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**Objectives:**

1. Review the pathogenesis and etiology of the most common complications of multiple myeloma (MM).
2. Describe the basics of testing for plasma cell dyscrasias.
3. Differentiate between monoclonal gammopathy of unknown significance (MGUS), smoldering myeloma (SMM), and MM.
4. BONUS: Understand the prognosis and natural course of MM.
5. BONUS: Recognize complications of MM and side effects of commonly used treatments.

**Teaching script instructions:**

Plan to spend at least 45-60 minutes preparing for this talk by reading through the Facilitator Guide and clicking through the Interactive Board to familiarize yourself with the animations. All clickable elements will be denoted as a rounded, shaded rectangle and/or a mouse cursor.

**Anticipated time to deliver the talk:**

* Objectives 1-3: 30 min
* Bonus objectives 4-5: 10-20 min (depending on depth of coverage)
* Cases: 10 min

Print out copies of the Learner’s Handout so they may follow along during the presentation and take notes as you expand on the decision tree and apply it through the practice cases. Begin with reviewing the objectives for the session.

**Introduction: (*Pathogenesis – Basic*)**Start with a brief review of the disorders that comprise plasma cell disorders - multiple myeloma (MM), monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), solitary plasmacytoma, Waldenström’s macroglobulinemia, primary amyloidosis (AL), heavy chain disease, POEMS syndrome, type I and II cryoglobulinemia. For this talk, we will just focus on MGUS, SMM, and MM.

*Click on each of the prompting buttons to briefly review lymphoid lineage, plasma cell function, and basic immunoglobulin structure.*

* *Lymphoid lineage:* Lymphoid progenitor cells differentiate into B cells which further differentiate into plasma cells once an antigen has been presented.
* *Plasma cell function:* Plasma cells can make IgG, IgM, IgD, IgA, and IgE.
* *Immunoglobulin structure:* Each immunoglobulin is comprised of a heavy chain and a light chain. Each light chain is either kappa (κ) or lambda (λ) in origin and in the absence of disease there is a relative balance of κ and λ light chains. A “clonal” expansion” will have an abnormally high proportion of either κ or λ. An M protein (also called a paraprotein, monoclonal protein, or M component) is a monoclonal immunoglobulin secreted by an abnormally expanded clone of plasma cells in an amount that is above the polyclonal immunoglobulin background. A clonal plasma cell population may produce an intact antibody such as IgG or IgA, primarily the serum free light chain component, or some amount of both.

**Objective 1: Review the pathogenesis and etiology of most common complications of MM (*Pathogenesis – Pathology*)**

Expansion of plasma cells in the bone marrow and large volumes of circulating M proteins wreak havoc and cause the clinical findings we see in plasma cell dyscrasias.

*Ask your learners to guess what clinical findings are a result of bone marrow infiltration, RANK-L production, and paraprotein (M protein) deposition. Click on each button to reveal the answer.*

* *Bone marrow infiltration:* Plasma cell infiltration in the bone marrow replaces normal cell lineages and leads to anemia and profound immunocompromise. Increased risk of infection is a result of impaired lymphocyte function and suppression of normal plasma cell function.
* *Increased RANK-L production:* Plasma cells release osteoclastic activating factors which leads to increased RANK-L production. Both factors lead to bone resorption, resulting in hypercalcemia and osteolytic bone lesions and fracture.
* *Paraprotein-production*: This leads to renal disease, with diverse pathology. In myeloma, this is most commonly cast nephropathy with an acute reduction in GFR. In other conditions like AL amyloid, it is often associated with nephrotic syndrome. In POEMs and Waldenström’s, this leads to neuropathy, but this is rare in MM.

**Objective 2:****Describe the basics of testing for plasma cell dyscrasias (*Testing – SPEP, UPEP, FLC*)**

SPEP: A serum protein electrophoresis (SPEP) is the standard screening method for the detection of multiple myeloma. It involves using electrophoresis to separate out the total protein in the blood by charge. Alpha1 includes HDL and alpha1 antitrypsin; Alpha 2 includes haptoglobin; Beta includes transferrin and C3; Gamma is the globulin region.

