

Diagnostic and therapeutic challenges in rare hematologic entities: monoclonal gammopathy of thrombotic and bleeding significance

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Abstract

Monoclonal gammopathies encompass a spectrum of clonal B-cell or plasma cell disorders characterized by the production of a monoclonal immunoglobulin. While most cases remain asymptomatic, certain clones can elicit organ or tissue injury through distinct pathogenic mechanisms, leading to the concept of monoclonal gammopathy of clinical significance (MGCS). Among the least recognized but clinically important MGCS entities are monoclonal gammopathy of thrombotic significance (MGTS) and monoclonal gammopathy of bleeding significance (MGBS), in which the M-protein directly interferes with hemostatic pathways, resulting in thrombosis or bleeding. These conditions remain underdiagnosed due to their heterogeneous clinical presentations and challenges in establishing causal relationships between the paraprotein and hemostatic abnormalities. MGTS and MGBS encompass diverse mechanisms, including cryoprotein formation, complement activation, coagulation factor inhibition, and von Willebrand factor or platelet dysfunction. Currently, there are no standardized diagnostic criteria or evidence-based treatment recommendations, and the role of anti-clonal therapy remains undefined. This perspective outlines an ongoing multinational initiative under the auspices of the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee (ISTH SSC) Subcommittee on Cancer-Associated Thrombosis and Hemostasis, aiming to define diagnostic pathways, propose classification and treatment criteria, and identify patients who may benefit from targeted therapies. A unified framework will improve recognition, diagnosis, and management of these rare yet clinically significant entities.

Introduction

Monoclonal gammopathies (MG) are a heterogeneous group of clonal disorders characterized by the presence of monoclonal immunoglobulin (M-protein) produced by a plasma cell clone (more often) or B-cell clone in the bone marrow. In most patients these clones are small and do not meet the criteria for overt hematologic malignancy requiring treatment and are termed monoclonal gammopathy of undetermined significance (MGUS). However, it has been established that small, otherwise benign clones, and low levels of M-protein may etiologically be linked to a broad range of heterogeneous but clinically significant entities, complications and symptoms grouped under the umbrella term monoclonal gammopathy of clinical significance

(MGCS).¹ One of the unique properties of the M-protein is its ability to interfere with the pathways of hemostasis, leading to either a thrombotic or bleeding phenotype.² Thus, the term monoclonal gammopathy of thrombotic significance (MGTS) was employed³ to describe patients presenting with thrombotic complications caused by clones not meeting the criteria for malignant disease. In analogy with MGTS, we also propose that the term monoclonal gammopathy of bleeding significance (MGBS) would be appropriate to use for patients who exhibit a clinically relevant bleeding phenotype in the context of an otherwise asymptomatic MG.⁴ Both MGTS and MGBS are rare diagnoses and their under-recognition is partly attributable to the difficulty in correlating with strong evidence the clinical symptomatology with the presence of the M-protein. The clinical

phenotypes can range from asymptomatic hemostatic abnormalities to life-threatening bleeding or thrombotic events. Establishing the diagnosis is, therefore, clinically relevant, and a key clinical question emerging is which patients would benefit from treatment against the B-cell/plasma cell clone or other targeted therapies. Moreover, the optimal criteria for evaluating treatment response remain undefined. Overall, there is currently a lack of definitions, diagnostic and treatment criteria and a proposed systematic approach. The aim of this perspective is to raise awareness, discuss the clinical challenges, and highlight the current knowledge gaps. Furthermore, we aim to outline a systematic, multinational effort supported by the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee (ISTH SSC) Subcommittee on Cancer-Associated Thrombosis and Hemostasis (CATH), intended to establish a framework for improving the recognition, diagnosis, and management of these entities, ultimately enhancing patients' outcomes.

Monoclonal gammopathy of thrombotic significance

A number of studies have linked MG to an increased risk of thrombosis, compared to that in the general population,⁵ but establishing causation is challenging. The iStopMM study, a large prospective population-based screening study, demonstrated that the presence of MGUS was associated with a 1.4 times higher risk of venous, but not arterial, thrombosis compared to that in the general population, suggesting MGTS in at least a subset of individuals with MGUS.⁶ Despite the lack of MG-specific studies reporting on age-related effects on thrombotic risk, given the association between MG and age, we expect that age-related effects on chronic low-grade inflammation (inflammaging),⁷ liver function, endothelial function, and coagulation factors such as factor VIII and von Willebrand factor (VWF) will also contribute to the observed increased risk of thrombosis. In addition, biomarker studies have shown a potential prothrombotic phenotype in MGUS patients compared to healthy controls involving platelet activation and hypercoagulability, such as higher D-dimer levels, elevated thrombin generation and increased procoagulant phospholipid activity.^{3,8-11} None of these studies has, however, demonstrated a link between biomarkers and clinical events. Several proposed mechanisms may be involved in the procoagulant phenotype observed, mediated through M-protein or non-M-protein pathways (Table 1).

