PERSPECTIVE ARTICLE

Monoclonal gammopathy of increasing significance: time to screen?

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Abstract

Monoclonal gammopathy (MG) is a frequently detected clonal B-cell or plasma-cell disorder. Importantly, every multiple myeloma (MM) case is preceded by MG. Although clinical algorithms now allow earlier treatment of patients with biomarkers of malignancy before MM-induced tissue damage (CRAB) occurs, most patients are still diagnosed late. It is important to revisit how MG should be managed in clinical practice and whether screening is required. As the prevalence of MG and other medical co-morbidities both rise with increasing age, the degree of contribution of MG to disease states other than malignant progression is often unclear. This can lead to monitoring lapses and under recognition of the organ dysfunction that can occur with monoclonal gammopathy of clinical significance (MGCS). Therefore, models of progression to MM and/or MGCS require further refinement. While MG is currently detected incidentally, a case for screening has been made with ongoing studies in this area. Screening has the potential benefit of earlier detection and prevention of both MGCS and delayed MM presentations, but important drawbacks include the psychosocial impact on individuals and resource burden on healthcare services. MG terminology should transition alongside our increasing understanding of the condition and genomic characterization that have already begun to revise the MG nomenclature. The biology of MG has been poorly understood and is often inferred from the biology of MM, which is unhelpful. We review the literature and case for MG screening in this paper. In particular, we highlight areas that require focus to establish screening for MG.

Introduction

The incurable plasma-cell malignancy multiple myeloma (MM) accounts for 2% of all cancer diagnoses and cancer deaths in the UK[1] and the USA.[2] MM is consistently preceded by well-defined earlier states termed monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM).[3,4] The recognition that a period of MGUS universally heralds MM, alongside the advent of less toxic MM therapies, have strengthened the argument for earlier intervention. As a result, therapeutic algorithms for MM have transitioned over the last decade to treating earlier stages of disease, in patients with biomarkers of malignancy and no end-organ damage, using standard anti-myeloma therapy.[5] However, the increasing focus on early intervention in MM highlights the need to re-assess methods of early detection, including screening.

Monoclonal gammopathy (MG) describes a clonal B-cell or plasma-cell dyscrasia leading to the production of a monoclonal protein discernible against a background of polyclonal immunoglobulins. Traditionally, MG is considered a benign premalignant condition and therefore research on MG has thus far concentrated on drivers of malignant transformation. However, there is growing evidence that MG can cause organ damage via mechanisms independent of tumor growth. For example, there has been increasing attention on the ability of small but 'dangerous' B-cell clones to cause paraprotein-mediated tissue damage, a phenomenon termed monoclonal gammopathy of clinical significance (MGCS). Furthermore, several large epidemiological studies have reported excess morbidity and mortality associated with a diagnosis of MG, with uncertain biological mechanisms.[6] Thus, accumulating evidence suggests that MG is of increasing significance.

Here, we outline current understanding, describing both the malignant and non-malignant mechanisms by which MG can cause tissue damage. Specifically, we question whether active systematic identification of MG cases

through population or targeted screening should be considered in the context of growing evidence of the clinical importance of this condition.

Monoclonal gammopathy: is it harmful enough to warrant screening?

The mechanisms by which different types of MG (Table 1) cause organ dysfunction and morbidity are incompletely understood. Although MG can lead to malignant transformation and paraprotein-mediated tissue damage, it has also been repeatedly associated with increased occurrence of other diagnoses (MGCS). The biological explanation for MGCS is even less well understood; it is possible that the mechanisms leading to cancerous and non-cancerous consequences overlap.

Malignant transformation

The prevalence of MG is 3.2% in those over 50 years and increases with age.[7,8] Non-IgM MG typically progresses to MM at a rate of 1% per year;[9] light-chain MG progresses to MM less frequently at a rate of around 0.3% per year,[10] while IgM MG progresses to B-cell malignancies such as Waldenström macroglobulinemia (WM) at a rate of 1.5% per year.[11] Rare cases of IgE and IgD MGUS/MM have also been described.[12,13]

Progression from MG to plasma-cell or B-cell malignancies is the principal cause of MG-related morbidity and mortality, and the risk of malignant progression is not uniform.[9] At present, there are two major risk predictors for progression to MM: (i) genomic and (ii) secreted protein profiles. Genomic myeloma-defining events, including MYC activation, driver gene mutations and mutant apolipoprotein B mRNA-editing enzyme, catalytic polypeptide (APOBEC) activity, help to distinguish indolent MG from MG with malignant potential.[14] In addition, secreted protein profiles are established risk factors for malignant transformation and include abnormal serum free light chain (SFLC) ratio, paraproteinemia >15 g/L, and non-IgG subtype.[15,16] Patients with no risk factors and those with all three risk factors (high-risk) have a 5% and 58% absolute risk, respectively, of MM progression at 20 years.[15] Further studies have identified baseline SFLC >100 mg/L,[16] immunoparesis[17] and pathologi-

Table 1. Definitions of conditions relating to monoclonal gammopathy.

