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

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Abstract:

Monoclonal gammopathies (MG) encompass a spectrum of clonal B- 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), where the M-protein directly interferes with hemostatic pathways, resulting in thrombosis or bleeding. These conditions remain underdiagnosed due to 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 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.

Keywords: Monoclonal Gammopathy, Monoclonal Gammopathy of Clinical Significance, Monoclonal gammopathy of Thrombotic Significance, Monoclonal Gammopathy of Bleeding Significance

Introduction

Monoclonal gammopathies (MG), are a heterogeneous group of clonal disorders characterized by the presence of monoclonal immunoglobulin (M-protein) produced by plasma cell (more often) or a B-cell or clone in the bone marrow. In most patients these clones are small and do not meet the criteria for overt hematological malignancy requiring treatment and are termed MGUS (monoclonal gammopathy of

undetermined significance). However, it has been established that small, otherwise benign clones, and low-level M-proteins may aetiologically 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 employed(3) 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, therefore, the diagnosis is 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 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 patient outcomes.

Monoclonal Gammopathy of Thrombotic Significance

A number of studies have linked MG to an increased thrombotic risk, compared to 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 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 FVIII 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, 9),(10),(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 MGTS

Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT)-like MGTS 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 IVIG, 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 a 89% rate of thrombosis recurrence in patients with APS and MG vs 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 the coagulation inhibitors

Antibodies against coagulation inhibitors have been reported in patients with multiple myeloma (MM) but not in MGUS. Acquired activated protein C resistance has been linked to an increased risk of thrombosis in MM, whereas MGUS patients show variable APC sensitivity(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 in MGUS-related type I cryoglobulinemia are expert opinion-based and depend on symptom severity; with agents targeting the B-cell or plasma cell clone leading to symptomatic improvement in up to 70% of patients(21-23). Though much less common, cryofibrinogen(24) and crystaloglobulins(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 patient. Increased risk of thrombosis is (29) driven by complement activation and intravascular hemolysis with subsequent platelet, blood cell activation and endothelial injury. The relative risk was 3.1 in one of the largest studies compared to matched controls(29). Recurrent thrombotic events could be an indication for treatment in patients not otherwise indicated, although cases in the literature are scarce to guide management. Options include B-clone targeting therapies(30) or complement inhibition which plays a central role in the pathogenesis of the syndrome(31).

Prothrombotic states of multifactorial etiology

Proinflammatory 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 contribute to the pathophysiology of AWS, such as accelerated degradation or clearance of circulating VWF following binding to the M-protein and circulating autoantibodies have been reported(35). Additionally, aberrant expression of glycoprotein Ib on abnormal plasma 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 employed(37) 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-αIIbβ3 and anti-GPIb–IX–V antibodies causing acquired Glanzmann and Bernard–Soulier syndromes, 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 hyporesponsiveness(8) 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, ITP was present at diagnosis in 6 cases.

Coagulation factor inhibitors

Clotting factor inhibition has been described in patients with MG. MGUS-related FXIII 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 FVIII 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 in patients with dysfibrinogenemia there is a theoretical increased risk of bleeding or thrombosis, no correlation with a clinical phenotype has been demonstrated.

Lupus Anticoagulant Hypoprothrombinemia Syndrome (LAHPS)

Much rarer, acquired factor II (prothrombin) deficiency in monoclonal gammopathy may be associated with lupus anticoagulant hypoprothrombinemia syndrome (LAHS)(46), a condition that can lead to significant bleeding due to marked reduction of circulating prothrombin levels. Prothrombin deficiency results from antiphospholipid 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 anticoagulant(48) 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 ISTH-SSC 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 syndrome(39) have been usually 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 likely yet 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 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 monoclonal gammopathy should not be automatically assumed to be causally related to the M-protein. Given the high incidence of monoclonal gammopathies 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 patient management. First-step evaluation with routine clotting assays, fibrinogen levels, and VWF assessment, followed by platelet function testing and FXIII 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 monoclonal gammopathy, the clinical context and the pattern of VWF deficiency may strongly support MGBS diagnosis, yet ELISA-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 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, where 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 reduction 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 VTE 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: (A) clinical evidence, (B) laboratory evidence, and (C) 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.

A. Clinical evidence:

Patients' 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 MGBS. A temporal relationship between recurrent breakthrough thrombosis with MG diagnosis 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 antiphospholipid syndrome, may coexist and do not safely exclude the diagnosis.

B. 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 (VWD) 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.

C. 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 IVIG in AVWS) supports the diagnosis. However, the optimal therapeutic approach and the M-protein levels correlating with symptom severity for each entity remain unknown.

