Para-proteinaemias

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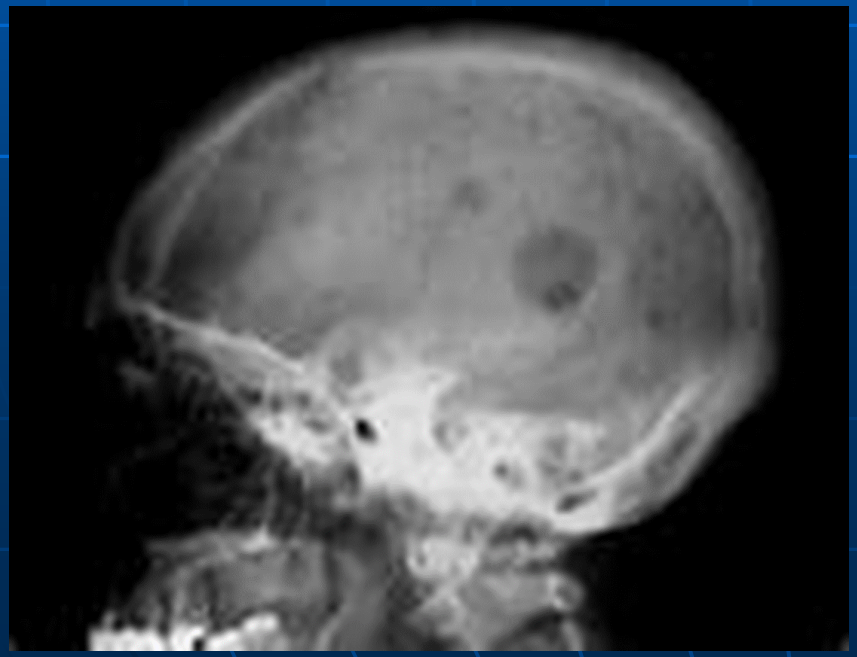
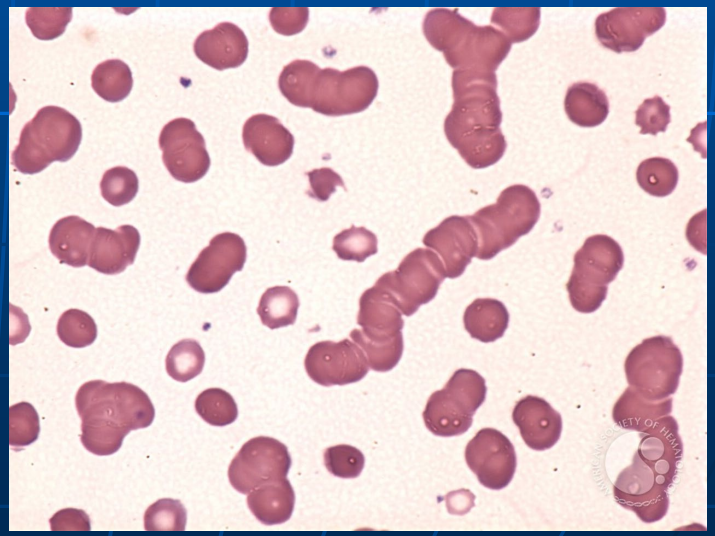




Para-proteinaemias

A gammopathy refers to over production of one or more classes of immunoglobulin. It may be:

Polyclonal: in association with acute or chronic inflammation as infection sarcoidosis, autoimmune disorders or some malignancies

Monoclonal: increase in a single Ig class may occur in association with or reduce level of other immunoglobulines.

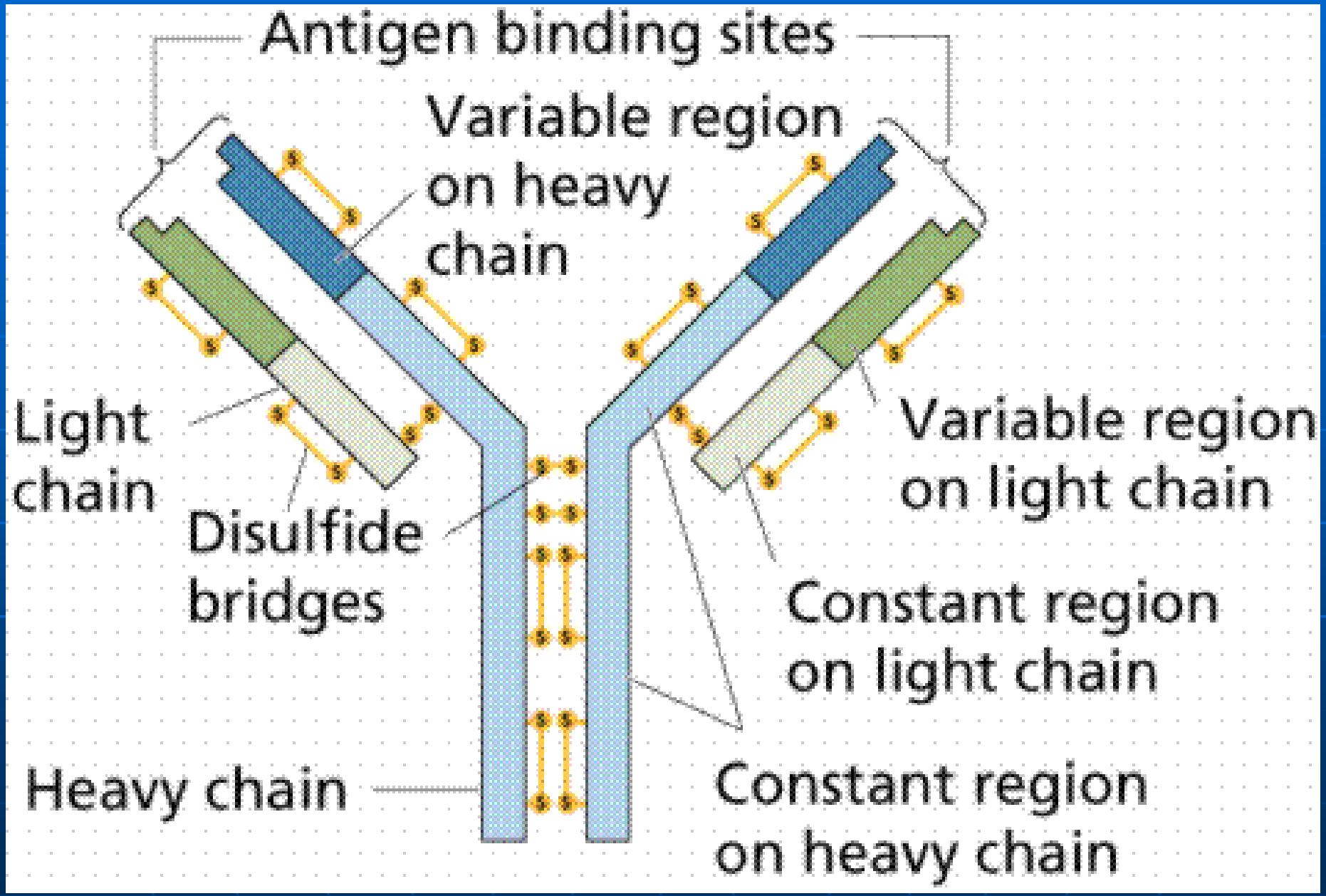
Gammopathies are detected by plasma Immmmunoelectrophoresis ,such monoclonal proteins also called M-proteins ,paraprotien or monoclonal Gammopathies ,occur as a feature of myeloma ,lymphoma, and amyloidosis.

