Myeloma

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Multiple Myeloma

- **Definition**
  B-cell malignancy characterised by abnormal proliferation of plasma cells able to produce a monoclonal immunoglobulin (M protein)

- **Incidence**:
  3 - 9 /100000 population / year
  elderly men age 68
  1.1% of malignancies in US
  modest male predominance
Multiple Myeloma

- In 1847 an article was published in *The Lancet* (1847; 2: 88-92) written by Dr. Henry Bence Jones in which he described the findings of one Dr. Watson in a patient whose only marked disease was mollities ossium (Osteomalacia). Describing his findings Dr Watson wrote:

  - "Dear Dr. Jones, The tube contains urine of very high specific gravity. When boiled it becomes slightly opaque. On the addition of Nitric Acid, it effervesces, assumes a reddish hue, and becomes quite clear; but as it cools assumes the consistence and appearance which you see. Heat reliquifies it. What is it?"

- This "peculiar substance" later came to be known as Bence Jones Protein.
Causes of Myeloma

- Genetic causes
  - The Mayo clinic found disease in 8 siblings out of 440 patients; these 8 siblings had different heavy chains but the same light chains.
  - Immunoglobulin heavy chain 14q32 and an oncogene (often 11q13, 4p16.3, 6p21, 16q23 and 20q11. (50%)
    - This mutation results in dysregulation of the oncogene which is thought to be an important initiating event in the pathogenesis of myeloma. The result is proliferation of a plasma cell clone and genomic instability that leads to further mutations and translocations.
  - HLA-Cw5 or HLA-Cw2

- Environmental or occupational causes: agriculture, food, petrochemical industries

- MGUS: 19% in 20 years.

- Radiation
Multiple Myeloma

- Clinical forms:
  - multiple myeloma
  - solitary plasmacytoma
  - plasma cell leukemia

- M protein:
  - is seen in 99% of cases in serum and/or urine
    - IgG > 50%,
    - IgA 20-25%
    - IgE IgD 1-3%
    - light chain 20%
  - 1% of cases are nonsecretory
Multiple Myeloma

- Clinical manifestations are related to malignant behaviour of plasma cells and abnormalities produced by M protein

- Plasma cell proliferation:
  - multiple osteolytic bone lesions
  - hypercalcemia
  - bone marrow suppression (pancytopenia)

- Monoclonal M protein
  - decreased level of normal immunoglobulins
  - hyperviscosity
Multiple Myeloma

Clinical symptoms:

- Bone pains, pathologic fractures eg back/ ribs/ shoulder
- Spinal cord compression in 20%
- Weakness and fatigue
- Renal failure (direct tubular injury, amyloidosis, plasmacytoma)
- Bleeding diathesis
- Neuropathy
- Pyogenic infection
- Decreased visual acuity
Myeloma – physical findings

- Pallor resulting from anemia.
- Ecchymoses or purpura.
- Bony tenderness, resulting from focal lytic destructive bone lesions or pathologic fracture. Pain without tenderness is typical.
- Neurological findings may include a sensory level change, weakness, or carpal tunnel syndrome.
- Extramedullary plasmacytomas, which consist of soft tissue masses of plasma cells, are not uncommon. (anywhere in body)
- Amyloidosis:
  - The shoulder pad sign
  - Macroglossia
  - Skin lesions that have been described as wax papules or nodules may occur on the torso, ears, or lips.
  - Postprotoscopic peripalpebral purpura strongly suggests amyloidosis. Patients may develop raccoonlike dark circles around their eyes following any procedure that parallels a prolonged Valsalva maneuver.
Multiple myeloma
Myeloma – laboratory investigations

- FBC, U+E, Ca, Uric acid, creatinine clearance.
- Serum protein electrophoresis, urine protein electrophoresis, and immunofixation
- 24 hour urine collection
- Quantitative immunoglobulin (ie, IgG, IgA, IgM) levels
- Beta-2 microglobulin important prognostic indicator, (elevated in renal insuff without myeloma)

- C reactive protein (marker of il 6, plasma cell growth factor)