Monoclonal gammopathy (MG) disorder	Definition	References
Non-IgM monoclonal gammopathy of undetermined significance (MGUS)	1. Serum monoclonal immunoglobulin ≤3 g/dL 2. Plasma cells in the bone marrow ≤10% 3. Absence of: lytic bone lesions, anemia, hypercalcemia, and renal impairment	5
IgM MGUS	1. Serum monoclonal immunoglobulin ≤3 g/dL 2. Lymphoplasmacytic cells in the bone marrow ≤10% 3. Absence of: constitutional symptoms or symptoms and signs of hyper-viscosity, anemia or lymphadenopathy	5
Light chain MGUS	1. Abnormal free light chain ratio (<0.26 or >1.65) with increased level of the appropriate involved light 2. Increased concentration of involved light chain 3. Complete loss of heavy chain immunoglobulin expression	5, 23
Monoclonal gammopathy of clinical significance (MGCS)	Organ dysfunction or damage caused by a MG-related clonal disorder via different mechanisms	23
Monoclonal gammopathy of renal significance (MGRS)	1. Hematologic clonal disorder producing a monoclonal paraprotein that causes renal injury 2. Absence of: light chain cast nephropathy, or monoclonal plasma-cell infiltration in kidney biopsy	27, 28
Monoclonal gammopathy of neurological significance (MGNS)	Peripheral neuropathy associated with a monoclonal paraprotein, without other obvious cause	23, 28
Monoclonal gammopathy of cutaneous significance	Varied group of MG-associated cutaneous presentations, some of which demonstrate a strong pathological link	37
Smoldering multiple myeloma (SMM)	1. Serum paraprotein (IgG or IgA) ≥30 g/L or urinary M-protein >500 mg/24 h and/or clonal bone marrow plasma cells 10-59% 2. Absence of myeloma-defining events* or amyloidosis	5

*Myeloma-defining events (SLiM-CRAB criteria): S: ≥60% plasma cells in bone marrow; Li: involved:uninvolved light chain ratio ≥100 (provided the involved light chain is >100 mg/L); M: two or more focal lesions on magnetic resonance imaging (>5 mm in size); C: hypercalcemia (>2.75 mmol/L or >0.25 mmol/L higher than upper limit of normal); R: renal insufficiency (serum creatinine >177 μmol/L or creatinine clearance <40 mL/min); A: anemia: hemoglobin <100 g/L or 20 g/L below lower limit of normal; B: one or more lytic bone lesion on X-ray, computed tomography or positron emission tomography/computed tomography (>5 mm in size).

cal SFLC N-glycosylation[18] to be additional risk factors for progression. Risk stratification using select parameters has since led to a distinct management pathway for high-risk MGUS involving additional investigations and more frequent follow-up in secondary care.[19]

Several risk stratification models of progression from IgM MG and smoldering WM to WM have also been proposed[20,21] and include measures of disease burden, such as bone marrow infiltration and IgM level, as well as immunoparesis, albumin and β_2-microglobulin levels. Wildtype MYD88 status has also been shown to be an independent risk factor for progression[21] and mortality[22] despite correlating with lower tumor burden at diagnosis.

Paraprotein-mediated tissue damage

MGCS has become a well-recognized entity that includes a wide range of non-cancerous MG-associated clinical presentations.[23,24] The mechanisms reported thus far include deposition of monoclonal immunoglobulin or amyloid fibrils (for example, in type I cryoglobulinemia and light chain amyloidosis; AL amyloidosis), autoantibody activity of the immunoglobulin (for example, anti-MAG antibodies in IgM-related neuropathy) and aberrant complement-activation (for example, in C3-glomerulonephritis and atypical hemolytic uremic syndrome).[23] The most recognized forms of MGCS are AL amyloidosis, monoclonal gammopathy of renal significance (MGRS), monoclonal gammopathy of neurological significance (MGNS) and monoclonal gammopathy of cutaneous significance.

