

# **An Approach to the Patient with Monoclonal Gammopathy**

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## **Overview**

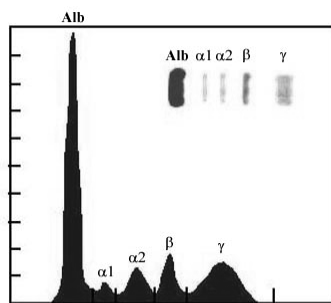
- **Define “monoclonal gammopathy”**
- **How do patients with monoclonal gammopathy present?**
- **Care of the patient with monoclonal gammopathy**

# Monoclonal gammopathy

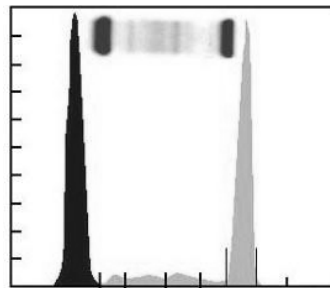
- The presence of an excessive amount of an immunoglobulin in serum

- IgG
- IgA
- IgM

# Monoclonal gammopathy



Normal SPEP



Abnormal SPEP

## **Monoclonal gammopathy**

- **Depending on the nature of the monoclonal gammopathy, patients may present with a wide range of conditions:**
  - **Asymptomatic, incidentally discovered**
  - **Critically ill with multi-organ system dysfunction**

## **Patient 1**

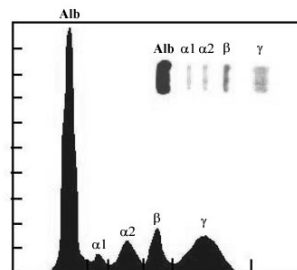
- **A 68 year old man presents for routine blood work. He has hyperlipidemia and receives regular blood work to monitor liver function tests related to his statin medication.**
  - **He has no complaints and feels well.**
  - **His examination is without abnormal findings.**

## Patient 1

- A 68 year old man presents for routine blood work. He has hyperlipidemia and receives regular blood work to monitor liver function tests related to his statin medication.
  - His LFTs show normal AST and ALT.
  - Total protein is 8.8 g/dL (normal 6.4-8.3 g/dL)
  - Albumin is 3.7 g/dL (normal 3.4-4.8 g/dL)

## Patient 1

- The patient has an unexplained, widened “protein gap”
  - Total protein is 8.8 g/dL (normal 6.4-8.3 g/dL)
  - Albumin is 3.7 g/dL (normal 3.4-4.8 g/dL)
- *PEARL: albumin typically accounts for about half of total protein in serum*



## Patient 1

- To investigate the elevated total protein:
  - SPEP
  - Quantitative immunoglobulin levels
  - Monoclonal immunofixation
- SPEP: “A prominent zone of restriction in the gamma region, suggestive of monoclonal gammopathy”

## Patient 1

- Quantitative immunoglobulins:
  - IgG (600-1500mg/dL) 1920 mg/dL
  - IgA (100-400mg/dL) 220 mg/dL
  - IgM (50-300mg/dL) 240 mg/dL
- Monoclonal immunofixation:
  - IgG kappa monoclonal protein 1145 mg/dL

## **Patient 1**

- **Further blood work is performed:**
  - **Normal blood counts**
  - **Normal metabolic panel and kidney function**
  - **Normal blood calcium level**

## **Patient 1**

- **The patient is referred to a hematologist for input**
  - **A bone marrow biopsy is normal except for 4% monoclonal plasma cells.**
  - **A radiograph skeletal survey is normal.**
- **The patient is given a diagnosis of “monoclonal gammopathy of uncertain significance”**

# **Monoclonal gammopathy of uncertain significance (MGUS)**

- **Definition of MGUS:**
  - **Monoclonal protein < 3 g/dL**
  - **Bone marrow plasma cells < 10%**
  - **Absence of signs or symptoms**

## **MGUS epidemiology**

- **Prevalence:**
  - **3.2% of Caucasians > 50 years old**
    - **5.3% in patients > 70 years old**
    - **More common in men than women**
    - **Prevalence is twice as high in African-Americans**
    - **2-3 fold increase in first degree relative of patient**
    - **Average age at diagnosis is 70 years**
  - **Cause is unknown**
    - **Higher prevalence in obesity, chronic antigen stimulation, pesticide exposure**

## **MGUS management**

- **MGUS**
  - **No treatment required**
  - **Patients must be followed, however, because of risk of progression to clinical malignancy:**
    - **Multiple myeloma**
    - **Amyloidosis**
    - **Waldenstrom's macroglobulinemia**
    - **Non-Hodgkin lymphoma**

## **MGUS management**

- **The overall risk of MGUS progressing to clinical malignancy is 1% per year**
  - **The actual observed rate is a bit lower because patients are far more likely to die of an unrelated condition in long term follow up**
  - **However, patients with MGUS require lifelong follow up as progression has been reported up to 30 years after index presentation**