- Serum viscosity in patients with CNS symptoms, nosebleeds, or very high M protein levels

- Skeletal survey, MRI scan, bone marrow
Multiple Myeloma

Laboratory tests

• ESR > 100
• Anaemia, thrombocytopenia
• Rouleaux in peripheral blood smears
• Marrow plasmacytosis > 10-15%
• Hyperproteinemia
• Urea, Creatinine, Ca all increased in 40%
• Beta 2 microglobulin
• Proteinuria
Diagnostic Criteria for Multiple Myeloma

**Major criteria**

I. Plasmacytoma on tissue biopsy

II. Bone marrow plasma cell > 30%

III. Monoclonal M spike on electrophoresis IgG > 35g/l,
    IgA > 20g/l, light chain > 1g/l in 24h urine sample

**Minor criteria**

a. Bone marrow plasma cells 10-30%

b. M spike but less than above

c. Lytic bone lesions

d. Residual normal immunoglobulin M (IgM) level of less than 50 mg/dL, IgA level of less than 100 mg/dL, or IgG level of less than 600 mg/dL

Diagnosis requires one major and one minor to be met or three minor
Staging of myeloma

- The following combinations of findings are used to make the diagnosis:
  - I plus b
  - I plus c
  - I plus d
  - II plus b
  - II plus c
  - II plus d
  - III plus a
  - III plus c
  - III plus d
  - a plus b plus c or a plus b plus d
• FIGURE 1. Patients with multiple myeloma show a "spike" in the or regions of the serum protein electrophoresis.
Myeloma Histology

Plasma cells are 2-3 times larger than typical lymphocytes; they have eccentric nuclei that are smooth (round or oval) in contour with clumped chromatin and have a perinuclear halo or pale zone. The cytoplasm is basophilic. Many descriptions of myeloma cells include characteristic, but not diagnostic, cytoplasmic inclusions, usually containing immunoglobulin.
Staging of Multiple Myeloma

- **Stage I involves all of the following:**
  - Hemoglobin > 10 g/dL
  - Calcium < 12 mg/dL
  - Radiograph showing normal bones or solitary plasmacytoma
  - Low M protein values (ie, IgG < 5 g/dL, IgA < 3 g/dL, urine < 4 g/24 h)

- **Stage II involves criteria that fit neither stage I nor stage III.**

- **Stage III involves any one of the following:**
  - Hemoglobin < 8.5 g/dL
  - Calcium level > 12 mg/dL
  - Radiograph showing advanced lytic bone disease
  - High M protein value (ie, IgG > 7 g/dL, IgA > 5 g/dL, urine > 12 g/24 h)

- **Subclassification A involves a creatinine < 2 g/dL.**

- **Subclassification B involves a creatinine > 2 g/dL.**
Multiple Myeloma

- Stage I is associated with median survival of longer than 60 months
- Stage II is 41 months
- Stage III is 23 months
- Stage B disease has a significantly worse outcome (e.g., 2-12 mo in 4 separate series).
Multiple Myeloma - Survival

[Bar chart showing survival rates over periods from 1971-1975 to 2000-2001 for men and women.]
Treatment of Multiple Myeloma

- No treatment indicated if patient is symptomatic (patient can be re-evaluated)
- < 70 years = autologous peripheral blood stem cell transplant
- Hematopoietic stem cells should be collected before the patient is exposed to alkylating agents.
- Chemotherapy is the preferred initial treatment for symptomatic MM in persons older than 70 years or in younger patients in whom transplantation is not feasible.
Treatment of myeloma – stem cell transplantation

- Peripheral blood stem cells are preferable to bone marrow transplantation. Autologous peripheral stem cell transplantation is applicable for more than half of patients with MM.

- Mortality 1-2%

Problems
1) Eradication of myeloma from the patient rarely occurs even with large doses of chemotherapy and/or radiation
2) Autologous peripheral blood stem cells are contaminated by myeloma cells or their precursors.
Treatment of Myeloma

• Initially: Vincristine + Doxorubicin (Adriamycin) IV for 96 hours; Dexamethasone po (VAD) for 3–4 months

• Dexamethasone +/- Thalidomide is being evaluated for initial therapy.

