Multiple Myeloma Symptoms, Pathophysiology and Diagnosis

Multiple myeloma is a monoclonal malignancy of plasma cells in the bone marrow resulting in their overproduction and production of large quantities of functionless immunoglobulins.

It is the second most common cancer affecting older people. The cause of this kind of disease is still not known.

The neoplastic event in myeloma may involve cells earlier in B-cell differentiation than the plasma cell. Interleukin (IL) 6 may play a role in driving myeloma cell proliferation.

Signs and symptoms of multiple myeloma

The most common presenting features of multiple myeloma are:

- Bone pain is usually in the back and ribs precipitated by movement.
- Radiculopathy secondary to spinal nerve roots compression.
- Respiratory tract infections. (Particularly with encapsulated organisms ie Pneumococcus and Haemophilus)
- Anemia. (Weakness, fatigue, and pallor)
- Renal failure. Hypercalcemia is the most common cause of renal failure
- Proteinuria.
- Fractures and,
- Dehydration.
- Hypercalcemia features such as polyuria, polydipsia, and altered mental status.
- Scans show lytic bone lesions.

CRAB mnemonic stands for C-High calcium levels, R-Renal problems, A-Anemia and B-Bone problems

In a typical individual vertebra is a site for hematopoiesis of the hematopoietic stem cells. Normal bone marrow has less than 5% plasma cells that secrete antibodies to protect the body.

The antibodies that are secreted by the plasma cells have a normal heavy and light chain.

In multiple myeloma, the hematopoietic stem cells shift production to mainly produce more B cells and plasma cells ending up with more than 10 % of plasma cells producing abnormal antibodies.

In about 75% of the cases, these abnormal antibodies produced have only light chains. These light chains are known as power proteins.

The main antibodies found associated with multiple myeloma are immunoglobulin A and immunoglobulin G.

Pathophysiology of Multiple Myeloma

Normal bone has three main types of cells.

- **Osteoblasts** which build up the bone,
- **osteoclast** which breaks down bones and
- **Bone marrow stromal cells** regulate hematopoiesis.

Osteoblasts in the presence of calcium and phosphates produce strong bones. Osteoclasts, on the other hand, break down bones by secreting hydrochloric acid. This results in the release of calcium and phosphorus into the blood. Osteoblasts and osteoclasts regulate each other.

Osteoclasts activation is regulated by osteoblasts that express RANKL (Ligand). (**Receptor activator of nuclear factor ? B**)The RANKL binds to RANK on the osteoblasts receptors stimulating osteoblast activity but osteoblasts secrete another molecule called osteoprotegerin (OPG) which inhibits the interaction, therefore, reducing osteoclast activity.

Osteoclastic activity is triggered via the osteoblasts' surface-bound RANKL activating the osteoclasts' surface-bound receptor activator of nuclear factor kappa-B (RANK).

RANKL is an apoptosis regulator gene, a binding partner of osteoprotegerin (OPG)

In multiple myeloma, the bone marrow stromal cells interact with these cancerous cells through receptors and cytokines. Adhesion of the multiple myeloma cells to the bone marrow stromal cells results in cytokine-mediated growth, survival, resistance, and migration. This means that the bone marrow stromal cells promote the growth and development of multiple myeloma cells.

These effects are due both to direct MM cell–BMSC binding and to induction of various cytokines, including IL-6, insulin-like growth factor type I (IGF-I), vascular endothelial growth factor (VEGF), and stromal cell-derived growth factor (SDF)-1?.

Multiple myeloma cells have the ability to release cytokines that can have effects on the body such as interleukin 6 which reduces osteoblast activity by inhibiting osteoblast progenitor cells to become osteoblasts, therefore, leading to reduced osteoblast numbers.

These malignant cells also release Dickhoff-1 DKK-1 which inhibits OPG produced by the osteoblast resulting in an increased osteoclast population. Multiple myeloma cells also stimulate osteoclast activity by producing the MIP alpha component and Rank L.

The osteoclasts can self-stimulate through bone marrow stromal cells and IL6. This image then results in the amplification of multiple myeloma cells in the bone marrow increasing osteoclast activity and reducing osteoclast activity in the bones.

With the amplified osteoclastic activity then there is an increased breakdown of the bones leading to an increased susceptibility to fractures and the development of bone lytic lesions and hypercalcemia.

In the blood, there is also paraproteins production with bits of light chains floating around. These types of proteins have also a negative effect on the body. They are produced by multiple myeloma cells.

These light chain types of proteins known as power proteins are small enough to get filtered through the glomerulus eventually causing kidney failure in about 20 - 30 % of the cases.

The light chains are then passed into the urine. This is one of the classical features of multiple myeloma known as **Bence Jones proteins**

Multiple myelomas also lead to anemia in various ways as follows:

1. Shifting of hematopoietic stem cells from myeloid progenitors to lymphoid progenitors to make more plasma cells.
2. Overproduction of plasma cells clogs up the bone marrow stopping the production of red blood cells.
3. Reduced erythropoietin production as a result of kidney failure also adds up to reduced erythropoiesis.
4. In addition, mild hemolysis may contribute to anemia.
5. Some of the patients may have megaloblastic anemia due to either folate or vitamin B12 deficiency.

Variants of multiple myeloma

- Solitary bone plasmacytoma - This is a single lytic bone lesion without marrow plasmacytosis.
- Solitary extramedullary plasmacytoma- This usually involves the submucosal lymphoid tissue of the nasopharynx or paranasal sinuses without marrow plasmacytosis.

Investigations

For a detailed discussion of the diagnosis and differential diagnosis of multiple myeloma you can get the theme in our previous article here:

- Diagnosis and differential diagnosis of multiple myeloma.

Blood and urine tests

Blood tests when performed on these patients can show;

- Anemia is most commonly normochromic, normocytic anemia.
- Increased paraproteins, (A paraprotein is a monoclonal light chain immunoglobulin known as Bence Jones protein.
- Serum B2 microglobulin is elevated in 75% of the cases.
- Diffuse hypogammaglobulinemia if the M component is excluded. Hypogammaglobulinemia is related to both decreased production and increased destruction of normal antibodies
- Reduced normal antibodies.
- Hypercalcemia due to increased bone breakdown.
- Increased urea and nitrogenous bases (BUN) and creatinine levels due to renal failure.
- **Urinary Bence Jones Protein**s, (A test for Bence-Jones protein involves acidification of the urine).
- Erythrocyte sedimentation rate is elevated
- Serum alkaline phosphatase is usually normal.

Patients with myeloma also have a decreased anion gap [i.e., Na+ – (Cl? + HCO3?)] because the M component is cationic, resulting in the retention of chloride.

Bone investigations

Bone marrow biopsy indicates more than 10% of plasma cells (Confirmatory).

Bone marrow aspiration

X-Rays indicate osteoporosis or diffuse osteopenia.

CT scan shows punched-out **lytic lesions**. (Mostly in the vertebrae, ribs, pelvic bones, and bones of the thigh and upper arm)

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