PARAPROTEINEMIC NEUROPATHIES

By

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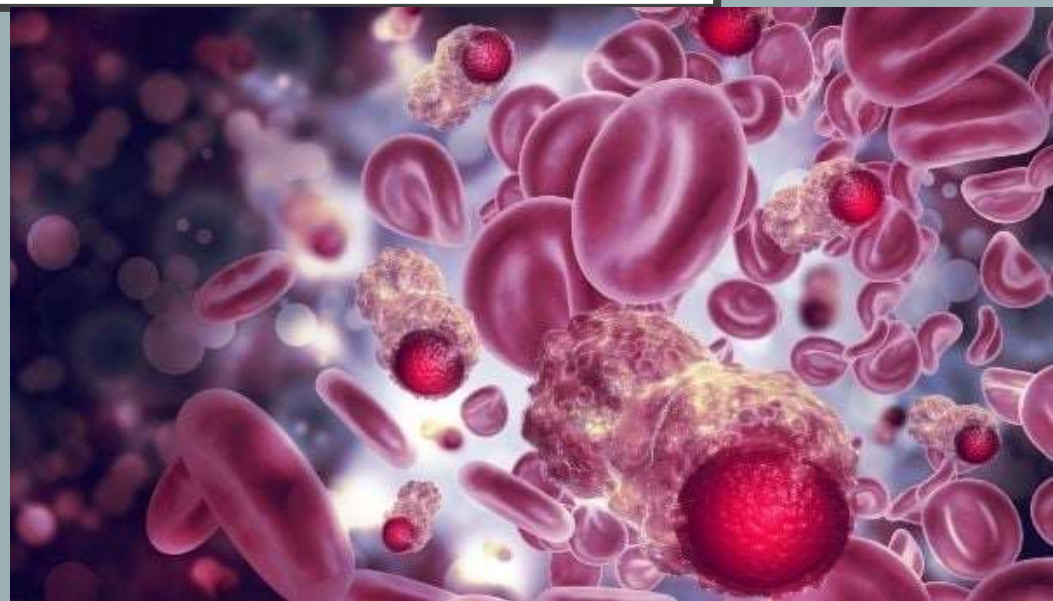
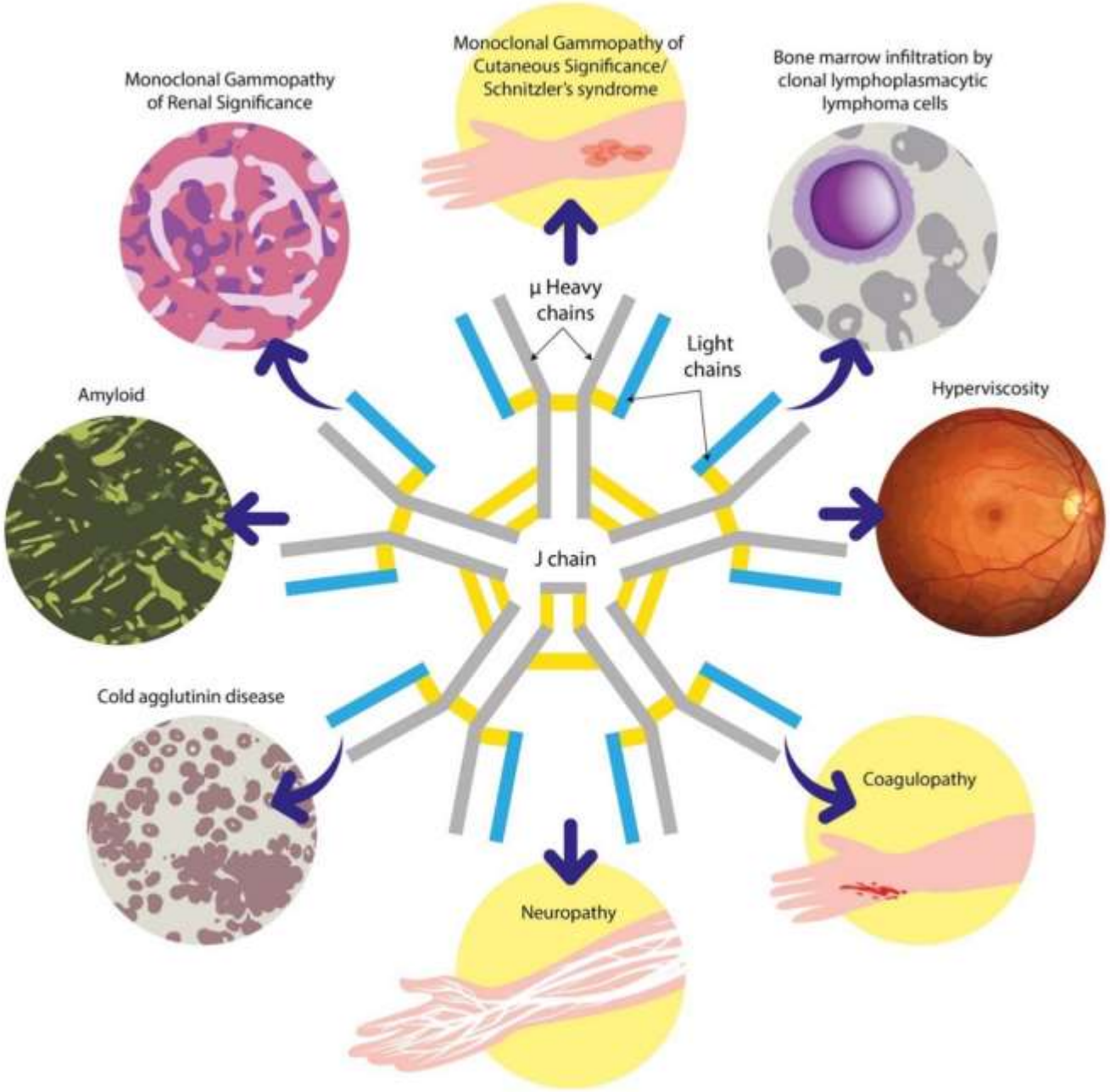
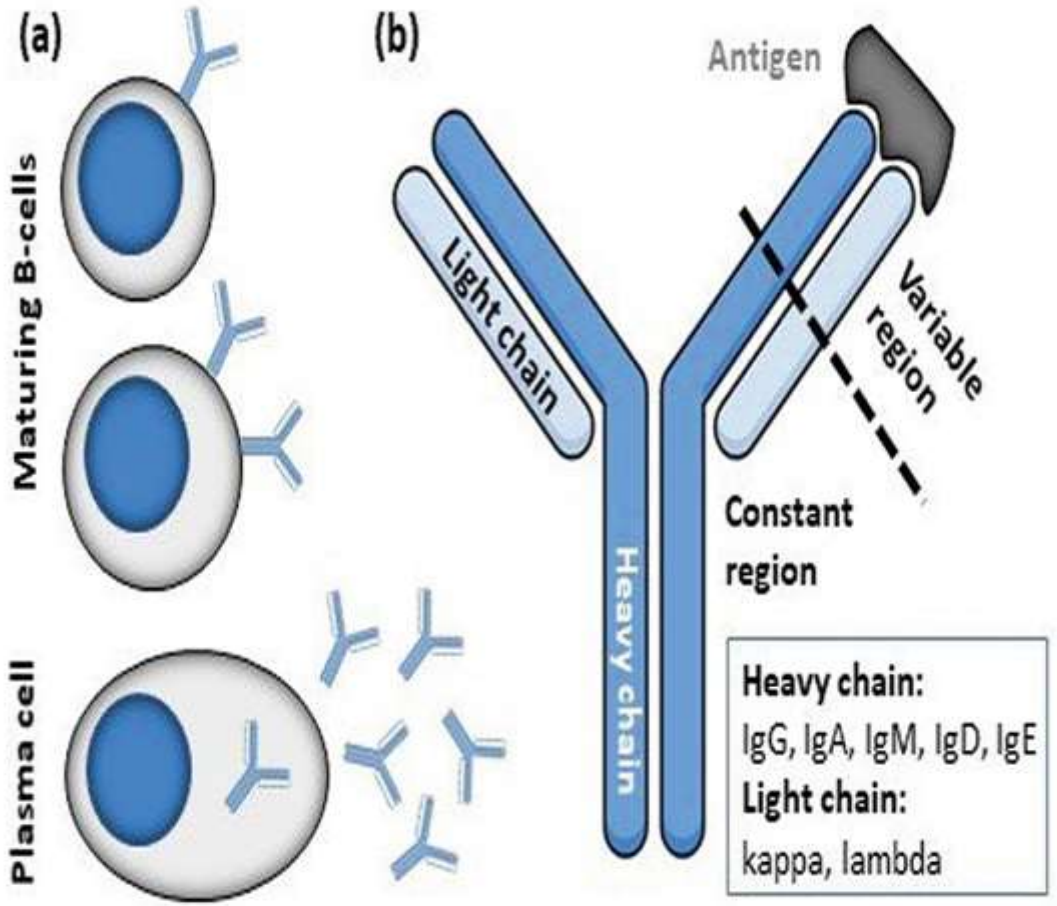


