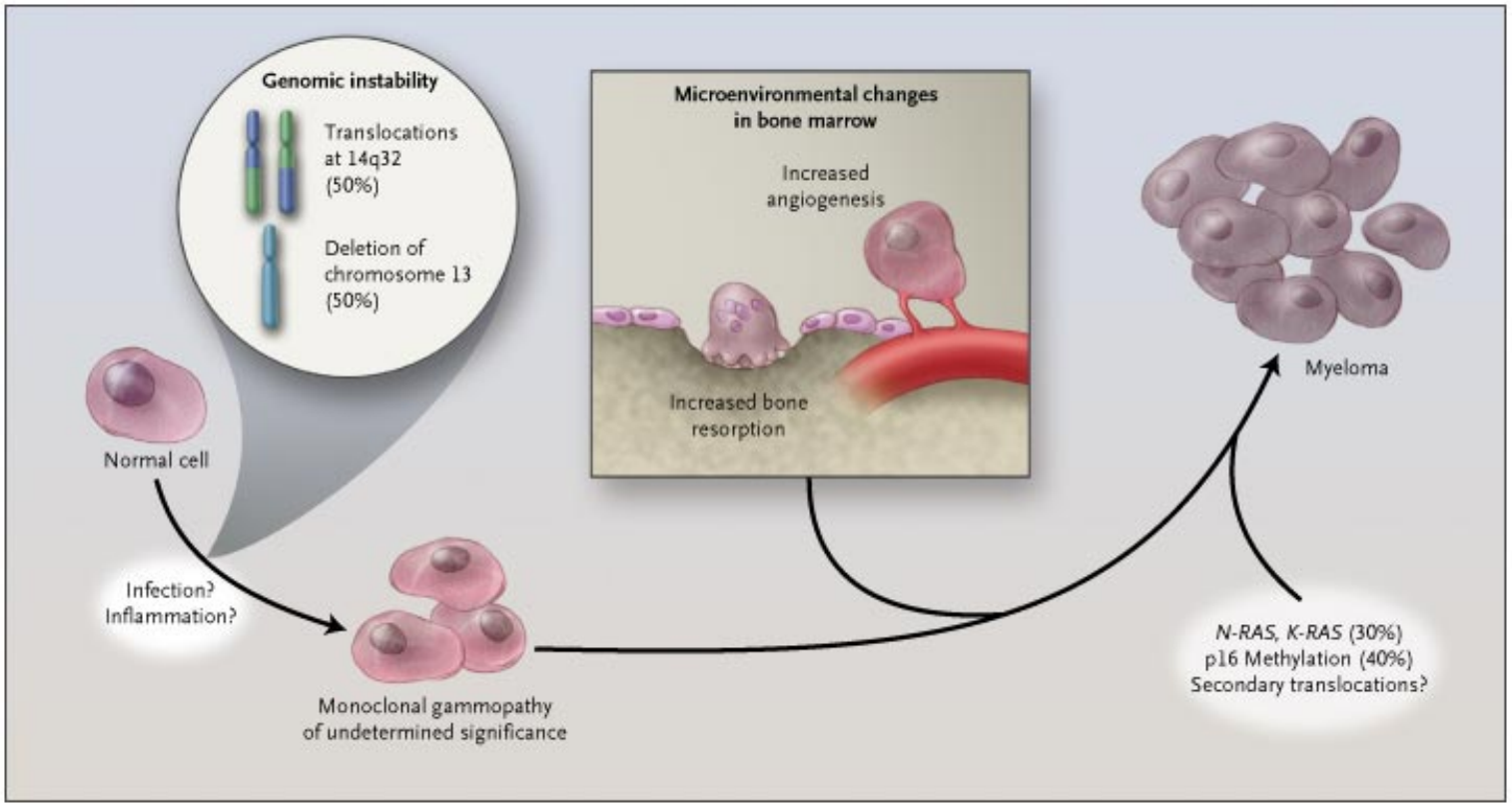
LearnMMORE:
MGUS and Smoldering Myeloma

Nick Burwick MD

off the mark.com by Mark Parisi

MICHAEL DISCOVERS THAT A CANTALOUPE IS ACTUALLY MUCH MORE EFFECTIVE AT KEEPING THE DOCTOR AWAY

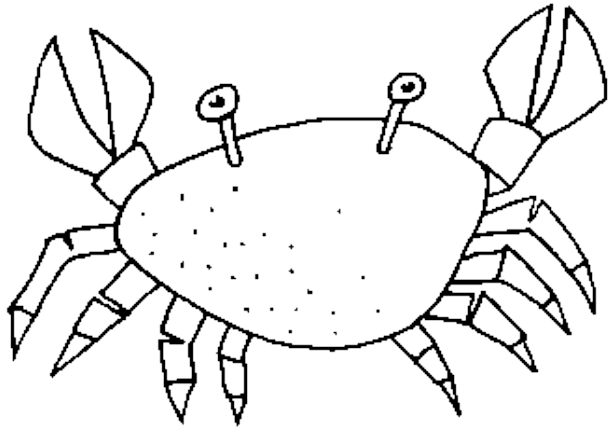


MGUS → Asymptomatic "Smoldering" MM → Symptomatic MM

Kyle R and Rajkumar S. N Engl J Med 2004

The NEW ENGLAND JOURNAL of MEDICINE

Symptomatic “Active” Multiple Myeloma



CRAB:

