Paraprotein is an immunoglobulin produced and secreted by one single clone of B-cells. Paraproteinemias are diseases that are associated with paraprotein production.

It is a well-known fact that we are born with a very little immunity of our own. All of the newborn’s immunoglobulins are passively acquired transplacentally from the mother. As the newborn faces the antigenic challenges of its new existence, antibodies are started to be produced. Each clone of plasma cells, which is supposedly produced from one single B-lymphoid cell, purposefully produces antibody to one antigenic stimulus. As the child grows and gets exposed to countless number of antigens, different clones of plasma cells are generated producing different types of immunoglobulins. The ultimate result of this process is production of many plasma cell clones producing a polyclonal spectrum of immunoglobulins. Serum protein electrophoresis shows that under the gamma globulin hump. We call it polyclonal because different clones of plasma cells produce different types of immunoglobulins.

If for some reason there is malignant proliferation of one single clone of plasma cells, producing one single type of immunoglobulin, we call this monoclonal immunoglobulin a paraprotein. Conditions producing paraproteins are called paraproteinemias.

**MULTIPLE MYELOMA (MM)**

Myeloma is a plasma cell neoplasia. It results from infiltration of the bone marrow by malignant plasma cells.

MM constitutes 1% of all malignancies and 10% of hematological malignancies. The incidence is around 50 per million in Caucasians and double that in black people. It is usually a disease of the elderly and middle-aged people.

The hallmark of MM is an increase in the number of abnormal looking plasma cells in the bone marrow, which are called myeloma cells. The second important feature of MM is the presence of paraprotein in the serum or urine in 98% of patients at the time of diagnosis. The third diagnostic feature of MM is the presence of lytic bone lesions, which is found in 70% of patients. 4% of patients only show osteoporosis. In one quarter of patients, skeletal survey is normal.

A normal plasma cell produces as many light chains as heavy chains, which are then assembled and secreted to the circulation. Myeloma cells differ from normal plasma cells in that in more than 50% of cases an excess of light chains are produced in relation to heavy chains. The light chains in MM are filtered by the glomeruli and when the tubular re-absorption capacity is exceeded, they appear in the urine. Detection of a homogenous band of light chains on urinary electrophoresis is of considerable diagnostic importance in MM and related disorders. This monoclonal band of light chains is referred to as Bence - Jones protein.
In 20% of cases of myeloma, no heavy chains are synthesized. In the majority of cases of this type of myeloma (variously referred to as Light Chain Disease or Bence Jones only Myeloma) no serum paraprotein is detectable on routine electrophoresis and the only abnormality is found in the urine. In consequence, cases may be overlooked if the urine is not examined. In these cases even ESR might be normal, because plasma paraprotein is not increased.

2% of cases of myeloma cannot synthesize paraprotein; these are referred to as non-secretory myeloma.

In summary, the three cardinal features of myeloma are:

1. Paraproteinemia or Bence-Jones protein in the urine.
2. Plasma cell infiltration of the bone marrow.
3. Lytic bone lesions on skeletal survey.

Minimal criteria for the diagnosis of MM is more than 10% plasma cells in the bone marrow and one of the followings:

- Paraprotein of more than 30 gm/L
- BJP
- Lytic lesions.

It is important to exclude connective tissue diseases, chronic infections, metastatic carcinoma and lymphoma.

5% of patients are asymptomatic at presentation although they fulfill the minimal criteria for the diagnosis of MM. Their M-protein is more than 30 gm/L and marrow plasma cells are more the 10%; however, they are not anemic, do not have lytic lesions and their calcium and creatinine are normal. The plasma cell proliferation index is also low. These patients have smoldering myeloma. These patients can remain asymptomatic for very long periods and need not be treated. Bone marrow labeling index is helpful to differentiate between this condition and MM.

Other prognostic factors in MM are CRP, S IL-6R, β2M, creatinine level and presence of plasma cells in the peripheral blood.

The concentration of serum paraprotein in an individual myeloma patient is closely related to the tumor cell mass, a feature that enables the growth and regression of the neoplastic cell population to be monitored with a precision unmatched in any other class of human neoplasm. By knowing the concentration of the paraprotein in the serum and few more features, one can estimate the plasma cell burden. This is now used as a cornerstone for staging MM.

**PATHOPHYSIOLOGY & CLINICAL FEATURES OF MM**

(A). **Bone marrow infiltration** by plasma cells can lead to pancytopenia. Anemia, neutropenia and thrombocytopenia can all happen in MM. Neutropenia can cause infection, and thrombocytopenia can lead to bleeding. Bone marrow infiltration also suppresses the immunity, adding another cause to liability to infection in these patients. Bleeding gradually causes anemia.

