Bone Disease in Plasma Cell Dyscrasias

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Courtesy of Dr. Ferris Hall
Objectives

- Characterization of the plasma cell neoplasms
- Radiologic work up of Multiple Myeloma
- A Visual Journey
  - Multiple Myeloma: Lytic
  - Multiple Myeloma: Osteopenic
  - *Sclerotic* Plasma Cell Neoplasms
    - Diffuse: Sclerotic Multiple Myeloma
    - Solitary: Sclerotic Plasmacytoma
    - Multifocal: POEMS
Definitions

- **Multiple Myeloma (MM)** = monoclonal malignant proliferation of plasma cells

- **Plasmacytoma** = discrete, solitary mass of neoplastic monoclonal plasma cells in either bone or soft tissue (extramedullary). Absence of multiple lesions, marrow plasmacytosis or other features of MM. Progresses to MM in 50-60%.

- **POEMS** = syndrome of Polyneuropathy, Organomegally, Endocrinopathy, Monoclonal gammopathy & Skin problems

- **MGUS** = Monoclonal Gammopathy of Undetermined Significance: Presence of M-protein in urine without evidence of multiple myeloma. With long term follow up 25% develop MM.
Multiple Myeloma

• Minimal diagnostic criteria:
  ♦ Presence of >10% plasma cells in the BM or plasmacytoma
  ♦ Serum or urine monoclonal protein
  ♦ Related organ or tissue impairment (↑ calcium, renal insufficiency, anemia, lytic bone lesions, hyperviscosity, amyloidosis, recurrent infections)

• Epidemiology: MM represents 1-2% of all malignant disease & 10-33% hematologic malignancies. Incidence increases with age. Men > Women. Blacks > Whites

• Presentation: Bone pain precipitated by movement = most common. Other common symptoms include weakness, fatigue and weight loss.
Staging of MM – Durie & Salmon

Based on staging and other prognostic indicators, median survival ranges from 5 years to 15 months.

Systemic tx is indicated for Stage II & III patients.

<table>
<thead>
<tr>
<th>Stage I – Low cell mass</th>
<th>Stage III - High Cell Mass</th>
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<tbody>
<tr>
<td>All of the following Present:</td>
<td>&gt;1 of the following:</td>
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<tr>
<td>• Hgb &gt; 10 g/dl</td>
<td>• Hgb &lt; 8.5 g/dl</td>
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<tr>
<td>• Serum IgG &lt; 5 g/dl</td>
<td>• Serum IgG &gt; 7 g/dl</td>
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<tr>
<td>• Serum IgA &lt; 3 g/dl</td>
<td>• Serum IgA &gt; 5 g/dl</td>
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<tr>
<td>• Normal serum calcium</td>
<td>• Serum calcium &gt; 12 mg/dl</td>
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<tr>
<td>• Urine monoclonal prtn excretion &lt; 4 g/day</td>
<td>• Urine monoclonal prtn excretion &gt; 12 g/day</td>
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<tr>
<td>• No generalized lytic bone lesions</td>
<td>• Advanced lytic bone lesions</td>
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Stage II – Intermediate cell mass  Fitting neither I nor III
The Skeletal Survey

The **skeletal survey** used at dx of MM to detect bone pathology for:

- Establishment of a baseline for future follow-up
- Assessment of fracture risk
- Staging

The **skeletal survey** in an adult consists of **plain radiographs** of the:

- skull (AP and lateral)
- ribs (AP global, AP on the lower thoracic grid, two oblique views)
- spine (AP and lateral of cervical, thoracic and lumbar areas)
- pelvis (AP)
- femurs (AP and lateral)
- humerus (AP and lateral)

**Bone scintigraphy** is less sensitive than plain films in identifying lytic lesions. Most lesions of MM are not apparent unless a fracture occurred or the lesion is in a healing phase.
MRI for lesion detection in MM?

Several studies suggest that MR is superior to radiographs for detection of lesions in the spine.

The Durie and Salmon staging system was developed in 1975 when only plain film was available to image the skeleton.

Currently, MRI is not standardly used in MM patients.

Spine imaging of the same patient using MRI and plain film

Role for PET?

By directly imaging the increased metabolic activity of the bone marrow PET may be able to:

- detect early lesions missed by skeletal surveys or MRI
- may be useful to monitor response to therapy

Currently PET is not commonly used for MM imaging.
What Causes Lytic Lesions in MM?

- Formation of osteolytic lesions involves uncoupling of bone resorption and formation

- Patients taking bisphosphonates (which inhibit osteoclasts) do not have an increase in bone formation within lytic lesions

- Long search for a secreted factor that activates osteoclasts

- Myeloma cells secrete RANKL to increase osteoclast activity and DKKI to inhibit osteoblasts, creating a bias toward negative bone balance

A Visual Journey by Case Series

• Multiple Myeloma: Lytic
  Patient 1: GW
  Patient 2: SL

• Multiple Myeloma: Osteopenic
  Patient 3: BV

• Sclerotic Plasma Cell Neoplasms
  ◦ Diffuse: Sclerotic Multiple Myeloma
    Patient 4: HM
  ◦ Solitary: Sclerotic Plasmacytoma
  ◦ Multifocal: POEMS
    Patient 5: OJ (Plasmacytoma)
    Patient 6: BP (Mixed lytic-sclerotic)
GW is a 71 y.o. female who presents to the EW with mild pain and an inability to walk. Labs indicate M-protein by electrophoresis.

