

Monoclonal gammopathy of significance

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Abstract

The presence of a monoclonal protein in the serum and/or urine is a common clinical condition that increases in incidence with age. Although the diagnosis is most often monoclonal gammopathy of undetermined significance (MGUS) there are many conditions associated with the presence of a monoclonal protein in a patient. Several of these are potentially life-threatening and the presence of the M protein should serve as a clue to these diagnosis. The size of the monoclonal protein has very little bearing on the association with other disorders. This concise review highlights the better known associations between monoclonal proteins and other symptoms, making them monoclonal gammopathy of clinical significance.

The concept of monoclonal gammopathy of undetermined significance (MGUS) was coined by Dr Robert A. Kyle in 1978 to describe a clinical state when a monoclonal protein is identified in a patient's serum or urine in the absence of evidence of end organ damage such as multiple myeloma, primary (AL) amyloidosis or Waldenstrom's macroglobulinemia.¹ The presence of a monoclonal protein by necessity infers the existence of clonal plasma cells in the bone marrow that produce the protein and for this reason, MGUS belongs to the spectrum of clonal plasma cell disorders. This group of conditions varies from the benign MGUS to the highly malignant primary plasma cell leukemia. The current diagnostic criteria for MGUS require that there are less than 10% clonal plasma cells in the bone marrow and the monoclonal protein concentration in the serum must be less than 30g/L (for IgG, IgA, and IgM).² In the case of immunoglobulin light chain MGUS, the involved immunoglobulin light chain (kappa or lambda) must be elevated and the monoclonal protein in the urine must be less than 500mg/24 hours.²⁻⁴

MGUS is common and found in 3.2% of the general population, with a prevalence that increases with age: 0.3% of the population younger than 50 years will have this protein, while up to 8% of the population above the age of 80 will have a detectable monoclonal protein.⁵⁻⁶ There are considerable ethnic differences in the prevalence of the condition and it is more common and appears at a younger age in African Americans.^{3,6-7} The main clinical significance of MGUS has been due to its risk of progression to multiple myeloma, amyloidosis or Waldenstrom's macroglobulinemia. It has been argued that MGUS is a necessary prerequisite for the development of multiple myeloma since retrospective analysis of serum samples from patients who subsequently developed multiple myeloma were found to have the signature monoclonal protein present sometimes for years in advance.⁸⁻⁹ However, this observation is not unexpected since kinetic studies from the 1960s showed that for a clonal plasma cell to grow and reach a clinically significant size, more than a

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decade has to pass.¹⁰ This seminal observation has been confirmed with more recent analysis.¹¹ Various models have been developed to try and determine the risk of progression to multiple myeloma at the time of diagnosis and provide some guidance on the frequency of follow up in this condition. Part of the problem with this approach relates to rigid cut-offs that have been imposed on the diagnostic categories (MGUS, smoldering multiple myeloma and multiple myeloma). The result is that there are patients who do not meet these rigid criteria and in such situations (as always) the clinical judgment of the physician becomes essential rather than following guidelines blindly.

In clinical practice, the diagnosis of MGUS may appear to be easy – the presence of the monoclonal protein without the ‘CRAB’ features that define multiple myeloma (hyperCalcemia, Renal failure, Anemia and Bone lesions). Moreover, there is the impression that when the size of the monoclonal protein is small (especially when much smaller than 30g/L), then the risk of multiple myeloma is trivial or non-existent and the label of MGUS quickly applied. This can expose the patient to potential harm for several reasons: (i) Such thinking will inevitably exclude patients with light chain multiple myeloma (maybe up to 10% of patients), (ii) eliminate from consideration patients with oligosecretory or non-secretory multiple myeloma (~3%), (iii) exclude the possibility of AL amyloidosis, and (iv) likely exclude from consideration important clinical conditions associated with MGUS. The list of ‘benign’ conditions associated with MGUS keeps increasing.¹² Therefore MGUS should only be diagnosed if the physician consciously excludes these conditions with a comprehensive history and physical examination and targeted testing as clinically indicated. The purpose of this review is to highlight the better known associations between MGUS and other conditions and discuss the relevant clinical features of these syndromes so as to increase awareness of these associations and facilitate diagnosis and therapy. Some of these associations lead to well defined clinical syndromes affecting several organ systems while other manifestations are restricted to single organs. It is important to emphasize that in general there is no linear association between the size of the monoclonal protein and the presence of associated diseases or syndromes and therefore, it is the

presence of the monoclonal protein that should be considered as an aid to the diagnosis or exclusion of these specific conditions.

