# Monoclonal gammopathy of undetermined significance

Monoclonal Gammopathy of Undetermined Significance (MGUS) is a build up of monoclonal antibodies produced by abnormal but non-cancerous plasma cells. In general, MGUS does not cause significant health problems and is almost always discovered by chance when laboratory tests are performed for other purposes. In this article, **Drs Siva Ramakrishnan and Venkitasamy Balakrishnan** discuss the diagnosis and management of MGUS in the elderly.

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In Monoclonal Gammopathy of Undetermined Significance (MGUS), abnormal plasma cells produce excess amounts of a monoclonal immunoglobulin (Ig), also called an M-protein, in the serum or urine of persons without evidence of Multiple Myeloma (MM), Waldenström macroglobulinaemia, primary amyloidosis, or other lymphoproliferative disorders.

In this condition, patients usually have a serum M protein level less than 3.0g/dl and the bone marrow contains less than 10 per cent plasma cells[1,2].

## Prevalence

The incidence of MGUS increases with age[3]. Several studies established that the prevalence of MGUS was one per cent in patients aged 50 years, three per cent in those over 70 years, 5.7 per cent in the over 80 year olds and 14 per cent in persons aged 90 years and above[3].

## Epidemiology

The epidemiology of MGUS mirrors that of myeloma, and is more common in blacks than Caucasians[4]. It is also seen more frequently in the US than in Asia. Of note, China has the lowest incidence of MGUS. The disease affects men more often than women and the prognosis of the former appears to be worse in some studies.

Patients with MGUS should be informed that there is a long-term risk of malignancy. Overall risk of progression to neoplasm is one per cent per year. For 10 years this risk is 12 per cent; for 20 years it is 25 per cent and for 25 years it is 30 per cent[5].

## Transient monoclonal gammopathy

Many conditions are associated with transient monoclonal gammopathy. M components are occasionally seen in non-lymphoid neoplasms such as carcinomas (colon, breast, prostate or other sites), in auto-immune disorders (Sjogren's syndrome, rheumatoid arthritis), transplants of inorganic material (silicone, valves) and in miscellaneous disorders (papula mucinosis, Gaucher's disease, cirrhosis, sarcoidosis)[6]. Transient M component has also been observed in patients recovering from various infections (viral hepatitis, cytomegalovirus infection) and after bone marrow transplantation.

## Diagnosis

Most of the patients will be accidentally diagnosed

**Table 1.** Comparison of clinical features of MGUS, Smoldering MM (SMM) and MM[7]

| Characteristic | MGUS | SMM | MM |
|---|---|---|---|
| Marrow plasma cells | <10 per cent | >=10 per cent | >=10 per cent |
| Serum M-spike | <3g/dL | >=3g/dL | >=3g/dL |
| Bence Jones protein | <1g/24 h | <1 g/24 h | >=1g/24 h |
| Anaemia | Absent | May be present | Usually present |
| Hypercalcaemia, renal insufficiency | Absent | Absent | May be present |
| Lytic bone lesions | Absent | Absent | Usually present. |

while investigating for some other medical problem. These patients should be differentiated from MM patients as MGUS patients are clinically asymptomatic. Patients with MGUS are compared with those with myeloma in *Table 1* and baseline investigations are listed in *Table 2*. MGUS does not require any active treatment except for regular follow up[4].

Patients with MGUS tend to do well, without major problems for a long time, but these patients should be followed as there is a risk of developing MM (65 per cent), macroglobulinaemia (six per cent), primary systemic amyloidosis (8.7 per cent), plasmacytoma (<one per cent) or malignant lymphoproliferative disorder (19.1 per cent)[8]. Over half of MGUS patients die of unrelated causes.

Symptoms of malignant conversion (fatigue, bone pain, renal failure, increasing anaemia, hypercalcaemia, loss of weight or loss of appetite) should be reviewed with the patient as the transition may be abrupt.

**Table 2.** Baseline investigations for MGUS[9]

- Full blood count
- Serum calcium, creatinine and albumin
- Serum protein electrophoresis
- Serum protein immunoelectrophoresis or immunofixation
- Immunoglobulin quantification
- Random urine for total protein and Bence Jones protein
- 24 hour for light chain quantification (if urine protein >500 mg/day)
- Bone marrow testing is not routinely done
- Indications include unexplained anaemia, hypercalcaemia, renal failure or symptoms suggestive of myeloma
- Skeletal surveys not routinely performed and will be performed if bony symptoms or symptoms suggestive of myeloma.

## Management

Patients will be managed with observation alone. There is no evidence to support the use of alkylatory based chemotherapy or bisphosphonates to delay progression.

Patient with asymptomatic MGUS with a M protein level that is stable and consistently less than 1.5g/dl should receive annual follow up[5]. For patients with M protein between 1.5 and 2.5g/dl, they should be followed up three to six months after initial diagnosis and if stable, they need to be followed up annually or sooner if any symptoms or complications occur.