Pathologic fracture

Multiple lytic lesions without sclerotic margins
Lytic MM: GW, Additional Radiographs

Lateral skull film with classic punched out lytic lesions of various sizes

Courtesy of Dr. Ferris Hall
DDx Multiple Punched-Out Lytic Lesions of Bone with Nonsclerotic Margins

Common:

• Arthritis (eg, gout, rheumatoid, osteoarthritis)
• Brown tumors of hyperparathyroidism
• Langerhans Cell Histiocytosis
• Metastases
• Multiple Myeloma
Lytic MM Patient 2: Disease Progression

SL was diagnosed in 1971 at age 28, initially with an isolated plasmacytoma.

10% of MM patients have an indolent course.

June 1976

April 1985

All films this slide courtesy of Dr. Ferris Hall
Complications of Bone Destruction

Lytic lesions may cause:

- hypercalcemia
- pathologic fractures
- loss of height
- cord compression
- osteoporosis

Additional Lesions

Pathologic Fracture

Courtesy of Dr. Ferris Hall
Osteopenia in MM

• Evidence for **diffuse bone loss** in 60% of multiple myeloma patients

• In 5% of patients bone loss occurs without focal lytic lesions

• Bisphosphonates often used for treatment of bone disease in MM. Use of pamidronate is associated with:
  
  ♦ **↓** pathologic fractures
  
  ♦ **↓** need for irradiation/surgery of bone
  
  ♦ **↓** spinal cord compression
  
  ♦ Prevention of hypercalcemia
  
  ♦ **↓** bone pain.
Osteopenic MM: Patient 3 - BV

History: BV is a 54 y.o. female diagnosed with MM following a fall onto her hip, which lead to the discovery of lytic lesions in the pubic bone, leukopenia, anemia, and an monoclonal IgG lambda spike. A confirming bone marrow biopsy showed greater than 30% plasma cells.

Compression Fracture

Lateral thoracic spine illustrates diffuse osteopenia
Osteosclerotic MM

- 3-4% plasma cell neoplasms are sclerotic
- Sclerotic plasma cell neoplasms can be divided into:
  - Solitary: Sclerotic plasmacytoma
  - Diffuse: Sclerotic MM
  - Multifocal: POEMS
- 85% sclerotic myeloma patients present with polyneuropathy
- More indolent course
- Affects younger patients
- Lambda > Kappa chains
Diffuse Osteosclerotic MM: Patient 4 - HM

History: HM is 77 y.o. woman who presented with DOE and pancytopenia. Initial work-up for lymphoproliferative disease prompted a CXR, CT, bone scan, skeletal survey and electrophoresis.

Bone “superscan” with symmetrically diffuse increase of tracer uptake and diminished renal activity.

Lateral spine radiograph of diffuse sclerosis.
POEMS

- Polyneuropathy – predominantly sensorimotor
- Organomegally – liver, spleen or lymph nodes
- Endocrinopathy – impotence, amenorrhea, gynecomastia, IGT
- Monoclonal gammopathy – myeloma in >50%, MGUS or others
- Skin Changes – hyperpigmentation, thickening, hirsutism
  - Rare!
  - Affected patients may not have all findings
  - Pathogenesis remains unknown
  - Skeletal findings usually on axial and proximal appendicular skeleton and are usually sclerotic or infrequently mixed lytic-sclerotic
Sclerotic Plasmacytoma POEMS Pt. 5: OJ

History: OJ is a 42 y.o. male who presented with back pain, endocrinopathy, parasthesias & leg weakness. IgG was slightly ↑, Bx diagnosed a plasmacytoma. MRI was performed to evaluate CC.

CT: well defined lytic lesion with sclerotic rim. No cortical destruction or bony expansion.

PET fusion: Homogenous focus of intense FDG uptake.

T1W MRI: lesion with a dark margin

T2W fat suppressed MRI: lesion with dark signal margin & high intensity central aspect.
Mixed Lytic-sclerotic POEMS
Patient 6: BP

BP is a 27 y.o. male who presents with gynecomastia, impotence & papilledema.

Plain film of the pelvis: multiple foci of sclerosis.

Round lytic lesion within sclerotic focus.

Courtesy of Dr. Ferris Hall.
Mixed Lytic-sclerotic POEMS

Patient PB’s Axial CT of the pelvis at the level of the lytic lesion seen on plain film

Courtesy of Dr. Ferris Hall
Summary

Plasma cell neoplasms are often first diagnosed radiologically.

Plain film & potentially MRI or PET findings influence tumor prognosis and therapy decisions.

Skeletal surveys may be supplemented by additional imaging modalities in the future for lesion detection and follow-up.
References

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