Cancer Association of South Africa (CANSA)

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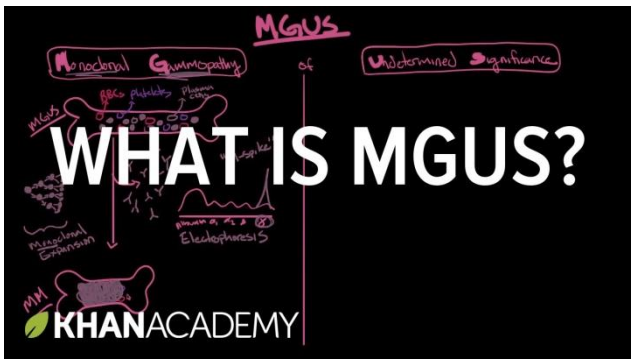
Fact Sheet
on
Monoclonal Gammopathy of Unknown Significance (MGUS)

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a condition in which an abnormal protein — known as monoclonal protein or M protein — is in a patient's blood. The protein is produced in a type of white blood cell (plasma cells) in the bone marrow.



[Picture Credit: MGUS]

It resembles multiple myeloma and similar diseases, but the levels of antibody are lower, the number of plasma cells (white blood cells that secrete antibodies) in the bone marrow is lower, it has no symptoms or major problems, although patients with MGUS have sometimes been reported to suffer from peripheral neuropathy, and no treatment is indicated. Peripheral neuropathy (PN) is damage to, or disease affecting nerves, which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected.

There is a risk of MGUS developing into a blood cancer, such as myeloma (cancer of the plasma cells) or lymphoma (cancer of the lymphatic system).

Kaseb, H., Annamaraju, P. & Babiker, H.M. 2020.
"Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic premalignant plasma cell disorder that is characterized by the presence of serum M-protein less than 30 g/L or 3g/dL, bone marrow (BM) clonal plasma cells less than 10%, absence of plasma cell myeloma (PCM) related end-organ damage (CRAB symptoms: hypercalcemia, renal insufficiency, anemia and, bone lesions) and absence of B-cell lymphoma or other disease known to produce an M-protein. MGUS is generally considered a preneoplastic disorder that does not always progress to overt malignancy. There are three distinct types of MGUS

1. Non-IgM MGUS
2. IgM MGUS: Non-IgM MGUS (IgG, IgA, IgD) accounts for the majority of MGUS cases and is characterized by a monoclonal plasma cell.
3. Light-chain MGUS

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Non-IgM MGUS may progress to a malignant plasma cell neoplasm. IgM MGUS may develop into Waldenstrom macroglobulinemia, immunoglobulin light chain (AL) amyloidosis, or lymphoma. Light chain MGUS (LC-MGUS) is characterized by a monoclonal protein that lacks the immunoglobulin heavy chain component. LC-MGUS may show progression to idiopathic Bence Jones proteinuria, light chain PCM, AL amyloidosis, or light chain deposition disease. According to a population-based cohort study, the risk of progression to multiple myeloma in patients with light-chain MGUS is 0.3%"

Incidence of Monoclonal Gammopathy of Unknown Significancer (MGUS)

Because monoclonal Gammopathy of Unknown Significance (MGUS) is not a cancerous condition in itself, the National Cancer Registry (2017) does not provide any information.

Seth, S., Zanwar, S., Vu, L. & Kapoor, P. 2020.

Purpose of the review: Monoclonal gammopathy of undetermined significance (MGUS) is a highly prevalent precursor condition in the general population, with an approximate 1% annual risk of progression to multiple myeloma (MM) or a related disorder. Our understanding of MGUS and its association with myriad clinical disorders, its progression to MM, and the genomic alterations in the setting of a conducive or permissive microenvironment has deepened considerably.

Recent findings: Data from gene expression profiling studies have underscored the heterogeneity in the risk of progression of MGUS to MM. Ongoing efforts are being directed toward precise identification of high-risk factors for progression and addressing the role of screening for MGUS in populations at higher risk of MGUS in order to diagnose this precursor condition early, and target modifiable risk factors. Ongoing clinical trials are assessing the role of therapeutic interventions to prevent MGUS from progressing. MGUS is a heterogeneous precursor condition with a risk for progression to symptomatic disease. Future directions are focusing on identifying high-risk populations of MGUS and smoldering multiple myeloma that may benefit with screening and/or early intervention.

