QUESTION 25
A 65-year-old woman presents with progressive lethargy and thoraco-lumbar pain.
Full blood examination shows:

- Haemoglobin: 102 g/L [113-159]
- Mean corpuscular volume (MCV): 102 fL [80-97]
- White cell count: 3.4 x 10^9/L [3.9-12.7]
  - Neutrophils: 1.6 x 10^9/L [1.9-8.0]
  - Lymphocytes: 1.0 x 10^9/L [0.9-3.3]
  - Monocytes: 0.5 x 10^9/L [0.3-1.1]
  - Eosinophils: 0.2 x 10^9/L [0-0.5]
  - Basophils: 0.1 x 10^9/L [0-0.1]
- Platelet count: 92 x 10^9/L [150-396]

A chest X-ray shows diffuse osteopenia but is otherwise normal.

55% of nucleated cells in the bone marrow aspirate have the appearance shown below (examples indicated by arrows).

The most likely diagnosis is:
A. Burkitt's lymphoma.
B. Amyloidosis.
C. Multiple myeloma.
D. Waldenström's macroglobulinaemia.
E. Metastatic carcinoma.

Presentation: pancytopenia
Bone Marrow – excess plasma cells

**Multiple Myeloma | IgG | excess plasma cells**
Multiple myeloma is characterized by the neoplastic proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin. This clone of plasma cells proliferates in the bone marrow and often results in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures. Other common clinical findings include anemia, hypercalcemia, and renal insufficiency. Recurrent bacterial infections (particularly during chemotherapy) and bleeding can occur, while the hyperviscosity syndrome is rare.

**CLINICAL MANIFESTATIONS**
Common complaints — Bone pain, particularly in the back or chest, and less often in the extremities, is present at the time of diagnosis in approximately 60 percent of patients. The pain is usually induced by movement and does not occur at night except with change of position. The patient's height may be reduced by several inches because of vertebral collapse.

- Weakness and fatigue are common (32 percent) and often associated with anemia.
- Fever occurs in less than 1 percent; when present, it is usually due to infection.
- A bleeding diathesis is uncommon.
- Weight loss is present in 24 percent of patients, one-half of whom have a weight loss of more than 9 kg.
- Patients may have symptoms related to complications of myeloma, such as hypercalcemia, renal insufficiency, or amyloidosis.

Physical findings —
- Pallor is the most frequent physical finding.
- Palpable hepatomegaly, splenomegaly, and lymphadenopathy are uncommon.
- Extramedullary plasmacytomas can occur as large, purplish, subcutaneous masses late in the course of the disease

Neurologic disease —
- Radiculopathy, usually in the thoracic or lumbosacral area, is the most common neurologic complication of multiple myeloma. It can result from compression of the nerve by a paravertebral plasmacytoma or rarely by the collapsed bone itself.
- Cord compression — Spinal cord compression from an extramedullary plasmacytoma or a bone fragment due to fracture of a vertebral body occurs in approximately 5 percent of patients; it should be suspected in patients presenting with severe back pain along with weakness or paresthesias of the lower extremities, or bladder or bowel dysfunction or incontinence. This set of symptoms constitutes a medical emergency; magnetic resonance imaging or computed tomographic myelography of the entire spine must be done immediately, with appropriate follow-up treatment by chemotherapy, radiotherapy, or neurosurgery to avoid permanent paraplegia.

Peripheral neuropathy —
- Peripheral neuropathy is uncommon in multiple myeloma and, when present, is usually due to amyloidosis.

CNS involvement —
- Intracranial plasmacytomas are rare and almost always represent extensions of myelomatous lesions of the skull.
- Leptomeningeal myelomatosis along with abnormal cerebrospinal fluid findings is uncommon but is being recognized more frequently, especially in advanced stages of the disease.
- Rare cases of encephalopathy due to hyperviscosity or high blood levels of ammonia, in the absence of liver involvement, have been reported

Other findings — A variety of other signs of systemic involvement can be seen in patients with multiple myeloma. Plane xanthomas involving the creases of the palms and/or soles may represent a paraneoplastic phenomenon. Plasmacytomas of the ribs occur and can present either as expanding costal lesions or soft tissue masses. Pleural effusion and diffuse pulmonary involvement due to plasma cell infiltration are rare and usually occur in advanced disease.

The incidence of infection is increased in multiple myeloma, with Streptococcus pneumoniae and gram-negative organisms being the most frequent pathogens. The propensity to infection results from an impairment in the antibody response, due to suppression of normal plasma cell function as manifested by hypogammaglobulinemia and, during chemotherapy - neutropenia.

Burkitt’s lymphoma| vacuoles | t(8;14)
-seen p2q10
Amyloidosis | cargo red stain lambda light chains
Immunoperoxidase stain of a bone marrow biopsy from a patient with primary (AL) amyloidosis. Evidence for a monoclonal plasma cell disease is provided by the intense staining for lambda light chains (left panel) with almost no staining for kappa light chains (right panel).

Immunofluorescence microscopy in light chain deposition disease involving the kidney. There is intense staining with anti-kappa light chain antibodies along the tubular basement membranes.

**Waldenström's macroglobulinaemia |IgM paraprotein**

Macroglobulinemia occurs in disorders in which there is proliferation of B-lymphocytes and plasma cells that produce an IgM monoclonal protein. This broad definition includes patients with monoclonal gammopathy of undetermined significance (MGUS) of the IgM type, chronic lymphocytic leukemia (CLL), a number of lymphoma variants, primary amyloidosis, and Waldenstrom's macroglobulinemia (WM).
Weakness, fatigue, weight loss and chronic oozing of blood from the nose and gums are the most common presenting features in WM.

Pallor due to anemia is a frequent finding in WM along with lymphadenopathy, hepatomegaly, and splenomegaly.

Diagnostic criteria:
- IgM monoclonal gammopathy regardless of the size of the M protein.
- Ten percent or greater bone marrow infiltration by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation with an intertrabecular pattern.
- Typical immunophenotype (e.g., surface IgM+, CD5+/−, CD10−, CD19+, CD20+, CD22+, CD23−, CD25+, CD27+, FMC7+, CD103−, CD138−);

Bone marrow smear from a patient with lymphoplasmacytic lymphoma and Waldenstrom's macroglobulinemia. The marrow consists largely of lymphoplasmacytic cells that have the nuclear spoke-wheel pattern of a plasma cell but the low cytoplasmic volume that is more characteristic of a small lymphocyte.
Metastatic carcinoma | clumping, overlapping nuclei, don't look like haemopoetic cells

Bone marrow aspirate from a patient with carcinoma metastatic to the bone marrow, illustrating the presence of a large clump of tumor cells (arrow), surrounded by normal marrow elements. Note that the cellular outlines within the clump of tumor cells are indistinct. This is not a characteristic of any group of cells normally seen in the bone marrow.