VITT-like monoclonal gammopathy of thrombotic significance

Vaccine-induced immune thrombocytopenia and thrombosis (VITT)-like MGTS is a term that has been employed to describe patients with anticoagulant-refractory, recurrent

thrombosis and intermittent thrombocytopenia secondary to the presence of anti-PF4 antibodies.¹²⁻¹⁴ At least six cases with detailed investigation have been described to date.^{12,13,15} Reference laboratories were used to confirm the diagnosis (using PF4-dependent immunoassays and washed platelet-activation assays) and the antibody clonotype was confirmed by mass spectrometry. Clonal plasma cell-directed therapy (daratumumab, bortezomib, cyclophosphamide) was initiated leading to remission of the clinical syndrome in most of these patients.^{12,13} Alternatively, other treatment options include inhibition of Fcγ receptor-mediated platelet activation with high-dose intravenous immunoglobulins and inhibition of signal-transduction pathways involving Fcγ receptors with Bruton tyrosine kinase inhibitors.^{12,13}

Antiphospholipid syndrome

Data also suggest that M-proteins could have antiphospholipid (aPL) antibody properties but no cases treated with anti-clonal therapy have been reported yet.¹⁶ No particular immunoglobulin subtype has been linked to aPL activity. Patients with thrombotic antiphospholipid syndrome (APS) and detectable M-protein have higher rates of recurrent thrombosis during treatment with anticoagulant therapy compared with those without a M-protein; one study demonstrated an 89% rate of thrombosis recurrence in patients with APS and MG *versus* 42% in patients with no MG.¹⁶ Further investigation is warranted to determine whether the coexistence of aPL antibodies in patients with MG exerts a synergistic effect, or whether a paraprotein with aPL antibody activity is inherently more thrombogenic than non-MG-related aPL.

Disorders of coagulation inhibitors

Antibodies against coagulation inhibitors have been reported in patients with multiple myeloma but not in MGUS. Acquired activated protein C resistance has been linked to an increased risk of thrombosis in multiple myeloma, whereas MGUS patients show variable sensitivity to activated protein C.³

Cryoproteins

M-protein may also act as a cryoprotein, leading to a prothrombotic clinical phenotype. Type I cryoglobulinemia, and less often type II, can fall within the spectrum of both monoclonal gammopathy of renal significance and MGTS, depending on clinical manifestations.¹⁷ Type I cryoglobulinemia is linked to MGUS in approximately 40% of cases. The cryoglobulin is usually IgM or IgG, and the disease presentation variable.^{18,19} Immune complexes in type II cryoglobulinemia activate complement pathways as demonstrated by the presence of complement components within cryoprecipitates, particularly in cryoglobulinemic glomerulonephritis.²⁰ Treatment recommendations for MGUS-related type I cryoglobulinemia are based on expert opinion and depend on symptom severity; agents targeting the B-cell

or plasma cell clone lead to symptomatic improvement in up to 70% of patients.²¹⁻²³ Although much less common, cryofibrinogen²⁴ and crystalglobulins^{25,26} are cryoproteins associated with vascular injury and thrombosis in large vessels.²⁴ Thrombotic complications are reported in 5-56% of patients with cryofibrinogenemia.^{24,27,28}

Cold agglutinin disease

Cold agglutinin disease is characterized in most patients by the presence of an IgMκ M-protein directed against erythrocyte antigens, with anti-I specificity and an optimal binding temperature of 3°C to 4°C. This induces erythrocyte agglutination and complement-dependent hemolysis via

activation of the classical pathway, which is predominantly extravascular but may involve terminal complement activation with intravascular hemolysis in some patients. An increased risk of thrombosis²⁹ is driven by complement activation and intravascular hemolysis with subsequent platelet and blood cell activation and endothelial injury. The relative risk was 3.1, compared to matched controls, in one of the largest studies.²⁹ Recurrent thrombotic events could be an indication for treatment in patients in whom it would not otherwise be indicated, although cases in the literature are scarce to guide management. Options include B-clone targeting therapies³⁰ or complement inhibition which plays a central role in the pathogenesis of the syndrome.³¹

Table 1. The main entities of monoclonal gammopathy of thrombotic or bleeding significance as well as possible pathophysiological mechanisms, diagnostic tools and management.