PARAPROTEINEMIA

- Paraproteins are immunoglobulins that are produced in excess by an abnormal clonal proliferation of B-lymphocytes or plasma cells.
- These monoclonal proteins exist as heavy chain subtypes (IgG, IgA, IgG, IgD and IgE). Also light chain subtypes such as kappa and lambda)
- Clonal proliferation may or may not occur in the context of a hematologic malignancy or a premalignancy.


Monoclonal Gammopathy of Renal Significance
Monoclonal Gammopathy of Cutaneous Significance/ Schnitzler's syndrome
Bone marrow infiltration by clonal lymphoplasmacytic lymphoma cells
μ Heavy chains
Light chains
Amyloid
Hyperviscosity
J chain
Cold agglutinin disease
Coagulopathy
Neuropathy


(a)
(b)
Antigen
Maturing B-cells
Plasma cell
Light chain
Heavy chain
Variable region
Constant region
Heavy chain:
IgG, IgA, IgM, IgD, IgE
Light chain:
kappa, lambda

INTRODUCTION

- A wide range of mature B cell disorders may be associated with a circulating paraprotein.

- Common disorders associated with monoclonal gammopathy are Multiple myeloma, POEMS syndrome, Plasmacytoma, Lymphoproliferative disorders, Lymphoplasmacytic lymphoma, Chronic lymphocytic leukemia.

- Despite associated with many conditions paraproteins mostly a monoclonal gammopathy of undetermined significance (MGUS) .

PARAPROTEIN NEUROPATHIES

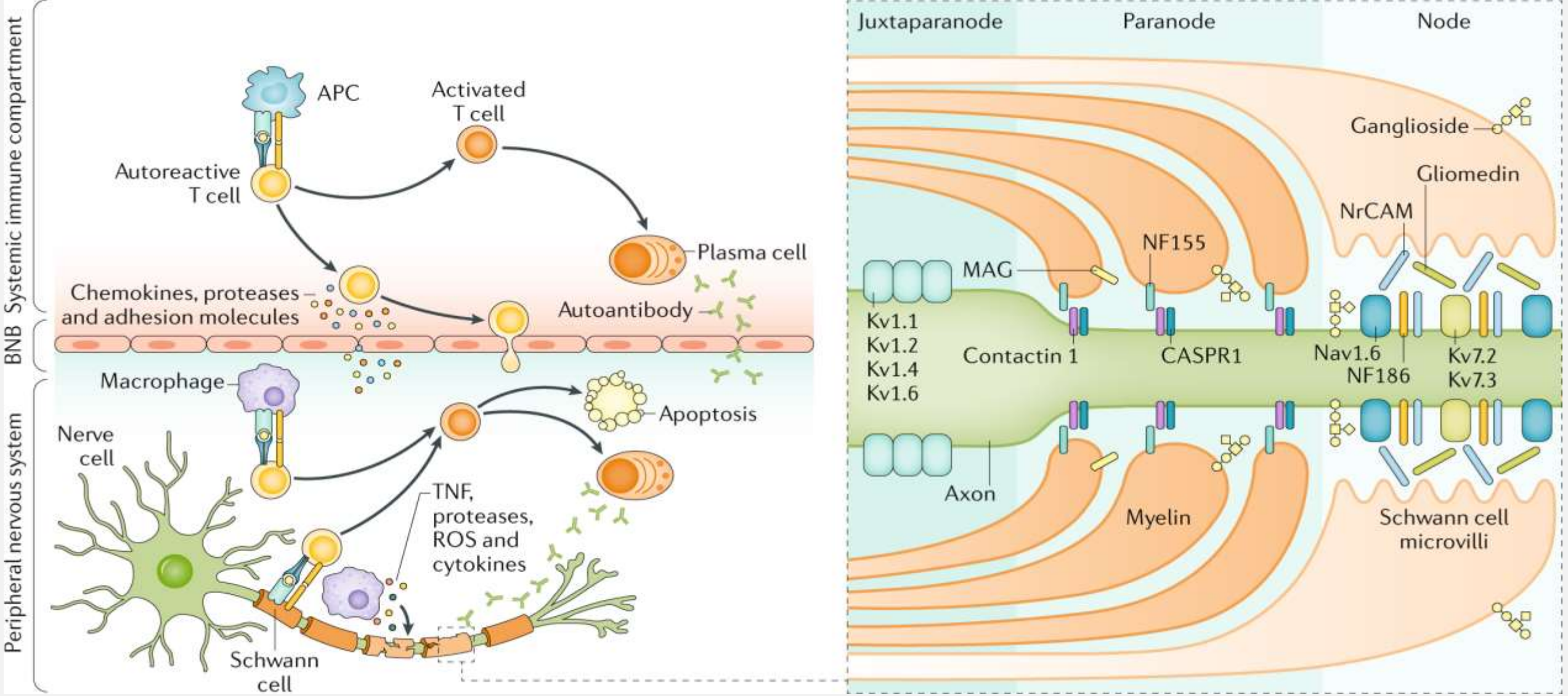
- Paraproteins and neuropathy are common and frequently coexist with each other.
- They are caused by interaction of antibodies with specific antigenic targets on peripheral nerves or by deposition of immunoglobulins or amyloid.
- Paraproteinemic neuropathies more commonly occur with IgM (50% to 75%) than with IgG or IgA monoclonal protein.

- Screening of paraproteinemia should always be a part of diagnosis when diagnosed with polyneuropathy.

