clinical-scale use. This is why for the time being clinical stratification models are important. These cover two areas of interest: first, the identification of populations who are at high risk for having MGUS or SMM and, second, the characterization of subjects with evolving SMM in whom the initiation of systemic therapy prior to the development of overt multiple myeloma will be beneficial. While a first true population-based screening study is underway but still far from its readout,7 there is clear evidence to support targeted screening in known high-risk groups. The incidence of MGUS is
as high as 25% in black people aged 50 years or older when having at least one family member with multiple myeloma. This incidence is also found in people with a different ethnic background aged 50 and older if at least two family members were diagnosed with multiple myeloma.\textsuperscript{8} Such a screening approach could result in placing subjects with high-risk SMM (still defined by clinical and laboratory parameters) on systemic therapy to prevent end-organ damage due to symptomatic multiple myeloma. With many studies including novel combinations still being under way, there is some evidence that treatment with lenalidomide and dexamethasone in high-risk MM prolongs progression-free and overall survival when compared to observation only.\textsuperscript{9}

A further layer of complexity in monoclonal gammopathies is the existence of very rare, non-malignant, albeit severely disabling entities, such as light-chain amyloidosis or renal, neurologic or myopathic disease for which the acronym “MGCS” (monoclonal gammopathy of clinical significance) was coined.\textsuperscript{2} These entities are typically characterized by their underlying low-burden plasma cell dyscrasias and by a wide spectrum of clinical symptoms. This highlights the need for more sensitive laboratory tests both with respect to confirm presence of a monoclonal gammopathy and for monitoring treatment response. The matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry has the potential to identify even small amounts of monoclonal proteins that go unrecognized by serum protein electrophoresis and serum immunofixation. A large study has proven its superiority in detecting monoclonal gammopathies in a defined screening cohort.\textsuperscript{10} Mass spectrometry could in the future replace serum immunofixation resulting in a higher accuracy to reliably detect gammopathies and exclude false-positive cases on immunofixation. The incremental benefit of this advanced technology is most likely to occur in low-level conditions. From a diagnostic perspective, certain “red flags” may serve as initial clues to the underlying clonal B-/plasma cell proliferation. Awareness is a prerequisite to allow for a timely diagnosis.

In conclusion, a complex and clinically significant spectrum of disease takes center stage in the current review.\textsuperscript{1} The authors touch on all topics that are currently under debate: the question whether screening for the “pre-symptomatic” condition is justified; the different mechanisms contributing to organ damage; the importance of early recognition of a monoclonal gammopathy; and the dilemma how to establish the best screening algorithm. The paper is an important contribution to field and will attract much interest of the readership.
References

1. Chen LY, Drayson M, Bunce C. Monoclonal gammopathy of increasing significance: time to screen? Haematologica. xxx
Figure 1. Considerations regarding diagnosis and surveillance of clonal B-/plasma cell diseases.
Screening / diagnostic aspects

- Laser
- Sample matrix
- Electric field generator
- Time-of-flight tube
- Detector

MALDI ToF MS spectrometry
*Enhanced sensitivity to detect small amounts of monoclonal protein*

Genomic / clinical aspects

Stable genomic situation
- Benign MGUS
  - Nil

Genomic instability
- Acquisition of driver mutations
- Progressive immune escape?

Overt malignant disease
- Multiple myeloma
- Lymphoplasmacytic lymphoma (Waldenström’s)

Definition of screening approaches / populations

Awareness “Red flags”

MGCS
- Kidney
- Nerve
- Skin
- Heart
- Blood cells
- Cornea
- Liver

iStopMM
Iceland Screens, Treats or Prevents Multiple Myeloma

Icelandic nationwide screening study

Plasma or B-cell clone

Differential immunoglobulin variable region gene usage