Entity	Pathophysiology	Diagnostic tools	Management*
Monoclonal gammopathy of thrombotic significance			
VITT-like ^{12,13}	M-protein with anti-PF4 activity forms immune complexes that cross-link platelet FcγRIIIa receptors, triggering intracellular signaling, procoagulant platelet formation, thrombin generation, and thrombosis with thrombocytopenia	Anti-PF4/UFH ELISA, anti-PF4 CLIA, functional platelet assays (SRA, HIPA, PEA)	Anti-clonal therapy (bortezomib, daratumumab, cyclophosphamide, etc.), IVIG, BTK inhibitors ^{12,13,15}
Antiphospholipid syndrome ^{**16}	M-protein or light chains possessing antiphospholipid activity	Anticardiolipin IgG, IgM and αβ2 GPI IgG, IgM antibodies using ELISA, lupus anticoagulant assay	No data on anti-clonal therapy
Coagulation inhibitor deficiency ^{***3}	Inhibitory action or enhanced clearance of coagulation inhibitors through binding of the M-protein, leading to reduced anticoagulant activity	Measurement of the activity and antigen levels of coagulation inhibitors (antithrombin, protein S, protein C)	No data on anti-clonal therapy
Acquired activated protein C resistance ³	Reduced APC-mediated inhibition of factors Va and VIIIa leads to increased thrombin generation	APC-R assays (clotting-based, chromogenic, thrombin generation-based)	No data on anti-clonal therapy
Cryoglobulinemia ²¹	Precipitation of M-protein (or immune complexes) at low temperatures	Detection of the cryoprecipitate in refrigerated serum, determination of the monoclonality and isotype of the precipitated immunoglobulin	Anti-clonal therapy based on disease severity (alkylating agents, rituximab, corticosteroids, bortezomib, IMiD) ²¹⁻²³
Cryofibrinogenemia ²⁴	Precipitation of immune complexes of M-protein with fibrinogen, fibrin and other plasma proteins at low temperatures	Detection of the cryoprecipitate in refrigerated plasma, not serum	Corticosteroids, alkylating agents ^{24,54}
Crystalglobulinemia ²⁶	Crystallization of M-protein into the tissues and the vasculature exacerbated at low temperatures	Visualization of crystals in tissue biopsies using light or electron microscopy	Anti-clonal therapy (alkylating agents, bortezomib, daratumumab, corticosteroids) ^{26,55}
Cold agglutinin disease ²⁹	M-protein acts as a cold agglutinin and activates the complement cascade, platelets and causes endothelial injury	Cold-agglutinin titration and presence of IgM M-protein by immunofixation	B-clone targeting therapies, ^{30,56} complement inhibition ³¹
POEMS syndrome ^{32,33}	Proinflammatory, pro-angiogenic cascade activation, VEGF increase, thrombocytosis, polycythemia, endothelial dysfunction	Clinical diagnosis: 2 mandatory criteria plus 1 of 3 major criteria and at least 1 minor ³⁴	Anti-clonal therapy; daratumumab, IMiD, cyclophosphamide ^{32,34}

Continued on following page.

Entity	Pathophysiology	Diagnostic tools	Management*
Monoclonal gammopathy of bleeding significance			
Acquired von Willebrand syndrome ³⁵	Accelerated degradation or clearance of circulating VWF due to M-protein binding Circulating autoantibodies against functional or non-functional VWF domains GPIIb-mediated adsorption of HMW VWF on malignant plasma cells	Closure time assessment with PFA, VWF:Ag, platelet-dependent activity of VWF, VWF:CB, FVIII:C, VWF multimer analysis, detection of inhibitory antibodies with mixing studies or ELISA	IVIg, cyclophosphamide, rituximab, ³⁷ anti-plasma cell therapy ³⁵
Acquired platelet function disorders ^{38,39}	Acquired Glanzmann thrombasthenia due to paraproteins that either block fibrinogen binding to αIIbβ3 or induce internalization of the αIIbβ3 integrin Acquired Bernard-Soulier syndrome*** due to binding or disruption of the GPIIb-IX-V complex resulting in defective platelet adhesion Through other undefined mechanisms	Platelet aggregation assay, phenotypic analysis of platelet activation markers and membrane receptors at baseline and after activation by flow cytometry, evaluation of stored and released platelet granule contents	Azathioprine, rituximab, IVIg
Immune thrombocytopenia ⁴¹	M-protein may target platelet antigens, most commonly GPIIb/IIIa and GPIIb-IX-V complexes, leading to platelet destruction	Platelet count, detection of antiplatelet antibodies	No data on anti-clonal therapies for MG-related ITP specifically, manage as per ITP guidelines
Clotting factor deficiencies ⁴²	M-protein-mediated neutralization of coagulation factors by binding to their functional domains and enhancing their proteolytic breakdown	PT, aPTT, determination of coagulation factor levels with one-stage clotting assays, or chromogenic assays, mixing studies	Rituximab and anti-plasma cell regimens ^{42,43}
Heparin-like anticoagulant**** ⁴⁸	Release of endogenous heparin-like substances such as heparan sulphate and chondroitin sulphate through unknown mechanisms	aPTT, mixing studies, thrombin time, reptilase time, anti-FXa assay	No data on specific therapy or anti-clonal therapies
Monoclonal gammopathy of thrombotic and bleeding significance			
Dysfibrinogenemia ⁴⁴	M-protein interference with fibrinopeptide release, fibrin polymerization, or FXIIIa cross-linking via antigen-antibody or nonspecific interactions and/or increased plasma viscosity	Fibrinogen activity by the Clauss method, fibrinogen antigen, PTderived fibrinogen, thrombin time, reptilase time	No data on specific therapy or anti-clonal therapies
Lupus anticoagulant hypoprothrombinemia syndrome***	Formation of prothrombin-antibody complexes targeting inactive epitopes, leading to accelerated prothrombin clearance	PT, aPTT, mixing testing, measurement of factor II with one-stage clotting assays or chromogenic assays, lupus anticoagulant assay, antiphosphatidylserine/prothrombin complex IgG, IgM antibodies using ELISA	No data on specific therapy or anti-clonal therapies