Mechanisms of Nerve Damage in Paraproteinemia

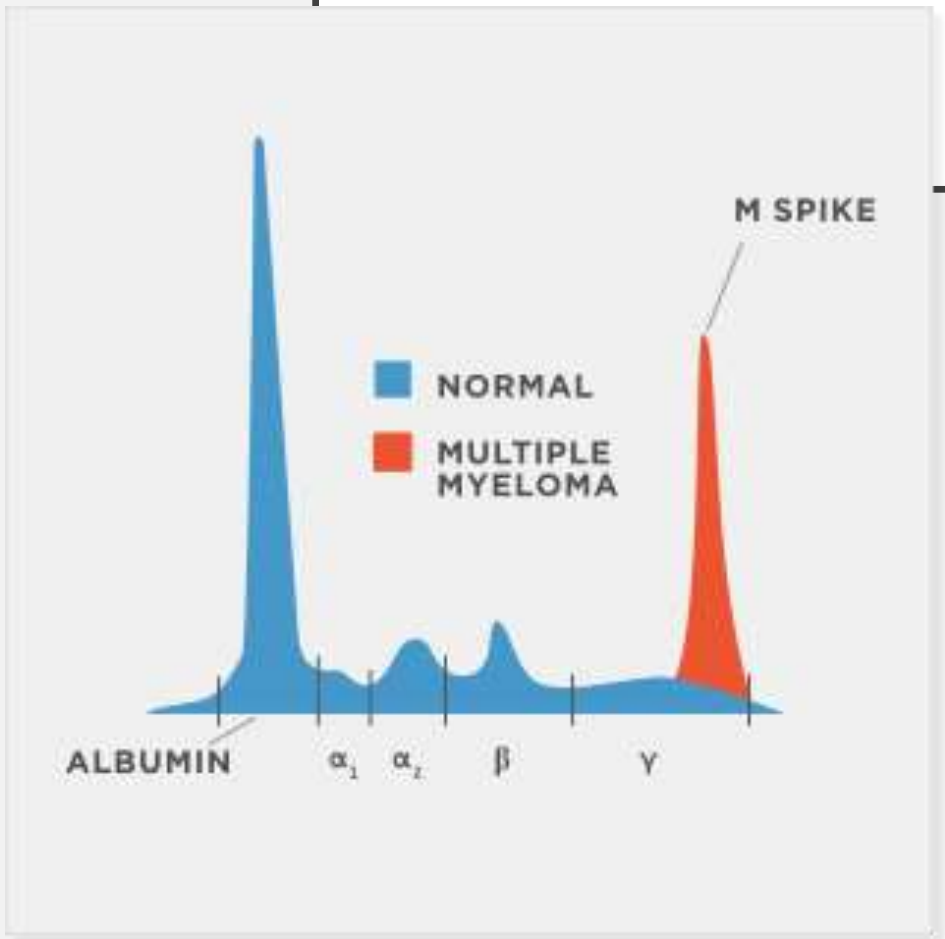
TABLE 9-3

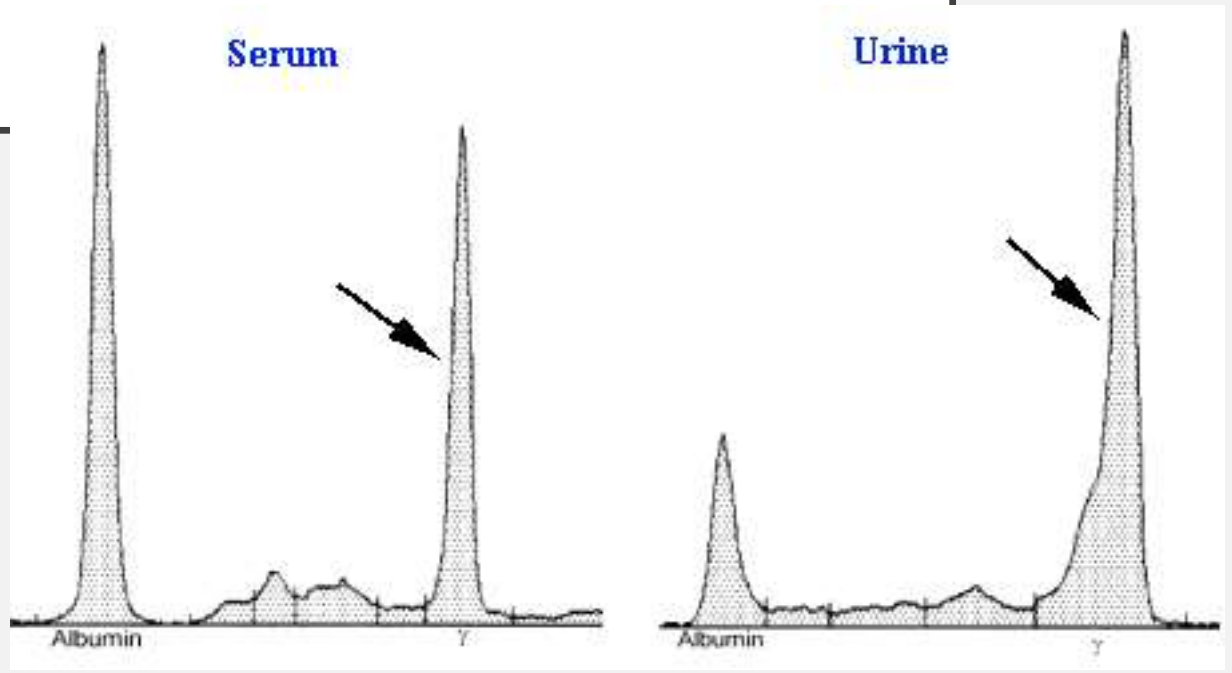
Mechanism	Disorders
Interaction of antibodies with specific antigenic targets on peripheral nerves	IgM anti-myelin-associated glycoprotein neuropathy, CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies)
Monoclonal protein deposition	Light chain amyloidosis
Overproduction of inflammatory cytokines	POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome
Infiltration of peripheral nerve by malignant cells	Neurolymphomatosis
Ischemic	Cryoglobulinemic vasculitis
Compressive	Plasma cell expansion in multiple myeloma, infiltration of ligamentous tissue (amyloid light chain) directly compressing adjacent nerves
Treatment related	Thalidomide- and bortezomib-induced neuropathy


Systemic immune compartment
BNB
Peripheral nervous system
APC
Activated T cell
Autoreactive T cell
Plasma cell
Chemokines, proteases and adhesion molecules
Autoantibody
Macrophage
Apoptosis
Nerve cell
TNF, proteases, ROS and cytokines
Schwann cell
Juxtaparanode
Paranode
Node
Ganglioside
Gliomedin
NrCAM
NF155
MAG
Kv1.1
Kv1.2
Kv1.4
Kv1.6
Contactin 1
CASPR1
Nav1.6
NF186
Kv7.2
Kv7.3
Axon
Myelin
Schwann cell microvilli

