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Does My Patient with a Serum Monoclonal Spike have Multiple Myeloma?

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Abstract

A monoclonal spike (M spike or paraprotein) on serum protein electrophoresis (SPEP) is a frequent finding in the general population and typically is pathognomonic of an asymptomatic, premalignant condition called monoclonal gammopathy of undetermined significance (MGUS). MGUS occurs in around 3% of people older than 50 and is associated with a lifelong, low, yet non negligible, risk of progression to multiple myeloma (MM) or a related plasma cell dyscrasia. It is generally an incidental diagnosis during the evaluation of patients complaining of various symptoms such as fatigue, forgetfulness, or neuropathy. While in most outpatient encounters the paraprotein is non pathogenic and cannot explain the presenting symptoms, both patients and physicians are faced with the medical, psychological and economic consequences of a premalignant diagnosis that is non curable, and the obligation (or lack thereof) for follow up. Lifelong annual medical evaluation and blood testing are currently recommended as a mean to early diagnose progression into asymptomatic (smoldering) or active MM. Recently the foundation of these recommendations have been challenged considering the low rate of progression and potential harm related to over-testing.

As MM remains an incurable disease, a timely diagnosis is crucial to establish an adequate plan of care and potentially prevent significant comorbidities such as pathologic fractures or kidney failure.

In this article we will discuss the criteria for diagnosis of MGUS, smoldering MM (SMM) and symptomatic MM; the risk factors for progression from MGUS and SMM to MM; the current recommendations for follow up of MGUS patients and diagnostic evaluation of suspected MM transformation.

Epidemiology of MGUS

The nomenclature monoclonal gammopathy of undetermined significance (MGUS) was introduced by Kyle in 1978, and since then the fundamental characteristics, natural history and diagnostic criteria of this condition have been extensively revised.[1] According to the most current International Myeloma Working Group consensus, MGUS is defined by the simultaneous presence of three criteria: 1) a monoclonal spike on serum protein electrophoresis (SPEP) of less than 3 g/dL; 2) bone marrow infiltration by monoclonal

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malignant plasma cells (PC) of less than 10% and; 3) the absence of any end organ damage related to multiple myeloma (MM), the so call CRAB (hyperCalcemia, Renal failure, Anemia and Bone lesions) criteria (Table 1).[2] Other diseases that can present with an M spike, such as chronic lymphocytic leukemia, B and T cell lymphomas, chronic myeloid leukemia and other PC dyscrasias (systemic AL amyloidosis, Waldenström's macroglobulinemia (WM) and heavy chain disease) should also be excluded before making a diagnosis of MGUS. Epidemiologic studies in the Olmsted County have estimated MGUS to affect around 3% of individuals age 50 or older and with prevalence increasing with age.[3] Of note, these data refer to a cohort heavily skewed toward Caucasian race and the 3% figure does not reflect the two-to-three fold higher incidence of MGUS in Afro-Americans and blacks from Africa or the decreased incidence in Asians and Mexicans in comparison to the white population.[4–8] A familial predisposition, with increased risk of MGUS in first degree relatives of MGUS patients, has also been observed.[9] MGUS carries a 1%/year unremitting, lifelong risk of transformation to hematologic cancer, mainly MM. Clinical research has focused on identifying predictive factors of progression and risk stratification models in order to provide appropriate patient counseling and guide follow up.[10–12]

Diagnosis and follow up of MGUS patients

In most instances, MGUS is an incidental diagnosis on blood work performed to investigate a variety of signs and symptoms.[13] The diagnosis is usually made by general practitioners in the ambulatory setting while evaluating complaints which are rather non specific such as fatigue, lack of stamina or forgetfulness or symptoms and signs worrisome for MM or amyloidosis such as back or bone pain, abnormal liver function tests or neuropathy. The evidence of a monoclonal spike on SPEP and/or an abnormal immunofixation (IF) is suggestive of a PC dyscrasia although it can occur in other diseases.[14] In the absence of clinical or diagnostic findings suggestive of MM, WM, amyloidosis, or other myeloid or lymphoid neoplasia, an M spike smaller than 3 g/dL on SPEP is pathognomonic of MGUS. Hypercalcemia, renal failure, anemia and bone lesions (CRAB criteria) need to be excluded or, when present, explained by another condition (i.e.: hypercalcemia secondary to primary hyperparathyroidism; renal failure secondary to diabetic or hypertensive nephropathy; iron deficient anemia in chronic gastrointestinal losses).[13] Free light chain (FLC) assay is recommended in newly diagnosed MGUS patients given its prognostic value.[11] Bone survey and/or bone marrow aspirate and biopsy are not mandatory part of the work up of patients with MGUS, in the absence of worrisome clinical presentation (excruciating or new, unremitting bone pain, neurologic symptoms, heart failure) or abnormal laboratory findings. Fat aspirate to exclude amyloidosis should only be performed when clinically indicated (i.e.: evidence of unexplained liver, heart, peripheral nerve or gastrointestinal tract abnormalities).[15]