The incidence of AL amyloidosis is around 12 cases per million person-years and the prevalence is around 30,000 to 45,000 cases in Europe and the USA.[25] As with many forms of MGCS, AL amyloidosis remains underdiagnosed and earlier detection is key to improving survival.[26] Presenting symptoms are often non-specific; therefore, a high index of clinical suspicion alongside screening tests for organ damage, such as albuminuria and cardiac biomarkers, can be key to an early diagnosis. Despite advances in treatments, the reported mortality rate is 25% within 6 months of diagnosis.[25]

MGRS represents a spectrum of MG-induced renal conditions diagnosed via renal biopsy and is defined as a hematologic clonal disorder producing a nephrotoxic monoclonal protein.[27,28] In an Austrian cohort of nearly 3,000 MGUS patients, the rate of MGRS (around 80% biopsy-proven) was 1.5%,[29,30] and the estimated prevalence of MGRS is 0.5% among people aged 70 or older in the general population.[31] However, accurate case detection is impacted by the rising prevalence of chronic kidney disease with age[32] and difficulty in obtaining histological diagnoses in an older cohort with multiple co-morbidities.

MGNS is defined as neuropathy caused by a monoclonal protein, and often requires input from a neurology specialist for diagnosis.[28] Peripheral neuropathy is a frequent finding in MG patients, with the prevalence being up to 30-50% in IgM MG patients, 5% in IgG MG, and 15% in IgA MG.[33] Furthermore, large population studies have demonstrated that MG patients have a 2.7-fold higher risk of peripheral neuropathy compared to matched controls[34] and a 5.9-fold higher risk of chronic inflammatory demyelinating polyradiculoneuropathy.[35] Despite diagnostic challenges, up to 50% of cases of demyelinating neuropathies are likely linked to a causal IgM MG,[36] with anti-myelin-associated glycoprotein (MAG) neuropathy accounting for a large proportion of cases.

Cutaneous manifestations of MG are classified into several subgroups. Group I conditions are pathologically caused by malignant or clonal plasma cells (for example, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin disease; POEMS), group II conditions are strongly associated with a MG, group III conditions are anecdotally linked to MG and group IV conditions are related to immunoglobulins or M-proteins that may or may not be clonal.[37] Treatments are generally specific to the dermatological condition, aside from group I/II conditions for which clonally directed treatment may be employed.

The true incidence and prevalence of MGCS are unknown due to suboptimal monitoring, lack of established diagnostic criteria and the reliance on multiple specialties to identify MGCS through a high index of suspicion. The main challenge in MGCS is distinguishing symptoms caused directly by the MG clone and its resultant monoclonal protein, and those that are merely coincidental; for example, only half of patients with clinically suspected MGRS have the condition on biopsy.[38] Evidence suggests that treatment of the underlying plasma-cell or B-cell clonal disorder can ameliorate symptoms and prevent irreversible organ damage in MGCS.[28] Further studies, both large-scale epidemiological and biological, are required to fully understand the etiology of MG-related disorders. In order to achieve this, thought needs to be given to how cohorts of MG patients can be established, and we hypothesize that improving detection and monitoring of MG will enhance recognition of MGCS cases to this end.

Other monoclonal gammopathy-related morbidity

Higher mortality rates in MG unrelated to malignant progression have been observed. A UK cohort study of 2,193 newly diagnosed MG patients demonstrated excess morbidity and mortality associated with the diagnosis.[39] MG patients had a 5-year overall survival of 71.9% compared to 80.1% in age-matched controls and were significantly more likely to have a higher comorbidity index score.[39] MG patients also had significantly higher rates of hospital attendance, particularly for renal and rheumatological issues, both prior to and after diagnosis.[39] Several large population-based studies show similar findings of increased morbidity and mortality associated with MGUS;[6,40,41] for example, in a

Swedish population study, MG patients had a survival ratio of 0.70 compared to matched population controls.[6] In keeping with these findings, results from the PROMISE study and Mass General Brigham Biobank, investigating patients at high risk of developing MG, demonstrated an increased all-cause mortality associated with patients who had screen-detected MG.[42]