Risk Factors for Monoclonal Gammopathy of Unknown Significance (MGUS)

Factors that increase one's risk of developing MGUS include:

- Age - the average age at diagnosis is 70 years.
- Race – Black Africans are more likely to experience MGUS than are white people. The incidence in other races is not clear.
- Sex - MGUS is more common in men.
- Family history - One may have a higher risk of MGUS if other individuals in one's family has the condition.

Khouri, J., Samaras, C., Valent, J., Meija Garcia, A., Faiman, B., Mathur, S., Hamilton, K., Nakashima, M. & Kalaycio, M. 2019.

"Monoclonal gammopathy of undetermined significance (MGUS) is commonly diagnosed in outpatients being worked up for an array of clinical concerns. It carries a risk of progression to myeloma and other lymphoproliferative disorders that, albeit low (1% per year), warrants regular follow-up. Patients with MGUS can be risk-stratified on the basis of the amount and type of their monoclonal protein as well as whether they have an abnormal light-chain ratio. Here, we provide a guide to the diagnosis, workup, and management of MGUS."

Causes of Monoclonal Gammopathy of Unknown Significance (MGUS)
MGUS is a rare condition that becomes slightly more common as people get older. It is more common in people with conditions that affect the immune system, such as rheumatoid arthritis and certain infections.

Monoclonal gammopathies result from an overproduction of a single abnormal clone of a plasma cell or B lymphocyte. The monoclonal immunoglobulin is recognised as a band of restricted migration on serum or urine electrophoresis (M-component). When the band represents a monoclonal free light chain, it usually is called a Bence Jones protein (BJP). In some cases, more than one clone may produce monoclonal gammopathies (biclonal or, very rarely, triclonal). Usually, the production of a M-component does not seem to be a response by the immune system to an offending immunogen. Still, in some cases, M-components with activity against immunogens from infectious agents have been identified. The exact meaning of this relationship remains obscure.

Signs and Symptoms of Monoclonal Gammopathy of Unknown Significance (MGUS)
MGUS is usually found during a blood test carried out for some other reason. It does not usually cause any symptoms. Occasionally, people with MGUS have numbness or tingling in their hands and feet, or problems with their balance. This may be due to damage to nerves (peripheral neuropathy) caused by the paraprotein in the blood.

MGUS has a number of clinical features. These include having a low level of protein (less than 30g/l) and less than 10 per cent plasma cells in the bone marrow: There is no damage to bones, calcium levels are normal, little or no protein is present in the urine, the kidney's function normally and there is no anaemia.

If symptoms are troublesome, or get worse, one may be referred to a neurologist (a doctor who specialises in conditions of the nervous system).

Most people who have abnormal proteins in their blood will never get worse. But in some cases, the following illnesses can develop:

- Multiple myeloma
- Non-Hodgkin lymphoma
- Plasma cell leukaemia
- Primary amyloidosis
- Solitary plasmacytoma
- Waldenstrom's macroglobulinaemia

Symptoms of monoclonal gammopathies vary among these conditions, but can include:
- Anaemia or low red blood cells counts
- Lack of energy (fatigue) or tiredness
- Weakness
- Pain in the bones or soft tissues
- Tingling or numbness in the feet or hands
- Infection that keeps coming back
- Increased bruising

- Bleeding
- Weight loss
- Headache
- Vision problems
- Swelling
- Mental changes

Lomas, O.C., Mouhieddine, T.H., Tahri, S. & Ghobrial, I.M. 2020.
"Monoclonal Gammopathy of Undetermined Significance (MGUS) is considered to be a benign precursor condition that may progress to a lymphoproliferative disease or multiple myeloma. Most patients do not progress to an overt condition, but nevertheless, MGUS is associated with a shortened life expectancy and, in a minority of cases, a number of co-morbid conditions that include an increased fracture risk, renal impairment, peripheral neuropathy, secondary immunodeficiency, and cardiovascular disease. This review aims to consolidate current evidence for the significance of these co-morbidities before considering how best to approach these symptoms and signs, which are often encountered in primary care or within a number of specialties in secondary care."