While the risk for progression to MM or a related malignancy (WM, amyloidosis) in MGUS patients is small, it is yet unremitting and life long. In the most updated consensus, the International Myeloma Working Group recommends a repeat SPEP for newly diagnosed MGUS patients at 6 months follow up.[2] If the M spike proves stable, complete blood counts, kidney function tests, serum calcium levels and SPEP should be performed yearly in patients with high risk features (see next section) in an attempt to promptly identify transformation to MM and avoid complications.[16] Patients with low risk MGUS could tentatively be assessed with laboratory studies every 2–3 years if clinical conditions are stable.[2] Patients should be informed to pay special attention to new onset bone pain, progressive fatigue or progressive confusion and to promptly seek medical attention if these arise. If there is suspicion for *in interim* progression to symptomatic MM, a detailed history and complete physical exam should be promptly performed by a physician, and diagnostic studies should be ordered as deemed appropriate to prove evolution to active disease.

Risk factors for progression and stratification models for MGUS patients

Retrospective epidemiologic studies showed non-IgG immunoglobulin subtypes (IgA, IgD or IgM), monoclonal component equal or higher than 1.5 g/dL and an abnormal FLC ratio (κ to λ ratio lower than 0.26 or higher than 1.65) to be risk factors for progression of MGUS to MM.[11]

A risk model has been proposed on the base of those factors by the Mayo Clinic group: patients presenting with all 3 risk factors had a risk of progression to MM of 58% over a period of 20 years. This likelihood was reduced to 37%, 21%, and 5% in MGUS patients presenting with two, one or no risk factors, respectively.[11]

The Spanish group has proposed a second risk progression model based on the preponderance of aberrant monoclonal PC in the bone marrow aspirate, evaluated by multiparametric flow cytometry.[12] A percentage of aberrant PC equal or exceeding 95% of the total bone marrow PC population and the presence of DNA aneuploidy were established as risk factors for progression to symptomatic MM. MGUS patients presenting with both risk factors carried a risk of 46% progression at 5 years versus 10% when only one risk factor was present and 2% when both were absent.

Two recent prospective studies lead by Weiss and Landgren provided useful information on the natural history of MGUS and outlined the challenges related with predicting progression to MM in the clinics.[17, 18] Both studies showed that MM is (almost) inevitably preceded by MGUS. In the Landgren's study, only half of the patients who evolved to MM presented with a yearly progressive rise in the M spike, while the other half had a relatively stable M spike until MM diagnosis, making a rising M spike only a partially reliable marker of disease transformation.

Epidemiology and diagnostic criteria for SMM, MM and PC dyscrasia variants

MM is further classified in smoldering (SMM) and active MM (referred simply as MM from now on). The former is a precancerous condition diagnosed by the presence of an M spike of 3 g/dL or higher and/or bone marrow invasion by malignant PC of 10% or more in the absence of end organ damage (CRAB) (Table 1).[2, 19] Differently from MGUS, patients with SMM have a risk of progression to active MM or related PC dyscrasia of 10%/year in the first 5 years, 3%/year in the following 5 years and 1%/year thereafter with a cumulative probability of progression over 70% at 15 years.[20] Bone marrow involvement by 10% or more MM cells, M spike equal or greater than 3 g/dL and an abnormal FLC ratio (equal or less than 0.125, or equal or exceeding 8) have been identified as risk factors for progression to active disease.[21] Current guidelines recommend close observation and monitoring with no active treatment for patients with SMM.[22] Yet, the paradigm of PC dyscrasia is evolving, with timing of active therapy for high risk SMM patients recently questioned, and early treatment being advocated, in an attempt to slow disease progression and possibly prolong survival.[23, 24] Three criteria need to be satisfied to diagnose MM: 1) bone marrow invasion with monoclonal PC or evidence of a plasmacytoma; 2) presence of an M spike on SPEP or urine protein electrophoresis (UPEP) or abnormal FLC ratio and 3) evidence of end organ damage related to the PC clone (any of the CRAB criteria or hyperviscosity, amyloidosis or recurrent infections) (Table 1).[2] True non secretory MM, which represents around 3% of all MM, is an exception to these criteria as an M spike is not identifiable on either SPEP or UPEP with IF.[2, 25, 26] True solitary plasmacytoma is a variant within PC dyscrasia and occurs in around 3–5% of the cases.[2, 27] It is characterized by a single area of monoclonal PC proliferation either within the bone (osseous plasmacytoma) or in the soft tissue