Multiple myeloma

This is a malignant proliferation of plasma cells.

Normal plasma cells are derived from B cells and produce immunoglobulins which contain heavy and light chains.

Normal immunoglobulins are polyclonal, which means that a variety of heavy chains are produced and each may be of kappa or lambda light chain type .


Antigen binding sites
Variable region on heavy chain
Light chain
Disulfide bridges
Variable region on light chain
Constant region on light chain
Heavy chain
Constant region on heavy chain

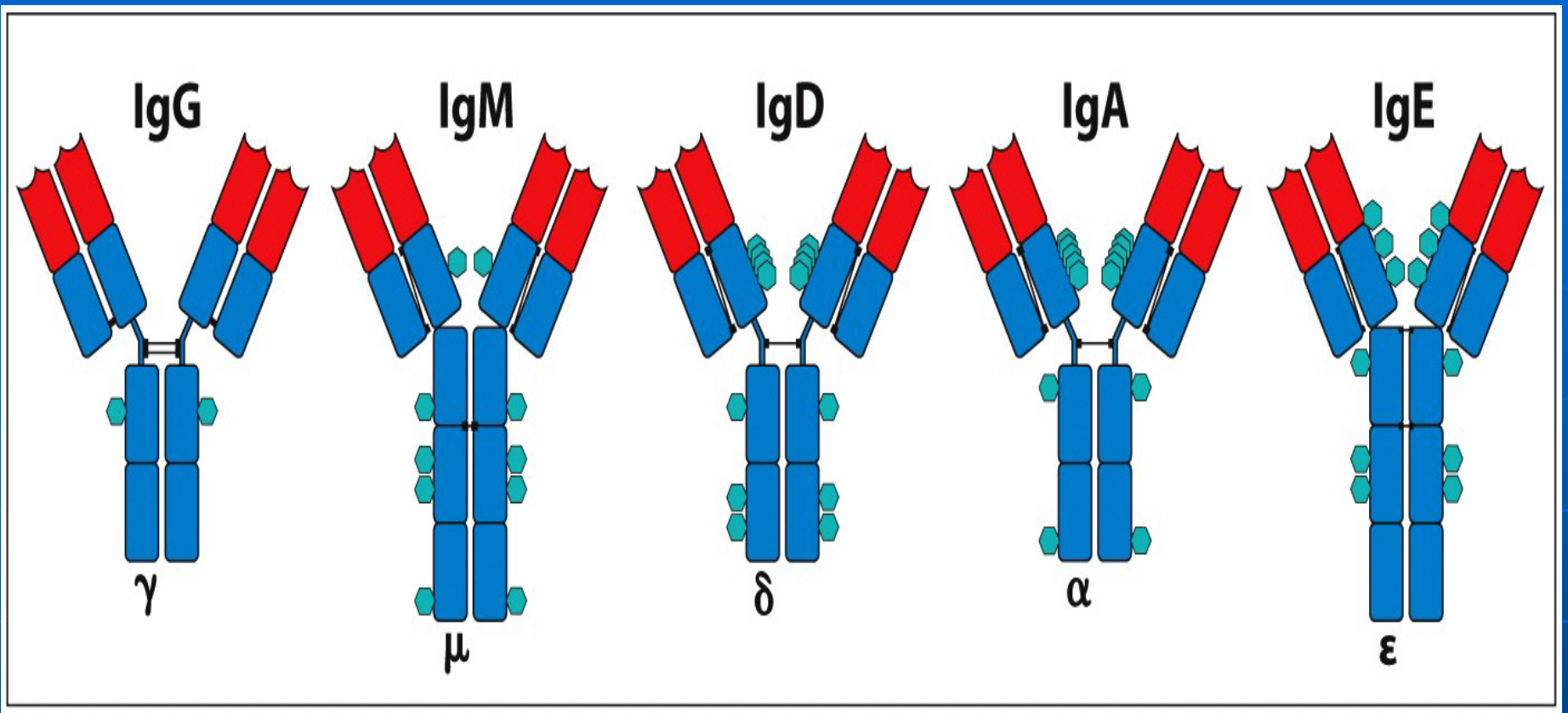


Figure 4.5 The Immune System, 3ed. (© Garland Science 2009)

In myeloma, plasma cells produce immunoglobulin of a single heavy and light chain, a monoclonal protein commonly referred to as a paraprotein. In some cases only light chain is produced and this appears in the urine as Bence Jones proteinuria and can be measured inthe urine or serum as free light chain.

The frequency of different paraprotien type:

IgG	55%
IgA	21%
Light chain only	22%
Other(D,E,Non secretory)	2%

The majority of plasma cells present in the bone marrow .
These cells produce cytokines ,which stimulate ostioclasts and result in bone absorption .the resulting lytic lesions cause bone pain ,fractures and hypercalcaemia .
Marrow involvement can result in anaemia and pancytopenia .

Clinical features:

Incidence is 4/100000 new cases per year .

Male:femle ratio 2/1

Age 60-70 years

The clinical manifestations arise from :

1-Presence of malignant plasma cells in the bone marrow.

2-Effects of monoclonal proteins in the blood or urine .

3-Immunologic deficiencies caused when the Ig production by remaining plasma cells is inadequate.

-Hyperviscosity:manifested by
A-Retinal bleeds
B-bruising
C-Heart failure
D-cerebral ischemia
E-Engorged retinal veins
-Excess light chain may result in Amyloidosis manifested by
A- carpal tunnel syndrome
B- nephrotic syndrome
C-panda eyes.

-Renal failure: caused by:

A- paraprotein deposition

B-hypercalcemia

C-ifection

D-NSAID

E-amyloid.

-spinal cord compression dueto

A-Bony collapse

B-Extradural mass

-anaemia :normochromic normocytic ,occasionally macrocytic.