* *Abnormal SPEP*: The SPEP allows you to identify and measure a monoclonal protein. The M spike is most commonly detected in the Gamma region but may also be seen in in the Beta or Alpha 2 regions.
* *Example SPEP*: Your results will often be shown in tabular form such as this. Note that the protein measured in the table includes both the polyclonal and monoclonal portion. The monoclonal protein will be a slightly lower value measured in a separate statement.
* *Example immunofixation (IFX)***:** Serum immunofixation is more sensitive than SPEP and also determines the heavy and light chain type of the monoclonal protein (i.e. IgG vs IgA). However, unlike SPEP, immunofixation does not give an estimate of the size of the M protein (i.e., its serum concentration), and thus should be done in conjunction with electrophoresis.You can also have a false positive with polyclonal elevation in IgG in things like infection. Thus, it is always important to combine this test with a test for clonality.
* *Sensitivity*:SPEP with immunofixation has 80% sensitivity to detect plasma cell dyscrasias.

UPEP: Traditionally, urine protein electrophoresis (UPEP) with urine immunofixation was used to increase the sensitivity of testing. This test detects free light chains (so called “Bence Jones” proteins) that are small enough to pass through the glomeruli, into the urine. Remember that urine protein on a dipstick is just albumin, so will miss Bence Jones proteins.

* *Why obtain a UPEP?*: Combined, SPEP + UPEP increases the sensitivity to 95%. However, this test must be collected on using a 24-hour urine collection; thus, there is a newer method used to screen for plasma cell dyscrasias which primarily produce serum free light chains.

FLC: kappa-lambda free light chain (FLC) assay isa newer method, which can replace the time-consuming UPEP as part of plasma cell disorder screening. This testmeasures the ratio of κ and lambda light chains in the serum.In normal circumstances, the ratio of κ to λ light chains is roughly equal and a normal ratio is 0.26-1.65.

*Click on each of the scenarios – “normal,” “κ disease,” “λ disease,” “ESRD,” and “MM”*

* *κ disease:* A ratio > than 1.65 suggests and κ clone due to overproduction of κ light chains.
* *λ disease:* A ratio <0.26 suggests a gamma clone due to overproduction of λ light chains.
* *ESRD:* Renal disease may cause reduced excretion of both kappa and lambda free light chains and elevate the ratio up to 3. Ratios > 4 or < .25 should raise high suspicion for plasma cell dyscrasia.
* *MM:* Ratio >100 or <0.01 with a high elevation of the effect serum free light chain may be diagnostic of MM.

*Ask your learners, “Why obtain a serum FLC?” and click to reveal the answer*.

Up to 16% of patients with multiple myeloma have “light chain” only disease that may be missed with SPEP alone. FLC in conjunction with SPEP increases sensitivity to ~ 99% and can replace UPEP, which requires a 24 h urine collection.

**Objective 3: Differentiate between monoclonal gammopathy of unknown source, smoldering myeloma, and MM. (*Differential*)**

Multiple myeloma exists on a spectrum of MGUS, smoldering myeloma, and MM. Presence and size of an M-spike on SPEP and immunofixation (and/or UPEP) is used in conjunction with bone marrow biopsy and the presence of end organ damage or myeloma-defining events to differentiate between these diagnoses. *Click on each of the diagnoses.*

**MGUS** *-* MGUS is defined as an M protein <3 g/dL in serum and <500 mg/24-hour period in urine as well as <10% clonal cells in the bone marrow and no signs of end organ damage. Specifically, we define end organ damage as the CRABI symptoms:

* **C**alcium ≥ 11 mg/dL
* **R**enal dysfunction with serum Cr ≥ 2 mg/dL
* **A**nemia with Hgb < 12 g/dL not from another etiology
* **B**oney lytic lesions, pathologic fracture
* **I**mmunodeficiency (hypogammaglobulinemia) with resultant recurrent infections.

**Smoldering myeloma** *-* Smoldering myeloma is when we can measure the M protein ≥3 g/dL or ≥500 mg/24-hour period or a bone marrow biopsy shows 10-60% plasma cells, but still no CRABI symptoms. This requires a thorough radiographic evaluation to ensure lytic lesions aren’t missed. While whole body x-rays are easy to obtain, they may miss small lytic lesions. MRI is more sensitive but may be challenging to obtain. PET/CT is the most sensitive modality and currently the gold standard for evaluation.

