



## Paraprotein-associated diseases: a complex relationship between monoclonal gammopathy of unknown significance and severe organ damage

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In this special issue we want to introduce new insights into a complex relationship between monoclonal gammopathy of unknown significance (MGUS) [1, 2], monoclonal gammopathy of renal significance (MGRS) [3], immunoglobulin light chain amyloidosis (AL) [4] and monoclonal gammopathy with clinical significance (MGCS) [5]. All of them are categorized as M-protein related diseases.

MGUS is a premalignant condition with an incidence of 3% for persons who are 50 years of age, with the incidence continuously increasing with age. MGUS and smoldering multiple myeloma (SMM) are defined by a measurable paraprotein (M-protein, M-spike or M-gradient), a detectable clonal plasma-cell or B-cell population in the bone marrow, and without any related organ damage.

Hematologists and oncologists are trained to be aware of progression from MGUS/SMM to multiple myeloma (MM). In rare cases, the premalignant condition does not progress into malignant uncontrolled cell growth like plasma-cells in MM but the clonal M-protein can acquire a “toxic” character and causes severe tissue damage or life-threatening organ dysfunction. It is important to realize that the severity of the injury is independent of the M-protein concentration. Very low levels of M-protein can induce severe and highly dangerous organ dysfunction.

In recent years, knowledge about the diverse categories of M-protein induced organ damages has been continuously growing. Intensive efforts have been made to improve awareness and clarify the complex

mechanisms of tissue and organ damage by a “toxic” M-protein. Delayed diagnosis and prolonged treatment-initiation often result in loss of organ function and may cause life-threatening systemic deterioration.

If there is suspicion of M-protein-induced tissue damage, the relationship between M-protein and organ dysfunction has to be clearly defined. The next most important step is timely treatment initiation to avoid irreversible long-term organ damage. In summary, awareness and early treatment are of pivotal importance for improvement of overall survival and restoration of organ function. These rare and complex diseases are summarized within two new concepts named monoclonal gammopathy of renal significance (MGRS) and monoclonal gammopathy of clinical significance (MGCS).

AL amyloidosis is an extensively studied rare disease. The mechanism of tissue damage is almost clarified. The clonal cell population produces a misfolded light-chain, forming insoluble extracellular fibrils and building amyloid depositions.

MGRS represents a very new entity within this concept that is currently of great research interest. The growing information about these complex interactions clearly supports and influences the awareness and daily routine in medical care of MGUS and SMM patients. It is important to note that by implementing simple biomarkers into the clinical routine parameter-checklist, organ function and even lives might be saved.

Due to the fact that final diagnosis and treatment initiation are based on an intensive workup including interdisciplinary collaboration between multiple disciplines (hematologists, nephrologists, cardiologists, pathologists, radiologists), patients with suspected paraprotein-associated tissue damage should be sent to a highly experienced center.

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With the intention to highlight the urgent need in awareness and early diagnosis of these rare diseases and to outline the complexity and intensive collaboration needed for diagnosis and treatment, we present a special edition of paraprotein-associated diseases.

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