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MONOCLONAL GAMMOPATHY OF CLINICAL AND UNDETERMINED SIGNIFICANCE

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a pre-malignant condition that arises when clonal B-lymphocytes or plasma cells secrete a monoclonal immunoglobulin protein (m-protein). To be diagnosed with MGUS, patients must have bone marrow clonal cell involvement of less than 10%, an m-protein concentration of <30 g/L, and no signs or symptoms related to the clonal proliferative process.

MGUS is a common condition and its prevalence increases with age; a large population screening study has shown that the prevalence of MGUS is approximately 3% among individuals above the age of 50, and increases to 5% among those above the age of 70.[1] Currently, the standard of care is not to screen for MGUS; therefore, patients often are incidentally diagnosed during the work-up of other comorbid conditions. Patients with MGUS are, by definition, asymptomatic and do not require treatment. However, recognizing this disorder is clinically relevant as there is a small (~1% per year) risk that MGUS will progress to multiple myeloma, a lymphoproliferative disorder, or systemic light-chain (LC) (AL) amyloidosis.[2] Therefore, expert consensus guidelines recommend that patients diagnosed with MGUS undergo lifelong serial clinical and laboratory monitoring for signs or symptoms of disease progression.[3] It is becoming increasingly recognized that there is a small subset of patients with a small B-cell or plasma-cell clone that would otherwise have met the criteria for MGUS; however, these patients have debilitating symptoms due to organ damage from the circulating m-protein. Therefore, the term "monoclonal gammopathy of clinical significance" (MGCS) was coined to differentiate these patients from asymptomatic patients with MGUS. The objective of this review is to broadly highlight when to investigate further for MGCS when evaluating a patient with a monoclonal protein.

Unlike with multiple myeloma or B-cell lymphoma, where symptoms are most often related to uncontrolled clonal cell proliferation resulting in high tumor burden and m-protein production, quiescent MGCS clonal cells cause symptoms from other mechanisms including cytokine production or the production of toxic m-proteins. Multiple mechanisms of tissue injury have been described: organized m-protein deposition into target tissues (i.e., systemic AL amyloidosis, Type 1 cryoglobulinemia); disorganized m-protein deposits (i.e., monoclonal immunoglobulin deposition disease [MIDD], proliferative glomerulonephritis with monoclonal IgG deposits [PGMNID]); auto reactivity of the m-protein (i.e., C1 inhibitor deficiency resulting in angioedema; IgM-associated peripheral neuropathy resulting in an anti-MAG [myelin-associated glycoprotein] ataxic polyneuropathy); complement pathway activation (i.e., C3 glomerulonephritis); and cytokine-mediated damage (i.e., vascular endothelial growth factor [VEGF] production in POEMS [Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, Skin changes] syndrome).[4] MGCS clinical syndromes can affect multiple organs simultaneously; however, commonly involved organs include the kidneys, nerves and skin. To diagnose MGCS, a thorough review of systems and physical

examination, and a high index of suspicion, are required when evaluating patients with a monoclonal gammopathy to identify red flags (**Table 1**).

Monoclonal Gammopathy of Renal Significance

MGCS affecting the kidneys is termed monoclonal gammopathy of renal significance (MGRS). Given that renal failure is a common manifestation of multiple myeloma, it is important to distinguish between a diagnosis of MGRS and multiple myeloma. The International Myeloma Working Group clearly states that only renal failure caused by cast nephropathy is considered a myeloma-defining renal event.[5] All other causes of renal injury due to plasma cell disorders are classified as MGRS. MGRS is a broad term for several different disorders that arise when an m-protein causes renal damage, and the underlying B-cell or plasma-cell clone does not meet criteria for treatment due to other end-organ damage (including patients with smoldering multiple myeloma or indolent Waldenström macroglobulinemia).[6] MGRS-related disorders include amyloid LC amyloidosis; MIDD; PGMNID; C3 glomerulopathy; thrombotic microangiopathy; monoclonal immunotactoid glomerulonephritis; Type 1 cryoglobulinemia; and LC proximal tubulopathy. A renal biopsy is required to identify the underlying disorder based on the location of m-protein damage within the nephron, the type of m-protein deposit (i.e, organized fibrils, immunoglobulin crystals, cryoglobulins, microtubules), and other characteristics of renal damage.