• Peripheral blood stem cells are collected following granulocyte colony-stimulating factor (G-CSF) +/- high-dose Cyclophosphamide.

• Transplant following high-dose chemotherapy and/or total body irradiation (TBI) followed by infusion of the peripheral blood stem cells

• Or: alkylating agents after stem cell collection until a plateau is reached + alpha-2-interferon (_2IFN) or no therapy until early relapse

• High dose Melphalan +/- TBI + peripheral stem cell transplantation (good performance status)

• Early or late transplantation

• No difference in single vs tandem transplants
Treatment of Multiple myeloma

- Allogeneic Bone Marrow Transplantation

- Graft contains no tumor cells.

- >90% are unsuitable due to age, lack of a HLA-matched sibling donor or inadequate renal, pulmonary or cardiac function.

- Mortality 25%

- In a report of 266 patients from the European Blood and Bone Marrow Transplantation registry, 51% obtained a complete response.

- The overall treatment mortality rate was approximately 40%. The actuarial survival was 30% at 4 years and 20% at 10 years.

- Mini allo transplants/ depletion of t cells
Chemotherapeutic agents

- Various combinations of therapeutic agents have been used because of the shortcomings of melphalan and prednisone.

- Melphalan and prednisone = response in 50–60% of patients. (4,930 persons from 20 randomized trials comparing melphalan and prednisone)

- Higher response rates with combination chemotherapy (60%) vs melphalan and prednisone (53%) (p < 0.00001).

- No significant difference in overall survival and no evidence that any group of patients benefited from receiving combination Chemotherapy.
Chemotherapeutic agents

- Combination chemotherapy for at least 1 year (may cause acute leukemia/myelodysplastic syndrome)

- 2-IFN in induction and maintainence following conventional chemotherapy (In a large meta-analysis Wheatley reported a survival benefit in both induction (p = 0.05) and maintenance (p = 0.03) with an increase in median response duration of six months in both settings)

- Close monitoring during plateau phase

- Same chemotherapy regimen should be reinstituted if relapse occurs after six months.

- Prednisone, 50 mg po every 48 hours can prolong plateau state and survival
Treatment of myeloma

- Treatment resistance - reversible effect. Some new treatment modalities may re-sensitize the tumor to standard therapy.

- *Relapsed disease* - bortezomib (or Velcade®)

- Bortezomib is a proteasome inhibitor.

- Lenalidomide (or Revlimid®), a less toxic thalidomide analog, is showing promise for treating myeloma.
Treatment of complications of myeloma

• Renal failure – adequate hydration, plasmapharesis, stop nephrotoxic meds.

• Anaemia – EPO


• Spinal cord compression

• Hypercalcaemia - bisphosphonates

• Hyperviscosity – plasmapharesis

• Emotional support
Disorder Associated with Monoclonal Protein

- Neoplastic cell proliferation
  - multiple myeloma
  - solitary plasmacytoma
  - Waldenstrom macroglobulinemia
  - heavy chain disease
  - primary amyloidosis
- Undetermined significance
  - monoclonal gammopathy of undetermined significance (MGUS)
- Transient M protein
  - viral infection
  - post-valve replacement
- Malignancy
  - bowel cancer, breast cancer
- Immune dysregulation
  - AIDS, old age
- Chronic inflammation
Monoclonal gammopathy of undetermined significance (MGUS)

- M protein presence, stable
- Levels of M protein: IgG < 3.5g  IgA < 2g  LC<1g/day
- Normal immunoglobulins - normal levels
- Marrow plasmacytosis < 5%
- Complete blood count - normal
- No lytic bone lesions
- No signs of disease
Monoclonal gammopathy of undetermined significance (MGUS)

- M protein
  - 3% of people > 70 years
  - 15% of people > 90 years
  - MGUS is diagnosed in 67% of patients with an M protein
  - 10% of patients with MGUS develop multiple myeloma
Thank you