*Clone-directed or other specific treatment indicated solely on the basis of bleeding or thrombotic events; anticoagulation and supportive therapy for bleeding not reported here. **Doyle *et al.* reported two cases with antiphospholipid syndrome who received anti-clonal therapy due to progression to high-grade lymphoplasmacytic lymphoma in addition to recurrent thrombotic episodes, and therefore the indication for treatment is not clear. ***Protein C deficiency, Bernard-Soulier syndrome, heparin-like anticoagulant and lupus anticoagulant hypoprothrombinemia syndrome have been described only in multiple myeloma patients. VITT: vaccine-induced immune thrombotic thrombocytopenia; M-protein: monoclonal protein; PF4: platelet factor 4; UFH: unfractionated heparin; ELISA: enzyme-linked immunosorbent assay; CLIA: chemiluminescent immunoassay; SRA: serotonin release assay; HIPA: heparin-induced platelet activation assay; PEA: PF4-dependent P-selectin expression assay; IVIg: intravenous immunoglobulin; BTK: Bruton tyrosine kinase; APC: activated protein C; APC-R: activated protein C resistance; IMiD: immunomodulatory drugs; POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; VEGF: vascular endothelial growth factor; VWF: von Willebrand factor; GPIIb: glycoprotein IIb (platelet receptor); HMW: high molecular weight; PFA: platelet function analyzer; VWF:Ag: von Willebrand factor antigen; VWF:CB: von Willebrand factor collagen-binding activity; FVIII:C: factor VIII coagulant activity; PT: prothrombin time; aPTT: activated partial thromboplastin time; FXIIIa: activated factor XIII; MG: monoclonal gammopathy; ITP: immune thrombocytopenia.

Prothrombotic states of multifactorial etiology

Pro-inflammatory and pro-angiogenic cascade activation may be implicated in the increased risk of thrombosis in POEMS syndrome, estimated to be as high as 20–30%.^{32,33} Contributing factors may include elevated levels of vascular endothelial growth factor, other cytokines, but also thrombocytosis, polycythemia and endothelial dysfunction.^{32,34}

Monoclonal gammopathy of bleeding significance

Bleeding disorders affecting all steps of hemostasis have been described in patients with MG. Although certain entities have only been reported in patients with multiple

myeloma, and not MGUS, the same underlying pathogenesis is likely shared between the two.

Acquired von Willebrand syndrome

Acquired von Willebrand syndrome (AWS) is the most well-recognized bleeding disorder in MGBS.³⁵ In M-protein-related AWS the bleeding phenotype may vary from mild to life-threatening and is independent of the degree of the deficiency.³⁶ There is no evidence that a specific immunoglobulin isotype determines the bleeding risk in MGBS. Various mechanisms have been reported to contribute to the pathophysiology of AWS, such as accelerated degradation or clearance of circulating VWF following binding to the M-protein and circulating autoantibodies.³⁵ Additionally, aberrant expression of glycoprotein Ib on abnormal plas-