Calcium Levels Increased

Renal Insufficiency

Anemia

Bone lesions- Lytic lesions or osteoporosis with compression fractures

Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)

*As outlined by the International Myeloma Working Group; British Journal of Haematology 2003

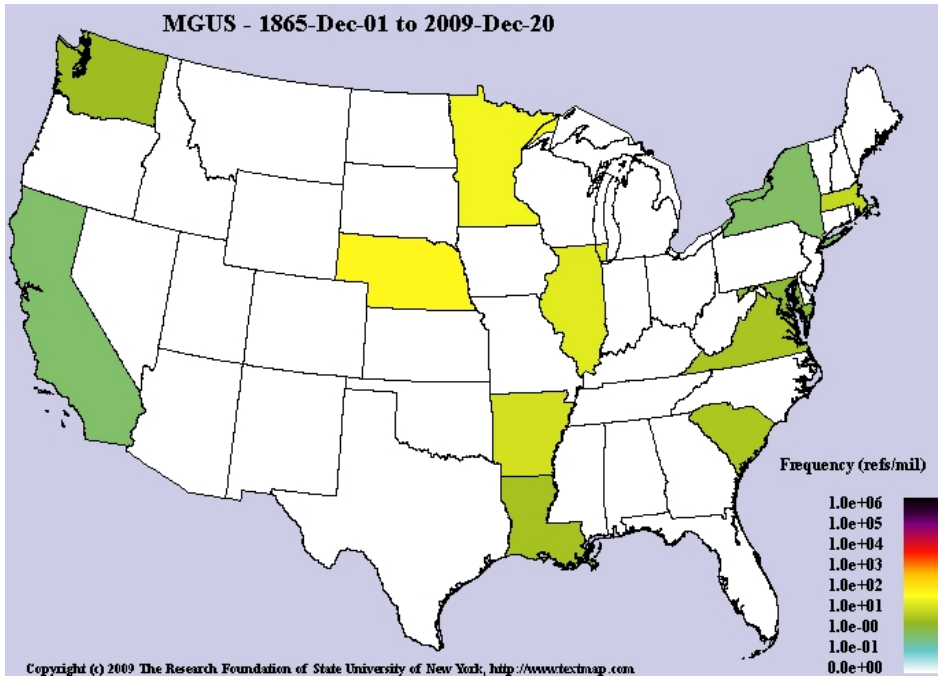
MGUS Prevalence

3.2% of age 50 or older

5.3% of age 70 or older

Size of M protein

<1.5g/dL in 80% of cases



Where is MGUS hot?

