Summer 7-2018

Multiple Myeloma

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What & Why

- Multiple myeloma [MM] is a complex hematologic malignancy. It is crucial for any practitioner to be aware of the pathophysiology, presenting clinical manifestations, differential diagnoses, implications for care, and other disease specific details to avoid misdiagnosis and provide proper treatment/referral.
- As a future nurse practitioner providing care in an orthopedic office in addition to the surgical environment there is a high likelihood of caring for a patient with this disease.
- American Cancer Society (2018) Estimates:
  - "30,770 newly diagnosed cases of MM in the United States
  - 12,770 deaths
  - 1 out of 132 life time risk of developing MM" (p.1)

Presentation: Multiple Myeloma

- Plasma cell malignancy, insidious onset
- Malignant plasma cells multiply in bone marrow and produce an overabundance of monoclonal protein (Michels & Peterson, 2017).
- Monoclonal protein produced: IgG, IgM, IgA (most commonly). IgE, IgD (rarely). Kappa or Lambda light chain proteins (Michels & Peterson, 2017).
- African Americans are twice as likely to develop MM compared to Caucasians. African Americans also present earlier in life (Michels & Peterson, 2017).
- 85% of patients diagnosed with MM are older than 65 years (Michels & Peterson, 2017).
- 65 years old is current median age of diagnosis (Brigle & Rogers, 2017).
- 46.6% 5 year survival rate (Brigle & Rogers, 2017).
- Findings on presentation for patients with multiple myeloma presented in Table 1 (Michels & Peterson, 2017).
- World Health Organization Classification, differentiation between:
  1. Multiple myeloma [MM]
  2. Monoclonal gammopathy of undetermined significance [MGUS]
  3. Solitary plasmacytoma of the bone
  4. Extraosseus plasmacytoma
  5. Monoclonal immunoglobulin deposition diseases

(Brigle & Rogers, 2017)

Underlying Pathophysiology

Plasma Cell Disease: Incurable, Heterogeneous

- Monoclonal plasma cell crowding in bone marrow due to overgrowth (Brigle & Rogers, 2017).
- Followed by increased production of immunoglobulins or immunoglobulin chains that also crowd other cells in bone marrow (Brigle & Rogers, 2017).

Pathogenesis of abnormal plasma cell production:

- Cyclin D protein dysregulation (early event).
- Almost always a progression from MGUS. (Brigle & Rogers, 2017).
- *Two karyotype subclasses of MM :*
- *1.Hyperdiploid-* chromosomes 3,5,7,9,11,19, and 21 contain extra copies or trisomies.
- *2. IgH Translocation-* at 14q32 of IgH locus with the possibility of various individual partner genes that all result in an upregulation of cyclin D proteins.
- 40% of MM cases are hyperdiploid (better prognosis than patients with any of the various IgH translocation abnormalities).
- 30% of MM cases present with IgH translocations.
- 15% of MM patients have both trisomies and IgH translocations.

(Brigle & Rogers, 2017)

Further genetic alterations that potentiate growth of abnormal plasma cells:

- Chromosome 13 loss
- MYC and RAS oncogene initiation
- Changes of chromosome 1 copies
- Demise of TP53 tumor suppressor activity (can indicate poor prognosis)
- Nuclear Factor kB (NF-kB) regulation is inactivated by mutations (presents late in disease stage).
- Adhesion molecules between MM cells and bone marrow stroma cells regulated by NF-kN cells. Downregulation results in MM cell growth outside of bone marrow and "development of stromal-independent plasma cell Leukemia" (Brigle & Rogers, 2017, p. 226).

Changes not related to gene sequencing (epigenetic events):

- DNA hypomethylation and hypermethylation in early progression of MGUS to MM and late stage MM respectively.
- Target genes related to DNA methylation include links to, "dexamethasone resistance, cell adhesion, and cell signaling" (Brigle & Rogers, 2017, p. 227).
- Increase in oncogene transcription and expression as result of histone demethylation.

(Brigle & Rogers, 2017)

Disease progression related to genetic complexity:

- Clonal evolution: clonal competition, survival of the fittest clone.
- Clones are more genetically complex and produce a dominant cell line as a result of diversity and aggression.