-Increased susceptibility to infections specially strept.pneumonia,hemophilus infuenzae due to decreased normal Ig production.

-tumours of plasma cells can also form outside the marrow (extramedullary plasmacytoma) presenting as a mass in the skin, lymph nodes, liver, spleen and other locations

Diagnosis: requires two of the following criteria:

1-Increased malignant plasma cells in the bone marrow.

2-Serum and or urinary paraprotein.

3-skletal lytic lesions.

Investigations

1-Blood film morphology:

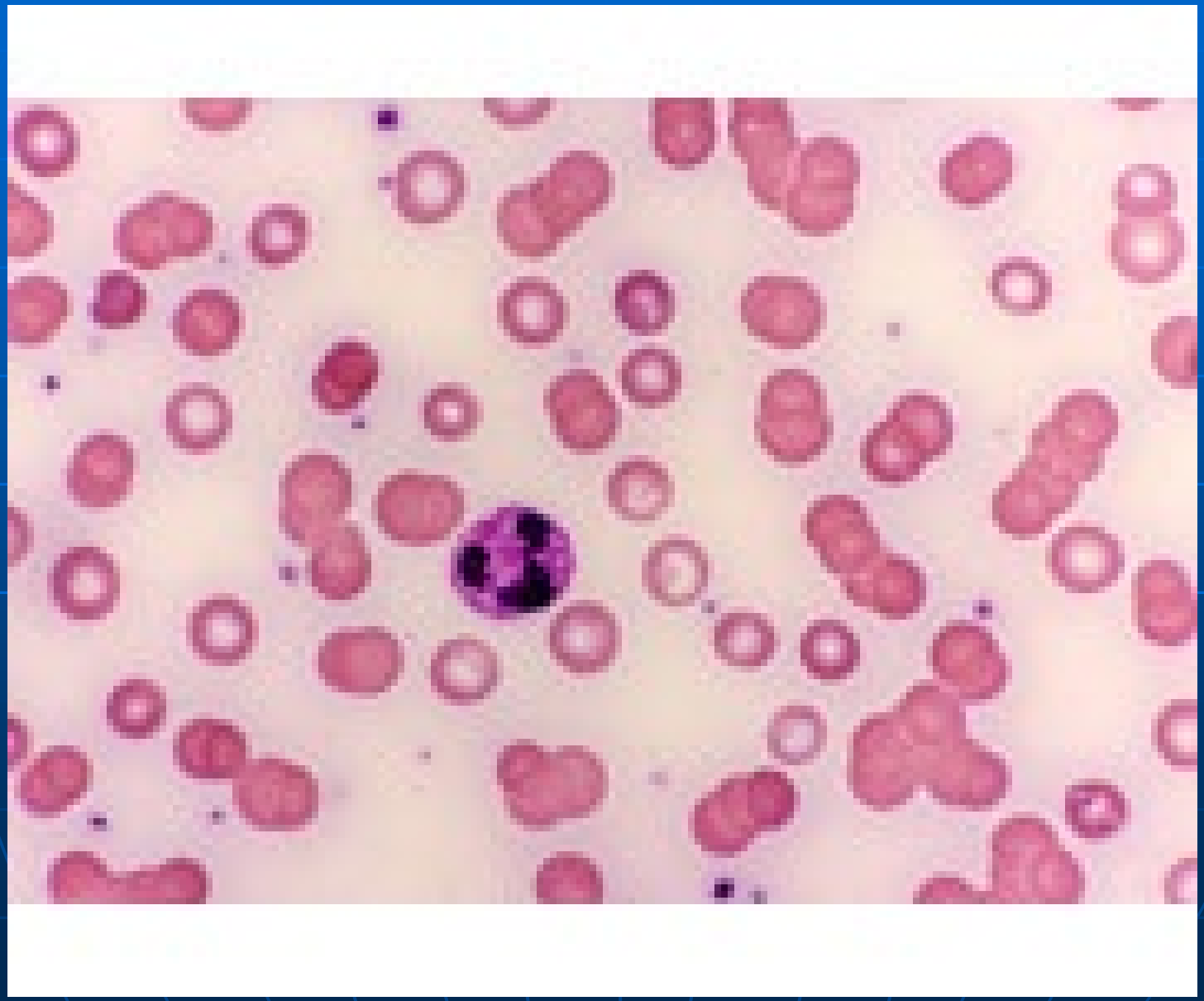
Anaemia, normochromic normocytic.occasionlly macrocytic

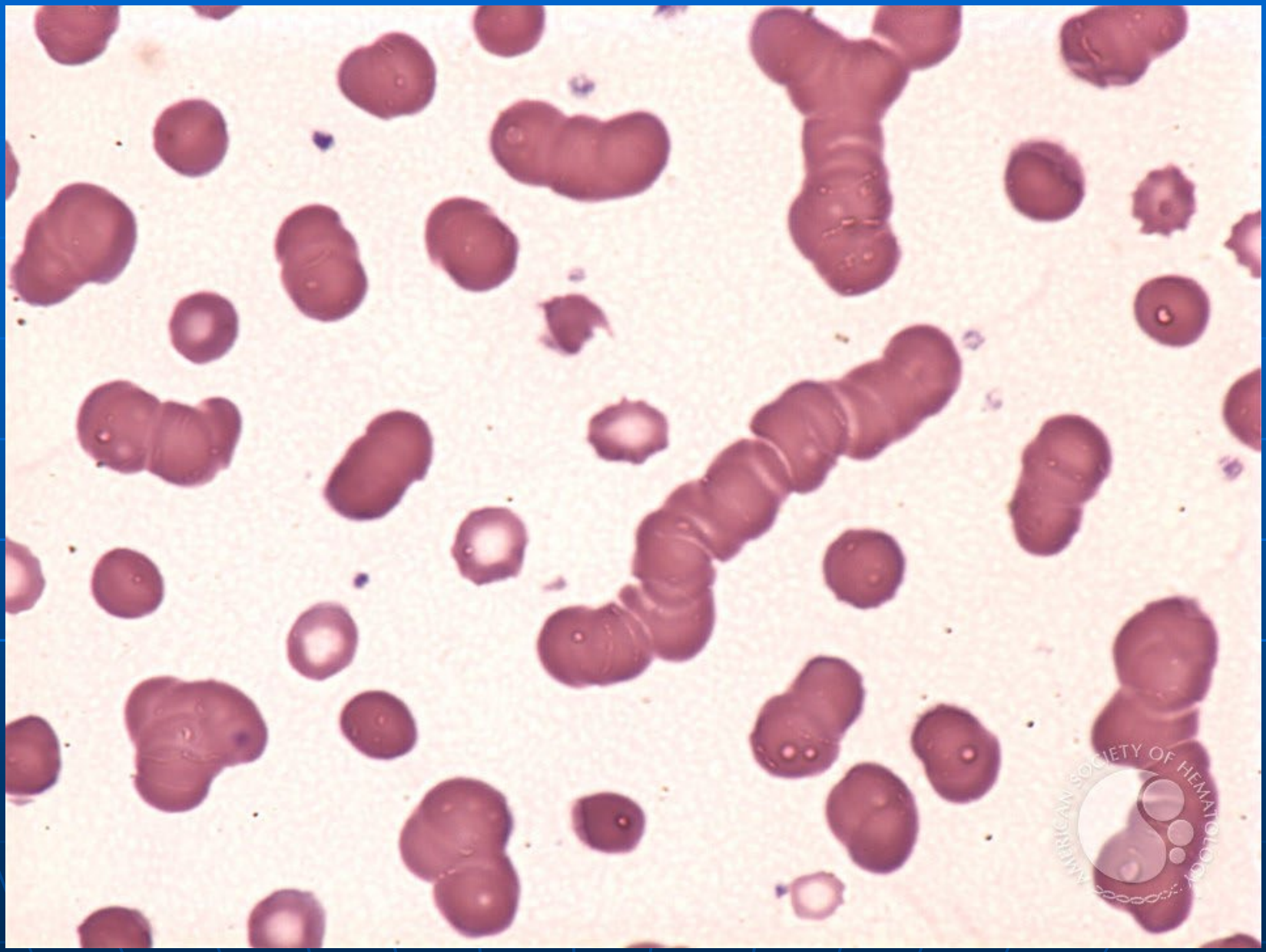
Leukoerythroplastosis ,nucleated erythrocytes and immature granulocytes **So**metimes present.