*Why should we care?* It is important to differentiate MGUS and SMM because the risk of progression with MGUS is 1% per year and the risk of progression with smoldering myeloma is 10% per year for the first 5 years and 5% per year over the following 5 years.

**MM** - MM is diagnosed when the M protein is ≥3 g/dL or ≥500 mg/24-hour period or a bone marrow biopsy shows 10-60% plasma cells AND there is presence of CRABI end organ damage or a MM defining event. Myeloma defining events established by the International Myeloma Working Group are:

* Marrow involvement >60%
* An extramedullary plasmacytoma
* An elevation in FLC greater than 100mg/dL with FLC ratio >100 or <0.1
* >1 focal lesion on MRI

There are several subtypes of MM with IgG and IgA being the most common. Light chain myeloma is the third most common subtype, representing ~ 16% of all cases of MM and can be missed by SPEP and immunofixation alone. Additionally, a subset of patients (up to 13%) with MM have oligo-secretory and non-secretory myeloma. The Revised International Myeloma Working Group uses the M protein spike to differentiate between these subtypes. Oligo-secretory myeloma will have M protein < 1 g/dL (or urine M protein <200 mg/24h), but frequently will have abnormal FLCs. Non-secretory myeloma completely normal SPEP and UPEPs and FLC ratios.

**Objective 4:**  **Understand the prognosis and natural course of MM (*Prognosis*)**

*A brief overview of the labs and testing required for prognostication and an understanding of the median survival of the disease is beneficial to general internists and should be taught as part of the core topic. Anticipated time for this review is 2 min.*

*An in-depth review of the assessment of prognosis of multiple myeloma is considered a bonus objective for higher level learners. Anticipated time for this review is 5 min.*

MM is a heterogenous disease with variable prognosis. The Revised International Staging System (R-ISS) is used to stratify patient’s risk. This system was developed based on a study of 3060 patients with newly diagnosed multiple myeloma from 11 international trial.

* *Stage I*: Serum β2-microglobulin <3.5 mg/L, *and* normal LDH, *and* standard-risk chromosomal abnormalities by iFISH, *and* serum albumin ≥ 3.5 g/dl. A β2-microglobulin, LDH, and albumin should be ordered after a new MM diagnosis to help with prognostication.
* *Stage III:* Serum β2-microglobulin ≥5.5 mg/L *and* elevated LDH *or* high risk FISH features including del(17p), t(4;14), or t(14;16).
* *Stage II* is when a patient meets neither criterion for stage I nor III.

|  |  |  |  |
| --- | --- | --- | --- |
| R-ISS Stage | Overall survival (5 years) | Progression free survival (5 years) | Median survival |
| I | 82% | 55% | Not reached |
| II | 62% | 36% | 83 months |
| III | 40% | 24% | 43 months |

 *Other prognostic factors -* There are other factors that affect prognosis including tumor factors such as proliferation rate, plasma cell leukemia and extramedullary disease and patient-related factors such as age, performance status, renal function.

**Objective 5: Recognize complications of MM and side effects of commonly used treatments (*Treatment – Natural History, Medication Toxicities, Complications*)**

**Natural History**: *a brief overview of the natural history (e.g., incurable disease, eventual relapse, and lifelong maintenance therapy) is beneficial to general internists and should be taught as part of the core topic. Anticipated time for this review is 2 min.*

*An in-depth review is considered a bonus objective for higher level learners. Anticipated time for this review is 5 min.*

MM is not a curable disease. The natural history for patients is that most patients will relapse and/or require lifelong therapy for maintenance of remission. This graphic shows a plot of the M-protein level over time. For most patients, the M-protein spike can be used to follow disease activity with higher M-spike correlating with worsening disease or relapse. Patients with oligosecretory, non-secretory, or light chain only subtypes of myeloma are followed using other parameters.

