Plasma Cell Neoplasms, including Multiple Myeloma

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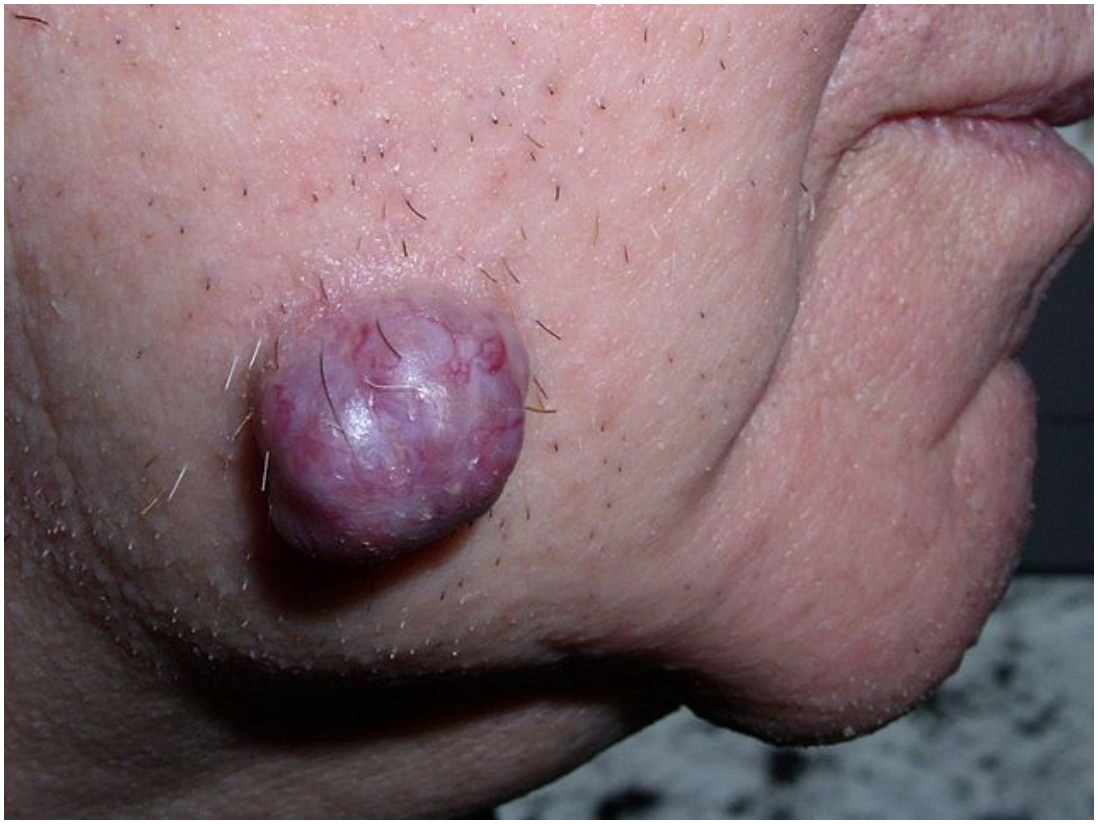
Plasma cell neoplasms are the cancers of plasma cells that are responsible for producing antibodies in our bodies. These abnormal plasma cells proliferate rapidly in the bone marrow causing extensive bone destruction. They also produce increased quantities of monoclonal immunoglobulins (M-protein) that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



Introduction

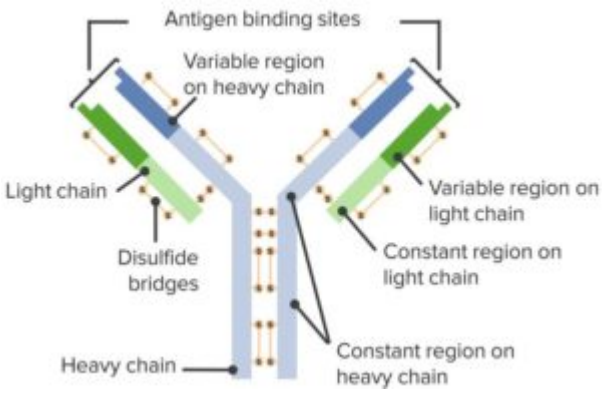


Image: Plasma cell neoplasms, by Lecturio

Plasma cells are 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 appears either in the bone marrow (medullary) or in various soft tissues (extramedullary).