MGUS Epidemiology

- Poorly understood
- Higher incidence in African Americans, and in those with first degree relatives with MGUS or Myeloma
- Exposures including atomic bomb survivors, pesticide applicators

Predictors of MGUS Progression

- Size of M protein (>1.5g/dl)
- Type of Immunoglobulin (IgA, IgM)
- Serum Free light chain ratio (abnormal)
- 1 risk factor (1% per year), 2 risk factors (2% per year), 3 risk factors (3% per year)

MGUS and Peripheral Neuropathy

- In patients with peripheral neuropathy- incidence of MGUS is 10%

- IgM MGUS predominant offender (50% of cases have antibodies against nerve proteins “anti-MAG antibodies”)

- 85-100% of patients with “POEMS” have MGUS with an associated peripheral neuropathy

MGUS and Peripheral Neuropathy

Table 1 IgM paraprotein is over-represented in patients with neuropathy

Paraprotein	Proportion with paraprotein AND neuropathy	Proportion with paraprotein WITHOUT neuropathy
IgM	50%	15%
IgG	35%	75%
IgA	15%	10%

(Modified with permission from: Ramchandren S, Lewis RA. Monoclonal gammopathy and neuropathy. Curr Opin Neurol. 2009 Oct;22(5):480–5) [91]

POEMS

- Polyneuropathy (mainly sensory)
- Organomegaly (organ enlargement)
- Endocrinopathies (such as thyroid abnormalities, low testosterone, diabetes)
- MGUS (usually IgA or IgG)
- Sclerotic bony lesions (seen on skeletal Xrays or CT)

POEMS

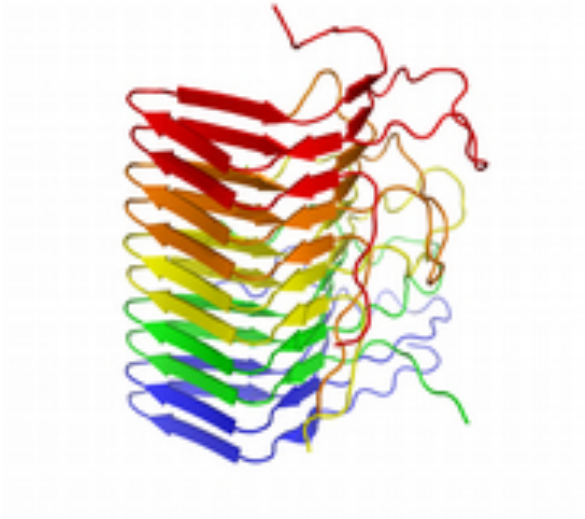
Other manifestations/associations:

- Castleman's disease (lymph node based disease- present in up to 30% of POEMS)
- Skin abnormalities
- Edema (swelling)
- Elevated protein levels of VEGF (vascular growth factor)

Light Chain Amyloidosis and Peripheral Neuropathy

- Peripheral neuropathy

symptoms often present for a long time prior to diagnosis



- Deposition of light chains,

mostly lambda in organs including nerves

- Causes predominantly painful neuropathy and also sensory and motor dysfunction

Amyloidosis and peripheral neuropathy

- In contrast to MGUS, there is systemic organ involvement (kidney, liver, heart, nerves)
- Biopsies of involved organs can identify amyloid deposition
- Requires Systemic Treatment to shut down light chain production

Treatment of peripheral neuropathy

- If there is evidence of myeloma, amyloidosis , or waldenstrom disease – Treat the underlying cause

- If no evidence of malignant process, treatment decision based on individual basis; if symptoms mild, surveillance often preferred (as treatment can exacerbate neuropathy)

IgM MGUS with anti-MAG antibodies

- Trials have demonstrated potential benefit to treat neuropathy associated with anti-MAG antibodies

- IV immunoglobulin (IVIG), Rituxan

(Treatment different than treating myeloma)

MGUS and skin disease

- Skin abnormalities commonly associated with MGUS and can be the presenting sign
- Includes vascular, inflammatory, fat deposition, and edematous abnormalities; several rare dermatologic conditions
- Schnitzler's syndrome: recurrent hives associated with IgM MGUS (also with fevers, bone aches, lymph node swelling)

