

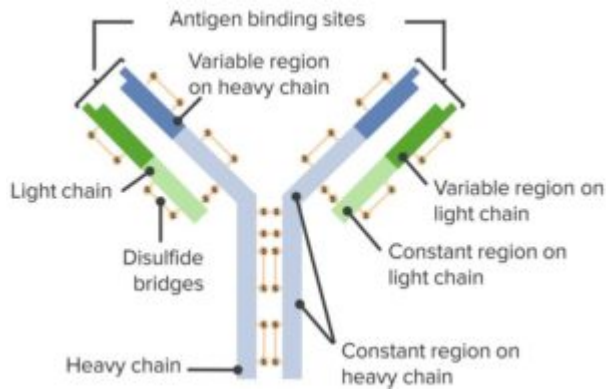
Plasma Cell Neoplasms including Multiple Myeloma

[See online here](#)

Plasma cell neoplasms are the cancers of plasma cells that are responsible for producing antibodies in our bodies. These abnormal plasma cells proliferate rapidly in the bone marrow causing extensive bone destruction. They also produce increased quantities of monoclonal immunoglobulins (M-protein) that build up in our body, leading to the thickening of the blood and damaging our kidneys.



Introduction



"Plasma Cell Neoplasms" Image created by Lecturio

Plasma cell neoplasms, as the name indicates, are the cancers of the plasma cells.

Plasma cells are the antibody-producing, fully differentiated, mature B-cells that have undergone somatic hypermutation and immunoglobulin heavy chain class switching.

A **plasmacytoma** is a solitary, separate, distinct mass of neoplastic plasma cells. It is present either in the bone marrow (medullary) or in various soft tissues (extramedullary).

Pathophysiology of Plasma Cell Neoplasms

The plasma cells are the antibody-producing, fully differentiated, mature B-cells that have undergone somatic hypermutation and immunoglobulin heavy chain class switching. These cells normally produce polyclonal immunoglobulins, which means a wide variety of immunoglobulins are produced with different heavy and light chains that help us combat infections. In plasma cell neoplasms, the immunoglobulins are

In plasma cell neoplasms, the monoclonal plasma cells proliferate rapidly and form a mass. These cells are large cells with a single nucleus and nucleolus along with the prominent Golgi apparatus, responsible for immunoglobulin production. These cells often have an eccentric nucleus.

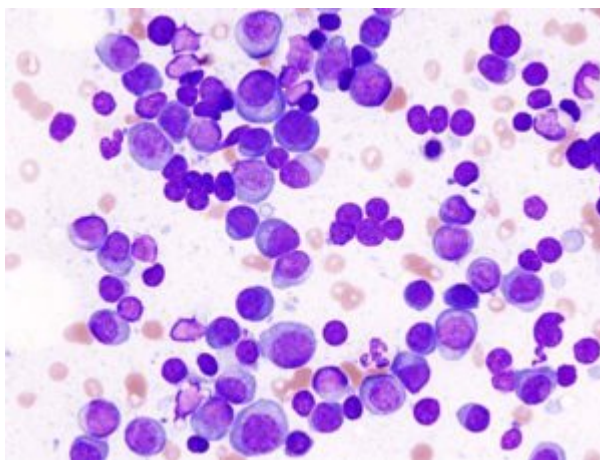


Image: "Multiple myeloma" by KGH. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

The neoplastic plasma cells produce **monoclonal** immunoglobulins, which means only a single type of immunoglobulin (M-protein) with the same heavy and light chain is produced by the malignant cells. The M-protein builds up in the body and may lead to kidney and widespread tissue damage. The increased neoplastic plasma cells do not fight infections but, ironically, prevent normal plasma cells from producing normal

immunoglobulins leading to an increased risk of infections.

Etiology of Plasma Cell Neoplasms

The exact etiology of plasma cell neoplasms is not yet known, however, certain theories have been put forward that may act as the triggering factors, such as chronic antigenic stimulation, chronic infections, chemical and radiation exposure.