Pathophysiology of Plasma Cell Neoplasms

Plasma cells typically produce polyclonal immunoglobulins, with different heavy and light chains that help combat infections. In plasma cell neoplasms, monoclonal plasma cells proliferate rapidly and form a mass. These cells are large, with a single nucleus and nucleolus, along with a prominent Golgi apparatus responsible for immunoglobulin production. These cells often have an eccentric nucleus.

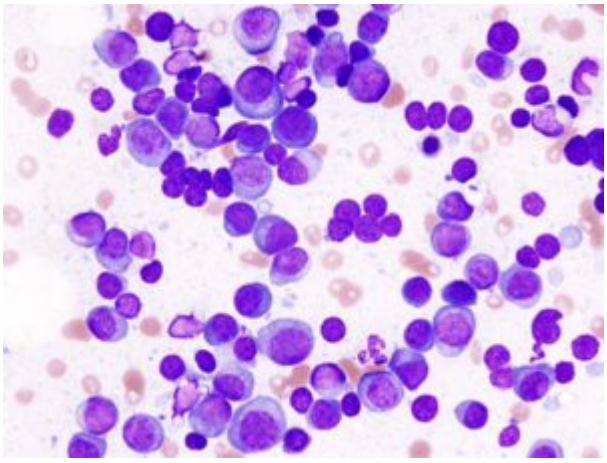


Image: Multiple myeloma, by KGH. License: CC BY-SA 3.0

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. Increased neoplastic plasma cells do not fight infections. Instead, they 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, chronic antigenic stimulation, chronic infections, or chemical or radiation exposure may be triggering

factors.

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, such as asymptomatic myeloma, nonsecretory myeloma, and plasma cell leukemia. A second classification is a plasmacytoma, 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)

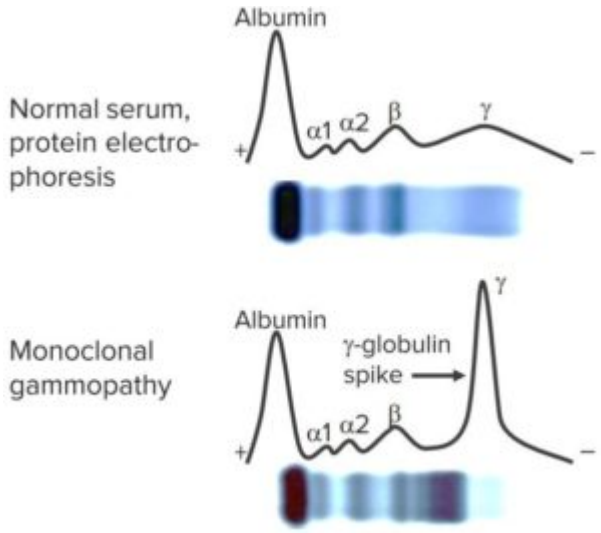


Image: Multiple myeloma, by Lecturio

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

Epidemiology

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

Pathophysiology

In MM, the neoplastic plasma cells produce specific 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 bone destruction, bone marrow involvement, and increased serum paraprotein. Standard clinical features include 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 elevated, and peripheral blood film may show **rouleaux formation**. **Hypercalcemia** is a common finding.