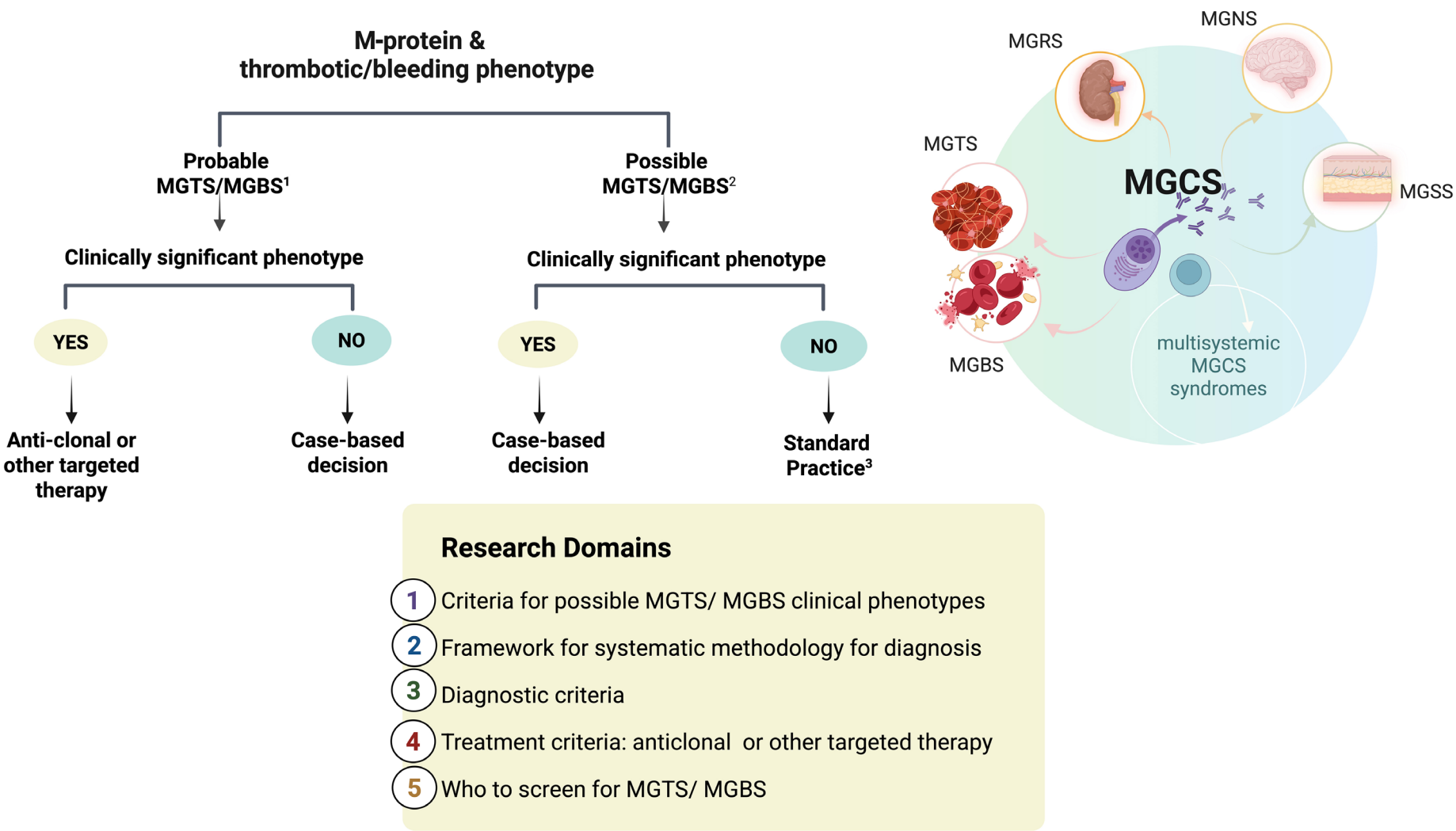


Figure 1. Summary figure. Monoclonal gammopathy of thrombotic significance (MGTS) and monoclonal gammopathy of bleeding significance (MGBS) are visualized in the context of monoclonal gammopathy of clinical significance. In a patient with suspected MGTS or MGBS, the first step is to demonstrate the etiological link between the monoclonal gammopathy and the clinical manifestation. ¹An etiological link includes the presence of clinical evidence plus laboratory evidence (probable). ²Weak or no etiological link is defined as the presence of clinical evidence only (possible), and no laboratory evidence or lack of an effective therapeutic trial. The second step is to assess the severity of the clinical phenotype. For patients with a clinically significant phenotype and a probable etiological link anti-clonal therapy or other targeted therapy is warranted. For patients with a probable etiological link but no clinically significant phenotype a case-based decision should be made. The same approach may be applied to probable cases that are reclassified as definite when a targeted therapy other than anti-clonal treatment (e.g., immunoglobulins in acquired von Willebrand syndrome) leads to reversal of laboratory abnormalities and improvement of the clinical phenotype. For patients with no clinically significant phenotype and a possible or no etiological link present, standard clinical practice is warranted. ³Standard clinical practice includes anticoagulation or supportive management for a bleeding phenotype. If a clinically significant phenotype is present and a possible or no etiological link is demonstrated then a case-based management decision should be made. Current research domains/challenges are outlined. MGCS: monoclonal gammopathy of clinical significance; MGRS: monoclonal gammopathy of renal significance; MGNS: monoclonal gammopathy of neurological significance; MGSS: monoclonal gammopathy of skin significance.