Multisystem

AL or AH amyloidosis

Almost 90% of all patients with amyloidosis will have a syndrome related to the deposition of immunoglobulin light (AL) or heavy chains (AH) or both (AL/AH).¹³ The deposited protein appears as an amorphous material on hematoxylin and eosin (H&E) staining and demonstrates apple-green birefringence with Congo red staining under plane polarized light. Diagnosis of amyloidosis depends on recognition of the various clinical syndromes that patients can present with. The major organs affected (alone or in combination) are the heart (restrictive cardiomyopathy), the kidneys (nephrotic syndrome), peripheral neuropathy, gastrointestinal involvement (upper gut: macroglossia, dysphagia, early satiety, unexplained nausea and vomiting; lower gut: constipation or diarrhea alternating with constipation), weight loss, carpal tunnel syndrome, liver involvement (non-tender hepatomegaly; elevated alkaline phosphatase), autonomic dysfunction, purpura (typically periorbital), and vascular disease (lower extremity or jaw claudication).¹⁴⁻¹⁵ In patients with symptoms of heart failure without hypertension or diabetes mellitus, amyloid cardiomyopathy is an important consideration, especially if there is left ventricular hypertrophy or a pseudo-infarction pattern on the electrocardiogram.¹⁵ The same approach applies to patients with unexplained nephrotic range proteinuria. The urine protein electrophoretic pattern can provide an important clue: if the protein is mainly albumin, AL amyloidosis needs to be excluded. If however, the protein is mainly due to the monoclonal immunoglobulin or light chains (‘Bence Jones proteinuria’) then multiple myeloma is much more likely. Although it is more common to have lambda light chains as a cause of amyloidosis, this cannot be used to exclude this disease. Indeed, perhaps 30% of patients with AL amyloidosis may have immunoglobulin kappa light chains. Diagnosis of amyloidosis depends on a tissue biopsy and it can never be excluded simply because the serum protein electrophoresis and immunofixation are negative. Nor is it excluded if the serum immunoglobulin free light chains are normal since patients can have non AL amyloidosis

or (rarely) even AL amyloidosis. The most accessible organs for biopsy include the bone marrow and subcutaneous fat – together they can identify amyloidosis in up to 90% of patients.¹³ If these are negative, then a biopsy of the major affected organ (e.g. kidney or heart) will yield the diagnosis. It is critical to identify the amyloidogenic protein properly to ensure appropriate therapy. Specifically, the presence of a monoclonal protein in the serum or urine does *not* guarantee that the amyloidosis is due to the plasma cell disorder and typing is the only definitive way to determine the identity of the causative protein.¹⁶ This is ideally done by laser capture micro-dissection followed by MALDI-TOFF mass spectrometry.¹⁷ Therapy of AL amyloidosis is complex and depends on the organs affected, their severity as well as the performance status of the patient.^{13,15,18} Although in many patients with AL amyloidosis the clonal plasma cell burden in the bone marrow is less than 10%, others may have higher fractions of plasma cells. Patients with a low plasma cell burden may be eligible for autologous stem cell transplant if they meet strict selection criteria.¹⁸ Other patients can be treated with a bortezomib based regimen.¹⁸ Ideally, such patients should be seen at a center of excellence for optimal staging and planning of care. It has to be emphasized that a patient with MGUS may have TTR amyloidosis affecting the heart and this possibility increases with older age. Therefore, if the amyloidosis syndrome appears to be restricted to the heart, a pyrophosphate scan should be performed to determine whether the amyloid deposits are TTR versus immunoglobulin related. If in doubt, then a cardiac biopsy should be performed to avoid the possibility of treating a patient with TTR amyloidosis using chemotherapy. This becomes also more relevant with the availability of tafamidis that can treat TTR amyloidosis.

POEMS syndrome

Patients who present with a progressive sensory or sensory-motor polyneuropathy should be tested for the presence of a monoclonal protein to diagnose or exclude the POEMS syndrome. This is an acronym standing for **P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal protein and **S**kin changes.¹⁹ The neuropathy and monoclonal proteins are cardinal features of the syndrome. Almost invariably, the M-protein is lambda light chain restricted and often is quite