MGUS and Skin Disease

- Rare cases of MGUS Associated with scleromyxedema

- Skin manifestations can respond to anti-myeloma treatment in severe cases

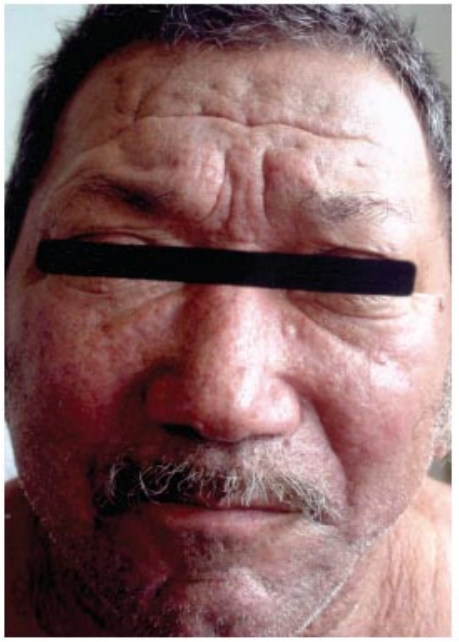
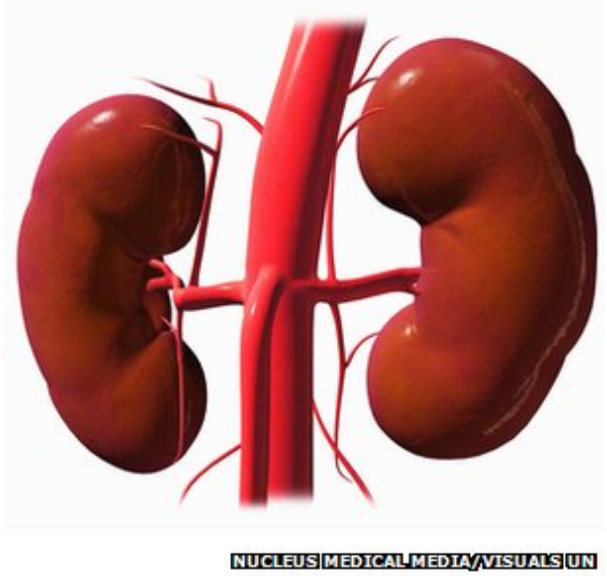


FIGURE 2: Diffuse face infiltration

Monoclonal Gammopathy of "Renal" Significance

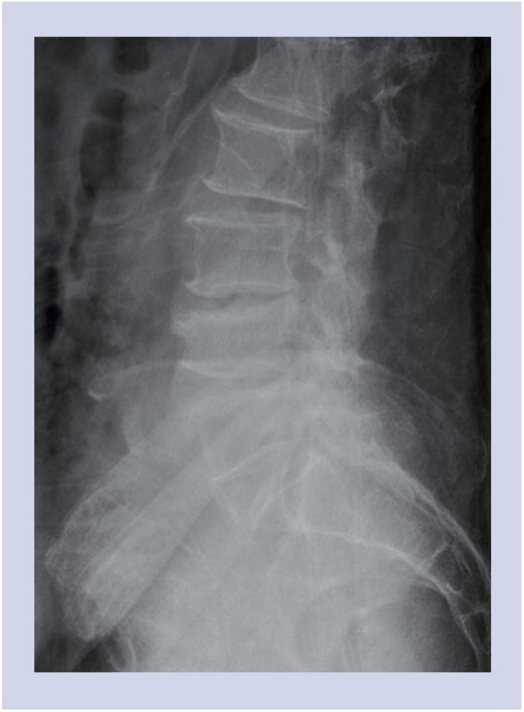
- MGUS can be associated with different kidney disorders (not meeting classic CRAB criteria)



- Kidney biopsy can determine if there are protein deposits in the kidney or evidence of kidney disease

- May require treatment to preserve kidney function

MGUS and Bone disease



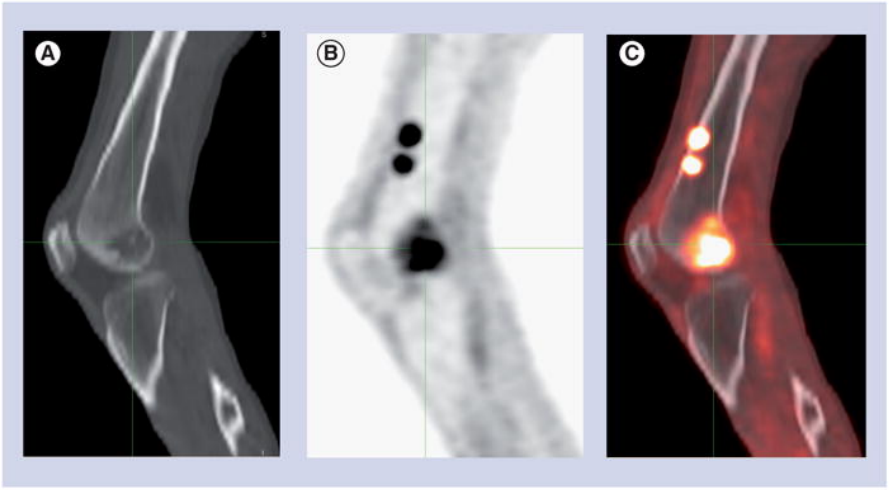
- Bone disease including osteopenia/ Osteoporosis, lytic lesions, and fractures are common in "Active" Myeloma