(B). **Paraproteins** are very viscous and eventually leads to hyperviscosity syndrome which is characterized by CNS symptoms of visual problems, lassitude, clouding of consciousness, vertigo, fits and even coma.
The body tries to compensate for the hyperviscosity by diluting the plasma. This hemodilution can further aggravate the anemia. So anemia in MM is caused by *marrow infiltration*, *bleeding from thrombocytopenia* and *hemodilution*. Paraproteins can coat the platelets and interfere with the clotting factors, adding yet two more causes to bleeding in these patients.

*Light chains* are very toxic to the kidneys and can precipitate in the tubules, causing considerable damage. **Renal failure** is a well-known sequela of MM. *Amyloidosis* is a well-known association to MM and deposition of the amyloid material in the kidneys can aggravate the degree of renal failure. As myeloma patients are prone to infections, *pyelonephritis* is another cause for renal failure. Renal failure is another cause of anemia in these patients (Anemia of Chronic Disorders).

(C). The myeloma cells produce an “Osteoclast Activating Factor = OAF” that activates the osteoclasts to eat the bone, creating punched-out **Osteolytic Bone Lesions**, which are one of the most important features of this disease. OAF has been identified as IL-1 and TNF. Osteoclasts also stimulate the plasma cells through a PDGF (Platelet Derived Growth Factor) and IL-6.

Bone pain is one of the cardinal features of Myeloma. It is present at diagnosis in approximately three quarters of patients. Myeloma itself is not a painful disease; being erosive rather than expansive lesions explains this phenomena. This is in contrast to other expanding tumors that can cause considerable pain because of its growth and pressure on the surrounding organs. The pain in MM only arises when sites which are subjected to stress and weight bearing are mechanically so weakened that they start to undergo deformation and incipient fractures (infarction). That is why bone pain is rare in the vault of the head, even though there is extensive bone destruction. **Pathological fractures** and **Vertebral collapse** are important features in MM. Approximately 10% of myeloma patients manifest evidence of spinal cord compression due to vertebral collapse &/or extension of the myeloma tissue from the vertebral body extradurally.

Calcium liberated from the eaten-out bony lesions can cause hypercalcemia, adding yet another causation to renal failure. So the causes of **Renal Failure** in MM are: Light chain damage, amyloidosis, pyelonephritis, hyperuricemia, hypercalcemia and plasma cell infiltration of the kidneys. Renal failure is a major cause of death in MM.

**Non-Specific Symptoms** of weakness, fatigue and malaise can arise from variety of different causes including anemia, uremia, hypercalcemia and Hyperviscosity.
STAGING OF MULTIPLE MYELOMA

It has been estimated that one trillion \((10^{12})\) plasma cells could weigh approximately one kilogram! That means if we can separate all the plasma cells from a MM patient and put it on a scale, it will weigh around one kilogram. Of course this is a practical impossibility. Fortunately, using few of the features of MM, one can come close to that assumption and make pretty a good guess of the mass of malignant cells. If the plasma cell burden in a 60 kg body weight patient is less than one kg, then it is a “Low Cell Mass” stage or Stage “I”. If it is more than two kg, then it is called “High Cell Mass” stage or Stage “III”. Between one and two kg, it is called “Intermediate Cell Mass” or Stage “II”.