ma cells leads to selective binding and adsorption of high molecular weight multimers on tumor cells.³⁵ Intravenous immune globulin has demonstrated efficacy in IgG-related AWS but is ineffective in IgM cases. Cyclophosphamide and rituximab have been employed³⁷ and clonal eradication with anti-plasma cell regimens has been effective.³⁵

Disorders of platelet number and function

M-protein may also target platelet membrane receptors causing thrombocytopenia or thrombocytopathy. M-protein-mediated anti- α IIb β 3 and anti-GPIb-IX-V antibodies causing acquired Glanzmann thrombasthenia and Bernard-Soulier syndrome, both associated with a bleeding phenotype, have been reported.^{38,39} Other unclassified disorders of platelet function have been documented in patients with MG, but correlation with bleeding symptoms is not consistent.^{11,40} On the contrary, *ex vivo* evidence suggests that platelet hyporesponsiveness⁸ observed in MGUS patients may result from a state of chronic platelet hyperreactivity at rest, ultimately contributing to an increased thrombotic risk. Nonetheless, evidence remains scarce, and M-protein-associated thrombocytopathy may be underestimated in clinical practice. Moreover, observations suggest a potential association between MGUS and immune thrombocytopenia.⁴¹ In a consecutive series of 228 MGUS patients, immune thrombocytopenia was present at diagnosis in six cases.

Coagulation factor inhibitors

Clotting factor inhibition has been described in patients with MG. MGUS-related factor XIII inhibitor leading to deficient ultrastructure of fibrin clots has been linked to severe hemorrhage and, similarly, a thrombin inhibitor was associated with severe recurrent bleeding responding poorly to rituximab and anti-myeloma regimens.⁴² A literature review identified 16 patients with MG-associated factor VIII inhibitor who received different anti-clonal regimens with variable outcomes.⁴³

Dysfibrinogenemia

Interference of the M-protein with fibrin polymerization has been associated with prolonged clotting times and mild coagulation factor deficiencies. These findings are relatively common in patients with MG, do not correlate with the severity of bleeding tendency and, in some patients, they are entirely asymptomatic. However, data on the incidence of abnormal clotting times specifically in MGUS are lacking whereas altered fibrin polymerization linked to specific binding of an immunoglobulin light chain to fibrinogen has been reported.^{44,45} Although there is a theoretical increased risk of bleeding or thrombosis in patients with dysfibrinogenemia, no correlation with a clinical phenotype has been demonstrated.

Lupus anticoagulant hypoprothrombinemia syndrome

Much rarer, acquired factor II (prothrombin) deficiency in

MG may be associated with lupus anticoagulant hypoprothrombinemia syndrome,⁴⁶ a condition that can lead to significant bleeding due to a marked reduction of circulating prothrombin levels. Prothrombin deficiency results from aPL antibodies directed against the phosphatidylserine-prothrombin complex, which are non-neutralizing but form immune complexes with prothrombin, leading to its accelerated clearance from the circulation. Concurrent bleeding and thrombosis have been described in the setting of systemic lupus erythematosus.⁴⁷

Heparin-like anticoagulant

Another rare but recognized cause of bleeding in MG is the presence of circulating heparin-like anticoagulant⁴⁸ which can lead to unprovoked or post-procedure bleeding and may respond to protamine sulfate, plasmapheresis, or clone-directed therapy.

Fibrinolytic disorders

Defects of the fibrinolytic pathway have been far less studied in MG,⁴⁹ and no cases of bleeding associated with fibrinolytic disorders in MGUS patients have been reported.

Spectrum and severity of bleeding manifestations

Overall, MGBS aims to encompass patients with a true clinical bleeding disorder. However, in some patients with MG, laboratory abnormalities do not translate into clinical symptoms; for example, mildly prolonged clotting times that are not associated with a defined bleeding entity rarely result in clinically relevant manifestations.⁵⁰ Moreover, even within a given entity, bleeding severity is variable and may not correlate with biological severity, as observed in AWS.⁵¹ Instead, it may relate to the underlying disorder, with ISTHSSC registry data showing more severe bleeding in AWS associated with lymphoproliferative disorders.⁵² Reported cases of MG-related acquired hemophilia,⁴³ Glanzmann thrombasthenia,³⁸ or Bernard-Soulier syndrome³⁹ have usually been associated with severe, life-threatening bleeding manifestations.

Identifying the challenges

A wide range of hemostatic abnormalities associated with bleeding or thrombosis of differing severity has thus been documented in association with MG, and numerous others are still likely to be identified. However, there are currently significant knowledge gaps that need to be addressed regarding both diagnostic pathways and optimal management of patients with possible MGTS/MGBS.