MGUS

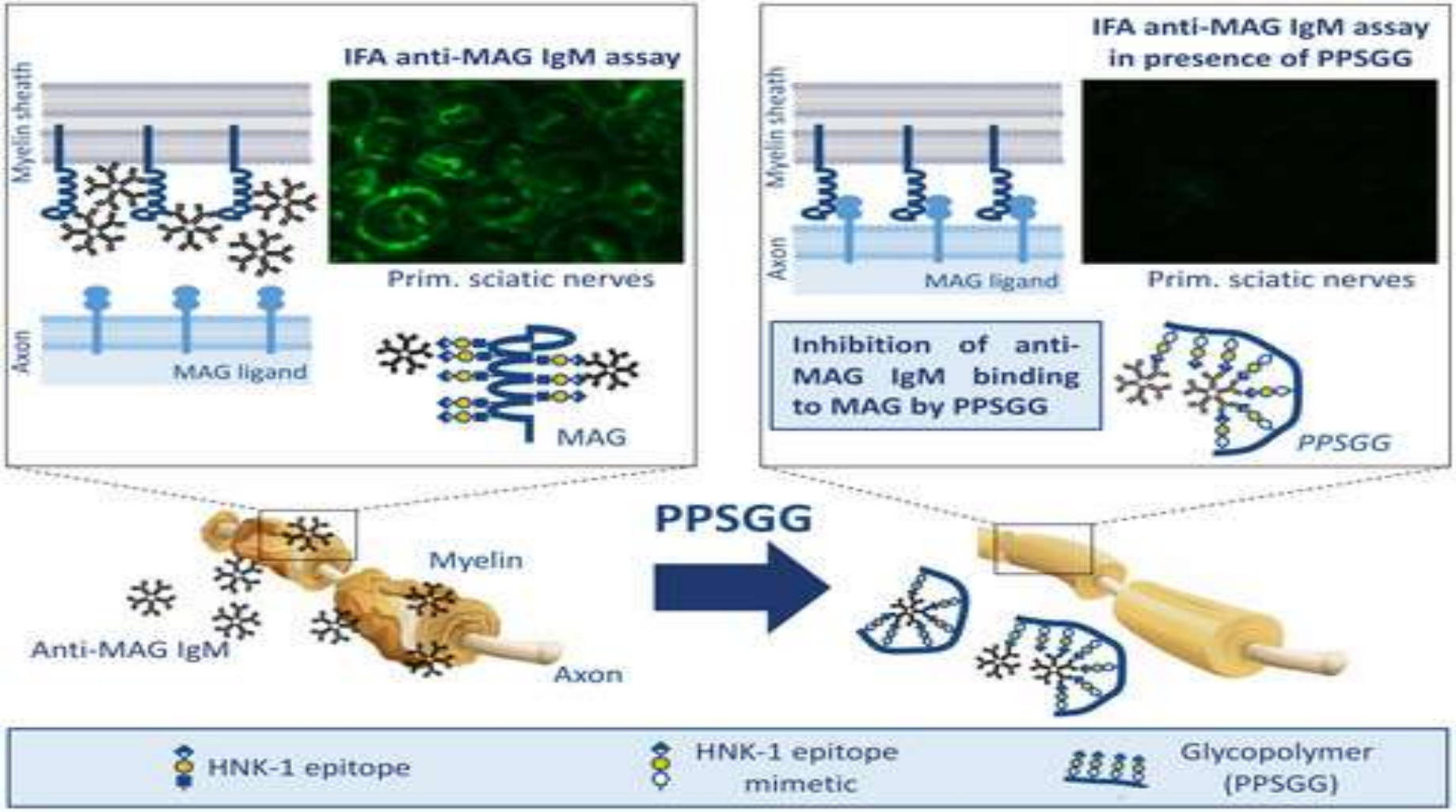
- Paraproteins most commonly occur as a monoclonal gammopathy of undetermined significance (MGUS).
- Characterized by the presence of monoclonal paraprotein in the blood less than 3 g/dL), plasma cells less than 10% on bone marrow examination, and lack of characteristic end-organ.
- The prevalence of MGUS increases with age, affecting 3.2% of people older than 50 years,
- The risk of progression to myeloma is 1%.


M SPIKE
NORMAL
MULTIPLE MYELOMA
ALBUMIN
α1
α2
β
γ


Serum
Albumin
γ
Urine
Albumin
γ

ANTI–MYELIN-ASSOCIATED GLYCOPROTEIN PERIPHERAL NEUROPATHY(ANTI-MAG)

- MAG is a transmembrane glycoprotein located in central and peripheral nerve within myelin localized in peri-axonal Schwann cell. It plays an important role in the formation of myelin and the interaction between axons and myelin.
- The phenotype is known as distal acquired demyelinating symmetric neuropathy (DADS) with monoclonal protein.
- High titers of anti-MAG antibody seen with paraproteins with kappa light chain.
- About 35% of patients with IgM neuropathy do not have any identifiable antibody and are classified as non–anti-MAG DADS.
- It is predominant in males and the elderly.


IFA anti-MAG IgM assay
Myelin sheath
Axon
MAG ligand
Prim. sciatic nerves
MAG
IFA anti-MAG IgM assay in presence of PPSGG
Inhibition of anti-MAG IgM binding to MAG by PPSGG
PPSGG
Anti-MAG IgM
Myelin
Axon
HNK-1 epitope
HNK-1 epitope mimetic
Glycopolymer (PPSGG)

ANTI-MAG

Presentation:

- Manifests with early sensory ataxia, resulting in gait impairment with absent or mild weakness and tremor.

Diagnosis:

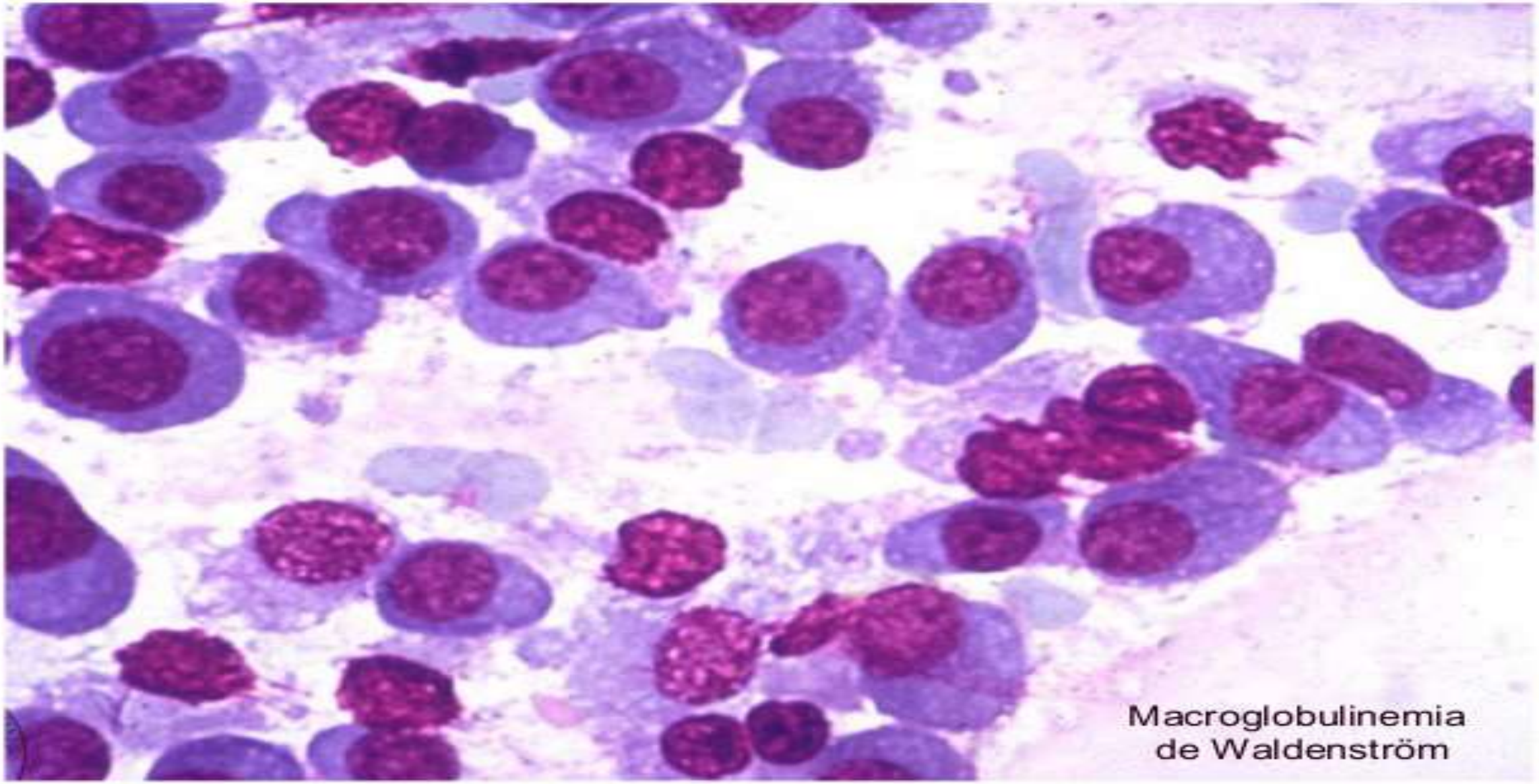
- Detection of anti-MAG antibody in 1000 Bühlmann/tu by serum ELISA.
- Nerve conduction studies demonstrate a uniformly slow conduction velocity with prolonged distal latencies and short terminal latency index.
- Nerve ultrasound studies demonstrate large cross-sectional area in cervical nerve root and and regional nerve enlargement.