<table>
<thead>
<tr>
<th>STAGE</th>
<th>CRITERIA</th>
<th>MYELOMA CELL MASS</th>
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<tbody>
<tr>
<td><strong>STAGE “I”</strong></td>
<td><strong>LOW CELL MASS</strong></td>
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<tr>
<td></td>
<td><strong>ALL</strong> of the followings:</td>
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<td></td>
<td>* Hb &gt; 10 gm/dL</td>
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<td></td>
<td>* Calcium equal or &lt; 3 mmol/L</td>
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<td></td>
<td>* X-Ray: Normal bones or a solitary lesion</td>
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<td></td>
<td>* Low Rate of Paraprotein Production:</td>
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<tr>
<td></td>
<td>(a) IgG paraprotein &lt; 50 gm/L</td>
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<tr>
<td></td>
<td>(b) IgA paraprotein &lt; 30 gm/L</td>
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<td></td>
<td>(c) Urine Light Chain &lt; 4 gm/ 24 hours</td>
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<td></td>
<td><strong>LESSTHAN ONE KILOGRAM OF PLASMA CELLS PER ADULT</strong></td>
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<td></td>
<td>(&lt; 0.6 TRILLION CELLS/ m²)</td>
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<td><strong>STAGE “II”</strong></td>
<td><strong>INTERMEDIATE</strong></td>
<td></td>
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<td></td>
<td>Fitting neither Stage I or III</td>
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<tr>
<td><strong>STAGE “III”</strong></td>
<td><strong>HIGH CELL MASS</strong></td>
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<tr>
<td></td>
<td><strong>ANY</strong> of the followings:</td>
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<td></td>
<td>* Anemia (Hb &lt; 8.5 gm/dL)</td>
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<tr>
<td></td>
<td>* Hypercalcemia (Ca++ &gt; 3 mmol/L)</td>
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<tr>
<td></td>
<td>* Advanced Lytic Bone Lesions</td>
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<td></td>
<td>* High Paraprotein Production Rate:</td>
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<tr>
<td></td>
<td>(a) IgG paraprotein &gt; 70 gm/L</td>
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<td>(b) IgA paraprotein &gt; 50 gm/L</td>
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<td>(c) Urine Light Chain &gt; 12 gm/ 24 hours</td>
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<td></td>
<td><strong>MORE THAN TWO KILOGRAM OF PLASMA CELLS PER ADULT</strong></td>
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<td>(&gt;1.2 TRILLION CELLS/ m²)</td>
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HEMATOLOGICAL ABNORMALITIES IN MM:

# Rouleaux formation in the peripheral blood. This is because of the viscous plasma that combines the red cells like stacks of coin.

# Very high ESR. This feature might not be seen in Light Chain Myeloma.

# Bluish proteinaceous background of the blood and marrow smears.

# Increased numbers of abnormal plasma cells in the marrow. Normally less than 5% of the marrow is composed of plasma cells. In MM, they are quite numerous.

Plasma cells are fried-egg appearing cells with deeply basophilic cytoplasm and eccentric nuclei. The cells are usually elliptical with coarse nuclear chromatin. In tissue sections, the nuclear chromatin strands radiate from a central core to the rim, giving it a cartwheel appearance. There is a large pale perinuclear halo representing the Golgi region that processes the synthesized immunoglobulins.

Myeloma cell morphology is very variable. It could look like a normal plasma cell or be more immature looking, larger and with nucleoli (Plasmablasts). Bi and multinuclear plasma cells are in favor of myeloma.
IMMUNOLOGICAL & BIOCHEMICAL FEATURES OF MM:

*. Serum and urine electrophoresis: In approximately 80% of cases of MM, an M-band is visible in serum electrophoresis. If the myeloma cells secrete only light chains, this serum M-band will not be seen and it is important to do urine electrophoresis to visualize the monoclonal band in the urine.

In more than half of the patients with MM the paraprotein is IgG; in a quarter of patients it is IgA; nearly 20% of patients only show light chains; in 2% of cases, no paraprotein is found. IgM paraprotein is not a feature of MM; it usually indicates Waldenstrom's macroglobulinemia.

*. Normal immunoglobulins are usually suppressed causing immune paresis.

*. Serum Calcium might be raised in up to half of the patients.

*. Urea, creatinine and uric acid are raised according to the state of the kidneys.

*. Serum Alkaline Phosphatase is usually normal or even reduced despite extensive bone damage. This is explainable because of the erosive nature of the disease and lack of osteoblastic activity.

RADIOLOGICAL FEATURES OF MM: Skeletal survey reveals evidence of bone lesions in three quarters of patients. 70% of myeloma patients have lytic bone lesions and 4% have osteoporosis. Skeletal survey shows punched-out, moth-eaten lytic lesions in the skull, thoracic cage, spine and pelvis.

MANAGEMENT: The average survival in MM is around 3 to 4 years. Median survival of up to six years can be expected with conventional chemotherapy for patients without adverse prognostic factors.

In general most patients will require therapy. Although cure cannot be attained in myeloma patients, supportive and ancillary therapy is just as important.

*. Physical activity should not be restricted to prevent more bone demineralization and hypercalcemia.

*. Rehydration, especially with normal saline, is of paramount importance to prevent renal failure.

*. Liberal use of analgesia and even morphia to keep the patient comfortable. In cases of severe pain or when there is spinal cord compression, local radiotherapy becomes a necessity.