Paraproteinaemia can cause an elevated ESR , but this is a non-specific test; only approximately 5% of patients with a persistently elevated ESR above 100 mm/hr have underlying myeloma.

Serum albumin and β2-microglobulin are measured for prognostic purposes, along with a cytogenetic analysis of the tumour cells.

Peripheral blood smear: normocytic, normochromic anemia, macrocytic anemia, rouleaux formation,

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Rouleaux formation is a term used to describe the stacking of red blood cell. The flat surface of the discoid RBCs give them a large surface area to make contact and stick to each other; thus, forming a rouleau. They occur when the plasma protein concentration is high, and because of them the ESR (erythrocyte sedimentation rate) is also increased. Rouleaux formation is a non-specific indicator of the presence of disease.

Causes of rouleaux formation :

Infections
Multiple myeloma
Waldenström's macroglobulinemia
Inflammatory and connective tissue disorders
Cancers

2-Bone marrow aspirate and trephine biopsy:

Plasma cells in the marrow more than 10%.

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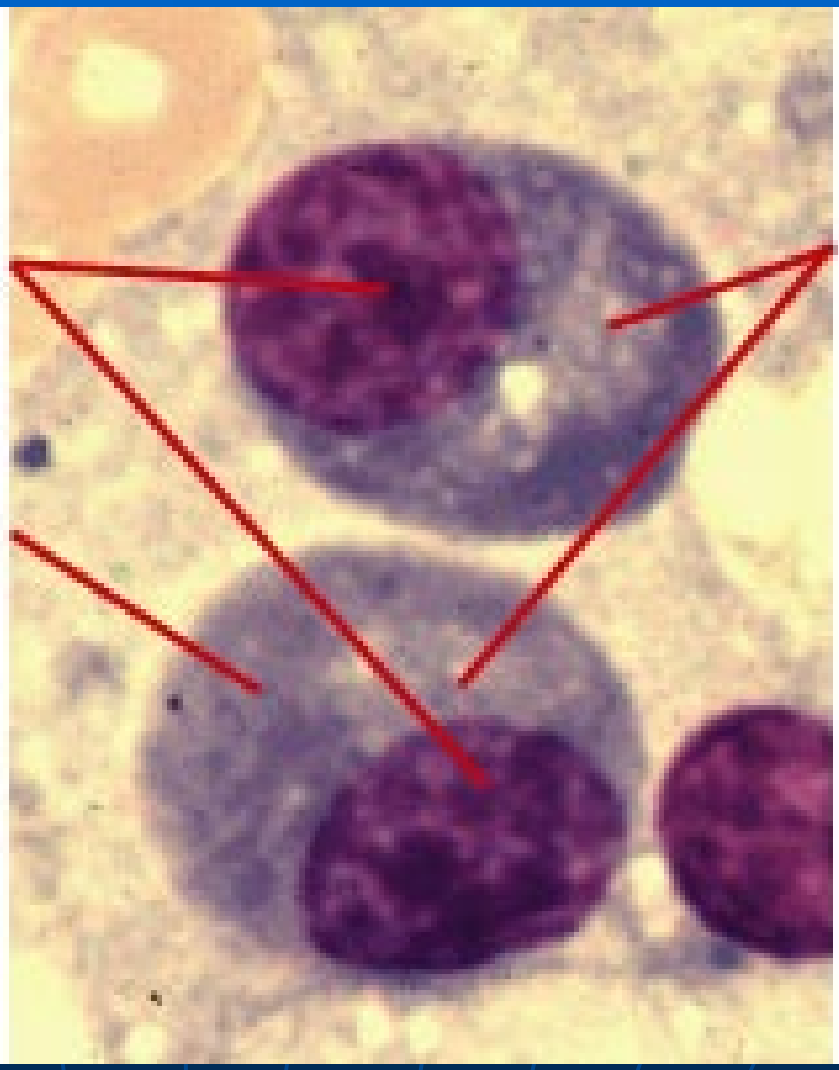
The cells bear characteristic morphologic features of plasma cells, round or oval cells with an eccentric nucleus composed of coarsely clumped chromatin, a densely basophilic cytoplasm, and a perinuclear clear zone containing the Golgi apparatus. Binucleate and multinucleate malignant plasma cells.