Treatment:

- Plasma Exchange, IVIG, Rituximab is considered as first line therapy.
- Newer anti–B-cell agents that cause more profound or sustained B-cell depletion are potential treatment strategies such as Obinutuzumab a anti-CD20 monoclonal antibody used in CLL.

WALDENSTRÖM MACROGLOBULINEMIA–ASSOCIATED PERIPHERAL NEUROPATHY

- Waldenstrom macroglobulinemia is a low-grade B-cell lymphoproliferative characterized by bone marrow infiltration by lymphoplasmacytic cells and IgM monoclonal gammopathy.
- Waldenstrom macroglobulinemia due to somatic variation in MYD88 gene, which codes for an adaptor protein in the B-cell receptor pathway.
- Neuropathy is common in patients with Waldenstrom macroglobulinemia.
- IgM binding to unidentified peripheral nerve antigens or less frequently, direct tumor cell infiltration of the nerves.
- When demyelinating, they are identical to IgM MAG neuropathy.


Macroglobulinemia
de Waldenström

CONT

Presentation:

- Cytopenia's, Hepatospleenomegaly, lymphadenopathy, hyper viscosity, cold agglutinin hemolytic anemia and polyneuropathies, glomerular disease, amyloidosis.

Diagnosis:

- Serum and urine electrophoresis with immunofixation, bone marrow biopsy, cold agglutin titer and electrophysiological studies shows Prolonged distal motor latency, low terminal and latency index.

Treatment:

- Chemoimmunotherapy like dexamethasone, rituximab cyclophosphamide are used bendamustine,rituximab or Bruton tyrosine kinase are used in treating Waldenstrom macroglobulinemia.
- Symptomatic treatment can be used in treating neuropathy but primary goal is treating the underlying cause.
- Bruton tyrosine kinase inhibitor ibrutinib are studied to use Waldenstrom macroglobulinemia

CRYOGLOBULINEMIA ASSOCAITED NEUROPATHY

- Cryoglobulins are immunoglobulins that precipitate in vitro temperatures less than <98.6°F and redissolve on rewarming .Its if two types.
- Type I cryoglobulinemia are monoclonal immunoglobulins like IgM, IgG, IgA, and light chain). It develops in the setting of monoclonal gammopathies. Mostly associated with MGUS, and B-cell lineage malignancy like multiple myeloma, Waldenstrom macroglobulinemia, or chronic lymphocytic leukemia.
- Type II is a mixed cryoglobulinemia and is usually associated with hepatitis C virus infection but may occur in lymphoproliferative disorders as well.
- Peripheral neuropathy manifests as a painful sensory neuropathy affecting predominantly small fibers sparing autonomic nerves, sometimes presenting as mononeuritis multiplex.