(extraosseous plasmacytoma), typically of the upper respiratory or gastrointestinal tract, in the absence of systemic disease and bone marrow involvement.[15] These patients can occasionally present with a small monoclonal component, but generally an M spike can not be identified on SPEP or UPEP. By definition, in solitary plasmacytoma, CRAB features must not be diagnosed, with the exception of the single plasmacytoma-related lytic lesion, for osseous plasmacytoma (Table 1).[15, 27] Plasma cell leukemia is defined by the presence of peripheral blood circulating PC exceeding 2×10^9/L or 20% of leukocytes and can be either primary (occurring *de novo*) or the leukemic transformation of a preexisting MM (secondary) (Table 1).[2] Around 60% of PC leukemia cases are primary.[28, 29]

In the Western World, MM accounts for over 10% of all hematologic malignancy and 2% of annual cancer-related deaths. According to the American Cancer Society almost 22,000 new cases of MM and 10,700 MM-related deaths are expected for 2012.[30] Although the past decade has witnessed a remarkable improvement in prognosis, mostly related to the introduction of novel chemotherapy agents such as thalidomide, lenalidomide and bortezomib, MM remains incurable and the current 5-year relative survival rate is estimated around 40%.[30]

Clinical presentation of MM

The clinical presentation of patients with MM can be explained by the abnormal proliferation of the malignant clone within the bone marrow and/or direct pathogenic effect of monoclonal immunoglobulin or free light chain secreted by the PC clone (Table 2). The former leads to suppression of normal hematopoiesis and immunoparesis and accounts for fatigue secondary to anemia, disorders of hemostasis due to thrombocytopenia, and recurrent infections, related to hypogammaglobulinemia or leukopenia.[14] Hypercalcemia, punched out lytic lesions and pathologic fractures can also be explained by the aberrant proliferation of myeloma cells in the bone marrow, although cytokine-driven bone reabsorption plays a prominent role (Table 2).[14, 31] Monoclonal immunoglobulin and free light chain can be directly toxic by immunodeposition in the kidneys, leading to either tubular or glomerular damage (cast nephropathy and light chain deposition disease, respectively) or by infiltration of a variety of organs (i.e.: heart, liver, small intestine, nerves) as in the case of systemic AL amyloidosis. Hyperviscosity syndrome can arise in case of particularly elevated paraproteinemia, especially if IgA or IgM, and can lead to cerebrovascular events and respiratory failure (Table 2).[32] Complications of solitary plasmacytoma include compression fractures and lytic lesions from osseous plasmacytoma, or extrinsic compression and/or invasion of vital structures such as bronchial tree, gastrointestinal tract, or lymph nodes in extraosseous plasmacytoma.[33–35]

Suspecting MM in a patient with a monoclonal spike

In order to diagnose a patient who has a monoclonal spike, with MM, end organ damage related to the PC dyscrasia must be present.[15] When the disease is overt, patients typically seek emergent medical attention due to MM-related complications, such as pathologic fractures, severe hypercalcemia or acute kidney failure. In these instances, the disease has declared itself and achieving a diagnosis in this acute setting may be easier than in the outpatient setting. In most cases, physicians are faced with the challenge of identifying MGUS patients who are progressing to MM in the ambulatory setting where presenting symptoms of MM transformation are typically more subtle. Despite providing stringent clinical follow up of patients with MGUS, a recent retrospective analysis showed that only a minority of asymptomatic patients will be diagnosed with MM on the sole base of abnormal laboratory work up.[36] The vast majority of patients are diagnosed either secondary to a major morbidity (i.e.: pathologic fracture, acute renal failure or severe hypercalcemia) or on

the base of work up of self reported symptoms, typically bone pain or asthenia and lack of stamina.[36] The complaint of new onset back pain in a patient with MGUS should prompt evaluation for lytic lesions while asthenia and lack of energy are usually secondary to anemia although uremia and hypercalcemia can present with similar aspecific symptoms.