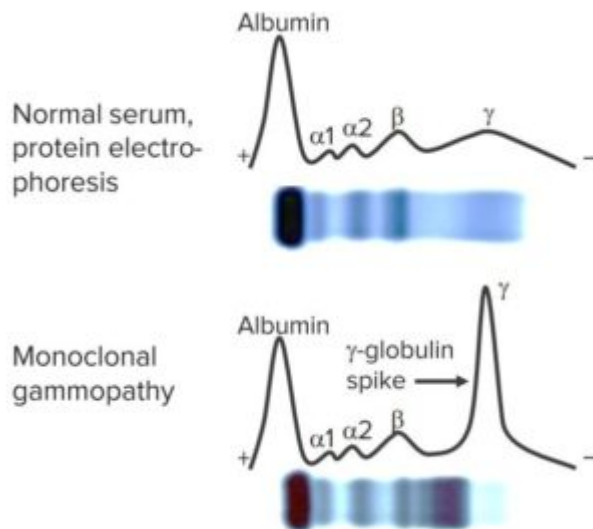
Classification of Plasma Cell Neoplasms

The World Health Organization (WHO) has classified plasma cell neoplasms into different groups. A simplified version of this classification is a monoclonal gammopathy of unknown significance and plasma cell myelomas like asymptomatic myeloma, nonsecretory myeloma, and plasma cell leukemia. A second classification is plasmacytoma, which can be divided into solitary plasmacytoma of the bone and extramedullary plasmacytoma.

Another classification of plasma cell neoplasms is according to their presentation, localized or diffuse.

- Localized plasma cell neoplasms include plasmacytomas, both solitary plasmacytomas of the bone and extramedullary plasmacytomas of the soft tissue.
- Diffuse lesions include multiple myeloma, plasma cell leukemia, and monoclonal gammopathy of unknown significance.

Multiple Myeloma (MM)



Multiple Myeloma. Image created by Lecturio

MM is characterized by the malignant proliferation of plasma cells within the bone marrow producing a monoclonal immunoglobulin (M-protein), mostly composed of immunoglobulin G (IgG) (>50% of cases). The rest of cases contain immunoglobulin A (IgA) (20%) or light-chain only (15%). It is an aggressive neoplasm that causes extensive bone destruction.

Epidemiology

The incidence of MM increases with age and the median age of presentation is 68 and 70 years in men and women, respectively. It is twice as common in men as compared to women. It accounts for 10% of all hematologic neoplasms.

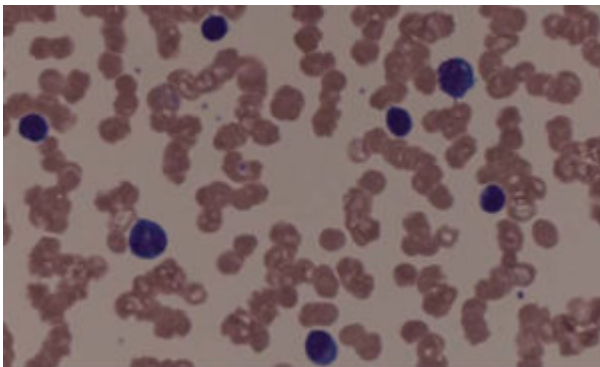
Pathophysiology

In MM, the neoplastic plasma cells produce certain cytokines that stimulate osteoclasts, which results in bone reabsorption and lytic lesions. This leads to bone pain, pathological fractures, and hypercalcemia. The bone marrow involvement results in normochromic normocytic anemia or pancytopenia.

Clinical Presentation

The clinical presentation of MM is related to the bone destruction, bone marrow involvement, and increased serum paraprotein. The common clinical features are bone pain, weakness, bleeding, anemia, infections, renal failure, fatigue, pathologic fractures, spinal cord compression, neuropathies, and hyperviscosity syndrome.

Anemia is normocytic and normochromic with low reticulocyte counts. ESR is typically raised and peripheral blood film may show **rouleaux formation**. **Hypercalcemia** is a common finding.



[Image](#): "Rouleaux formation" by Michail Charakidis, David Joseph Russell. License: [CC BY-SA 2.0](#)

International Myeloma Working Group (IMWG) criteria for the diagnosis of Multiple Myeloma is > 10% clonal bone marrow plasma cells or a biopsy-proven bone or extramedullary plasmacytoma.

Plus one or more of the following features of end-organ damage:

- Serum calcium > 1 mg/dL higher than the upper limit of normal or > 11 mg/dL
- Creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL
- Hemoglobin < 10 g/dL
- Radiographic evidence of > 1 osteolytic lesion

The most common causes of death in these patients are:

Renal failure: It is largely due to light-chain depositions in the kidney (Bence-Jones protein), renal amyloidosis, hypercalcemia, and hyperuricemia. The raised serum creatinine is present in half of the patients at the time of diagnosis.

Infections: The excessive monoclonal immunoglobulins are non-protective and, ironically, they decrease the production of normal protective immunoglobulins.