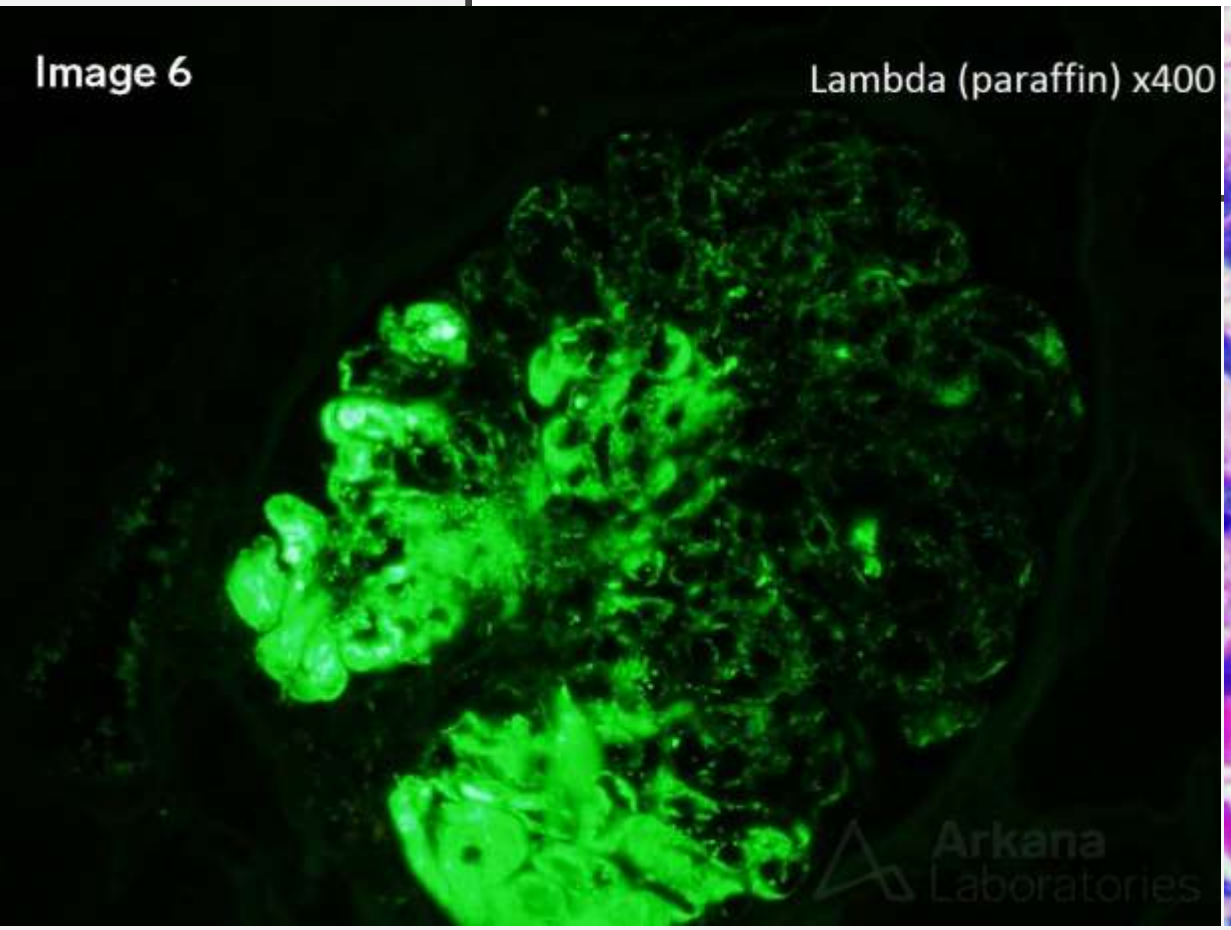
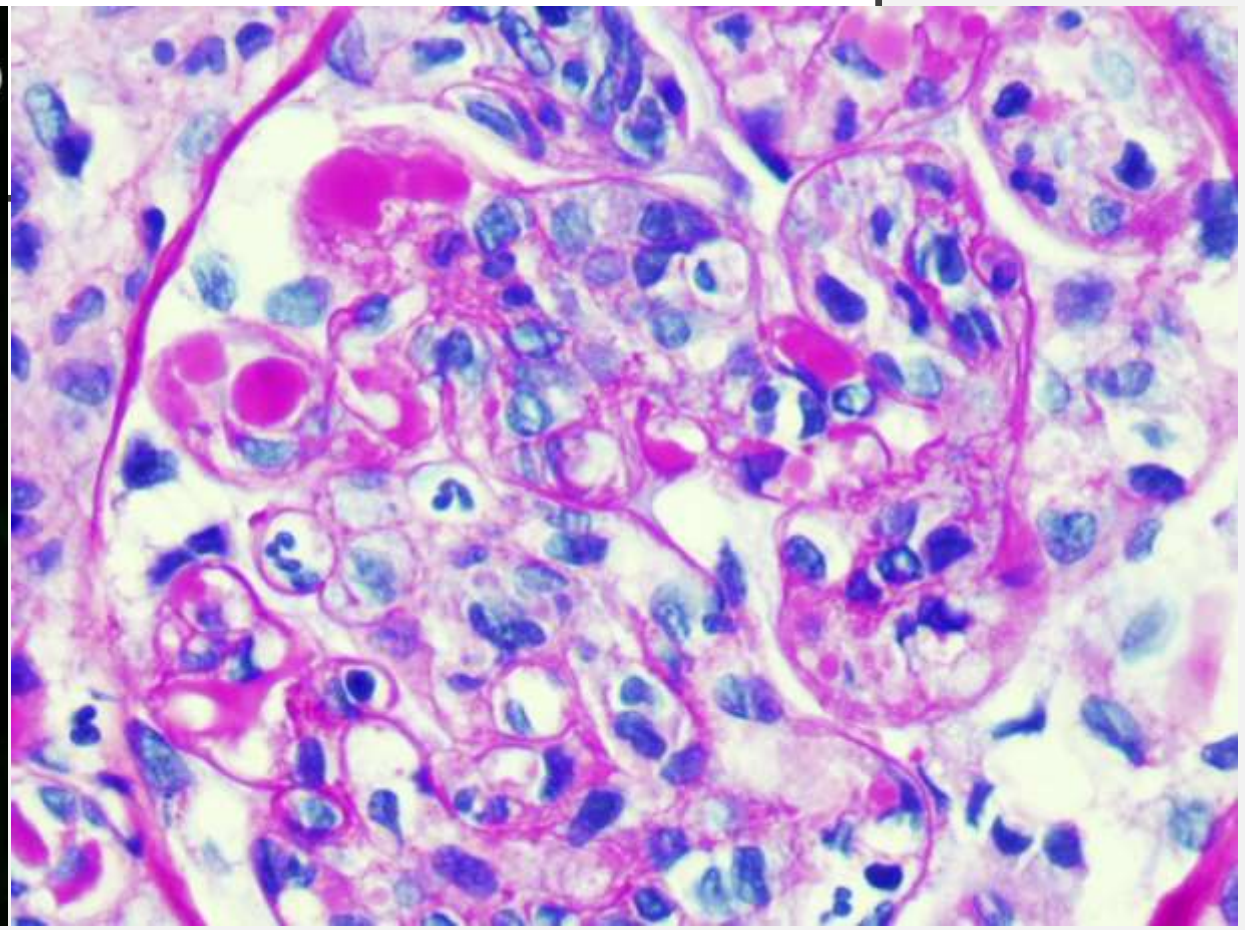


Image 6
Lambda (paraffin) x400
Arkana
Laboratories



CONT.

Presentation:

- Manifest with livedo reticularis, purpura, cutaneous ulcers, gangrene, AIHA and neuropathy.
- Pain can be a distinguishing feature of cryoglobulinic neuropathy.

Diagnosis:

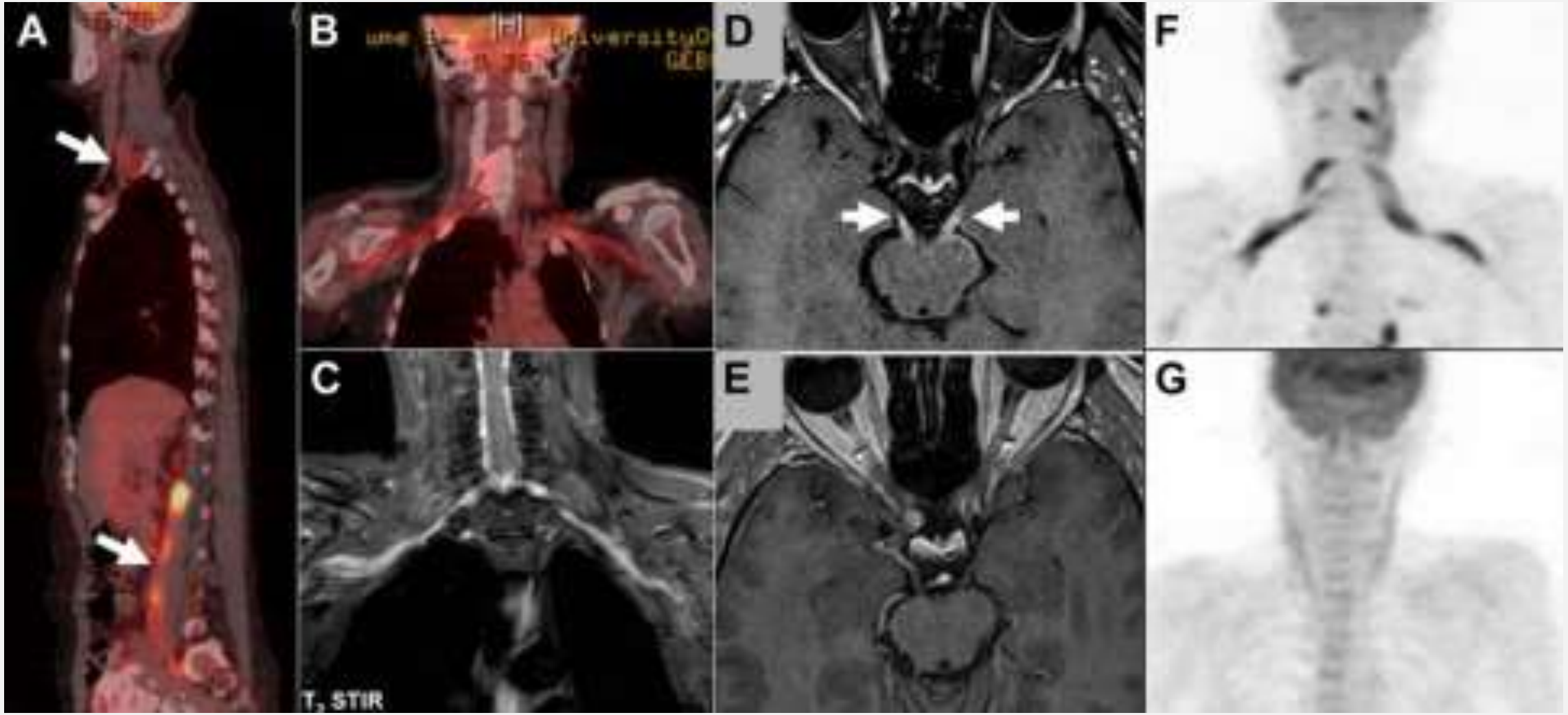
- Low C4 complement level, detection of cryoglobulins in serum, Immunofixation.

