

## An Approach to the Patient with Monoclonal Gammopathy

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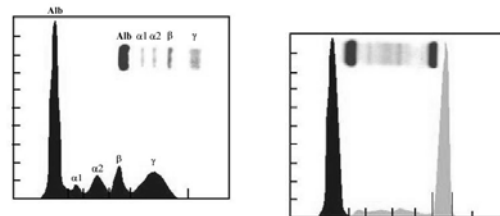
## Monoclonal gammopathy

- The presence of an excessive amount of an immunoglobulin in serum
  - IgG
  - IgA
  - IgM

## Overview

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

## 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

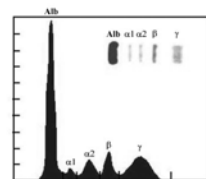
- A 68 year old man presents for routine blood work. He has hyperlipidemia and receives regular blood work to monitor liver function tests related to his statin medication.
  - His LFTs show normal AST and ALT.
  - Total protein is 8.8 g/dL (normal 6.4-8.3 g/dL)
  - Albumin is 3.7 g/dL (normal 3.4-4.8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

## Patient 1

- 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

- 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

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

## 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

- 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 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 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

- 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

## 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 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

## 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

- 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

- 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

- 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

- 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

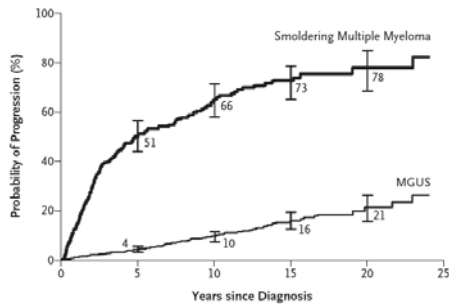
## Smoldering myeloma

- 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 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

## 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

## Risk of progression

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

## 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.
  - 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.
  - 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:
    - 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

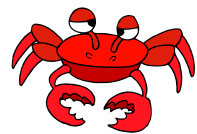
- A bone marrow biopsy reveals 64% monoclonal plasma cells
- A radiographic skeletal survey shows numerous lytic lesions with compression fractures in the lumbar spine
- The patient is diagnosed with multiple myeloma

## 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

## 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

## 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

- 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

## 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