small in size.²⁰ Immunofixation of the serum is essential so as not to miss the small protein that is critical for diagnosis. The neuropathy is typical of a chronic inflammatory demyelinating type and can progress over a matter of weeks. Involvement of the respiratory muscles is common and many patients may require supplemental oxygen for dyspnea or hypoxemia. Pulmonary function studies show a ‘restrictive pattern’ with low inspiratory and expiratory pressures due to respiratory muscle weakness. Hepatomegaly, splenomegaly and lymphadenopathy are common. The endocrinopathies vary and can affect any endocrine system of the body with hypogonadism being the most common.²¹ The skin changes are protean and include clubbing, leukonychia, hypertrichosis, hyper or hypopigmentation and cherry angiomas as well as acrocyanosis.²² Other features are captured by a second acronym: PEST. **P**apilledema is common in the absence of intracranial pathology. **E**rythrocytosis and **T**hrombocytosis and also not infrequent and sometimes patients are diagnosed with a myeloproliferative neoplasm. However, careful examination of the bone marrow as well as molecular testing will exclude clonal erythrocytosis or thrombocytosis.²³ Serositis is common leading to fluid retention either as lower extremity edema or ascites. Pleural effusions are frequent even in the absence of heart disease. Vascular endothelial growth factor (VEGF) levels are often quite high in POEMS syndrome and in the correct clinical context are highly suggestive of the diagnosis although the test is not specific.²⁴ Proper therapy of patients with POEMS syndrome is associated with a rapid decline and normalization of VEGF. Patients typically have sclerotic bone disease (in contrast to the lytic lesions of multiple myeloma) that are best detected by PET/CT. Therapy of POEMS syndrome depends on whether the cause is an osteosclerotic plasmacytoma or diffuse infiltration of the bone marrow by clonal plasma cells (often in low numbers). For a solitary sclerotic lesion, radiation therapy is the standard of care but if there is diffuse marrow involvement, chemotherapy or autologous stem cell transplantation is the best approach.²⁵ The peri-transplant care of these patients can be quite challenging due to their multisystem disorder, problems with fluid retention and respiratory muscle weakness. These patients seem to be a significant risk of peri-engraftment syndrome that

needs to be promptly diagnosed and treated with glucocorticosteroids.

Idiopathic Capillary leak syndrome (Clarkson's disease)

Patients with Clarkson's disease present with repeated episodes of hypotension followed by fluid retention.²⁶ Often the patient is diagnosed with dehydration and given large volumes of intravenous fluids to raise the blood pressure. However, a careful history will fail to find any reasonable mechanism for the dehydration. The clue to the diagnosis is the presence of hemoconcentration (elevated hemoglobin and hematocrit) with concomitant low serum protein and albumin concentrations: this combination is pathognomonic of the phenomenon of capillary leak. The patient will have no evidence of chronic liver disease, nephrotic syndrome or a protein losing enteropathy that would otherwise explain the low serum protein and albumin. Nor would there be any evidence for an acute infectious or inflammatory insult that could lead to extravasation of fluid and protein. Over the course of a few days these laboratory anomalies will return to normal as the episode of capillary leak resolves. The mechanisms that trigger these sporadic and potentially life threatening episodes are unclear and they can occur anywhere and at any time. Patients with this syndrome will have a monoclonal protein that in the proper context would help establish the diagnosis. Often patients are misdiagnosed as septic shock or with angioedema, cardiac dysfunction or autonomic failure but a complete blood count and serum albumin and protein during an acute episode provide the evidence for hemoconcentration and in the presence of the monoclonal protein (typically an IgG kappa)²⁷ establish the diagnosis. Therapy is with monthly intravenous immune globulin that is generally very effective.²⁸ Other patients may be treated with beta agonists as well as theophylline.²⁹

Scleromyxedema

Scleromyxedema is a multisystem disorder due to the deposition of immunoglobulins in various organs including the skin (waxy papules or plaques) and internal organs such as the gastrointestinal tract, the heart and rarely the central nervous system. Patients often present with joint and skin stiffness, tightening and thickening of the skin, dysphagia, or even seizures. When restricted

to the skin, the condition has a better prognosis. Involvement of the heart, lungs or brain is associated with a guarded prognosis. It has similarities to systemic sclerosis except for the waxy papules that may occur on the fingers, behind the ears, or over extensor surfaces (e.g. elbow). Patients will also have a monoclonal protein in their serum but typically there will be very few plasma cells in the bone marrow.³⁰ The disease can be rapidly progressive and therefore prompt recognition is important. Immunomodulatory drugs such as lenalidomide are highly effective. Patients may also have an excellent and prolonged response to autologous stem cell transplantation.³¹ Intravenous immune globulin may also be effective, although it has to be given long term.³²

TEMPI syndrome

A syndrome characterized by **T**elangiectasis, **E**rythrocytosis with elevated **E**rythropoietin levels, **M**onoclonal protein, **P**erinephric fluid collections and **I**ntrapulmonary shunting was initially reported in 2011 and since then several more cases have been described.³³⁻³⁴ The patient may have extreme erythrocytosis and with a very high erythropoietin level suggesting a reactive increase in erythrocytes. Patients will have hypoxemia due to intrapulmonary shunting which may be quantitated using radionuclide approaches. The causative role of the plasma cell disorder in this syndrome is supported by resolution of symptoms and sign with therapy directed at the clonal plasma cells. Bortezomib based therapy³⁵ or even autologous stem cell transplantation³⁶ may lead to long term disease control.