Treatment:

- Plasmapheresis and Immunosuppression such as glucocorticoids and rituximab for patient with rapidly progressing or life-threatening outcomes. Treat underlying systemic or hematologic condition.

NEUROLYMPHATOSIS ASSOCIATED NEUROPATHY

- Neurolymphomatosis is a rare manifestation of non-Hodgkin lymphoma and characterized by direct malignant lymphocytic invasion of the peripheral nervous system.
- It can affect cranial nerves, peripheral nerves, and nerve roots or plexus, and thus, the clinical picture is extremely heterogeneous presenting with neuropathies.
- Neurolymphomatosis should, therefore, be considered in all patients with lymphoma with unexplained peripheral nervous system dysfunction with an asymmetric distribution and rapid progression of neurologic symptoms.


A
B
D
F
C
E
G
T, STIR

CONT.

Presentation:

Manifest with painful radiculopathies, cranial neuropathies, mononeuropathies, polyradiculopathies.

Diagnosis:

- Nerve biopsy is the gold standard test for the diagnosis of neurolymphomatosis, but neuroimaging and PET-CT have greatly.
- CSF studies show elevated protein, low glucose, and elevated white blood cell count.

Treatment:

- Steroids alone only provide short-lived symptom control.
- Addition of rituximab to chemotherapy has been shown to significantly improve the survival of patients.
- Salvage ESHAP therapy (etoposide, methylprednisolone, cytosine arabinoside, and cisplatin) followed by BEAM (BCNU, etoposide, cytarabine, melphalan) chemotherapy with stem-cell transplant.

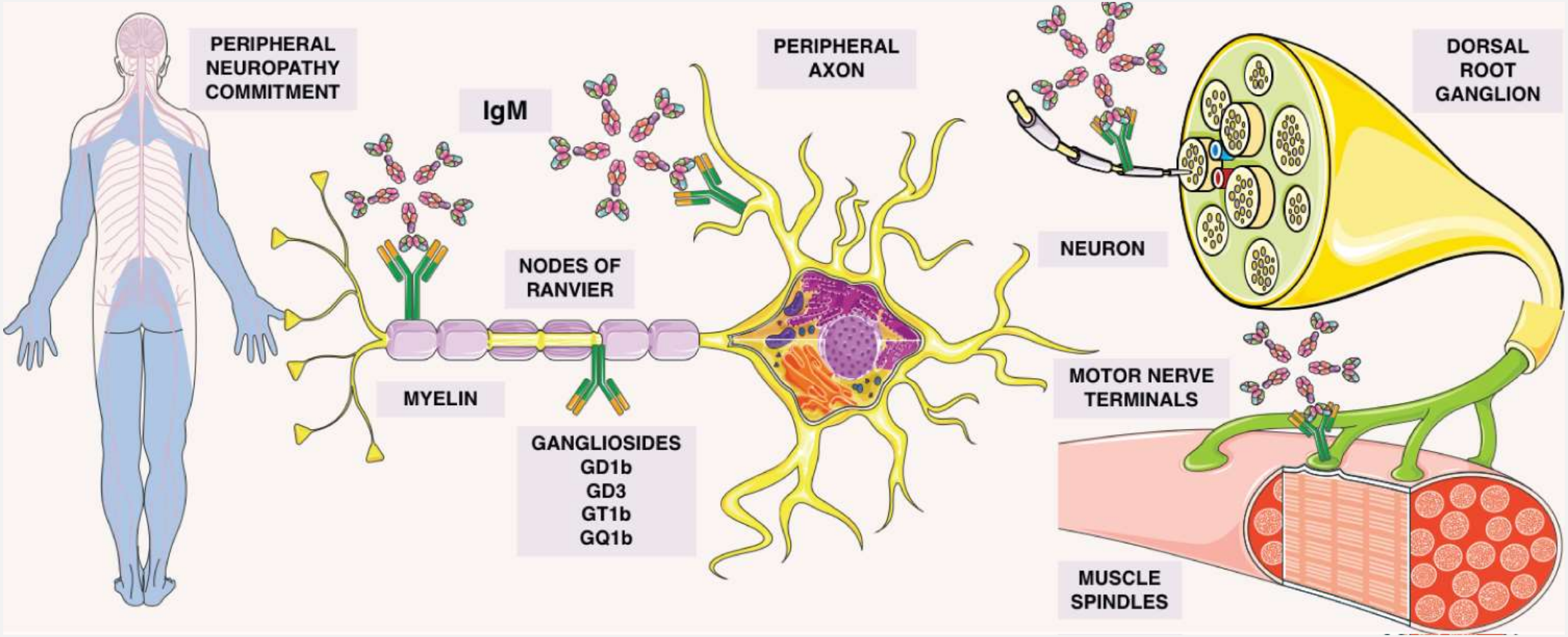
CANOMAD AND CANDA

- CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein,

cold agglutinins, and disialosyl antibodies).

CANDA (chronic ataxic neuropathy with anti-disialosyl IgM antibodies)

- It is sensory ataxic neuropathies associated with disialosyl antibodies, monoclonal proteins, and cold agglutinins characterized by chronic neuropathy with sensory ataxia, areflexia, and motor weakness occasionally involving the ocular motor and bulbar muscles.
- The exact pathogenesis is not fully understood, but evidence suggests that direct damage to dorsal root ganglia


PERIPHERAL NEUROPATHY COMMITMENT
IgM
PERIPHERAL AXON
DORSAL ROOT GANGLION
NODES OF RANVIER
NEURON
MYELIN
MOTOR NERVE TERMINALS
GANGLIOSIDES
GD1b
GD3
GT1b
GQ1b
MUSCLE SPINDLES

CONT.

Presentation:

- Symptoms include sensory ataxia, areflexia, and bulbar and oculomotor weakness with relative preservation of limb motor function.

Diagnosis:

Diagnosis is based on neurologic examination findings, presence of IgM antibodies, and elevated serum IgM paraprotein.

- Acquired demyelinating features are common findings on electrodiagnostic studies.
- Nerve ultrasound studies of four patients with CANOMAD demonstrated features of an acquired demyelinating polyneuropathy.

Treatment:

- IVIg and rituximab-based regimens were the most effective therapies.
- Rituximab is most effective in halting the disease progression.

POEMS SYNDROME

- A rare multiorgan paraneoplastic disorder associated with plasma cell dyscrasia.
- POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin changes).
- The pathogenesis of POEMS syndrome is not well understood but related to cytokine imbalance outlined by excessive production of multiple proinflammatory and angiogenic cytokines, including endothelial growth factor (VEGF).
- The most common type of monoclonal protein in POEMS syndrome is IgA followed by IgG, and the light chain is almost always lambda.