Diagnostic investigations in MGUS patients evolving into MM

A complete physical exam and careful history is mandatory and crucial in guiding diagnostic work up in MGUS patients suspected to be evolving into MM. Plain x-ray with dedicated views of the affected area should be performed in every MGUS patients complaining of unremitting, excruciating or rapidly progressive bone pain. MRI spine should be promptly performed if an impending vertebral fracture or spinal cord compromise (i.e.: cord compression or cauda equina) is suspected, to provide emergent radiation therapy or surgical stabilization so that permanent neurologic damage may be avoided. MRI also proves helpful in confirming MM evolution as signal is abnormal in case of pathologic bone marrow infiltration. PET-CT may be useful in the evaluation of new onset bone pain in patients with MGUS, suspected to be evolving to MM. Active disease will appear as FDG-avid bone marrow uptake.[37] Its use is recommended if a strong suspicion for lytic lesions or pathologic fractures is present but standard radiologic studies are negative. MRI and PET-CT are useful techniques to evaluate solitary plasmacytoma and CT-guided biopsy of these lesions should be obtained, whenever possible, to provide a definitive diagnosis.[15] While patients with true solitary plasmacytoma do not require systemic therapy and treatment is either localized radiation or surgical resection, they need to be closely followed given their higher risk of evolution to systemic MM.[15, 34, 35]

Progressive, worsening symptoms of asthenia and malaise in a patient with known MGUS should be evaluated, at minimum, with complete blood counts and peripheral blood smear, creatinine and calcium in order to exclude anemia, kidney failure or hypercalcemia. In a minority of cases, MGUS patients will progress to amyloidosis whose symptoms are related to the organ involved by the disease. In the case of cardiac amyloid, both conduction system and pump function can be affected, resulting in electrophysiologic abnormalities or heart failure. Hepatitis and liver failure related to amyloid deposition can initially present with non specific symptoms such asthenia and unintentional weight loss. GI involvement can presents with dysmotility, malabsorption, diarrhea, or recurrent gastrointestinal bleeding. Peripheral neuropathy, including bilateral carpal tunnel syndrome, can occur frequently in patients with amyloid and is typically multi-focal.[38]

If evolution to MM is suspected on the basis of clinical presentation and laboratory results, a unilateral bone marrow aspirate and biopsy is mandatory to confirm diagnosis and plan adequate treatment. Cytogenetics, FISH analysis and labeling index should be performed on bone marrow aspirate for risk stratification.[15, 39] In order to provide staging and to estimate disease burden, LDH, β2-microglobulin, albumin, serum free light chain ratio, quantification of serum immunoglobulins, SPEP with IF and 24 hour urine collection with UPEP and IF should be obtained after initial laboratory testing. Two staging systems are currently available for MM: the Durie-Salmon and the International Staging System (ISS).[40, 41] The former is more intuitive from a clinical standpoint, but at times difficult to objectify; while the latter provides useful prognostic information based upon two commonly available and standardized lab values: albumin and β2-microglobulin. Should amyloidosis be suspected, a Congo-red stain on fat aspirate and bone marrow is warranted. This stain can be requested on other pathologic specimens, if available, to confirm organ involvement by amyloidogenic light chain deposition. Referral to a specialist in hematology/oncology should be prompt in order to provide counseling and establish appropriate, timely treatment.

The importance of an early diagnosis in MM

Two recent studies, one from the United Kingdom and one from the United States, showed that diagnosis of MM after evaluation of symptoms such as fatigue or back pain, tends to be significantly delayed (over 3 months) in the ambulatory setting.[42, 43] Although no impact on overall survival was noticed in either study, there was a higher incidence of complications and hospitalizations during the interim time between first medical evaluation and diagnosis, thus emphasizing the negative impact on patient quality of life. Multiple factors were identified as playing a role in the delay, including the aspecific nature of MM presenting symptoms, which are common in the aging population and tend to be prematurely dismissed as benign. In this sense, a pre-existent diagnosis of MGUS should serve as an important reminder for both patients and physicians to carefully evaluate any change in current health status, especially if progressive or unremitting.