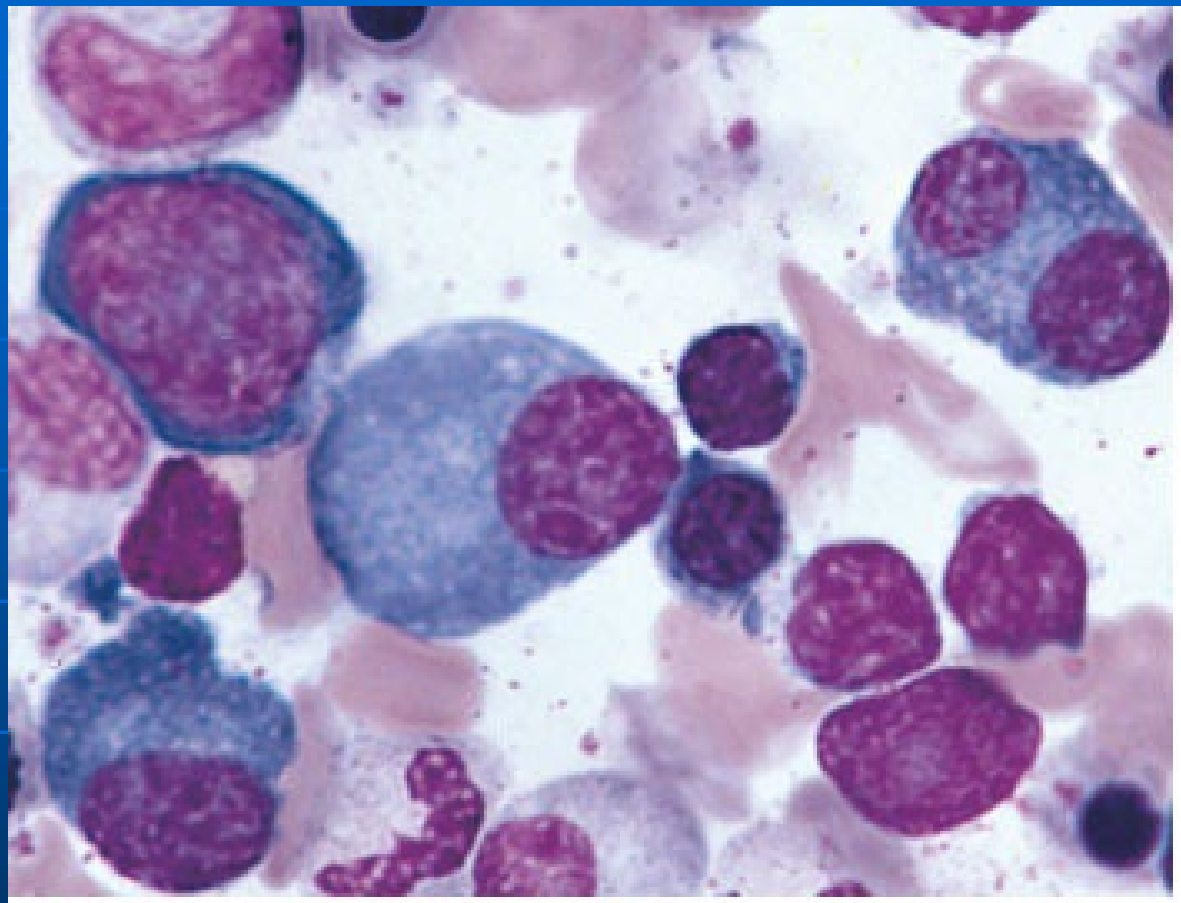
Eccentric nucleus

Abundant,
blue cytoplasm

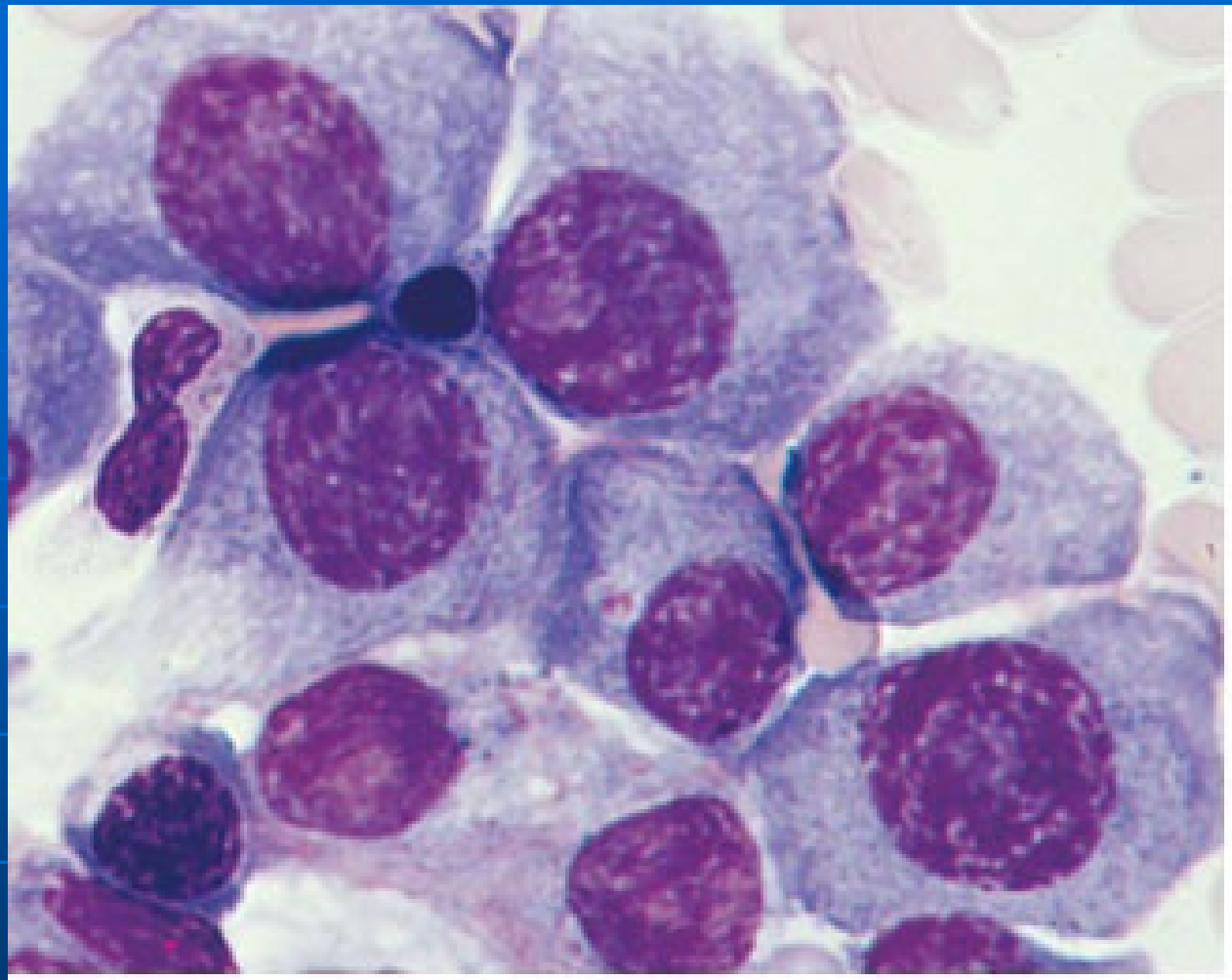


Golgi

Plasma cells



Source: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: *Williams Hematology*, 7th Edition: http://www.accessmedicine.com