Cast nephropathy occurs when free LCs (FLCs) aggregate with uromodulin (Tamm-Horsfall glycoprotein) causing intratubular renal casts and resulting in acute kidney injury. Patients with cast nephropathy typically have an involved FLC >1500 mg/L, high serum creatinine, and proteinuria due to renal excretion of LCs (also known as Bence-Jones proteinuria), resulting in abnormally high urine protein to creatine ratio (uPCR) relative to the urine albumin to creatinine ratio (uACR).[7] In contrast, MGRS-related disorders most commonly present with low m-protein levels, proteinuria (typically >1.5 g/day, and predominantly albuminuria given that the majority of MGRS-related disorders cause glomerular injury) even with a preserved glomerular filtration rate (GFR), microscopic hematuria or a rapid loss of kidney function.[8]

Clinical features associated with MGCS			
Dermatologic Findings	**Consider...**	**Neurologic Findings**	**Consider...**
Yellow plaques	Necrobiotic xanthogranuloma	Ascending length-dependent sensory neuropathy (parasthesia), autonomic neuropathy, carpal tunnel syndrome	AL amyloid
Angioedema	Acquired C1 esterase deficiency	length-dependent demyelinating motor >> sensory neuropathy	POEMS
Chronic urticaria	Schnitzler's syndrome	Ataxia	CANOMED
Acrocynanosis, purpura, livedo reticularis	Type 1 cryo.	Polyneuropathy	Cryoglobulinemia
Hyperpigmentation, hypertrichosis, white nails, acrocyanosis, flushing, hemangiomas, plethora	POEMS	Distal ascending symmetric neuropathy, sensory ataxia	DADS-M
Renal Findings	**Consider...**	**Cardiac Findings**	**Consider...**
Proteinuria (mainly albuminuria), CKD, microscopic hematuria, hypertension	MGRS (AL amyloid, MIDD, PGMNID, C3 glomerulopathy, TMA, MIGN, type 1 cryo., LCPT)	HFpEF, concentric LVH, low QRS on ECG, arrythmia	AL amyloid, MIDD

Table 1. *A summary ok key clinical features (if unexplained base on concomitant medical history) that should prompt further evaluation for MGCS in patients with MGUS.*
Abbreviations: ***cryo:*** *cryoglobulinemia ,* ***AL:*** *light chain,* ***CKD:*** *chronic kidney disease,* ***MIDD:*** *monoclonal immunoglobulin deposition disease,* ***TMA:*** *thrombotic microangiopathy,* ***MIGN:*** *monoclonal immunotactoid glomerulonephritis,* ***LCPT:*** *light chain proximal tubulopathy,* ***POEMS:*** *polyneuropathy organomegaly endocrinopathy m-protein sclerotic lesions,* ***DADS-M:*** *distal ascending demyelinating symmetric lgM ,* ***CANOMAD:*** *chronic ataxic neuropathy ophthalmoplegia lgM m-protein cold agglutinins disialosyl antibodies.*

These red flags should prompt an evaluation with a renal biopsy, as MGRS without other systemic features is ultimately a pathologic diagnosis.

Neurological MGCS

Although neurological symptoms are common in the general population, MGCS-related syndromes have classical neurologic presentations. AL amyloidosis can be associated with a progressive length-dependent, small fiber, axonal neuropathy presenting with burning, pain and paresthesias, autonomic dysfunction (postural hypotension, gastrointestinal [G] dysmotility, erectile dysfunction), and carpal-tunnel syndrome from median nerve compression due to soft tissue enlargement.[9] Isolated neurological manifestations with AL amyloidosis are rare, therefore a thorough review of systems (as described below) is needed to identify other potential organ involvement. POEMS syndrome is characterized by progressive, length-dependent, ascending, symmetrical, sensorimotor demyelinating peripheral neuropathy, where motor symptoms are often dominant and debilitating.[10] IgM-related neuropathy classically presents as a distal, acquired, demyelinating, symmetric (DADS-M) neuropathy affecting large sensory fibers and presenting with sensory ataxia. DADS-M neuropathy classically affects older males and is a diagnosis of exclusion among patients with an IgM m-protein. Anti-myelin-associated glycoprotein (MAG) antibodies have been associated with DADS-M neuropathy, however the presence of anti-MAG auto-antibodies is a not a specific finding.[9] CANOMAD is a rare condition characterized by chronic sensory ataxia, ophthalmoplegia, an IgM m-protein, cold agglutinins, and disialosyl antibodies.[11]