Treatment Decision of MGTS /MGBS

An appropriate therapeutic approach will be structured around two key pillars a) the likelihood of a MGTS/MGBS diagnosis: possible/probably/definite b) 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 VWD 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 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 seek to: a) 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 through a Survey Study. In addition, the survey will aim 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 b) Form a panel of experts who 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 anti-clonal or other treatment initiation. Finally, clearly set criteria for screening patients with bleeding or thrombotic episodes for monoclonal gammopathy 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 in these patients.

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	Pathophysiology	Diagnostic tools	Management**
MGTS			
VITT-like(12, 13)	M-protein with anti-PF4 activity forms immune complexes that cross-link platelet FcγRIIa receptors, triggering intracellular signaling , procoagulant platelet formation, thrombin generation, and thrombosis with thrombocytopenia	anti PF4/UFH Enzyme-linked immunosorbent assays (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 aβ2 GPI IgG, IgM antibodies using Enzyme- linked immunosorbent assays (ELISA), Lupus Anticoagulant assay	No data on anti-clonal therapy
Coagulation inhibitors 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 the isotype of precipitated immunoglobulin	Anti clonal therapy based on disease severity (alkylating agents, Rituximab, corticosteroids, bortezomib, IMiDs) (21-23)
Cryofibrinogenemia(24)	Precipitation of immune complexes of M-protein with fibrinogen, fibrin and other plasma proteins et 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, corticostreroids) (26, 55)

Cold agglutinin disease(29)	M-protein acts as a cold agglutinin and activates 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, IMiDs, cyclophosphamide (32),(34)
MGBS			
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 GPIb-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 (BSS)** due to binding or disruption of the GPIb-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 GPIb–IX–V complexes, leading to platelet destruction	Platelet count, detection of anti-platelet 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	PT, aPTT, determination of coagulation factors levels with one-stage clotting	Rituximab and anti-plasma cell regimens(42),(43).

	enhancing their proteolytic breakdown.	assays, or chromogenic assays, mixing studies	
Heparin-like anticoagulant** (48)	Release of endogenous heparin-like substances like heparan sulphate and chondroitin sulphate through unknown mechanisms	aPTT, mixing studies, Thrombin time, Reptilase time, anti-Xa assay	No data for MG patients
MGTS/MGBS			
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 , PT-derived fibrinogen , Thrombin time, Reptilase time	No data on specific therapy or anti-clonal therapies
Lupus Anticoagulant Hypoprothrombinemia Syndrome (LAHPS)**	Formation of prothrombin–antibody complexes targeting inactive epitopes, leading to accelerated prothrombin clearance.	PT, aPTT, mixing testing, measurement of FII with one-stage clotting assays or chromogenic assays, Lupus Anticoagulant assay, anti-PS/PT IgG, IgM antibodies using Enzyme- linked immunosorbent assays (ELISA)	No data on specific therapy or anti-clonal therapies

Table 1 Main MGTS/MGBS entities including possible pathophysiological mechanisms, diagnostic tools and . MGTS, monoclonal gammopathy of thrombotic significance; MGBS, monoclonal gammopathy of bleeding significance; 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 (PEA); APC, activated protein C; APC-R , activated protein C resistance; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; VEGF: vascular endothelial growth factor; GPI, glycoprotein I; IVIG, intravenous immunoglobulin; VWF, von Willebrand factor; GPIb, glycoprotein Ib (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; BSS, Bernard-Soulier syndrome; PT, prothrombin time; aPTT, activated partial thromboplastin time; FXIIIa, activated factor XIII.

* 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.

** Protein C deficiency; Bernard Soulier Syndrome, Heparin-like anticoagulant and Lupus Anticoagulant Hypoprothrombinemia Syndrome (LAHPS) have been described only in Multiple Myeloma patients.

