Paraproteinaemia

A paraprotein is a monoclonal immunoglobulin or light chain present in the blood or urine; it is produced by a clonal population of mature B cells, most commonly plasma cells.[1]

Paraproteinaemia represents a group of related diseases characterised by an unbalanced or disproportionate proliferation of immunoglobulin-producing cells, usually from a single clone. These cells frequently secrete a structurally homogeneous immunoglobulin (M-component) and/or an abnormal immunoglobulin. Plasma cell disorders can be considered as a spectrum of conditions ranging from monoclonal gammopathy of undetermined significance (MGUS), through asymptomatic, to symptomatic myeloma.[1]

Epidemiology

The incidence of a paraprotein is 3.2% in people aged over 50 years.[1]

Causes

- Artefacts: heparinised blood sample.
- MGUS:[2]
  - MGUS is defined by a low level of paraprotein <30 g/L, bone marrow plasma cells <10% and the absence of myeloma-related organ or tissue damage (predominantly renal, skeletal or bone marrow impairment).
  - Patients are often elderly and in good health.
  - MGUS requires no therapy and the overall risk of progression to myeloma is 1% per year.[1]
  - Follow-up must be continued indefinitely because multiple myeloma, amyloidosis, macroglobulinaemia or related disorders may occur.
- Haematological:
  - Cold agglutinin disease: IgM paraprotein.
  - Paroxysmal cold haemoglobinuria: Donath-Landsteiner antibody.
  - Warm antibody haemolytic anaemia.
- Malignant neoplastic conditions:
  - Heavy chain diseases: there are 3 variants - gamma, alpha and mu heavy chain disease.[3] The alpha variant is most common, occurring particularly in people from the Mediterranean and Middle East and often presenting with weakness, fatigue and fever.
  - Waldenström's macroglobulinaemia: clinically similar to multiple myeloma, lymphoma and chronic lymphatic leukaemia. Often presents with nonspecific weakness and fatigue but any system can be involved. Diagnosis is by serum electrophoresis and bone marrow aspiration. Treatment of symptomatic patients includes chemotherapy and supportive therapy aimed at the correction of anaemia and hyperviscosity.
  - Chronic lymphocytic leukaemia.
  - Myeloma:[1]
    - Myeloma remains incurable with a median survival of 3-4 years.
    - Autologous stem cell transplant can prolong survival.
    - Thalidomide in combination with dexamethasone has an emerging role in the treatment of myeloma.
  - Non-Hodgkin's lymphoma.
  - POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes).
Non-malignant systemic disease:[1]
- Autoimmune disease: rheumatoid arthritis, scleroderma, Hashimoto's thyroiditis, cryoglobulinaemia.
- Cutaneous disease: pyoderma gangrenosum, necrobiotic xanthogranulomatosis.
- Liver disease: hepatitis, cirrhosis.
- Infectious disease: tuberculosis, bacterial endocarditis.

Miscellaneous syndromes:
- Schnitzler’s syndrome (chronic, non-pruritic urticaria associated with recurrent fever, bone pain, arthralgia or arthritis, and a monoclonal IgM gammopathy).

Presentation
- May be discovered incidentally.
- Often nonspecific presentation with fever, malaise, and bone pain.
- Clinical indications for screening for M-protein:[1]
  - Malaise and fatigue.
  - Bone disease (persistent back pain, osteopenia or lytic lesions).
  - Impaired renal function.
  - Normochromic normocytic anaemia ± pancytopenia.
  - Hypercalcaemia.
  - Recurrent bacterial infections.
  - Hyperviscosity.
  - Nephrotic syndrome, cardiac failure, malabsorption.
  - Peripheral neuropathies, carpal tunnel syndrome.
  - Incidental persistent elevated erythrocyte sedimentation rate (ESR).

Investigations
The differentiation of benign paraproteinaemia from neoplastic states is based on the absence of bone marrow disease, a relatively low and constant concentration of serum paraprotein, the absence of urine light chain excretion and normal levels of other serum immunoglobulins.

- Serum protein electrophoresis showing M-protein: total protein and protein electrophoresis with paraprotein quantification, paraprotein typing, immunoglobulins G, A, M; beta-2-microglobulin.[4]
- FBC, blood film, ESR: underlying cause - eg, hypercalcaemia, high total protein, and high ESR in patients with myeloma.
- Urine protein: Bence Jones' proteins (usually indicate multiple myeloma, amyloidosis or Waldenström’s macroglobulinaemia).
- Bone marrow aspiration and trephine biopsy.

Management
Management will depend on the underlying cause.

Prognosis
This will depend on the underlying cause. Prognosis is often poor.

However, in patients with benign monoclonal gammopathy, patients are asymptomatic and there is no evidence of impairment of antibody response or bone marrow function.

Further reading & references

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