## **MGUS management**

- **There is no way to tell if an individual with MGUS will progress or not, however:**
  - **Monoclonal protein > 2g/dL = 40% life time risk**
  - **IgA or IgM has 2-fold increase risk than IgG**

## **Patient 1**

- **Conclusion:**
  - **The patient has been observed on a 6-month basis without evidence of disease progression.**
  - **At two years follow up, he will begin annual re-evaluation of his MGUS**

## **MGUS key points**

- **Almost always an incidental finding**
  - **Remember to check the protein gap on LFTs!**
- **No treatment indicated**
- **Most patients will not progress to malignancy**
  - **However, virtually all patients require life long follow up**

## **Patient 2**

- **A 58 year old woman presents for her annual examination. She feels well.**
  - **Her past medical history includes hypertension for which she takes atenolol.**
  - **Her examination is without abnormalities**

## **Patient 2**

- **A 58 year old woman presents for her annual examination. She feels well.**
  - **She recently attended a “health fair” at her employer’s request and presents results of blood work obtained at the event.**

## **Patient 2**

- **On review, her blood counts are normal.**
- **Her comprehensive metabolic panel is entirely normal except for:**
  - **Total protein is 9.0 g/dL (normal 6.4-8.3 g/dL)**
  - **Albumin is 3.9 g/dL (normal 3.4-4.8 g/dL)**

## Patient 2

- This asymptomatic patient also has an unexplained protein gap.
- Her SPEP reveals: “a marked zone of restriction in the gamma region compatible with a paraprotein:

## Patient 2

- Quantitative immunoglobulins:
  - IgG (600-1500mg/dL) 650 mg/dL
  - IgA (100-400mg/dL) 2930 mg/dL
  - IgM (50-300mg/dL) 52 mg/dL
- Monoclonal immunofixation:
  - IgA kappa monoclonal protein 2745 mg/dL

## **Patient 2**

- **She sees a hematologist:**
  - **A bone marrow biopsy which shows 23% monoclonal plasma cells**
  - **A radiographic skeletal survey shows no lytic lesions**
- **She is diagnosed with “smoldering myeloma”**

## **Smoldering myeloma**

- **Definition:**
  - **Monoclonal IgG or IgA protein > 3 g/dL**
    - **or**
  - **>10% clonal plasma cells in bone marrow**
  - **Absence of clinical signs or symptoms**

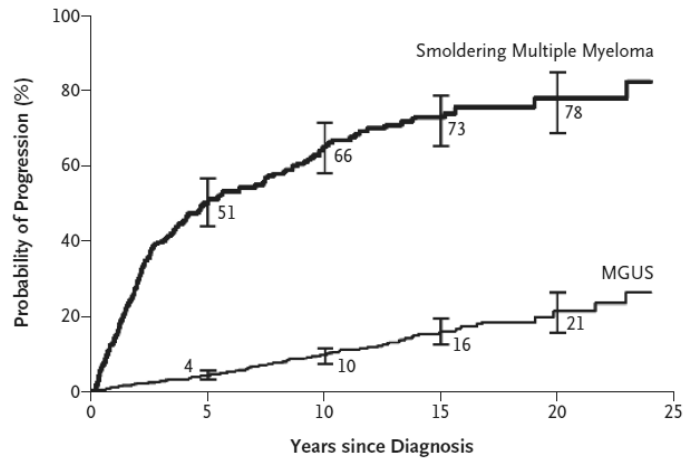
## **Smoldering myeloma**

- **Smoldering myeloma:**
  - **Accounts for about 8% of all cases of multiple myeloma**
  - **Median age 64**
  - **More common in men than women**
  - **Often an incidental diagnosis**

## **Smoldering myeloma management**

- **No treatment required\***
  - **Clinical trials are currently evaluating early intervention**
- **Patients are typically assessed every 3-4 months for signs or symptoms of progression**
- **Most commonly patients progress to multiple myeloma or amyloidosis**

# Risk of progression



*New Eng J Med 2007;356:2582*

# Risk of progression

Variable:	progression (%)		
	5	10	15
<b>Monoclonal protein:</b>			
> 4 g/dL	80	80	90
< 4 g/dL	47	64	71
<hr/>			
IgA		66	77
80			
IgG		46	62
71			
<hr/>			
<b>Bone marrow plasma cells (%)</b>			
< 20		36	53
61			
20-50	68	82	92
> 50		85	93
100			

## **Smoldering myeloma management**

- **Patients are typically assessed every 3-4 months for signs or symptoms of progression**
- **In this case, Patient 2 has been followed for nearly 30 months now without evidence of progression.**
  - **She is considering participation in an early intervention clinical trial at present**