The reason for increased morbidity and mortality in non-malignant MG patients is unclear but may be related to the increased rate of other medical conditions. The link between MG and bone fractures as well as osteoporosis is well established,[43-45] and a recent study demonstrated a detection rate of MGUS of one in 13 patients with osteoporotic fractures in the fracture clinic screened for MM.[46] Further studies have also confirmed a higher risk of thrombophlebitis[44] and a two-fold increased risk of developing viral and bacterial infections.[47] MG patients in the Swedish cohort had a significantly increased risk of co-existing medical conditions such as ischemic heart disease, and renal disorders.[6] Furthermore, a recent Korean study demonstrated a concurrent diagnosis of hypertension, hyperlipidemia, diabetes, and osteoarthritis in 80% of patients with MG followed up for 10 years.[48]

The challenge with these MG disease-associations is demonstrating causality, given that most patients being tested for MG are older and more likely to have pre-existing medical diagnoses, leading to inherent bias in these studies. However, as epidemiological evidence continues to accumulate, it becomes increasingly important to initiate thorough investigation into the possible biological causes of MGCS-associated morbidity and define an ICD-10 code to capture data more reliably. Clonal hematopoiesis of indeterminate potential (CHIP), an analogous but more genetically defined precursor state, has in recent years been associated with increased atherosclerosis,[49] with loss of TET2 function in hematopoiesis proven to accelerate atherogenesis in murine models. This demonstrates the potential of clonal hematopoietic disorders to cause organ pathology and supports the need to further investigate the relationship between MG and other disease states. An etiological role of chronic inflammation and immune stimulation in MG is plausible[50] and needs to be explored.

Monoclonal gammopathy: the importance of early detection and intervention

That MM is preceded by MG creates the opportunity for early intervention and possible prevention. The argument for early detection of MG includes improving quality of life for MM patients through reduced end-organ complications and potentially improving survival of MM patients. In addition, early identification of MG could, in theory, lead to earlier intervention and better outcomes for non-malignant MG-related morbidities and MGCS.

Less than 10% of MM patients are diagnosed at the MG stage[51] and it is estimated that by the time patients are formally diagnosed with MG, the clonal disorder has been present for at least 10 years.[52] Currently, a diagnosis of MM requires significant burden of disease meaning that, *de facto*, most MM diagnoses occur in a late stage of disease. Real-world data from Europe have demonstrated that around 85% of patients present with International Staging System stage II/III disease and over 50% present with at least two bone lesions.[51] Further cohort studies have shown that the median time from symptom onset to MM diagnosis is around 4 to 6 months, and while this diagnostic delay was not associated with adverse survival, it likely contributed to the significant burden of MM-related complications seen in a large proportion of patients at diagnosis.[53] Therefore, by the time most patients are diagnosed with MM, the time for early intervention has been missed. Screening would lead to earlier detection of MG, including MGCS, MM and WM; however, current guidelines do not recommend this due to the lack of clinically proven low-toxicity interventions at the precursor stage.[19,43,54,55]

There is some evidence that knowledge of prior MG before MM diagnosis can improve survival, although whether this is solely due to early detection remains unclear.[56] MG patients under regular monitoring have been shown to suffer significantly fewer major complications (such as dialysis use, cord compression and fracture) at MM diagnosis, and significantly improved disease-specific and overall survival when compared to patients with MG who were not actively managed.[57] However, these studies may suffer from lead-time bias. Importantly, the first screening study for MG, iStopMM,[58] has shown higher detection rates of B- and plasma-cell malignancies through screening; however, whether this enhanced detection will lead to clinical benefit is unknown. Further refinement of risk prediction in MG, using novel genomic[59] and biochemical[18] biomarkers, may help to define a groups of high-risk MG patients who would benefit from high-intensity follow-up and early intervention, as well as a low-risk MG group who may need less frequent or no monitoring.

Studies investigating low-toxicity treatments at the precursor stage are ongoing. Treatment of SMM with lenalidomide-dexamethasone and single-agent lenalidomide has been shown to improve progression-free survival in two randomized controlled trials[60,61] and to delay organ damage.[62] However international consensus on the treatment of SMM has not been reached. While the National Comprehensive Cancer Network recommends lenalidomide treatment for SMM, the European Myeloma Network does not advocate treatment of SMM outside of a clinical trial setting.[63] A phase II study (CENTAURUS) demonstrated