If M protein is more than 2.5g/dl, patients need to be followed up in two to three months and then again in three to four months. If stable, this follow up should be done annually. Patients will have their blood work done two weeks prior to clinic visits and the following tests should be performed with each visit[10]:

- Full blood count
- Serum calcium, creatinine and albumin
- Serum protein electrophoresis
- Immunoglobulin quantification
- Random urine for total protein and Bence Jones protein.

If the patient develops symptoms like fatigue, bone pain, renal failure, increasing anaemia, hypercalcaemia, loss of weight or loss of appetite, then they should be investigated with bone marrow testing and skeletal survey to rule out malignant conversion. Only in six per cent of the population did monoclonal protein disappear without apparent cause[4].

**Table 3.** MGUS risk stratification[12]

| Risk group | Criteria | 20 year risk of progression |
|---|---|---|
| Low | M protein <1.5g/dl and normal kappa/lambda ratio | seven per cent |
| Intermediate | Either M protein >1.5g/dl or abnormal kappa/lambda ratio | 26 per cent |
| High | Both M protein >1.5g/dl and abnormal kappa/lambda ratio. | 46 per cent |

## Biology

In most cases of chronic MGUS there is no known cause but a genetic predisposition is clear[11]. Gains of chromosome three are most common, occurring in 39 per cent of patients, followed by chromosome 11 (25 per cent), seven (16.7 per cent), and 18 (5.6 per cent).

Immunoglobulins (Ig) are divided into five classes (IgA, IgD, IgE, IgG, IgM), and Ig subclass distribution for MGUS includes approximately 70 per cent IgG (mostly IgG1), 12 per cent IgA, 15 per cent IgM and three per cent biclonal gammopathy (a gammopathy in which the serum contains two distinct monoclonal immunoglobulins).

In each Ig molecule there are a pair of heavy chains, which may be either gamma alpha, mu, delta or epsilon type, and a pair of light chains, which may be either kappa or lambda. In some pathological conditions, there is a proliferation of one antibody-producing plasma cell leading to excess production of light chains of one specific kind. These free monoclonal light chains can be found in urine and plasma and were first isolated in 1847 by Henry Bence-Jones. Consequently, they

are known as Bence-Jones proteins. Sixty-one per cent of patients with MGUS have excess kappa light chain whereas 39 per cent have excess lambda light chain[5].

Patients with IgM and IgA MGUS are more likely to progress to malignancy[7]. Also Rajkumar *et al* found that MGUS patients with an abnormal kappa/lambda ratio have significantly higher risk of progression to malignant change than with those with normal ratios[12]. In addition, two recent studies suggested that serum free light chains[13] can also be used for risk stratification (*Table 3*).

## Conclusion

MGUS patients should be diagnosed early and be monitored regularly. It is important to differentiate MGUS from MM as no treatment is indicated for MGUS except for the regular follow up[10]. The low risk patients can be followed up with their family doctor whereas high risk patients should be followed up in a hospital ■ GM

***Conflict of interest: none declared***

## References


1. Brigden ML. The search for meaning in monoclonal protein: is it multiple myeloma or monoclonal gammopathy of undetermined significance? *Postgrad Med* 1999; **106**(2): 135–42
2. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders. *Br J Haematol*. 2003 Jun; **121**(5): 749–57
3. Kyle RA, Bladé J, Rajkumar SV. Monoclonal gammopathies of undetermined significance. In: Malpas JS, Bergsagel DE, Kyle RA, Anderson KC, eds. Myeloma: Biology and Management. 3rd ed. Philadelphia, Pa: Saunders; 2004: 315–352
4. Mohamad H. Monoclonal Gammopathies of Uncertain Significance. eMedicine article last updated: February 19,2002
5. Kyle RA, Therneau TM, Rajkumar SV, *et al*. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2002; **346**: 564–69
6. Alexanian R, Dimopoulos D. The treatment of multiple myeloma. *New Engl J Med* 1994; **330**: 484–9
7. Baldini L, Guffanti A, Cesana BM, *et al*. Role of different hematologic variables in defining the risk of malignant transformation in monoclonal gammopathy. *Blood* 1996; **87**: 912–18
8. Kyle RA, Therneau TM, Rajkumar SV, *et al*. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2002; **346**: 564–69
9. Crawford J, Eye MK, Cohen HJ. Evaluation of monoclonal gammopathies in "well" elderly. *Am J Med* 1987; **82**(1): 39–45
10. Kyle RA. Benign monoclonal gammopathy: after 25 to 35 years of follow up. *Mayo Clin Proc* 1993; **62**(1); 26–36
11. Nilsson T, Lenhoff S, Rylander L. High frequencies of chromosomal aberrations in multiple myeloma and monoclonal gammopathy of undetermined significance in direct chromosome preparation. *Br J Haematol*. 2004; **126**(4): 487–94
12. Rajkumar SV, Kyle RA, Therneau TM, *et al*. Presence of an abnormal serum free light ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance (mgus). *Blood* 2004; **104**(11)
13. Rajkumar SV, Kyle RA, Therneau TM, *et al*. Presence of monoclonal free light chains in the serum predicts risk of progression in monoclonal gammopathy of undetermined significance. *Br J Haematol* 2004; **127**(3): 308–10