Diagnostic Tests

The bone marrow biopsy is the single most specific test for multiple myeloma. The presence of > 10% of plasma cells often constitutes the diagnosis. The other diagnostic tests needed are:

- Complete blood count (CBC) with peripheral smear: for anemia, pancytopenia, and rouleaux formation
- Skeletal survey: for osteolytic lesions
- Serum and urine protein electrophoresis: for M-protein and Bence-Jones protein, respectively
- BUN and creatinine: renal failure
- Serum calcium
- Albumin and beta-2 microglobulin: prognostic indicators

Staging

The International Staging System (ISS) is a simple risk assessment algorithm to predict the prognosis of patients with multiple myeloma. It uses 2 laboratory serum tests, albumin, and beta-2 microglobulin levels.

	Criteria	Median Survival (years)
Stage I	Serum β_2 -microglobulin < 3.5 mg/L Serum albumin \geq 3.5 g/dL	5.2
Stage II	Not stage I or III	3.6
Stage III	Serum β_2 -microglobulin \geq 5.5 mg/L	2.4

Management

The management of multiple myeloma depends upon the disease stage. The advanced stages are managed with chemotherapy with or without hematopoietic stem cell transplantation (HSCT).

Various chemotherapeutic combination regimens have been used and outcomes have been progressively improving. The common therapeutic agents used in MM are **thalidomide, melphalan, prednisolone**, and more recently, the proteasome inhibitor, **bortezomib**. Bisphosphonates are used to reduce bone pain and fractures. In addition to the basic chemotherapy, radiotherapy may also be used. The HSCT is efficient in early stages of the disease and prolongs survival.

The supportive treatment is provided to treat hypercalcemia (hydration/diuresis), hyperuricemia (hydration/allopurinol), bone pain and fractures (bisphosphonates) and anemia (erythropoietin). These patients should be vaccinated to prevent the infections.

Asymptomatic Plasma Cell Myeloma

This condition is similar to MM, but these patients are asymptomatic and there is no evidence of end-organ damage.

Diagnostic criteria for asymptomatic plasma cell myeloma:

- Elevated serum monoclonal protein (> 3 g/dL).
- $> 10\%$ clonal plasma cells in the bone marrow.
- No evidence of end-organ damage, namely hypercalcemia, renal insufficiency, and anemia (laboratory signs of lytic lesions of bone).

Monoclonal Gammopathy of Undetermined Significance (MGUS)

MGUS is characterized by increased monoclonal immunoglobulin (M-protein) in the serum or urine, produced by the premalignant monoclonal plasma cells. It is an asymptomatic condition and is often detected incidentally on serum electrophoresis done for other reasons.

MGUS is the most common plasma cell neoplasm comprising about two-thirds of all the cases. Its incidence increases with age and is present in around 5% of the population over 70 years.

Diagnostic criteria for MGUS are serum M-protein present < 30 g/dL and $< 10\%$ clonal plasma cells on bone marrow aspiration. Also, the absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions or amyloidosis that can be attributed to MM. Another criterion is no evidence of other B-cell lymphoproliferative disorders.

It is important to differentiate MGUS from MM because the treatment options are different. The MGUS is a benign condition and treatment is conservative. The patients should be followed over time as there is an increased risk of transformation into multiple myeloma.

Plasma Cell Leukemia

Plasma cell leukemia is characterized by high blood levels of malignant plasma cells. It is an aggressive rare variant of MM. It can occur primarily as an initial manifestation, comprising about 2–5% of all plasma cell neoplasms, or secondarily due to the leukemic transformation of MM.

The clinical presentation of plasma cell leukemia is similar to MM and other leukemias, such as anemia, infections, bleeding, bone pain, hepatomegaly, splenomegaly, renal dysfunction, hypercalcemia, and lytic bone lesions. The significant hepatic involvement or pleural effusions containing malignant plasma cells often suggests the diagnosis of plasma cell leukemia.

The diagnosis is initially based upon an evaluation of the CBC and peripheral blood smear showing increased monoclonal plasma cells comprising of $\geq 20\%$ of peripheral blood white cells or absolute plasma cell count of ≥ 2000 /mCL. The other features of MM will also be present, such as bone marrow aspiration and biopsy revealing $\geq 10\%$ monoclonal plasma cells; serum and urine protein electrophoresis showing increased monoclonal

immunoglobulins.

A plasma cell leukemia diagnostic criteria is the presence of clonal plasma cells in peripheral blood, $> 2 \times 10^9/L$ or $> 20\%$ of leukocytes.

The plasma cell leukemia has a very poor prognosis. The median survival is less than a year, with 1/4th of the patients dying within the first month. The aggressive chemotherapy with VDT-PACE (Velcade [Bortezomib], **D**examethasone, **T**halidomide, **CisP**latin, **A**driamycin [Doxorubicin], **C**yclophosphamide, and **E**toposide) followed by hematopoietic cell transplantation has been instated without much success.