the safety and activity of an anti-CD38 monoclonal antibody, daratumumab, as a single agent in intermediate- and high-risk SMM patients.[64] A small phase II study of carfilzomib, lenalidomide, and dexamethasone including high-risk SMM patients demonstrated minimal residual disease-negative responses in 11 of 12 patients,[65] which is significant given minimal residual disease negativity correlates with improved survival.[66] There is an ongoing debate surrounding the goal of treating SMM – to delay progression *versus* cure – and studies are currently addressing this. Studies investigating treatment at the MG stage are also underway. For example, phase II studies investigating treatment of high-risk MG patients with both daratumumab (NCT03236428) and isatuximab (NCT02960555) are ongoing and a phase I trial is evaluating the role of rifaximin in patients with MG (NCT03820817).[67] Potential opportunities exist for early intervention studies in MG targeting the microenvironment. This strategy is supported by single-cell RNA sequencing studies that have identified early changes in the bone marrow immune microenvironment in MG.[68,69] A study on patients with bi-clonal gammopathy highlighted that MG clones can be more difficult to eliminate with standard myeloma treatment because of having a very low proliferative fraction.[70] A combination approach with simultaneous targeting of the clone and its resident microenvironment may be required and warrants further investigation.

The value of early detection in asymptomatic WM (including IgM MGUS and smoldering WM) is less clear. There is evidence that the progression rate of smoldering WM to WM decreases after the first 5 years[71] and prior studies have also shown that the overall survival of patients with smoldering WM and the general population is similar.[72] Accordingly, early treatment before the symptomatic stage in WM has not thus far been recommended, and therefore the benefits of early detection of IgM MG to prevent malignant progression may be limited. However, the role of early detection in improving outcomes for IgM MGCS patients requires further study. Enhanced pick-up of IgM MG may lead to earlier diagnosis of IgM-related neuropathy as well as other IgM-related disorders, in which clonally targeted treatments have been effective.[73]

Monoclonal gammopathy: is screening warranted?

Does monoclonal gammopathy meet screening criteria?

The purpose of screening is to identify asymptomatic individuals at higher risk of developing a particular disease so that they may benefit from early intervention that can lead to improved survival or quality of life. The benefits to those who screen positive must also outweigh any potential harm to those who screen negative. International screening principles have been widely used to guide the development of screening programs,[74] such as the breast, cervical and colorectal cancer screening initiatives in the UK,[75–77] which have been shown to reduce mortality. MG fulfils many of the criteria for screening (Table 2). However, two main contentions exist: firstly, whether the collective health risk of MG on a population level is great enough to warrant screening, and secondly, whether an effective intervention for MG exists to reduce mortality and morbidity. These contentions to MG screening require re-appraisal in the context of new emerging evidence. It is also important to consider population *versus* targeted screening, which may have implications for the risk-benefit ratio of testing.

Who, if anyone, should we screen for monoclonal gammopathy?

As early interventions for MG continue to develop, it is also important to consider which population group would benefit the most from screening. A recent review of National Health Service screening programs highlighted targeted screening as a means of improving cost-effectiveness and reducing the risk-to-benefit ratio by focusing on individuals at a higher risk of developing the condition.[78] Several well-established risk factors for MG provide a strong basis for defining a population for targeted screening, including increasing age,[7] male gender,[7] black ethnicity[79] and having a first-degree relative with MG.[80] Other potential risk factors for MG, such as high body mass index[81] and immune-related conditions,[50] may further contribute to delineating a high-prevalence group suitable for screening. The PROMISE study is an example of targeted screening of those within a higher-prevalence group, and includes adults aged over 40 years old, identified as Black/African American or with a family history of myeloma or a precursor state.[42] Interim 3-year data on the first 2,960 participants screened demonstrated a 10% prevalence of MG,[42] a higher rate than previous estimates in the Minnesota cohort,[7] which therefore helps to corroborate this approach.

An alternative strategy would be opportunistic screening, for example combining serum protein electrophoresis with other primary care screening blood tests, such as cholesterol. A recent study demonstrated an increased prevalence of MG (5.3%) in unselected emergency medical admissions,[82] which also highlights medical inpatients as a possible group for opportunistic screening.[83] However, further prospective evidence is required to assess the long-term implications of opportunistic screening as an approach.