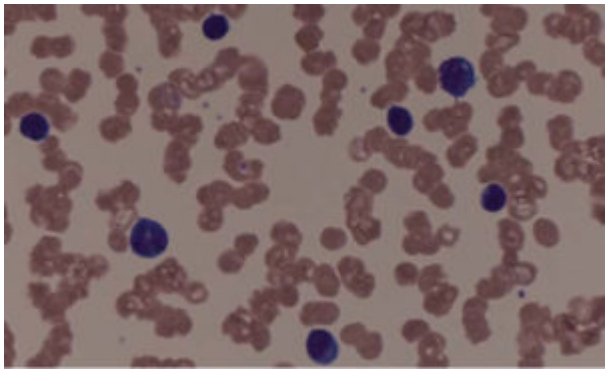


Image: Rouleaux formation, by Michail Charakidis, David Joseph Russell. License: CC BY-SA 2.0

International Myeloma Working Group (IMWG) criteria for diagnosing 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 mainly due to light-chain depositions in the kidney (Bence-Jones protein), renal amyloidosis, hypercalcemia, and hyperuricemia. The elevated serum creatinine is present in half of the patients at the time of diagnosis.

Infections: The excessive monoclonal immunoglobulins are non-protective and 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 for renal failure
- Serum calcium
- Albumin and beta-2 microglobulin for prognostic indicators

Staging

The International Staging System (ISS) is a simple risk assessment algorithm to predict the prognoses of patients with multiple myeloma. It uses two 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 ≥ 3.5 g/dL	5.2
Stage II	Not stage I or III	3.6
Stage III	Serum β_2-microglobulin ≥ 5.5 mg/L	2.4

Management

Managing multiple myeloma depends upon the disease stage. 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,** the proteasome **prednisolone,** and, more recently, the proteasome inhibitor, bortezomib. Bisphosphonates are used to reduce bone pain and fractures. In addition to chemotherapy, radiotherapy may also be used. The HSCT is efficient in the early stages of the disease and prolongs survival.

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

Asymptomatic Plasma Cell Myeloma

This condition is similar to MM, but these patients are asymptomatic with 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 that is produced by 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 cases. Its incidence increases with age and is present in around 5% of the population over 70.

Diagnostic criteria for MGUS are serum M-protein present < 30 g/L or < 3 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, 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. MGUS is usually a benign condition, calling for conservative treatment. However, patients should be followed over time since there is an increased risk of progression to 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 CBC results and a peripheral blood smear showing increased monoclonal plasma cells comprised of ≥ 20% of peripheral blood white cells or an absolute plasma cell count of ≥ 2000/mcL. The other features of MM will also be present, such as bone marrow aspiration and biopsy, revealing ≥ 10% monoclonal plasma cells, serum and urine protein electrophoresis, showing increased monoclonal immunoglobulins.

A plasma cell leukemia diagnostic criterion is clonal plasma cells in peripheral blood, > 2 × 109/L, or > 20% of leukocytes.

Patients with plasma cell leukemia have very poor prognoses. The median survival is less than a year; 1/4th of patients die within the first month. The aggressive chemotherapy with VDT-PACE (Velcade (Bortezomib), **D**examethasone, **T**halidomide, Cis**P**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 prefer 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.

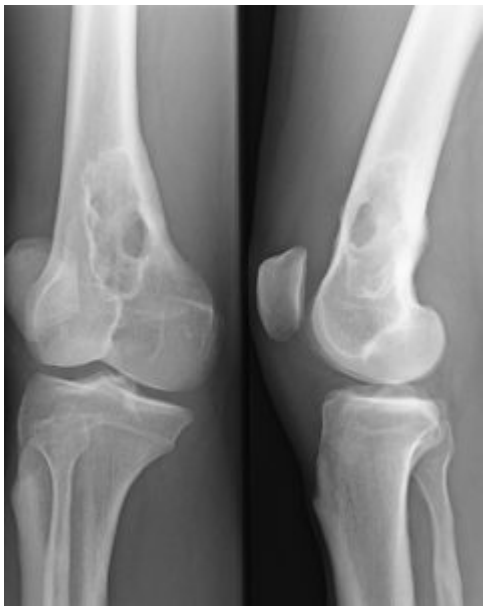


Image: Plasmocytome lytique tiers inf femur, by Grook Da Oger. License: Public Domain

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 ≤ 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

Local radiation therapy is the recommended treatment for SBP. Patients with peripheral plasmacytomas that do not involve the spine may be candidates for surgical resection along with 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. Extramedullary plasmacytomas are most common in 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 ≤ 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.

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

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

Notes