Solitary Plasmacytomas of the Bone (SBP)

SBPs constitute approximately 2-5% of all plasma cell neoplasms. They are more common in males and their incidence increases with age. The SBPs have a preference for the axial skeleton, most commonly involving thoracic vertebrae, although any bone can be involved.

The clinical presentation of SBPs ranges from asymptomatic incidental finding to pain, pathological fractures, and/or spinal cord compression depending upon the involved bone.



[Image](#): "Plasmocytome lytique tiers inf femur" by Grook Da Oger. License: [Public Domain](#)

The diagnostic criteria for SBP are radiographic evidence of a single bone lesion due to monoclonal plasma cell plus exclusion of MM by:

- Bone marrow aspirate showing $\leq 5\%$ of plasma cells.
- Serum or urine monoclonal proteins (low or absent).
- The absence of anemia, hypercalcemia or renal impairment.
- Preserved levels of uninvolved immunoglobulins.

The local radiation therapy is the recommended treatment for SBP. For peripheral plasmacytomas, not involving the spine, surgical resection is another option in addition to local radiation therapy.

Extramedullary Plasmacytomas of the Soft Tissue

The extramedullary plasmacytomas constitute only 3% of all plasma cell neoplasms. Like SBPs, they are more common in males and their incidence increases with age. The extramedullary plasmacytomas have a preference for the soft tissues of the head and neck (80%), followed by the gastrointestinal tract.

Diagnostic criteria for extramedullary plasmacytoma are soft tissue biopsy-proven monoclonal plasma cell neoplasms plus exclusion of MM by:

- Bone marrow aspirate showing $\leq 5\%$ of plasma cells.
- Serum or urine monoclonal proteins (low or absent).
- The absence of anemia, hypercalcemia or renal impairment.
- Preserved levels of uninvolved immunoglobulins.

The patients with extramedullary plasmacytoma may be asymptomatic for years or may present with vague features, such as rhinorrhea, sore throat, epistaxis, anorexia, hemoptysis, hoarseness or epigastric fullness. They may be confused with other carcinomas and lymphomas.

The local radiation therapy is the recommended treatment for extramedullary plasmacytoma. If the lesion is surgically resectable, then surgery has good long-term results.

Review Questions

The correct answers can be found below the references.

1. A 70-year-old woman complains of right thigh pain for 2 months, which is not relieved with the regular analgesics. She has also noticed increased fatigability during the same period. The CBC revealed pancytopenia. Bone marrow examination revealed clusters of plasmablasts, as well as atypical plasma cells that comprise 12% of all nucleated cells. An X-ray revealed multiple lesions in the right femur. What is the most likely diagnosis?

- A. Multiple myeloma
- B. Monoclonal Gammopathies of Undetermined Significance
- C. Waldenstrom Macroglobulinemia
- D. Solitary plasmacytoma of bone
- E. Plasma cell leukemia

2. A 66-year-old Afro-American man presents to you with a history of multiple fractures after trivial falls. On systemic inquiry, the patient confirms an elevated thirst and severe fatigue even at rest. Laboratory investigations reveal anemia and hypercalcemia. The urine exam reveals raised light chains of immunoglobulin (Bence-Jones protein). What neoplasm might be suspected according to the findings listed above?

- A. Multiple myeloma
- B. MGUS
- C. Hodgkin lymphoma
- D. Non Hodgkin lymphoma
- E. Bone sarcoma

3. Which of the following is considered a characteristic for MGUS?

- A. >30 g/dL of serum M-protein
- B. <30 g/dL of serum M- protein
- C. <10 g/dL of serum M-protein
- D. Absence of M-protein in the blood serum
- E. None of above

References

[Pathology of Plasma Cell Neoplasms](#) via [emedicine.medscape.com](#)

[Plasma Cell Neoplasms \(Including Multiple Myeloma\) Treatment \(PDQ®\)-Patient Version](#) via [cancer.gov](#)

[Plasma Cell Neoplasms \(Including Multiple Myeloma\)—Patient Version](#) via [cancer.gov](#)

[Bone marrow immunohistology of plasma cell neoplasms](#) via [ncbi.nlm.nih.gov](#)

[Multiple Myeloma Differential Diagnoses](#) via [emedicine.medscape.com](#)

Correct answers: 1A, 2A, 3B

Legal Note: Unless otherwise stated, all rights reserved by Lecturio GmbH. For further legal regulations see our [legal information page](#).

Notes