- Early bone disease also thought to be present in MGUS and Smoldering myeloma

- 1.6 fold increased risk of fracture at 10 years compared to matched controls (independent of size of M protein)

MGUS and bone disease

- Skeletal survey has been the gold standard imaging modality



- Requires ~30% bone destruction for detection of lytic lesions

- Newer more sensitive modalities for detecting bone disease include CT, PET, and MRI


I want a second opinion.
CatsKills College
Kim Wenk
©:Original•Artist:•Search•ID:•kwan93
Rights•Available•from•CartoonStock•com

Cat Scan

MGUS and Bone Disease

- Whole body MRI commonly used here to rule out occult bony disease in SMM and selective MGUS patients
- In one study, 68% of patients had their disease upgraded by MRI
- In another study of 668 patients, 139 patients with normal skeletal surveys were found to have abnormalities on MRI

MGUS and Bone Disease

- Treatment with bisphosphonates improves survival and decreases skeletal-related events in Myeloma patients
- Currently guidelines restrict use to those w/ symptomatic myeloma
- Studies in MGUS have shown no difference in survival or the rate of progression to myeloma (though studies show improved bone density, and less skeletal events)

MGUS and clotting abnormalities

- MGUS can be associated with increased bleeding or clotting risk
- Acquired von Willebrand disease or hemophilias
- High risk of clotting in myeloma but may also be elevated risk in MGUS
- In one series of 310 patients, 6.1% developed deep vein thrombosis over a period of 4 years

Summary

- MGUS is often indolent in the majority of cases
- Risk factors for progression include high M protein, IgA/IgM subtype, and abnormal light chains
- There are many systemic manifestations of MGUS. Not necessarily “benign”

MGUS and diet/nutrients

- There are reports of curcumin decreasing M protein levels in some patients with MGUS
- Active component of the indian spice tumeric; Anti-inflammatory and immunosuppressive properties
- The immunosuppressive properties at high doses could be counter-productive (dampens the anti-tumor responses of immune cells)…some evidence for this in the lab

MGUS and diet/nutrients

- Vitamin D important for bone metabolism; most common nutritional deficiency

- Associated with skeletal abnormalities, chronic diseases such as cancer

- One study demonstrated prevalence of Vitamin D deficiency increased with increasing stage of myeloma

- I found no studies of whether vitamin D supplementation risk of progression from MGUS to myeloma (we generally recommend daily Calcium + Vitamin D for MGUS patients for bone health)

MGUS and anti-oxidants

- Green Tea- a compound found in green tea (EGCG) has been found to kill myeloma cells in the lab. (Also incidentally may block the action of Velcade- avoid if on therapy)

- Resveratrol- found in grapes, red wine, blueberries; kills myeloma cells in the lab; One trial of resveratrol (5 grams daily) in myeloma suspended due to development of kidney failure in several patients

MGUS and peripheral neuropathy

- We generally recommend 3 nutritional supplements for those with peripheral neuropathy:

-alpha lipoic acid

-acetyl-l-carnitine

-Vitamin B6

- Omega 3 fatty acids-

may also promote nerve health and has anti-inflammatory properties (bleeding risk at high doses, >3g/day)

"I'd like some dry broiled fish, sliced cucumbers, and fresh mixed berries. If you don't have that, I'll take a triple bacon cheeseburger, jumbo fries and a cookie dough shake!"