First, these conditions are rare and likely underrecognized, partly due to limited awareness and restricted access to the

specialized coagulation assays and laboratory techniques required for their diagnosis. Nevertheless, it is essential to identify the clinical phenotypes that truly warrant further investigation. Thrombosis or bleeding occurring in a patient with a known or newly diagnosed MG should not be automatically assumed to be causally related to the M-protein. Given the high incidence of MG in the general population, avoiding overdiagnosis and subjecting patients to unnecessary investigations is also crucial. A personal history suggestive of an acquired disorder, together with the clinical features of the event, such as severity, response to standard treatment, and presence or absence of predisposing factors, are important elements to consider. In MGBS, defining the specific hemostatic defect is crucial for the patient's management. First-step evaluation with routine clotting assays, fibrinogen levels, and VWF assessment, followed by platelet function testing and factor XIII activity measurement, should allow characterization of the abnormality in most patients.

The most challenging task is to demonstrate direct evidence that the M-protein is causally responsible, as assays used in clinical practice cannot reliably establish its pathogenic role. For example, in patients with AWS associated with MG, the clinical context and the pattern of VWF deficiency may strongly support a diagnosis of MGBS, yet enzyme-linked immunosorbance-based assays or mixing studies are usually negative.⁵³ Similarly, in VITT-like MGTS, positive anti-PF4 antibodies are typically sufficient to link thrombosis to an M-protein with anti-PF4 activity, based on the entity's established pathophysiology. In such cases, diagnosis relies on the available evidence even without direct proof of causality. However, for certain entities, the underlying pathophysiology remains insufficiently characterized, limiting diagnostic certainty and underscoring the need for further mechanistic studies. Standardization of these specialized assays across reference centers is urgently needed to minimize inter-laboratory variability. Developing clearly set diagnostic pathways, criteria and novel assays for recognized entities would help guide clinicians in the process. Furthermore, employing sophisticated techniques may help to identify surrogate markers for thrombotic and bleeding risk, as well as previously unrecognized disorders.

The other significant knowledge gap pertains to the scarcity of evidence-based data necessary to inform treatment decisions, including which MGTS or MGBS patients require targeted therapy beyond standard anticoagulation or hemostatic therapy. MGTS/MGBS should be clearly differentiated from the thrombotic or bleeding complications observed in patients with overt multiple myeloma, in whom there is an unquestionable indication for anti-clonal therapy. In contrast, for MGTS or MGBS, the need for anti-clonal treatment remains limited at present and should be carefully individualized. For example, although VITT-like MGTS represents a landmark discovery of a distinct pathogenic

entity that accounts for catastrophic thrombotic syndromes and requires targeted management beyond standard anticoagulation, the therapeutic approach to most other M-protein-associated thrombotic entities remains far less defined. When is it justifiable to administer therapy against the B-cell/plasma cell and when should we target alternative pathways?

Equally important is the need to establish criteria for evaluating treatment efficacy. Should response be defined by reductions in thrombotic or bleeding events or modifications of biomarkers? How should we evaluate treatment outcomes, and what criteria should be used to define response? These issues currently remain areas of significant uncertainty.

Finally, an important emerging question is identifying which patients with clinically relevant thrombotic or bleeding events should be screened for MG. Should all patients with unprovoked venous thromboembolism be considered for testing and if MGUS is diagnosed, should it alter the duration of anticoagulation therapy?

Conceptual framework for a diagnostic and treatment approach

Outlining definitive diagnostic and therapeutic criteria and providing a guiding algorithm is beyond the scope of this Perspective. In the context of the ISTH SSC on CATH project, we do, however, provide an outline of a provisional diagnostic approach and briefly discuss treatment indications based on available knowledge.

In the current state of knowledge, a graded level of evidence may be applied to classify the degree of suspicion for MGTS and MGBS. A provisional framework to guide recognition of an MGTS/MGBS entity can be based on three key elements: (i) clinical evidence, (ii) laboratory evidence, and (iii) response to a therapeutic intervention. A definite diagnosis should fulfil all three criteria. A probable diagnosis may be based on clinical and laboratory evidence, whereas a possible diagnosis relies solely on clinical evidence.

Clinical evidence

The patient having a history suggestive of an acquired disorder is a strong indicator of MGTS/MGBS. New-onset bleeding manifestations, along with the absence of a personal or family history in favor of an inherited bleeding disorder, favor a diagnosis of MGBS. A temporal relationship between recurrent breakthrough thrombosis with a diagnosis of MG in a previously asymptomatic patient can raise suspicion of MGTS.

The absence of an alternative explanation may strengthen suspicion. However, the presence of certain conditions, such as APS, may coexist and do not safely exclude the diagnosis.

Laboratory evidence

Disorders of hemostasis with a known mechanistic link to the M-protein and a characteristic laboratory pattern, such as type 2A von Willebrand disease or the presence of anti-PF4 antibodies, support a diagnosis of MGBS or MGTS even in the absence of direct proof of causality. However, in cases with less convincing evidence, additional pathophysiological studies may be required, although these are difficult to implement in routine clinical practice and are largely confined to research settings.