(Brigle & Rogers, 2017)

Table 1. Findings on Presentation for Patients with Multiple Myeloma (Michels & Peterson, 2017)

Symptom or Laboratory Finding	Percentage of Patients
Anemia (hemoglobin < 12 g per dL [120 g per L])	73
Bone pain	58
Elevated creatinine (> 1.3 mg per dL [115 µmol per L])	48
Fatigue or generalized weakness	32
Hypercalcemia (calcium > 10.1 mg per dL [2.52 mmol per L])	28
Weight loss	24

Significance of Pathophysiology: Bone Marrow Microenvironment

Bone marrow: location of myeloma cell growth and expansion

- 2 compartments of bone marrow: 1) cellular 2)non-cellular
- *Cellular compartment:* hematopoietic and non-hematopoietic cells: Myeloid cells, T and B lymphocytes, natural killer cells (NK), osteoclasts, bone marrow stromal cells, bone marrow-derived mesenchymal stromal cells, fibroblasts, osteoblasts, adipocytes, endothelial cells, blood vessels
- *Non-cellular compartment:* Extracellular matrix, cytokines, chemokines, growth factors, exosomes produced by cellular compartment.
- *Both compartments and their interactions crucial to MM progression*

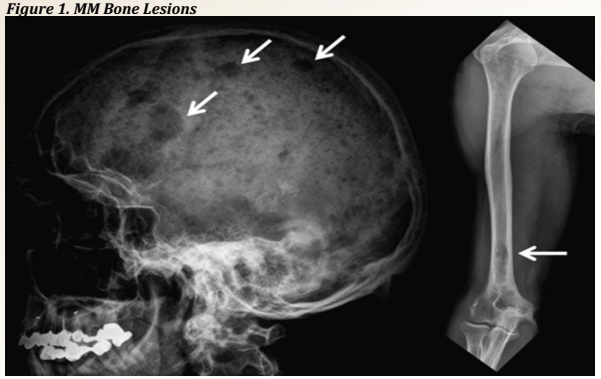
(Brigle & Rogers, 2017)

Bone marrow stromal cells: adhere to MM cells and, "support tumor cell proliferation, migration, drug resistance, and expression of anti-apoptotic proteins" (Rigle & Rogers, 2017, p. 227)

- Activate NF-kB to secrete cytokines which enhances the growth, adhesion, and overproduction of MM cells.
- Interleukin (IL)-6 a major cytokine involved in vascular endothelial growth factor (VEGF) secretin which increases vascularity inside the bone marrow.
- Enable microRNAs (miRNAs) to promote MM cell growth and overproduction through exosome release, also may have effect on drug resistance

(Brigle & Rogers, 2017)

Figure 1. MM Bone Lesions



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Bone marrow-derived mesenchymal stem cells

- "pluripotent potential" (can develop into fibroblasts, adipocytes, osteoblasts. (Rigle & Rogers, 2017, p. 228)
- Support growth and overproduction of MM cells through secretion of adhesion molecules, cytokines, and chemokines.

Osteoblast and Osteoclast activity

- Osteoblast suppression
- Osteoclast activation due to MM cell secretion of cytokines. IL-6 secretion by osteoclast stimulates further MM cell proliferation
- Overall increase of osteolysis leading to bone lesions (Figure 1).
- *Therapy targeting osteoclasts is key in major reduction or delay in skeletal pathology related to MM.*

(Brigle & Rogers, 2017)

Adipocytes

- Secrete leptin, adiponectin, IL-6 which are involved in MM cell growth.
- Large quantity of adipocytes in bone marrow

Endothelial Cells

- Promote neovascularization in bone marrow
- Contribute to overproduction of MM cells by supplying massive quantity of IL-6.

Immune System Alterations

- Increase in immunosuppressive cells (CD4+ Tregs
  - Enhanced in bone marrow because of increased levels of IL-6 and a growth factor.
  - Encourage osteoclast proliferation
- Increase in apoptotic ligands and receptors
- Decrease, suppression, and alternation of function in antitumor mediated cells (CD8+ cytotoxic T cells and NK cells)

(Brigle & Rogers, 2017)

Signs & Symptoms

Nonspecific:

- nausea, vomiting, weakness, fatigue, weight loss, recurrent infections, anemia, bone pain, renal dysfunction, hypercalcemia, pathologic fractures. Refer to Table 1 (Michels & Peterson, 2017).

Asymptomatic

- Patients may present without symptoms but MM is then discovered by laboratory analysis and findings of hypercalcemia, proteinuria, and anemia. (Michels & Peterson, 2017)

Long Term Effects: Serum Hyperviscosity and dysfunctional plasma cell infiltration and production of monoclonal light chains leads to end organ damage (Michels & Peterson, 2017).