Complications of Monoclonal Gammopathy of Unknown Significance (MGUS)
Complications and sequelae of Monoclonal gammopathy of unknown significance (MGUS) includes:
- Malignant Myeloma
- Paraproteinaemia
- Peripheral neuropathy
- AL amyloidosis
- Peripheral demyelination

Gonzalez-Lugo, J.D., Bachier-Rodriguez, L., Goldfinger, M., Shastri, A., Sica, R.A., Gritsman, K., Mehta, V., Kabarriti, R., Goel, S., Verma, A., Braunschweig, I., Kornblum, N. & Mantzaris, I. 2020.
"Monoclonal Gammopathy of Undetermined Significance (MGUS) is a pre-malignant clonal plasma cell disorder, with 25 to 30% life-long risk of progression to multiple myeloma (MM).[1] It is usually asymptomatic, but infrequently associated with several serious conditions, such as neuropathies, glomerulonephritis, and acquired angioedema.[2] Moreover, a higher risk of infection and deep venous thrombosis has been reported in patients with MGUS."

Diagnosis and Treatment of Monoclonal Gammopathy of Unknown Significance (MGUS)
No treatment is usually recommended for patients with MGUS. However, if preventive clinical trials are available, patients should be encouraged to participate.

Ravindran, A., Lackore, K.A., Glasgow, A.E., Drake, M.T., Hobbs, M.A., Kourelis, T., Kumar, S., Kyle, R.A., Leung, N., Muchtar, E. & Go, R.S. 2020.
Objectives: To determine the indications for prediagnostic testing, subsequent diagnoses found, and follow-up practices in patients who were incidentally diagnosed with monoclonal gammopathy of undetermined significance (MGUS).

Patients and methods: From our prospective MGUS database, we identified 329 patients residing in southeastern Minnesota who were diagnosed from January 1, 2011, through December 31, 2014, and followed up at Mayo Clinic.
Results: Most test orders came from nonhematologists (n=310, 94.2%). The top 5 indications were neuropathy (n=65, 19.8%), renal disease (n=45, 13.7%), anemia (n=42, 12.8%), bone disorder or connective tissue pain (n=42, 12.8%), and cutaneous disease (n=19, 5.8%). Hypercalcemia was an infrequent indication (n=9, 2.7%). The final diagnosis for all neuropathy evaluations was sensory/motor neuropathy-not otherwise specified, with 18.7% having IgM MGUS. Chronic kidney disease-not otherwise specified, iron deficiency, and osteoporosis/osteopenia were the most common subsequent diagnoses for test indications of renal disease, anemia, and bone disorder or connective tissue pain, respectively. Most patients (n=213, 64.7%) had 1 or more follow-up visit during the study period. A minority were followed by hematologists (43.5%, n=143). Patients with low-risk MGUS comprised 45.0% (n=148) of the cohort. Male patients and younger patients were more likely to be followed up than their counterparts (P<.01). About one-third (n=27, 32.1%) of patients 80 years or older (n=84) continued to have regular follow-up visits. Hematologists were more likely to follow patients with MGUS more closely than nonhematologists (P<.001). However, the intensity of follow-up was not based on MGUS risk.
Conclusion: Monoclonal protein testing is commonly performed for signs and symptoms not typically associated with lymphoplasmacytic malignancies. There is a significant variation in MGUS follow-up between hematologists and nonhematologists (P<.001) that is not based on risk factors or clinical practice guidelines.

Ho, M., Patel, A., Goh, C.Y., Moscvin, M., Zhang, L. & Bianchi, G. 2020.
"Multiple myeloma (MM) is a highly heterogenous disease that exists along a continuous disease spectrum starting with premalignant conditions monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) that inevitably precede MM. Over the past two decades, significant progress has been made in the genetic characterization and risk stratification of precursor plasma cell disorders. Indeed, the clinical introduction of highly effective and well-tolerated drugs begs the question: would earlier therapeutic intervention with novel therapies in MGUS and SMM patients alter natural history, providing a potential curative option? In this review, we discuss the epidemiology of MGUS and SMM and current models for risk stratification that predict MGUS and SMM progression to MM. We further discuss genetic heterogeneity and clonal evolution in MM and the interplay between tumor cells and the bone marrow (BM) microenvironment. Finally, we provide an overview of the current recommendations for the management of MGUS and SMM and discuss the open controversies in the field in light of promising results from early intervention clinical trials."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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