*. Hypercalcemia should be avoided at all costs. Rehydration, steroid and many other effective medications are available to treat hypercalcemia.

Melphalan and Prednisolone are the mainstay of treatment. Melphalan is used in the dose of 1 mg/kg body weight divided on five days and given nearly every five weeks. Prednisolone is added in the dose of 60 mg daily (15 mg q.i.d.) for five days. Repeat WBC and platelet counts two to three weeks after each cycle. Patient must be neutropenic or thrombocytopenic at mid cycle to achieve maximum tolerable chemotherapy. Treatment should be continued until a plateau is reached then a pause might be justified; otherwise, it might be needed continuously.

We use VAD “Vincristine, Adriamycin & Dexamethasone” for most of our patients in Kurdistan. Younger patients benefit from multiple stem cell autotransplantation. Thalidomide, Lenalidomide and other antiangiogenesis agents are new additions. Bortezomib is used for refractory cases.
WALDENSTRÖM’S MACROGLOBULINEMIA (WM)

This is an uncommon condition, seen most frequently in men over 50 years of age, which behaves clinically as a slowly progressive lymphoma. There is proliferation of cells that produce a monoclonal IgM paraprotein and resemble both plasma cells and lymphocytes (lymphoplasmacytoid cells). The dominant clinical picture of Waldenström’s macroglobulinemia results from macroglobulinemia (hyperviscosity) and diffuse cellular infiltrates (lymphadenopathy, bone marrow involvement, etc).

WM usually starts insidiously with fatigue and weight loss. Hyperviscosity syndrome may result in visual disturbances, lethargy, confusion, muscle weakness, CNS symptoms and signs, and congestive heart failure.

IgM paraprotein increases blood viscosity more than equivalent concentrations of IgG or IgA and small increases above 3 gm/L in concentration lead to large increases in viscosity. The retina may show variety of changes; engorged veins, hemorrhages, exudates and a blurred disc. If the macroglobulin is a cryoglobulin, features of cryo-precipitation e.g. Raynaud’s phenomena may be present. Bleeding and anemia from the effects of macroglobulins have been discussed in the MM section.

Moderate lymphadenopathy and hepato-splenomegaly are frequently seen.

WM can be diagnosed by detecting monoclonal IgM which is usually more than 15 gm/L. Bone marrow shows pleomorphic infiltration by small lymphocytes, plasma cells, lympho-plasmacytoid cells, immature lymphoid cells and mast cells. ESR is usually very high. Peripheral blood lymphocytosis with some plasmacytoid cells is usual.

BENIGN MONOCLONAL GAMMOPATHY

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE “MGUS”

Three percent of healthy adult population and 10% of elderly people above 80 years show a paraprotein in their serum without any definite evidence of myeloma, macroglobulinemia or lymphoma. It is not associated with Bence–Jones proteinuria or bone lesions and the percentage of plasma cells in the bone marrow is not in the range of diagnosing MM (usually less than 10%). The paraprotein concentration in the serum is usually less than 10 gm/L and remains stable for prolonged periods of time. When these patients were followed for 10 years, 20% of them transformed to myeloma or lymphoma; so the term benign monoclonal gammopathy is not right and MGUS should be used. In MGUS, patients are usually asymptomatic but they should be followed up regularly to rule out future development of myeloma or if the paraprotein causes problems e.g., cryoglobulinemia, peripheral neuropathy & CHAD.

To differentiate MGUS from myeloma, trephine biopsy might be quite helpful. In myeloma, the plasma cells are usually seen in clusters rather than being diffuse. In the marrow aspirate, plasmablasts are in favor of myeloma rather than MGUS.

HEAVY CHAIN DISEASES

These are rare syndromes characterized by the production of the α, γ or u heavy chain immunoglobulins and soft tissue tumors either as malignant lymphoma or plasmacytoma. Alpha heavy chain disease is common in Arabs and usually affects the gastrointestinal tract. Immunoproliferative Small Intestinal Disease “IPSID” is a well-described disease usually associated with intestinal infections.

POEMS Syndrome: Seen with 1% of MM. It is Polyneuropathy; Organomegaly; Endocrinopathy; Myeloma (Osteosclerotic) & Skin changes.

Amyloidosis: Seen in 5% of MM patients and 20% of light chain only Myeloma. Amyloid deposits are accumulations of the light chains that are produced by myeloma cells. Deposition in the kidney contributes to the renal failure. Cardiac Amyloidosis is a terminal problem. Macroglossia and skin depositions are the other sequel of amyloidosis.