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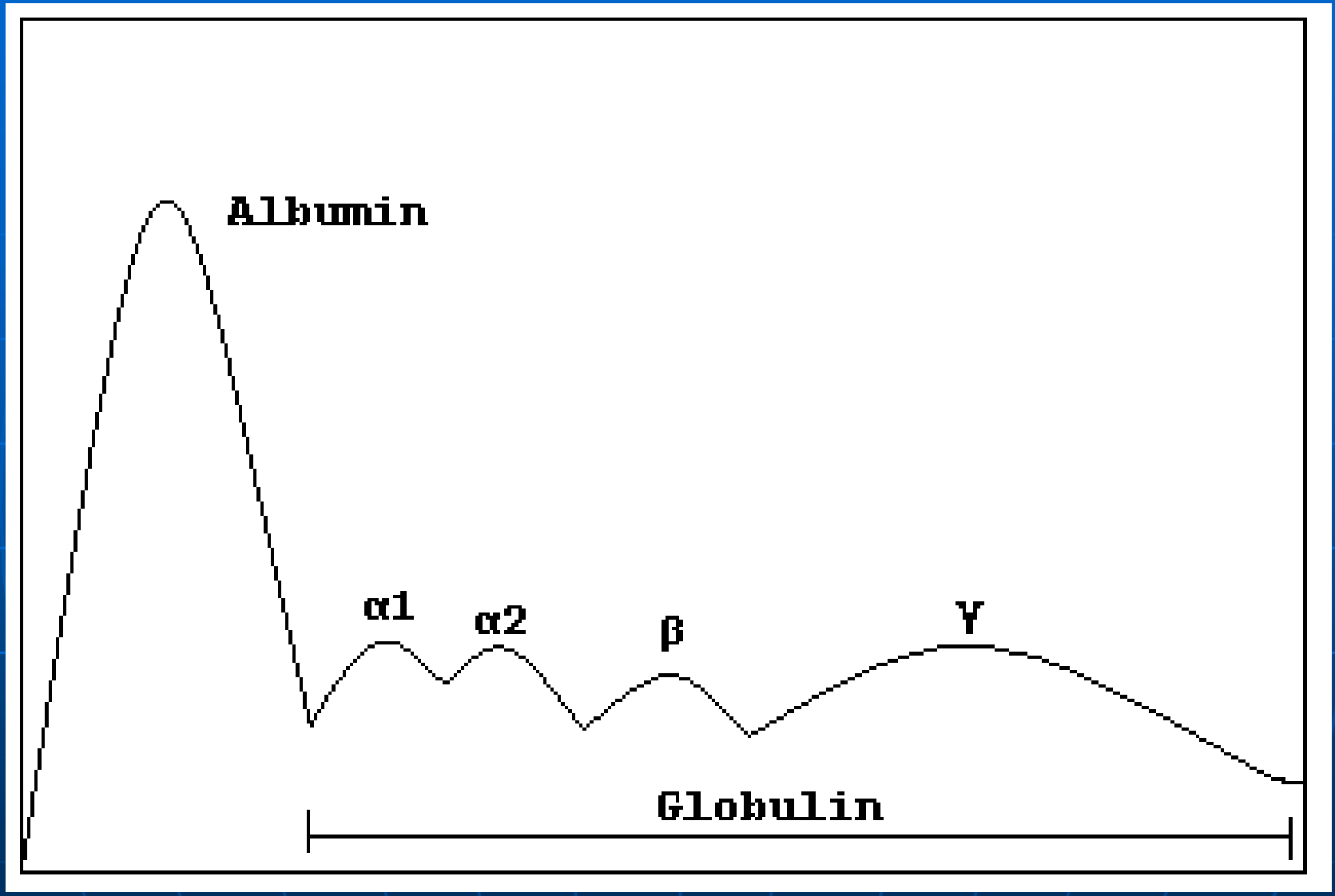
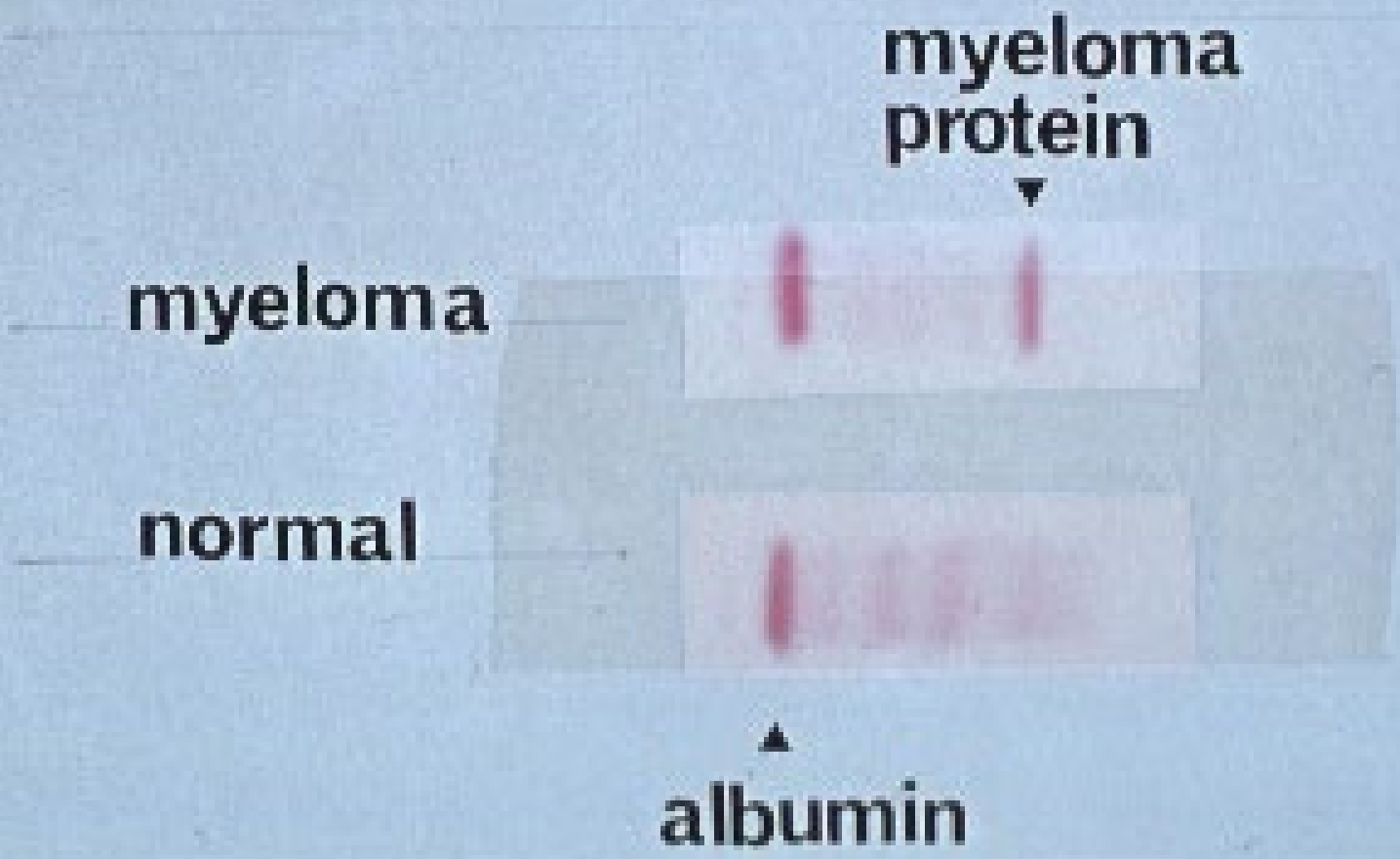
Myeloma cells