Population screening carries the highest resource burden and risk of psychosocial impact on otherwise healthy individuals. A population-based MG screening study ongoing in Iceland, iStopMM, has screened 75,422 individuals over the age of 40 and identified 3,725 individuals with MGUS.[58] Patients were randomized to three arms: no follow-up,

standard follow-up according to current practice, or an intensive diagnostic and follow-up pathway. After 3 years of follow-up, MG patients in the intensive follow-up arm of the study had significantly higher detection rates of lymphoproliferative disorders, specifically smoldering WM, SMM and MM,[84] demonstrating that early detection of these malignancies through screening is possible. Results from longer-term follow-up are required to determine whether this enhanced detection translates into better outcomes for patients.

Table 2. Interrogation of suitability of asymptomatic monoclonal gammopathy for screening using Wilson and Junger's principles of early disease detection.

Wilson & Junger principles of early disease detection[74]	Criteria met?	Explanation	References
The condition sought should be an important health problem	Contentious	MM is an incurable life-limiting hematologic malignancy and accounts for 2% of all cancer deaths in the UK MGUS is not infrequent; the age-standardized prevalence in UK is estimated at 8.7/100,000 and prevalence increases with age However, absolute risk of progression to MM remains low at 0.5-1% per year MG can lead to morbidity through MGCS independently of progression to MM	1,6,8,9,39,45
There should be an accepted treatment for patients with recognized disease	Contentious	Identification and routine monitoring of MGUS may improve outcomes and survival upon progression to MM Risk stratification helps to identify high-risk MGUS patients who have higher rates of progression to MM and in whom early intervention may be more valuable There are no proven low toxicity treatments to eliminate MGUS clones Treatment of early MM at the asymptomatic SMM stage improves survival MGUS patients have excess morbidity and mortality independently of progression to MM; screening may help early identification of MGCS such as MGRS and prevent irreversible end-organ damage	15,56,57,60,62
Facilities for diagnosis and treatment should be available	Yes	Phlebotomy and laboratory services are available and widely accessible	
There should be a recognizable latent or early symptomatic stage	Yes	It is well established that MGUS constantly precedes MM as a precursor state	3
There should be a suitable test or examination	Yes	Diagnosis of MG via peripheral blood serum protein electrophoresis and immunofixation has a high sensitivity and specificity	94
The test should be acceptable to the population	Yes	The blood test diagnosis for MG is non-invasive and convenient	
The natural history of the condition should be adequately understood	Yes	Large longitudinal studies have helped our understanding of the natural history of MGUS Further studies are required to understand MGCS	9
There should be an agreed policy on whom to treat as patients	Yes	IMWG guidelines for MGUS	19
The cost of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole	Unknown	Future prospective studies may help to determine whether screening for MG can be cost-effective The blood test required for diagnosis is inexpensive	
Case-finding should be a continuing process and not a "once and for all" project	Yes	If MG screening is justified and of proven benefit in a particular population, continual screening could need to be organized	

MM: multiple myeloma; MGUS: monoclonal gammopathy of undetermined significance; MG: monoclonal gammopathy; MGCS: monoclonal gammopathy of clinical significance; SMM: smoldering multiple myeloma; MGRS: monoclonal gammopathy of renal significance. IMWG: International Myeloma Working Group.

Limitations to screening for monoclonal gammopathy

Despite significant advances in early intervention and risk identification, the potential adverse effects of screening for MG need to considered carefully. A consensus evidence-based treatment for MG that improves morbidity and mortality by preventing malignant progression or allowing for earlier treatment of MGCS is required. The diagnosis of a pre-malignant condition through positive MG screening in otherwise "well individuals" would inevitably create health anxiety. Both the iSTOPMM and PROMISE studies have incorporated patient questionnaires to measure the psychosocial impact of screening for MG. Thus far, the PROMISE study has shown no significant difference in cancer-related anxiety or health-related quality of life in participants who screened positive for MG,[42] however much longer follow-up is required to determine the true psychological impact of screening in these patients. As with all screening programs, there is the potential of over-diagnosis,[85] which leads to the possibility of over-treatment. Furthermore, MG screening would likely create significant time and cost burdens on primary care clinicians requesting and interpreting the test results, as well as specialist teams monitoring high-risk MG patients. Uncovering unexpected MG cases would increase referrals to myeloma and cancer specialist services, at a great cost to already strained health services. The resource burden to specialist teams could be offset if screening were shown to be successful in preventing cases of advanced malignant disease. Furthermore, a recent study identified that using a modified monoclonal antibody threshold of 10 g/L and an extended range of SFLC ratios (0.15-3.36) excluded 89% of MGUS but importantly still identified 99% of MM patients.[86] Thus, a strategy for screening for MG that does not overload hematology referrals querying MM appears possible.