* *Induction* - The treatment starts with induction therapy. A three-drug regimen is better than 2, and recent research suggests 4 drugs may be better than 3 in appropriate patients. This is usually achieved with a combination of proteasome inhibitors, immunomodulatory agents, steroids, and/or monoclonal antibodies. Specific drugs and complications of these medications used in are further discussed in the “Med Tox” page.
* *AutoSCT* -If feasible, inclusion of autologous stem cell transplant (auto-SCT) remains an important part of therapy for many patients. While this is a tough treatment, there is a survival benefit, and so those up to age 75, ECOG <3, and absence of cirrhosis and severe HF should all be considered by a referral to a transplant center.
* *Maintenance –* Maintenance therapy is used to keep patients in remission. Most patients are maintained on a reduced form of therapy, often indefinitely, after achieving response to initial treatment*.*
* *Relapse and Treatment Intensification -* Patients are followed with serial laboratory monitoring of M protein until relapse, at which point treatment would be intensified again with use of new agents.
* *Subsequent relapses - The* cycle of relapse and remission continues indefinitely.

**Medication Toxicities**: *a brief overview of common toxicities of MM therapies is beneficial to general internists and should be taught as part of the core topic (e.g., all causing some degree of myelosuppression, GI irritation and increased risk of infections; immunomodulatory agents increasing risk of VTE/arterial thrombosis and the need for VTE prophylaxis when on therapy). Anticipated time for this review is 2 min.*

*An in-depth review is considered a bonus objective for higher level learners. Anticipated time for this review is 5 min.*

The most common medications used to treat MM are proteosome inhibitors (such as bortezomib/Velcade and carfilzomib/Kyprolis), immunomodulatory agents (such as Lenalidomide/Revlimid and Pomalidomide/Pomalyst), steroids, and monoclonal antibodies [daratumumab or Isatuximab (anti-CD38) and elotuzumab (anti-SLAMF7)].

* *Proteosome Inhibitors -* The most common side effects of the proteosome inhibitors are myelosuppression, GI irritation, and neuropathy. It’s important to note that this medication puts you at high risk for herpes zoster reactivation and patients should be on continuous shingles prophylaxis.
* *Immunomodulatory Agents -* The most common side effects of the immunomodulatory agents are also myelosuppression, GI irritation, and infections. These patients are also at high risk for VTE and arterial thrombosis and should take prophylaxis using an aspirin or full anticoagulation. This decision is made by their primary oncologist based off risk factors for VTE.
* *Steroids -* Patients may remain on high dose steroids for extended periods of time and should be considered for infection (specifically PJP) prophylaxis, GI prophylaxis, and prevention of osteoporosis.
* *Monoclonal Abs -* There are new treatments for plasma cell dyscrasias emerging every year. Three of the most common for MM (daratumumab, isatuximab and elotuzumab) have similar side effects of myelosuppression, GI irritation, and immunosuppression. Patients may also experience acute infusion reactions, dyspnea, edema, and arthralgias.

**Complications**:

* *Anemia -* Check patients for iron deficiency or other reversible causes of anemia. Some patients may require supportive transfusions.
* *Immunodeficiency -* If patients experience very frequent infections, consider checking IgG levels. If IgG <500, IVIg could be considered.
* *Hypercalcemia -* Many patients are hospitalized for symptomatic hypercalcemia. Bisphosphonates are the mainstay of therapy for hypercalcemia of malignancy. IVF and other temporizing measures such as calcitonin and IVF can be used in conjunction.
* *Boney lytic lesions -* Patients with boney/lytic lesions should get vitamin D supplementation (Ca if not hypercalcemic), a bisphosphonate with systemic therapy, and potentially palliative radiation. These patients are high risk for complications and may be sensitive to other approaches so avoiding surgery unless necessary.
* *Renal disease -* Worsening renal function or myeloma kidney is a serious complication. Providers should give IV fluids to a target urine output of 3L/day and concurrently correct hypercalcemia. It is important to start systemic therapy urgently once diagnosis is confirmed.

**Take Home Points:**

1. MM, MGUS, and smoldering myeloma are plasma cell dyscrasias involving abnormal expansion of plasma cells. These lead to complications CRABI - hyperCalcemia, Renal dysfunction, Anemia, Boney lesions, and Immunodeficiency.
2. An SPEP with immunofixation and serum FLCs are used to make the diagnosis of MM. Adding a UPEP or FLC improves the sensitivity of an SPEP. However, a UPEP is cumbersome to obtain and is rarely used.
3. MM can be differentiated from smoldering myeloma and MGUS by the degree of M-protein spike, degree of bone marrow involvement, and signs of end-organ damage (CRAB complications).

**References:**

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3. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification, and response assessment of multiple myeloma. Leukemia 2009; 23: 3-9.