



REVIEW

Monoclonal gammopathy: The good, the bad and the ugly

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ABSTRACT

Monoclonal gammopathy of undetermined significance (MGUS) is a condition characterized by the presence of a monoclonal gammopathy (MG) in which the clonal mass has not reached a predefined state in which the condition is considered malignant. It is a precursor to conditions such as multiple myeloma or lymphoma at a rate of ~1%/year. Thus, from a hematologic standpoint, MGUS is a fairly benign condition. However, it is now recognized that organ damage resulting from just the MG without the need MM or lymphoma can occur. One of the most recognized is nephropathy secondary to monoclonal gammopathy of renal significance (MGRS). Other well-recognized conditions include neuropathies, oculopathies and dermatopathies. Some conditions such as autoimmune diseases and coagulopathies are less common and recognized. Finally, systemic involvement of multiple organs is well described in several entities. In all of these conditions, the role of the MG is no longer insignificant. Thus, the term MGUS should be avoided when describing these entities.

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Contents

1.	Introduction	223
2.	Impact of MGUS on survival independent of MM development	224
3.	Nephropathies	224
4.	Dermopathies	225
5.	Neuropathy	226
6.	Autoimmune disorders	226
7.	Ocular manifestations	227
8.	Immunodeficiency	227
9.	Coagulopathy	227
9.1.	Thromboembolism	227
9.2.	Acquired von Willebrand disease	228
10.	Multi-systemic disease	228
10.1.	AL amyloidosis	228
10.2.	POEMS syndrome	228
10.3.	CANOMAD	228
10.4.	TEMPI syndrome	229
11.	Conclusion	229
11.1.	Practice points	229
11.2.	Research agenda	229
	Conflict of interest	229
	Acknowledgements	229
	References	229

1. Introduction

Monoclonal gammopathy is a condition in which a monoclonal immunoglobulin or its fragment is produced by clonal proliferation of

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cells in the B lymphocyte lineage. The spectrum of hematologic conditions capable of producing a monoclonal gammopathy includes monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), plasmacytoma, Waldenström macroglobulinemia (WM), chronic lymphocytic lymphoma (CLL), and other low grade lymphomas. [1] Of these, MGUS is the most common occurring in 3% of the population older than 50 years. It is defined by 3 criteria: <3 g/dL of monoclonal (M) protein, <10% plasma cells in the bone marrow, and no evidence of end organ damage. While it is a known precursor of malignant hematological disorders, such MM, immunoglobulin light chain (AL) amyloidosis, and WM, patients generally progress to these disorders at an average rate of ~1% per year.[2] As a result, most patients never develop a plasma cell malignancy and because of this MGUS has gained a relatively benign reputation. Unfortunately, this is not entirely accurate.

In the seminal paper titled “Monoclonal gammopathy of undetermined significance. Natural history in 241 cases”, Dr. Robert Kyle was very astute and careful in choosing the title.[3] The term was controversial because terms such as essential, idiopathic, asymptomatic and even benign were being used at the time to describe monoclonal gammopathy (MG) which occurred without MM or lymphoma. The importance of “undetermined significance” was validated by studies showing a constant percentage of patients progressed at a rate that never plateaus.[2] More recently, it has been recognized that nearly all cases with MM are preceded by a period of MGUS.[4] Replacing the terms with more “benign” connotations with “undetermined significance” was one of the most important contributions to this field.

In addition to the risk of malignant transformation, MG has been a wide variety of disorders that are not related to direct invasive or destructive properties of the clone.[5,6] In fact, in patients with AL amyloidosis, one of the most lethal disorders, only 8% of patients meet criteria for MM proving that small clones are not only capable of producing disease but can also be quite dangerous.[7,8] MG is most often detected as an incidental finding in patient's serum. The diagnosis of MG has increased in recent years, undoubtedly related to the increased screening of patients with common disorders such as anemia and renal impairment and the increased sensitivity of modern assays. As a result, there is an increasing recognition of the clinical significance in its own right and its association with a number of clinical entities, in which the monoclonal protein and not the clonal mass is implicated as a causative factor. Some causative associations certainly exist; however, given the relatively high prevalence of MGUS in the general population, many reported disease associations are possibly coincidental.[9] Therefore, careful consideration of this entity in each individual clinical scenario is required. In addition, since by definition MGUS cannot have end organ damage, it should not be used in the context where a pathologic condition is attributed to the monoclonal gammopathy.