Conclusions and remarks

A monoclonal spike is a frequent finding in the general population. It is typically incidentally diagnosed as MGUS or SMM and requires no treatment, although follow up is warranted due to a lifelong risk of progression to MM or related malignancies. Despite close laboratory follow up, most of the patients with MGUS are diagnosed with MM between medical visits due to new onset of complications, such as pathologic fractures, or symptoms, predominantly bone pain and fatigue. Patients with MGUS should be encouraged to report to their physician any new symptom and promptly seek medical attention to decide whether further diagnostic studies are indicated. Physicians should carefully evaluate such patients with a detailed history and physical examination, obtain laboratory and radiologic studies deemed necessary to achieve a diagnosis, and promptly refer to hematology-oncology specialists for initiation of treatment. A delay in the chain of events that leads to MM diagnosis can be a cause of significant morbidity and poor quality of life for patients, and every effort should be made to diagnose patients early in the course of their illness.

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Table 1

Diagnostic criteria of plasma cell dyscrasia

The table synthesized the most recent diagnostic criteria for plasma cell dyscrasia according to the International Myeloma Working Group.

	M spike		BM		CRAB[#]	Comments
MGUS	< 3 g/dL	AND	< 10%	AND	Absent	Diagnosis requires exclusion of other lymphoproliferative diseases
SMM	≥ 3 g/dL	OR	≥ 10%	AND	Absent	
MM	Any concentration on SPEP/UPEP	AND	Any % or presence of plasmacytoma	AND	Present	Truly non secretory MM is an exception as an M spike can not be identified on SPEP, UPEP or FLC
PC Leukemia[^]	Absent/Present	AND	Absent/Present	AND	Absent/Present	Defined by the presence of peripheral blood circulating clonal PC > 2×10^9/L or 20% of leukocytes
Solitary Plasmacytoma	Absent[§]	AND	Absent	AND	Absent	Defined as a single site of abnormal PC proliferation in the bone (osseous) or soft tissue (extraosseous)

[#]: Hypercalcemia is defined as total serum calcium higher than 11.5 mg/dL; renal insufficiency is defined by a serum creatinine exceeding 2 mg/dL or estimated glomerular filtration rate less than 40 ml/min; anemia is defined by hemoglobin less than 10 g/dL or less than 2 g/dL the normal reference values; bone lesions include lytic lesions, pathologic fractures or severely osteopenic bone disease. Hyperviscosity, recurrent infections related to hypogammaglobulinemia and amyloidosis represent evidence of end organ damage as well.

[^]: PC leukemia is further classified into primary when occurring *de novo*, or secondary, when it represents the leukemic phase of MM.

[§]: a small M spike can be occasionally seen.

Abbreviations: M, monoclonal; BM, bone marrow invasion by monoclonal malignant plasma cells; CRAB, hypercalcemia, renal failure, anemia, bone lesions; MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; MM, multiple myeloma; PC, plasma cell; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; FLC, free light chain.

Table 2
Pathogenesis of symptoms and signs in multiple myeloma

The table synthesized some of the most frequently occurring signs and symptoms of MM with their pathogenic correlate.

Signs and symptoms	Diagnostic findings	Pathogenic mechanisms	Bibliography
Bone/back pain, cord compression, cauda equina	Lytic lesions, pathologic fractures, severe osteopenia	Myelophthisis, increased osteoclastogenesis, osteoblast inhibition, solitary plasmacytoma	31, 35
Fatigue, malaise	Anemia	Myelophthisis, decreased EPO, hemolysis	44, 45
	Renal Failure	Light chain deposition, cast nephropathy, hypercalcemia-induced vasoconstriction, amyloidosis, urate nephropathy	46, 47
	Hypercalcemia	Bone reabsorption secondary to myelophthisis and cytokine release	48, 49
	Hepatitis, liver failure	Amyloid infiltration, MM cell infiltration	38, 50
Recurrent infections	Hypogammaglobulinemia, leukopenias	Myelophthisis	51, 52
Neurologic symptoms	Polyradiculopathy, ischemic strokes, altered mental status	Amyloid deposition, cryoglobulinemia type I, hyperviscosity, hypercalcemia, uremia	32, 53
Respiratory distress	Infiltrative cardiomyopathy, arrhythmias, pleural effusions, pulmonary edema	Cardiac or pulmonary amyloid, plasmacytoma, malignant pleural effusions, hyperviscosity	32, 38, 54
Purpura, petechiae, bleeding, acrocyanosis	Cryoglobulinemia type I, thrombocytopenia, hyperviscosity	M spike deposition, myelophthisis, hyperviscosity	32, 55

Abbreviations: EPO, erythropoietin; M, monoclonal.