Response after therapeutic intervention

Normalization or improvement of the clinical syndrome and/or laboratory abnormalities following anti-clonal or other appropriate therapy (e.g., a therapeutic trial of intravenous immunoglobulins in AWS) supports the diagnosis. However, the optimal therapeutic approach and the M-protein levels correlating with symptom severity for each entity remain unknown.

Treatment decisions for monoclonal gammopathy of thrombotic or bleeding significance

An appropriate therapeutic approach will be structured around two key pillars: (i) the likelihood of a MGTS/MGBS diagnosis: possible/probable/definite; and (ii) the severity

of the clinical phenotype. In the setting of a definitive diagnosis, the decision to treat the underlying disorder in the absence of other indications should depend on the severity of clinical events and a careful assessment of the bleeding/thrombotic risk *versus* the toxicity of anti-clonal regimens. However, no clear definition of severity exists, and this threshold may differ between MGTS and MGBS patients. Based on currently available data from small case-series, anti-clonal therapy has demonstrated efficacy and could be administered after careful consideration in VITT-like MGTS, cryoglobulinemia, crystalglobulinemia, cold-agglutinin disease and POEMS syndrome. Variable efficacy has been reported with anti-clonal therapy for severe cases of von Willebrand disease and severe cases of clotting factor inhibitors. The choice of the anti-clonal treatment regimen is also based on scarce data, which further complicates the decision to initiate treatment of the underlying malignancy.

ISTH SSC on CATH project on monoclonal gammopathy of thrombotic and bleeding significance

The aim of the ISTH SSC on CATH project on monoclonal gammopathy of thrombotic and bleeding significance is to organize the existing body of knowledge and expand on it, addressing the key gaps and challenges in the current

Table 2. Identified gaps and planned actions in the diagnosis and management of monoclonal gammopathy of thrombotic and bleeding significance.

Research priority/domain	Current gaps/challenges	Planned ISTH SSC actions	Type of action
Recognition and case identification	Underdiagnosis of cases, diagnostic challenges; poorly defined current state of diagnostic and management practices	International survey to assess recognition, screening and management practices and current challenges	Survey
Diagnostic criteria and etiological link	No standardized criteria; limited access to specialized assays; uncertain link between M-protein and phenotype	Systematic review and expert panel to propose diagnostic/ classification criteria and algorithms; sample centralization for complex cases	Systematic review; expert consensus and position statement; laboratory network
Management and therapeutic decision-making	Lack of guidance on when to initiate anti-clonal therapy or assess response; evidence mainly from case reports	Propose criteria for therapy initiation and treatment response through expert consensus and literature review	Position statement; propose practical guidance
Data and evidence gaps	True prevalence, clinical spectrum, and outcomes unknown; absence of registry data	Establish international registry via ISTH SSC networks to collect standardized diagnostic and clinical data	Registry creation
Future research and collaboration	Pathophysiological mechanisms remain poorly defined; lack of translational studies	Use registry data to guide mechanistic and therapeutic research; foster collaborations and grant proposals	Research collaboration

ISTH SSC: International Society on Thrombosis and Haemostasis Scientific and Standardization Committee.

state of knowledge in this field. Table 2 summarizes the identified gaps and planned actions. Among these, the MGTS/MGBS working group has identified the following key research priorities. Experts in the fields of hemostasis and plasma cell disorders will be invited to contribute their knowledge and experience to advance understanding in this emerging clinical issue. The project will include a survey and the formation of a panel of experts.

The survey study will seek to examine current clinical practices regarding diagnostic pathways, the availability of laboratory investigations, and subsequent management of patients who present with MG and have significant bleeding or thrombotic complications. Another aim of the survey will be to try to appreciate the frequency with which a causal relationship between M-protein and hemostatic complications is established and to estimate the proportion of patients without a definitive diagnosis.

A panel of experts will be formed which will employ a mixed-method approach to reach a multidisciplinary position statement using data from a systematic literature review and the survey to formulate practical guidance for clinicians. The panel will define and propose provisional

criteria for the diagnosis of MGTS and MGBS and for initiation of anti-clonal or other treatment. Finally, clearly set criteria for screening patients with bleeding or thrombotic episodes for MG will be proposed.

It is hoped that this effort will encourage further investigation into this evolving area of significant clinical relevance. Delving into the mechanisms through which the M-protein interferes with hemostasis may pave the way for the development of targeted therapies offering an adapted therapeutic approach for these patients.

Disclosures

No conflicts of interest to disclose.

Contributions

DF and VG conceived the article, defined its scope, and coordinated the work. DF, VG, and EK drafted the initial manuscript. EK, DA, AD, and ET contributed clinical and scientific expertise. All authors contributed to the interpretation of available evidence, critically revised the manuscript, and approved the final version.

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