In this review, we tried to summarize some of the more common disorders associated with MG. The conditions selected generally have a higher degree of certainty for a causative relationship between the condition and the MG and not just associative. Thus, to adhere to the definition, once end organ damage occurs, the term MGUS is no longer appropriate to describe the monoclonal gammopathy. These monoclonal gammopathies are clinically significant and as such should be properly denoted.

2. Impact of MGUS on survival independent of MM development

Population-based studies have demonstrated a reduced survival in patients with MGUS as compared to matched controls secondary to both malignant and non-malignant causes, implicating MGUS as a possible independent determinant of mortality.[10] A large population based cohort study of 17,398 patients tested for MGUS conducted at Mayo Clinic identified 605 cases of MGUS. In addition to previously reported associations of MGUS, it also found increased rates of

osteoporosis, vertebral and hip fractures as well as previously unpublished significant associations with hyperlipidemia and superficial thrombophlebitis.[9]

Given that MGUS is a precursor condition for several plasma cell dyscrasias, it follows that MGUS patients also have an increased risk of dying from MM, Waldenström's macroglobulinemia or other lymphoproliferative malignancies. However, mortality is also increased for several other conditions outlined in a large Swedish cohort study of patients with MGUS.[10] In this study, the survival of 4259 patients with MGUS was compared to matched controls. The fifteen-year survival rate was indeed inferior for MGUS patients (0.70). Patients with MGUS had an increased risk of dying from conditions such as other hematologic malignancies, amyloidosis, bacterial infections, ischemic heart disease, liver and renal disease. It is important to remember that while studies such as the above suggest mechanisms causally related to the monoclonal immunoglobulin, it may also be explained by underlying disease that led to the detection of MG. Identification of true disease associations with MG is of major importance because it sheds light on both the pathogenesis of MG itself and on the associated disorder. Based on these and other studies, the major categories of disease seen to be associated with MG include: renal, neurological, autoimmune, ocular and infectious diseases in addition to thromboembolic and bleeding diatheses.[9–12] These will be reviewed below and potential causal relationships discussed.

3. Nephropathies

Renal impairment is a diagnostic component of MM which is associated with a higher early mortality and reduced overall survival if present at diagnosis in MM.[13–15] Cast nephropathy, acute tubular necrosis resulting from hypercalcemia or nonsteroidal anti-inflammatory drugs, AL amyloidosis, monoclonal immunoglobulin deposition disease of the Randall type (MIDD), and light chain proximal tubulopathy (with or without Fanconi syndrome) have all been described with MM as causes of renal impairment.[15–17] In recent years however, more and more pathological renal conditions are attributed to clonal plasma cell disorders that do not satisfy the diagnostic criteria for MM. Unfortunately, glomerulonephritis that occurred in the absence of MM were misclassified and undertreated.[8,17–19] Given their morbidity, they are more appropriately described by the term “monoclonal gammopathy of renal significance” (MGRS).[16] This term is now used to distinguish nephrotoxic monoclonal gammopathies from those that are not. The notion that Bence Jones protein is directly toxic to the kidney is well documented in animal studies.[20] Despite this, MGRS is often underappreciated in clinical practice since patients with renal dysfunction often have other plausible explanations for their deteriorating renal function and the monoclonal protein is considered coincidental rather than causal.

MGRS nephropathies regroup all renal disorders caused by monoclonal immunoglobulins secreted by nonmalignant B-cell clones. By definition, patients with MGRS do not meet the criteria for overt MM or lymphoma. The clonal biology is generally most consistent with MGUS or smoldering MM in plasma cell clones, monoclonal B-cell lymphocytosis (MBL) in CLL clones or B-cell lymphoproliferative disorder or low-grade B-cell lymphomas in lymphoma clones. It is important to note that MGRS can be secreted by any clone of the B-cell lineage that produces a circulating MG. The spectrum kidney lesions seen in MM can also be seen in CLL and WM.[21,22].

MGRS is associated with significant morbidity as a result of the renal damage (and sometimes systemic involvement) induced by the monoclonal protein.[23] Early recognition is crucial since the kidney has a limit capability for repair and prompt treatment is vital.[24] Rapid and complete suppression of immunoglobulin secretion is required to improve outcomes. The spectrum of renal diseases in MGRS is wide, including old entities such as AL amyloidosis and newly described lesions, particularly proliferative glomerulonephritis with monoclonal

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