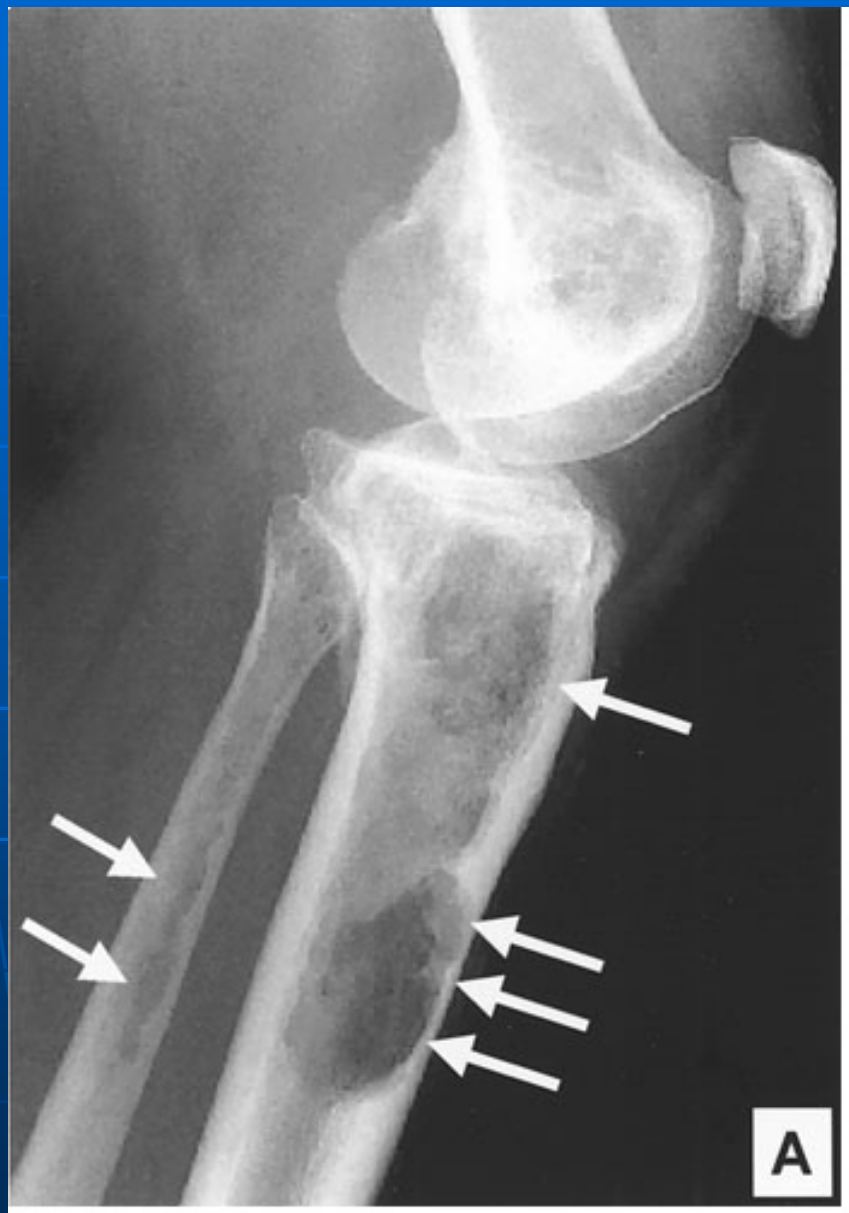
Bone marrow aspiration, plasma and urine electrophoresis, and a skeletal survey are thus required; the latter is classically a series of plain X-rays, but more often now low-dose CT scan or whole-body MRI is performed. Normal immunoglobulin levels, i.e. the absence of immunoparesis, should cast doubt on the diagnosis


Albumin
α1
α2
β
γ
Globulin

Serum protein electrophoresis in myeloma



-Urea,creatinine,electrolytes,ureate:
Renal function.
-Blood calcium,Albumine:
Presence of hypercalcaemia.
-Bleeding time,coagulation screen:
Degree of haemostasis.
-MRI spine:
Spinal cord compression.
-X-RAY(skeletal survey) +Alkaline phosphatase:
Presence of lytic lesion , bone fractures
In the absence of fractures, the plasma alkaline phosphatase and isotope bone scan will be normal despite the lytic lesions.