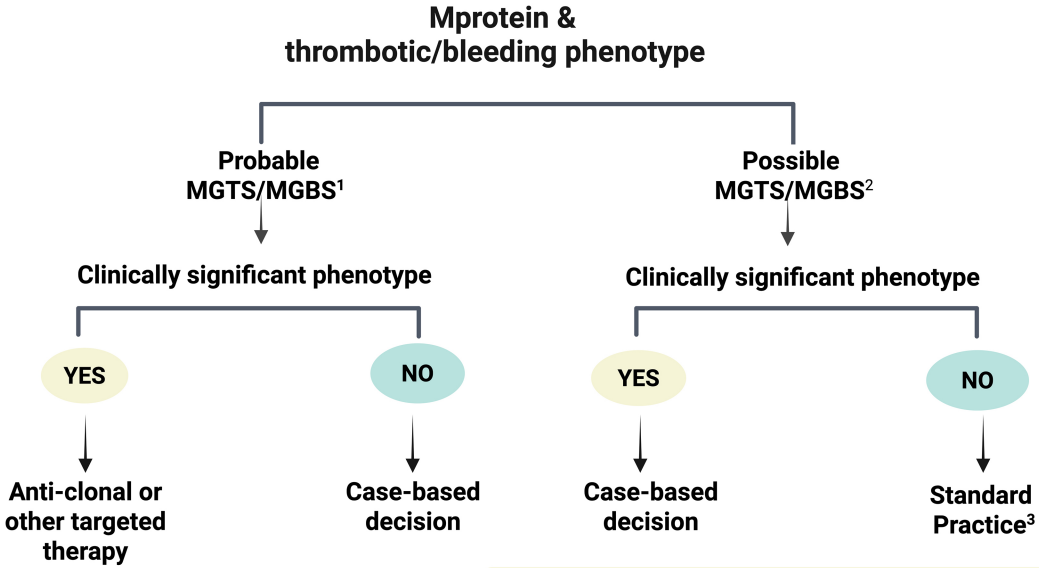
*** Doyle et al. report two cases with antiphospholipid syndrome who received anti-clonal therapy due to progression to high-grade lymphoplasmacytic lymphoma in addition to recurrent thrombotic episodes, and therefore the indication for treatment is not clear.

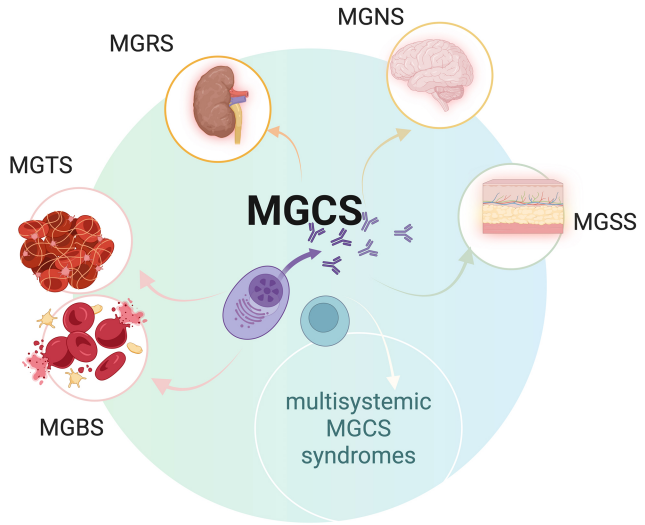
Research priority/ Domain	Current Gaps / Challenges	Planned ISTH SSC Actions	Type of Action
Recognition and Case Identification	Underdiagnosis of cases, diagnostic challenges. Poorly defined current state of diagnostic and management practices.	International survey to assess recognition, screening and management practices and current challenges.	Survey
Diagnostic Criteria and Etiologic 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	Pathophysiologic mechanisms remain poorly defined; lack of translational studies.	Use registry data to guide mechanistic and therapeutic research; foster collaborations and grant proposals.	Research collaboration

Table 2. Identified Gaps and Planned Actions in the Diagnosis and Management of MGTS/MGBS

Figure 1

Summary Figure. Monoclonal Gammopathy of Thrombotic (MGTS) and Bleeding Significance (MGBS) is visualized in the context of Monoclonal Gammopathy of Clinical significance (MGCS). In a patient with suspected MGTS or MGBS, the first step is to demonstrate the aetiological link monoclonal gammopathy and the clinical manifestation. [1] An aetiological link includes the presence of clinical evidence plus laboratory evidence (probable).[2] Weak or no aetiological 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 aetiological link anti-clonal therapy or other targeted therapy is warranted. For patients with a probable aetiological 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., IVIG in AWS) leads to reversal of laboratory abnormalities and improvement of the clinical phenotype. For patients with no clinically significant phenotype and a possible or no aetiological link present, standard clinical practice is warranted. [3] Standard clinical practice includes anticoagulation or supportive management for a bleeding phenotype. If a clinically significant phenotype is present and a possibly or no aetiological link is demonstrated then a case-based management decision should be made. Current research domains/ challenges are outlined. MGRS : Monoclonal Gammopathy of Renal Significance, MGNS : Monoclonal Gammopathy of Neurological Significance, MGSS : Monoclonal Gammopathy of Skin Significance.





Research Domains

1. Criteria for possible MGTS/ MGBS clinical phenotypes
2. Framework for systematic methodology for diagnosis
3. Diagnostic criteria
4. Treatment criteria: anticlonal or other targeted therapy
5. Who to screen for MGTS/ MGBS