Smoldering Myeloma (SMM)

- >10% plasma cells in the bone marrow
- No evidence of symptomatic Myeloma (no CRAB Features)
- Risk of Progression:

5% per year x 5 years

3% per year x 3 years

1% per year x 10 years

Median time to progression- 4.8 years

Management of SMM

- Current recommended strategy is for observation with close surveillance
- Historically, studies had failed to show a survival benefit to early intervention
- Older drugs also had significant toxicities (alkylators, thalidomide, etc).

The case for treating high risk smoldering myeloma: PETHEMA study

- High risk defined as

>10% bone marrow plasma cells

AND >3g/dl M spike

Or

- 1 of the above,

and >95% plasma cells abnormal (by flow) as well as immunoparesis (suppressed immunoglobulins)

Treatment Schedule in PETHEMA study

- Lenalidomide/Dex for 9 cycles, followed by lenalidomide maintenance (10mg) x 15 months

- Patients in abstention arm more likely to develop symptomatic disease at 3 years (76% vs 23%)

- Treatment group had improved survival (94% vs 80%)

Pethema Study: some caveats

- Escalation of treatment was allowed for asymptomatic “biochemical” progression in treatment arm
- 23% of patients discontinued study in Treatment arm (vs 5% in observation arm)
- 1 death and 12% serious adverse advents in treatment arm (vs 3% in observation arm)

Pethema Study: some caveats

- 40% of SMM patients identified solely by flow cytometry (not widely available)
- Cytogenetics not taken into account. Yet there is data that proteasome inhibitors may be beneficial in high risk subtypes (4:14, del 17p)
- Long-term use of lenalidomide could effect stem cell collection/ Controversy in harvesting stem cells from SMM patients

"WHAT'S ALL THIS ABOUT YOU REFUSING TO TAKE YOUR PLACEBO?"

Ongoing studies in SMM

- US study of Revlimid for high-risk SMM patients (some similarities to PETHEMA study, but no dex)
- 33% response rate
- 4.6% experienced a serious adverse event, with 2 deaths
- At 17 months, 2 patients progressed on therapy

Ongoing Studies in SMM

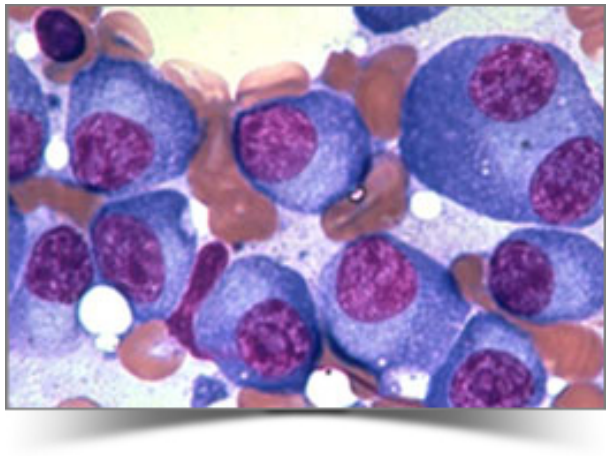
- Low dose Velcade for the study of bone health and disease progression in SMM patients (9 cycles);
- No progressions at the 20 month period; 46% patients had improvement in bone density
- Caveat- bisphosphonates not allowed

Ongoing studies in SMM

- NIH study of Carfilzomib/Lenalidomide/Dex , followed by lenalidomide maintenance in high risk SMM
- Treatment for 8 cycles, followed by maintenance for 2 years
- Out of 9 patients completing 4 cycles, 100% had a very good response or better
- No patients have progressed thus far (early); one pt discontinued due to heart failure

Patients with high-risk SMM who should be considered for treatment*

- Bone Marrow Plasma cells >60% (~2-3% of patients)



- Free light chain ratio >100 (as many as 15% of patients)

- MRI bone marrow with greater than one focal lesion (as many as 15% of patients)

- In these patients risk of progression in 2-3 years is 80% or higher

* Based on consensus panel recommendations Blood 2013

Summary

- Current guidelines still recommend surveillance for all MGUS/SMM patients without CRAB criteria
- There is data demonstrating benefit in treating high risk patients with Lenalidomide/Dex, but there are important caveats to consider
- Further clinical studies are necessary in this patient population

Thank you

- Email with questions

nburwick@fhcrc.org