Monoclonal gammopathy of renal significance

The nephrotoxic potential of monoclonal proteins have been known for a long time. The best characterized is myeloma cast nephropathy where monoclonal immunoglobulin light chains form casts that obstruct the renal tubules leading to renal failure.³⁷ This is a common presentation of multiple myeloma and perhaps 30% of patients will present with primarily renal dysfunction as the sole manifestation of multiple myeloma. These patients typically have very high monoclonal protein levels both in the urine and serum. Very high serum immunoglobulin free light chains in a patient with renal failure are highly suggestive of myeloma cast nephropathy and signal the need for urgent therapy

to salvage kidney function.³⁸ However, monoclonal proteins can cause a wide variety of renal pathologies, even when present in low concentrations. AL amyloidosis was discussed earlier in this review. More recently, the concept of monoclonal gammopathy of renal significance (MGRS) was proposed and it encompasses a spectrum of renal conditions.³⁹

Membranoproliferative glomerulonephritis

In a recent series of patients with membranoproliferative glomerulonephritis (MPGN) who did not have any associated infection, connective tissue disorder, any evidence of complement dysregulation or other malignancies, 41% were found to have monoclonal deposits (usually IgG3) and complement that were identical to those in the circulation and/or urine and of the same isotype as the clonal plasma cells in the bone marrow.⁴⁰ These deposits appear granular on histology and present with the typical hematuria proteinuria, hypertension and impaired renal function. Often the monoclonal protein is kappa light chain restricted. Therapy directed at the plasma cells is critical to salvage kidney function. A bortezomib based regimen such as cyclophosphamide, bortezomib and dexamethasone (CyBORd) is generally recommended.⁴¹

Immunotactoid glomerulonephritis

Patients with this condition present with a 'nephritic syndrome' namely, an active urine sediment that includes hematuria and proteinuria, azotemia and hypertension. Biopsy of the kidney shows organized microtubular deposits of immunoglobulins, typically IgG in contrast to the disorganized monoclonal deposits seen in *monoclonal immunoglobulin deposition disease*.

Acquired Fanconi syndrome

This syndrome is normally suspected in patients with hypophosphatemia with a low potassium and low serum uric acid levels in the context of significant azotemia. A metabolic acidosis without an anion gap is also present. As an acquired type of renal tubular acidosis, patients with have glycosuria and aminoaciduria. Most often, patients have a kappa light chain restricted monoclonal protein and they may have immunoglobulin crystals in the proximal tubules on renal biopsy. Therapy of the underlying plasma cell

disorder often leads to improvement of the acquired Fanconi phenotype.⁴²

Neurologic syndromes

Sensorimotor peripheral neuropathy

In patients who present with an acquired, distal demyelinating and symmetric neuropathy, monoclonal protein should be performed, especially if a clear etiology of the neuropathy (e.g. hereditary, diabetes mellitus, alcohol and medication effect) cannot be established. The strongest association between MGUS and neuropathy is for patients with a monoclonal IgM. Many of these patients will have anti-myelin associated glycoprotein (MAG) antibodies, although these are not specific. Non-IgM related neuropathy often presents as length dependent sensory motor neuropathy to classic chronic inflammatory demyelinating polyneuropathy (CIDP) with predominantly motor nerve involvement. Often patients with IgM related neuropathy will have features of demyelination on EMG while IgG related neuropathy is often associated with electro-diagnostic features of axonopathy. In all these patients, AL amyloidosis and POEMS syndrome need to be excluded. Given the relatively high frequency of MGUS in the population above the age of 50, it has been difficult to prove a causal association between MGUS and neuropathy, except perhaps for IgM (43). Therapy is often unsatisfactory and includes intravenous immunoglobulin, plasmapheresis, rituximab or in patients with Waldenström's macroglobulinemia bendamustine with rituximab. Given the limited data of a link between IgG and CIDP, patients who present with the latter should be treated with standard therapy such as plasmapheresis, IVIG or glucocorticosteroids.