Monoclonal gammopathy: unanswered questions and future steps

Genomic studies have begun to provide explanations for the heterogeneity of MG and SMM.[87] Recent advances in low-input whole-genome sequencing in MG and MM has led to the delineation of two distinct entities within asymptomatic MG: those with a low burden of myeloma-defining genomic events and indolent phenotype, and those with sufficient myeloma-defining genomic events to cause malignant transformation.[88] Increasing availability and use of these technologies could provide enhanced molecular inspection of the plasma- and B-cell clones in MG patients. The mechanisms that trigger an indolent phenotype MG to become a malignant phenotype and whether there are genetic drivers associated with MGCS are yet to be understood.

Fluorescence *in situ* hybridization panels frequently fail to identify genetic abnormalities in MG patients. Use of targeted gene panels such as the Myeloma Genome Project next-generation sequencing panel, which comprises 228 genes/exons for mutations, six regions for 40 translocations, and 56 regions for copy number abnormalities, could overcome this limitation.[89] This panel can be employed in a routine diagnostic laboratory and detailed genomic characterization could serve as a potential predictor of disease progression. Recent observation of higher rates of pathological N-glycosylation noted in cold hemagglutinin disease as well as AL amyloidosis provides vital routes to develop proteomic research to better understand causality of these post-translational modifications.[90]

It is inescapable that a major stumbling block to introducing MG screening approaches is the lack of early intervention options that could be applied in MG to prevent progression to either MGCS or MM. If such safe and affordable interventions were available, the arguments for screening would be significantly changed. Making this a reality will require novel research focused on the biological features of MG, which are likely to be distinct from MM and which represent a potential Achilles' heel for an MG clone. For example, one biological question yet to be addressed is: what is the repopulating cell responsible for maintaining early-stage MG? In MM, it is widely accepted that plasma cells are the propagating cells.[91] However, the involvement of the B-cell hierarchy in earlier stage plasma cell dyscrasias has been under-investigated and may provide potential interventional strategies in earlier stage disease.

Monoclonal gammopathy terminology

As the genomic and biological understanding of MG progresses it is important that the field also updates the MG terminology to reflect this transition. There is increasing recognition of the need to move from "cancer burden to cancer genomics".[92] With the recent characterization of myeloma-defining genomic events using whole-genome sequencing,[14] three simplified genetically defined (rather than clinically defined) myeloma categories have been proposed: MG, early MM and MM.[88] Using in-depth genomic and biological characterization of monoclonal gammopathies, MGCS-defining events and features of 'benign' MG should be identified (Figure 1).

Conclusion

Recent research has started to unpick the 'undetermined' aspect of MGUS, with accumulating evidence that MG is