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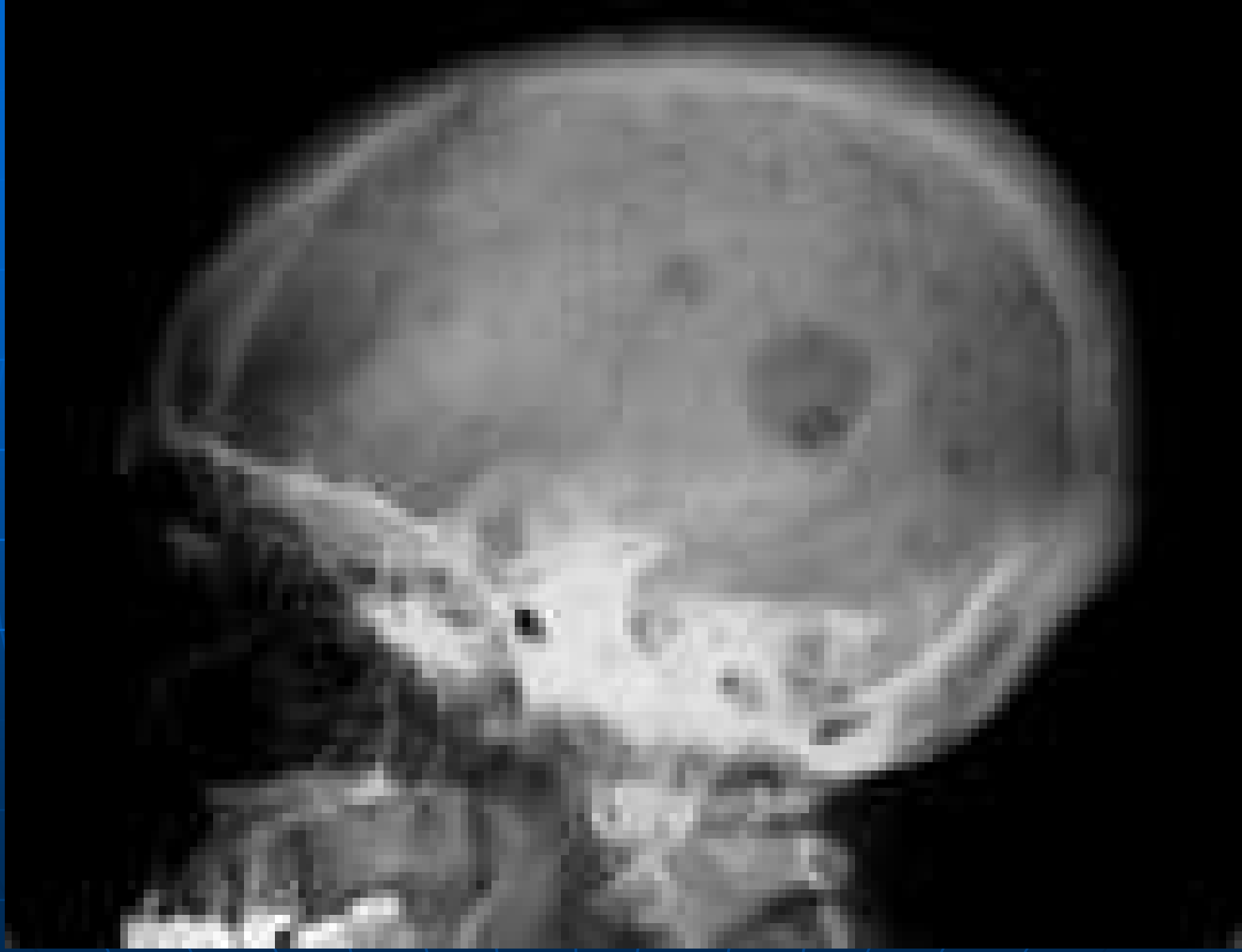

Management

If patients are asymptomatic with no evidence of end-organ damage (e.g. to kidneys, bone marrow or bone), treatment may not be required.
So-called asymptomatic myeloma should be monitored closely for the development of end-organ damage.

Immediate support

-High fluid intake to treat renal impairment and hypercalcaemia
-Analgesia for bone pain
- Bisphosphonates for hypercalcaemia and to delay otherskeletalrelated events .
-Allopurinol to prevent urate nephropathy
-Plasmapheresis, if necessary, for hyperviscosity
-Antibiotic prophylaxis with levofloxacin during the first 3 months of therapy.

Chemotherapy with or without HSCT

Patients are initially assessed for their fitness and eligibility for autologous HSCT and treatment pathways vary accordingly. Myeloma therapy has improved with the addition of novel agents, initially the immunomodulatory drug thalidomide and more recently the proteasome inhibitors bortezomib and carfilzomib, the second- and third-generation immunomodulatory drugs lenalidomide and pomalidomide and the anti-myeloma antibodies daratumumab and isatuximab, which binds to CD 38 on the malignant plasma cell

-For first-line therapy in older patients who are unsuitable for transplant, thalidomide combined with the alkylating agent melphalan and prednisolone (MPT) has increased the median overall survival to more than 4 years.

-Lenalidomide is approved first-line treatment for patients not eligible for transplantation and who are intolerant of, or unsuitable for, thalidomide.

-Thalidomide and lenalidomide both have anti-angiogenic effects against tumour blood vessels and immunomodulatory effects.

Both can cause somnolence, constipation, peripheral neuropathy and thrombosis, though lenalidomide has a better side-effect profile.

It is vital that females of child-bearing age use adequate contraception, as thalidomide and lenalidomide are teratogenic. Treatment is administered until paraprotein levels have stopped falling. This is termed ‘plateau phase’ and can last for weeks or years.

In younger, fitter patients considered eligible for transplant, standard treatment includes first-line therapies, such as cyclophosphamide, thalidomide and dexamethasone (CTD) or bortezomib (Velcade), thalidomide and dexamethasone (VTD) to maximum response, and then autologous HSCT. This improves quality of life and prolongs survival, but does not cure myeloma.

In all patients who have achieved maximal response, lenalidomide maintenance has been shown to prolong the response.

When myeloma progresses, treatment is given to induce a further plateau phase.
In the UK, the proteosome inhibitor bortezomib and lenalidomide have been used as second- and third-line therapy, as appropriate.
However, as they have been used more frequently in the first or second line with prognostic benefit, subsequent relapses are more difficult to treat. Pomalidomide, carfilzomib and daratumumab show promise in relapsed/refractory disease and are increasingly used. Patients who respond may benefit from a second autologous HSCT.

Radiotherapy

This is effective for:

1- localised bone pain not responding to simple analgesia.

2- pathological fractures.

3- emergency treatment of spinal cord compression complicating extradural plasmacytoma.

Bisphosphonates

Long-term bisphosphonate therapy reduces bone pain and skeletal events. These drugs protect bone and may cause apoptosis of malignant plasma cells. There is evidence that intravenous zoledronate in combination with anti-myeloma therapy confers a survival advantage over oral bisphosphonates. Osteonecrosis of the jaw may be associated with long-term use or poor oral hygiene and gum sepsis; regular dental review, including a check before starting therapy, is therefore important.

Prognosis

The international staging system (ISS) identifies poor prognostic features, including a high β2-microglobulin and low albumin at diagnosis (ISS stage 3, median survival 29 months).

Those with a normal albumin and a low β2-microglobulin (ISS stage 1) have a median survival of 62 months.

Increasingly, cytogenetic analysis is used to identify poor-risk patients, e.g. t(4;14), del(17/17p), t(14;16), t(14;20), non-hyperdiploidy and gain(1q).

Use of autologous HSCT and advances in drug therapy with the newer agents have increased survival.

Over one-third of patients are now surviving for 5 years, compared with only one-quarter 10 years ago. The outlook may improve further with new drugs and combinations of treatments.

THANK YOU