Sporadic late onset nemaline myopathy

This is a rare acquired myopathy that generally presents after the age of 40 years. Patients present with a sub-acute progressive, proximal/axial (or less likely distal) muscle weakness often associated with dysphagia and respiratory muscle weakness. Symptoms may be asymmetric in some patients. Muscle enzymes are normal but the EMG shows fibrillation and myopathic features.⁴⁴ At least half of these patients will have a monoclonal protein. Muscle biopsy establishes the diagnosis by the presence of nemaline structures. Various treatment options are

available including autologous stem cell transplant⁴⁵ or lenalidomide with dexamethasone that may lead to long term disease control.⁴⁶

Skin

Acquired C1 esterase inhibitor deficiency

Activation of bradykinin release can lead to angioedema that is life threatening if it affects the tongue or upper airways. This results from the activation of the contact phase with kinin production in the absence of C1-esterase inhibitor. Although the most common cause of C1 esterase inhibitor deficiency is genetic, acquired forms of the disease exist and in one large series of 92 patients, a monoclonal protein was identified in 28.⁴⁷ Antibodies against C1 esterase inhibitor were found in 17 of these patients. Most of the patients had MGUS, although several had multiple myeloma or AL amyloidosis.

Cryoglobulinemia

Cryoglobulins are proteins that precipitate in a temperature dependent manner. Their thermal stability may be quite variable and as a result they may be asymptomatic or associated with severe symptoms. Classically, cryoglobulins are divided into 3 types: Type 1 with a monoclonal protein (IgG or IgM), Type 2 with a monoclonal protein (IgM) and polyclonal IgG with a positive rheumatoid factor assay and Type 3 with only polyclonal immunoglobulins. Type 1 is invariably associated with a clonal plasma cell disorder, typically multiple myeloma. Patients generally present with Raynaud's phenomenon although they can also have vasculitis symptoms such as skin ulcers, livedo reticularis, purpura mononeuropathy or mononeuritis multiplex as well as renal manifestations including azotemia, proteinuria or a 'nephritic syndrome'.⁴⁸ Patients with Type 1 or Type 2 cryoglobulinemia will have a detectable monoclonal protein. In general for these patients therapy directed at the plasma cell or lymphoproliferative clone is indicated.⁴⁸

Schnitzler syndrome

Schnitzler syndrome (SchS) is a rare acquired inflammatory disorder characterized by recurrent episodes of 'urticaria' and the presence of a monoclonal protein, typically an IgM.⁴⁹⁻⁵² Other associated features include fever, an acute phase response (usually with florid elevation of the

sedimentation rate and CRP), anemia, neutrophil leukocytosis as well as thrombocytosis. Many patients will have bone or joint pain and imaging studies, especially PET/CT may be helpful in defining the sclerotic bone lesions or the presence of the 'hot knee' sign that is often present.⁵³ Diagnosis is based on the 'Strasbourg criteria'.⁵⁰⁻⁵¹ Typically the urticaria will respond to systemic glucocorticosteroids but will recur once therapy is tapered. Often the skin lesions migrate from one location to another over the course of 48 to 72 hours and may be itchy. Biopsy of the skin lesions shows a predominantly neutrophilic dermal infiltrate without evidence of vasculitis. The serum ferritin is normal, in contrast to adult onset Still's disease. Complement levels are also normal and help to distinguish from hypocomplementemic urticarial vasculitis. Diagnosis of the syndrome is important since effective therapy in the form of anakinra, an interleukin 1 inhibitor, is highly effective. Patients will respond rapidly and completely to this therapy, although it will have to be given continuously.⁵⁰⁻⁵²

Necrobiotic xanthogranuloma

Patients with necrobiotic xanthogranuloma present with skin plaques that may be pink to red in color, or subcutaneous nodules with a predilection to occur around the orbit, flexural areas and the trunk.⁵⁴⁻⁵⁵ In a significant number of patients, the lesions may ulcerate. Histologically, the dermis and subcutaneous tissue have a granulomatous infiltrate with bands of hyaline necrobiosis as well as Touton giant cells. Cholesterol clefts, lymphoid nodules with or without germinal centers, and focal accumulation of plasma cells may also be present. Helper T cells may be found in the granulomas. Immunologic studies will confirm that these are non-X histiocytosis. Many patients will have an associated monoclonal protein (usually Ig) and a significant number will have hyperlipidemia and low levels of C4. Therapy directed at the plasma cell disorder usually results in a complete resolution of the necrobiotic xanthogranulomas.⁵⁶

Conclusion

The spectrum of conditions associated with monoclonal gammopathy is ever increasing¹² and recognition of the association between monoclonal proteins and other clinical features may assist in establishing the diagnosis of life threatening conditions. Although many patients with

monoclonal gammopathy may turn out to have MGUS and that simply need follow up, we cannot afford to miss important associated conditions. The size of the monoclonal protein has no predictive value with respect to the disease associations that need to be carefully excluded based on the old fashioned history and physical examination and targeted testing.

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