## **Smoldering myeloma key points**

- **No treatment required**
  - **Consider referral for clinical trial participation**
- **Risk of progression:**
  - **much higher for SM than MGUS**
  - **Risk of progression is highest in first 5 years**
  - **IgA, high monoclonal protein or high bone marrow plasma cells increase risk of progression**



## **Patient 3**

- **A 62 year old man is brought into the clinic by his daughter.**
  - **She says over the past two days he has become increasingly confused and disoriented.**
  - **He was seen about 3 months ago for back pain that seemed to improve with a short course of non-steroidal anti-inflammatory medication**

## **Patient 3**

- **A 62 year old man is brought into the clinic by his daughter.**
  - **On examination:**
    - **Temperature 100.2 HR 115 RR 24 BP 160/94**
    - **Pale, disoriented to place and time**
    - **Mucous membranes very dry**
    - **tachycardic, regular**
    - **Abdomen is tender to palpation**

## Patient 3

- A 62 year old man is brought into the clinic by his daughter.
  - Basic laboratory results show:
    - WBC 14 K/uL (normal 4-10 K/uL)
    - Hemoglobin 8.2 g/ dL (normal 13-17 g/dL)
    - Platelets 122 K/uL (normal 150-400 K/uL)

## Patient 3

- A 62 year old man is brought into the clinic by his daughter.
  - Basic laboratory results show:
    - Total protein is 10.2 g/dL (normal 6.4-8.3 g/dL)
    - Albumin is 3.2 g/dL (normal 3.4-4.8 g/dL)
    - BUN 44 mg/dL (normal 6-20mg/dL)
    - Creatinine 2.4 mg/dL (normal 0.8-1.2mg/dL)
    - Calcium 13.8 mg/dL (normal 8-10 mg/dL)

## Patient 3

- The patient is transferred to a local emergency room and admitted to hospital
  - Hypercalcemia is treated with IV fluids
  - He is seen by a consultant from hematology

## Patient 3

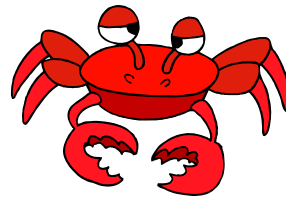
- Quantitative immunoglobulins:
  - IgG (600-1500mg/dL) 4225 mg/dL
  - IgA (100-400mg/dL) 50 mg/dL
  - IgM (50-300mg/dL) 35 mg/dL
- Monoclonal immunofixation:
  - IgG kappa monoclonal protein 3928 mg/dL

## Patient 3

- A bone marrow biopsy reveals 64% monoclonal plasma cells
- A radiographic skeletal survey shows numerous lytic lesions with compression fractures in the lumbar spine
- The patient is diagnosed with multiple myeloma

## Multiple myeloma

- A monoclonal protein
- Clonal plasma cells in bone marrow
- Signs and symptoms of disease:
  - Calcium elevation
  - Renal insufficiency
  - Anemia
  - Bone disease
    - Also: hyperviscosity, recurrent infections



## **Multiple myeloma**

- **20,000 new cases annually in USA**
- **About 75,000 patients living with MM**
- **About 12,000 deaths annually**
  
- **Incurable**
- **Prevalence of disease is rising**
- **Cause is essentially unknown**

## **Multiple myeloma**

- **NEW information!**
  - **Multiple myeloma is universally preceded by MGUS**
  
  - **New treatments have improved survival**
    - **6 new FDA approved therapies in last 6 years**
    - **Median survival doubled in last 10 years**
  
  - **Treatment paradigms rapidly changing**
    - **Consider referral to multiple myeloma center**

## **Patient 3**

- **The patient received aggressive in hospital care**
  - **His serum creatinine normalized**
  - **He was started on induction treatment and achieved remission**
  - **He underwent high-dose chemotherapy with autologous bone marrow transplantation**
  - **He is alive and well in remission 4 years out from index presentation**

## **Multiple myeloma key point**

- **Index of suspicion:**
  - **Early presentation with non-specific signs and symptoms**
    - **Back pain (lytic bone disease)**
    - **Mental status changes (hypercalcemia)**
    - **Fatigue (anemia)**
    - **Recurrent / unusual infections**
    - **Pain in extremities (hyperviscosity)**
  - **Renal insufficiency (hypertension / diabetes)**

# Monoclonal gammopathy

- MGUS
- Smoldering myeloma
- Multiple myeloma
  
- Also seen in:
  - Amyloidosis (usually just in urine)
  - Waldenstrom's macroglobulinemia (IgM)
  - Chronic lymphocytic leukemia and non-Hodgkin lymphoma

## More information

- <http://cancer.osu.edu>
  - KEYWORD SEARCH: Myeloma
  
- MGUS
  - *JAMA* 2010;vol304:2397-404
- Smoldering myeloma
  - *J Clin Oncol* 2010;vol 28: p 690-7
- Multiple myeloma
  - *New Eng J Med* 2011;vol 364: p 1046-60