Diagnostic Criteria According to Michels and Peterson, 2017:

"Both criteria must be met:

(1) Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma

(2) Any one or more of the following myeloma-defining events: Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

Hypercalcemia: serum calcium > 1 mg per dL (0.25 mmol per L) higher than the upper limit of normal or > 11 mg per dL (> 2.75 mmol per L)

Renal insufficiency: creatinine clearance < 40 mL per minute per 1.73 m2 (0.67 mL per second per m2) or serum creatinine > 2 mg per dL (177 µmol per L)

Anemia: hemoglobin > 2 g per dL (20 g per L) below the lower limit of normal, or a hemoglobin value < 10 g per dL (100 g per L)

Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or positron emission tomography/CT Clonal bone marrow plasma cells ≥ 60% Involved: uninvolved serum free light chain ratio ≥ 100 (involved free light chain level must be ≥ 100 mg per L) More than one focal lesion on MRI studies (≥ 5 mm size) " (p. 376, Table 3).

Implications for Care

International Staging System using serum beta2-microglobulin and albumin levels

- International Myeloma Working Group (IMWG) recently presented new *Revised International Staging System* to include chromosomal alterations. Predicts, "progression free and overall survival and has been recommended for use in future studies". (Michels & Peterson, 2017, p.378)

Implications for Care

Treatment

- *Myeloablative chemotherapy using two or three drug combinations and autologous stem cell transplantation (ASCT)*

Common chemotherapy drugs used

- Corticosteroids: dexamethasone, methylprednisolone, prednisone
- Alkylating agents: Melphalan (Alkeran), cyclophosphamide
- Immunomodulatory drugs: thalidomide, lenalidomide(Revlimid)
- Proteasome inhibitors: bortezomid (Velcade), carfilzomib (kyprolis)

(Michels & Peterson, 2017, p.380)

Special Treatment Considerations

- Avoid nephrotoxic medications and studies using contrast media due to renal dysfunction
- Acute kidney injury with MM: at least 3L per day of intravenous normal saline in addition to dexamethasone to decrease serum light chain if elevated.

(Michels & Peterson, 2017)

Bone Modifying Agents

- Zoledronic acid (Reclast), pamidronate, denosumab
- Refer to the American Society of Clinical Oncology's 2017 Clinical Practice Guidelines update cited in the additional sources section for specific recommendations, selection, dosing, duration, and monitoring of BMAs with MM

(Anderson, Ismaila, & Kyle, 2017)

High Risk of Thromboembolic Events

- Prevention with low-molecular-weight-heparin or warfarin with target INR of 2 to 3 (American Society of Clinical Oncology).
- Stratify thromboembolic risk factors for treatment and consider aspirin alone for low-risk patients (IMWG).

(Michels & Peterson, 2017, p.380)

High Risk of Recurrent and/or Life Threatening Infection

- Vigilance and speed in recognition and treatment
- May use prophylactic antibiotics: Trimethorprim/sulfamethoxazole, fluoroquinolone, penicillin
- Intravenous immune globulin
- Prophylactic antivirals if taking proteasome inhibitors due to risk of varicella-zoster virus
- Immunizations: pneumococcal pneumonia, Haemophilus influenza, influenza virus, especially for stem cell transplant patients.

Anemia Common with MM : Restrictive transfusion policy supported for hemoglobin levels less than 7 g per dL (Michels & Peterson, 2017).

Conclusion

*Providers should be aware of evaluation and management of MM in relation to other plasma cell dyscrasias for prompt diagnosis and treatment***.** Refer to Figure 1 in the March 2017 American Family Physician Journal Article, Volume 95, Number 6, *Multiple Myeloma: Diagnosis and Treatment* for an excellent flowchart to assist with management and treatment (Michels & Peterson, 2017).

Providers should also be aware of plasma cell diseases that progress to MM (MGUS and Smoldering MM) (Brigle & Rogers, 2017).

Overall diagnostic workup for suspicion of MM includes, "lab studies, urine studies, bone marrow biopsy, and radiographic evaluation" (Brigle & Rogers, 2017, p.231).

For *specific diagnostics* refer to Seminars in Oncology Nursing Volume 33, Number 3, *Pathobiology and Diagnosis of Multiple Myeloma* (Brigle & Rogers, 2017, Table 7, p. 231).

Current findings confirm survival improvements for patients with MM.

- Populations that should be considered regarding survival improvement: older populations (75+ years) and minority populations (Costa et al., 2016)

Significant expansion of molecular pathophysiology of MM over the last decade has allowed progression of study of various MM pathogenesis pathways (Lawasut et al., 2013).

References Cited & Additional Sources

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