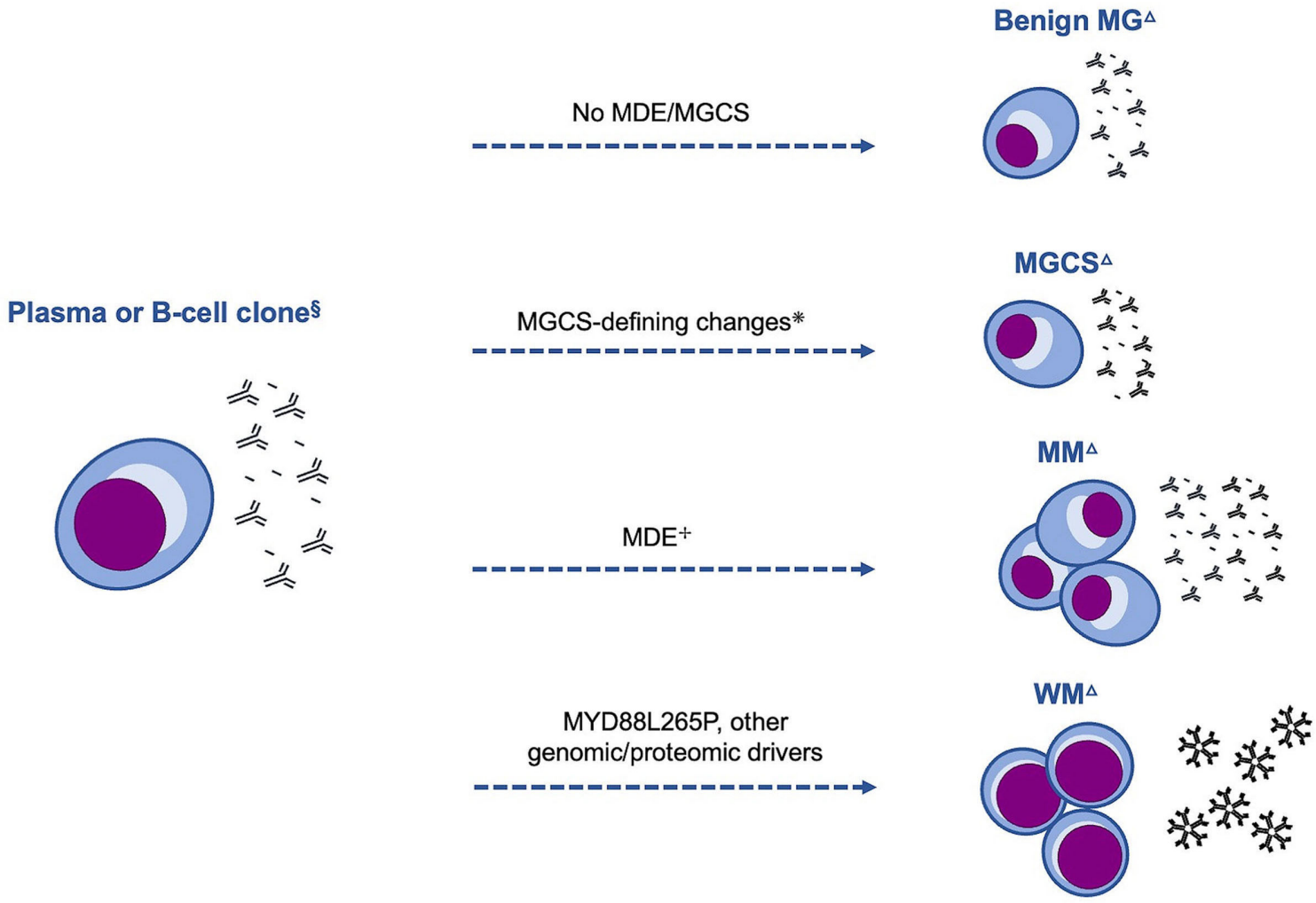

Figure 1. Proposed schema for classification of monoclonal gammopathies. §The cell intrinsic/extrinsic factors that lead to the persistence and/or progression of plasma/B-cell clones are still unknown. *The events, e.g. genomic/proteomic changes, defining monoclonal gammopathy of clinical significance have not yet been defined and require further research. +Myeloma-defining events have recently been described.[88] △The interplay and relationship between benign monoclonal gammopathy, monoclonal gammopathy of clinical significance and multiple myeloma/Waldenström macroglobulinemia is not fully understood; it is not clear whether the genomic and biological drivers of these conditions are shared or distinct. MG: monoclonal gammopathy; MDE: myeloma-defining event; MGCS: monoclonal gammopathy of clinical significance; MM: multiple myeloma; WM: Waldenström macroglobulinemia.

heterogeneous and more clinically significant than initially thought.[88,93] MG is perfectly poised as a condition in which early detection and intervention could make a significant impact on the morbidity and mortality of patients by preventing irreversible organ damage. Despite recent advances, such as improved risk stratification of MG patients, effective treatment of asymptomatic SMM and enhanced awareness of MGCS, further prospective data are needed before widespread screening of MG can be recommended. Results from a single randomized trial of screening for MG (iStopMM) are eagerly awaited and a large prospective observational MG study in the UK is underway (SECURE study; NCT05539079). We believe that more trials of MG screening and monitoring are warranted, as enhanced risk stratification of both malignant progression and identification of MGCS is likely to provide benefit to patients. Continual re-appraisal of the balance between risk and benefit of a targeted screening program for MG is required as the field of early intervention continues to evolve. Further research into the biology of MG as an independent entity is important to understanding MGCS-defining genomic and molecular events and will help to inform methods of effective early therapeutic intervention.

Disclosures

MD owns shares in Abingdon Health. LYC, CB, KR have no conflicts of interest to disclose.

Contributions

LYC wrote the manuscript. LYC, CB, KR, and MD developed the concept of the article, edited several revisions of the paper and approved the final manuscript.

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Data-sharing statement

For data requests, please contact the corresponding author via email.

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