Cutaneous MGCS

MGCS-related dermatological disorders have a wide variety of manifestations. Schnitzler syndrome is characterized by chronic urticaria, an IgM monoclonal protein, recurrent fevers, bone remodelling, and neutrophilic infiltrates on skin biopsy.[12] Patients with scleromyxedema have generalized papular and sclerodermoid cutaneous eruptions,[13] whereas patients with necrobiotic xanthogranulomas present with yellow-orange papules and nodules typically involving the eyelids.[14] TEMPI syndrome is a rare disorder characterized by telangiectasias, an elevated erythropoietin level along with erythrocytosis, perinephric fluid collections, and intrapulmonary shunting, in addition to a monoclonal gammopathy.[15] MGCS-related cryoglobulinemia is most commonly Type I, and cutaneous findings occur due to small vessel vascular occlusion and include cold-induced purpura, urticaria, livedo reticularis, and ulceration. Palpable purpura, as a manifestation of small-vessel-vasculitis, is more commonly found in patients with Type 2/3 cryoglobulinemia, which is less common in patients with underlying lymphoproliferative or plasma cell disorders.[16] POEMS syndrome, described in greater detail below, can also present with hyperpigmentation, hypertrichosis, white nails, acrocyanosis, flushing, hemangiomas, and plethora.[10]

References: 1. ADCETRIS (brentuximab vedotin) Product Monograph. Seagen, Inc. June 11, 2021.

Multisystem MGCS: Systemic Light-Chain Amyloidosis

Amyloidosis is characterized by the deposition of misfolded proteins in a proteolysis-resistant beta-pleated sheet. Although multiple proteins are amyloidogenic, systemic AL amyloidosis is caused by the deposition of monoclonal light-chain proteins. The clinical symptoms of systemic AL amyloidosis can vary and can mimic chronic complications of other common disorders such as Type 2 diabetes mellitus and hypertension, which can lead to prolonged delays in diagnosis.[17] Most commonly, AL amyloidosis presents with cardiac involvement (heart failure with preserved ejection fraction [HFpEF], thickened ventricular walls with low voltages on electrocardiogram, dyspnea on exertion, arrythmias and renal involvement (nephrotic syndrome, renal failure). Other signs and symptoms include soft tissue deposition (macroglossia, obstructive sleep apnea, carpal tunnel syndrome); liver involvement (hepatomegaly and increased alkaline phosphatase); peripheral or autonomic neuropathy; GI involvement; periorbital purpura; and coagulopathy due to an acquired factor X deficiency.[18]. A diagnosis of amyloidosis requires histological evidence of apple-green birefringent amyloid fibrils when the biopsied tissue is stained with Congo red and viewed under polarized light. In patients with clinical symptoms of AL amyloidosis and a detectable serum or urine m-protein, a combined fat pad aspirate and bone marrow biopsy stained for Congo red has a sensitivity of 90% for detecting amyloid deposits.[19] Once Congo red positive amyloid deposits have been found, the type of amyloid needs to be identified; mass spectrometry is the preferred method for isotyping as it has a high sensitivity and specificity.[20]

Multisystem MGCS – POEMS

Patients with POEMS syndrome present with polyneuropathy and a monoclonal (almost always lambda-restricted) plasma-cell proliferative disorder. Patients also require at least one major criteria (sclerotic bone lesions, an elevated vascular EGF level or concomitant Castleman disease) and one minor criteria (organomegaly; extravascular volume overload; endocrinopathy excluding Type 2 diabetes mellitus and thyroid disorders; skin changes as described above; papilledema; thrombocytosis; or polycythemia).[10] Patients diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP) who do not respond to conventional CIDP treatment should flag a high clinical suspicion for POEMS syndrome, as POEMS syndrome is often misdiagnosed as CIDP.

Conclusion

Although specific treatments for MGCS-related disorders are beyond the scope of this review, significant symptoms related to MGCS often warrant the use of clone-directed therapy to inhibit the production of the problematic m-protein. Therefore, having a high clinical suspicion for MGCS-related disorders is necessary to allow early identification and treatment prior to the onset of debilitating symptoms.

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