Mandatory major criteria

1. **Polyneuropathy (typically demyelinating)**
2. **Monoclonal plasma cell-proliferative disorder (almost always lambda)**

Other major criteria (one required)

3. **Castleman disease**
4. **Sclerotic bone lesions**
5. **VEGF elevation**

Minor criteria

6. Organomegaly (**splenomegaly**, hepatomegaly or **lymphadenopathy**)
7. Extravascular volume overload (**edema**, pleural effusion or ascites)
8. Endocrinopathy (adrenal, **thyroid,** pituitary,gonadal, parathyroid and **pancreatic)**
9. **Skin changes (hyperpigmentation,** hypertrichosis, **sclerodermoid changes, eruptive hemangiomata,** plethora, acrocyanosis, flushing, clubbing**, facial atrophy**, white nails)
10. Papilledema
11. Thrombocytosis/polycythemia

Other symptoms and signs

Clubbing, **weight loss**, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea

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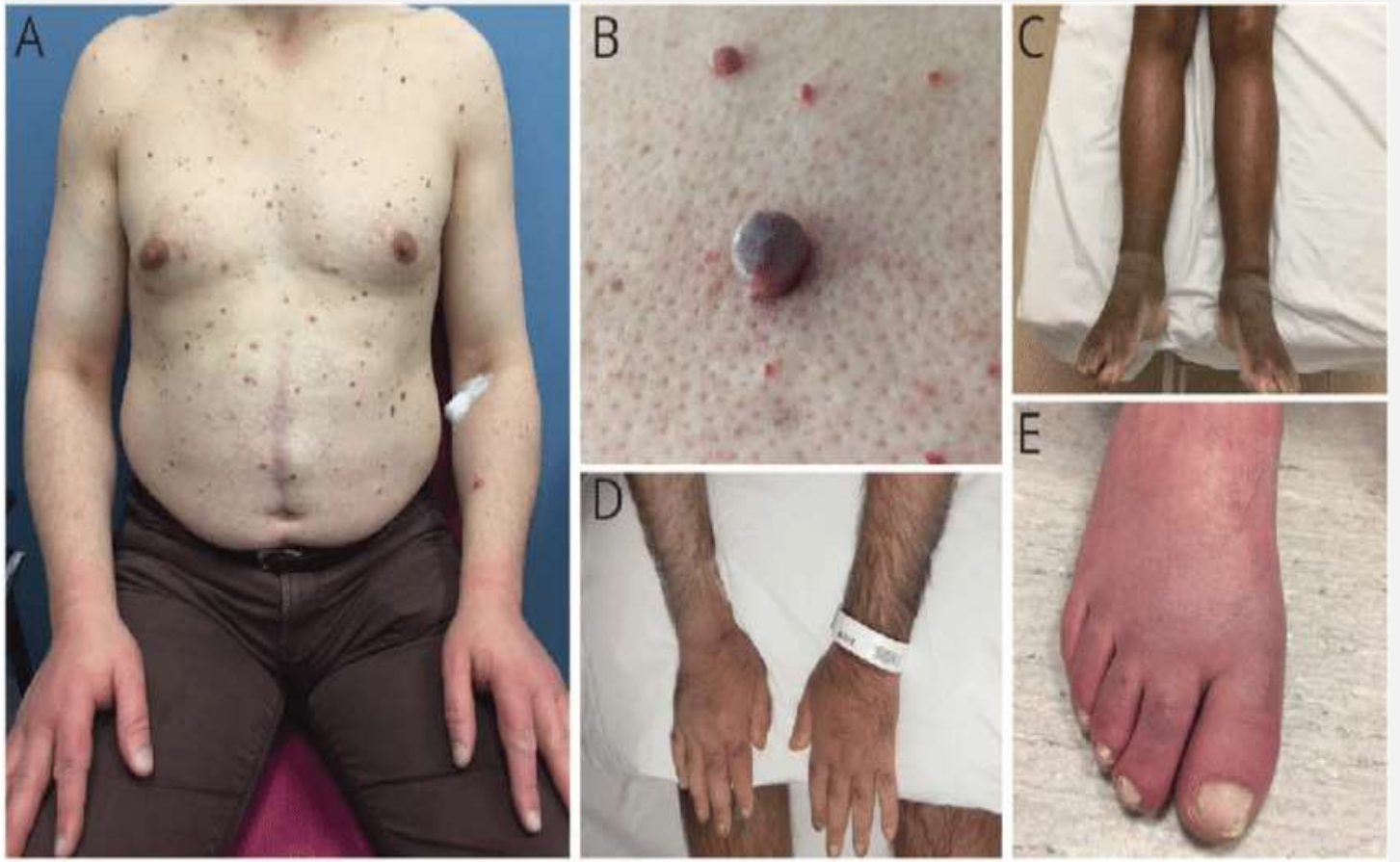
POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin signs; VEGF, vascular endothelial growth factor.
Criteria and symptoms of our patient are in bold.



CONT.

Further Diagnosis:

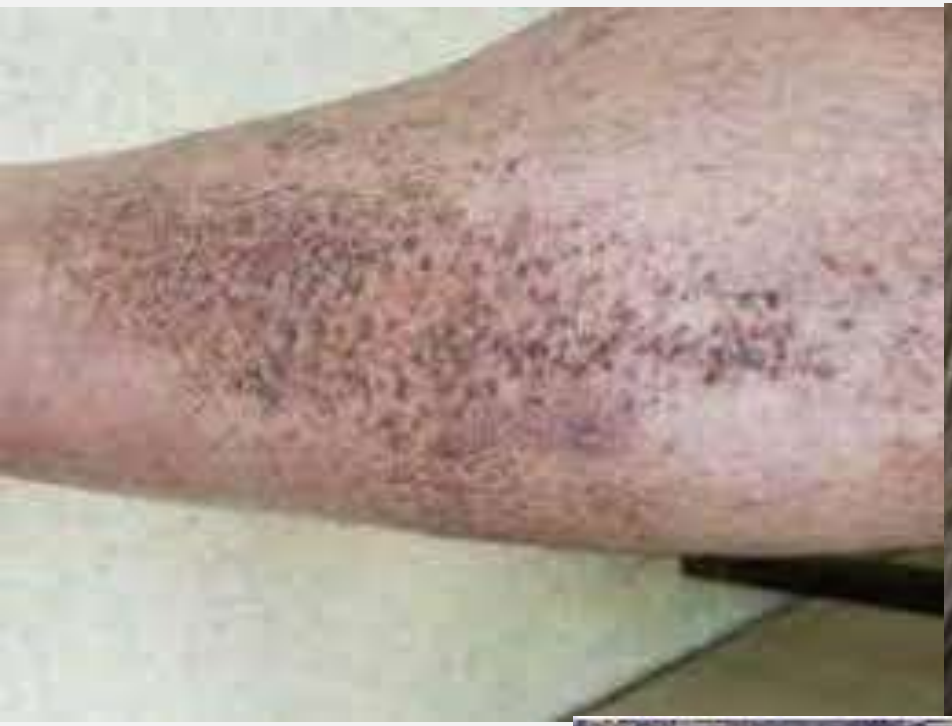
- Electrodiagnostic studies show prominent demyelinating neuropathy with secondary axonal loss and characteristic patterns such as conduction block, conduction slowing is prominent in the intermediate nerve segments and CMAPs and sensory nerve action potentials (SNAPs) of the lower limbs.
- Nerve biopsy reveals demyelination with uncompacted myelin. POEMS syndrome demonstrates moreaxonal degeneration and epineural neovascularization.
- Elevated serum and plasma levels of VEGF >200 pg/mL.
- N-terminal propeptide type I collagen has been identified as a novel marker for the diagnosis.

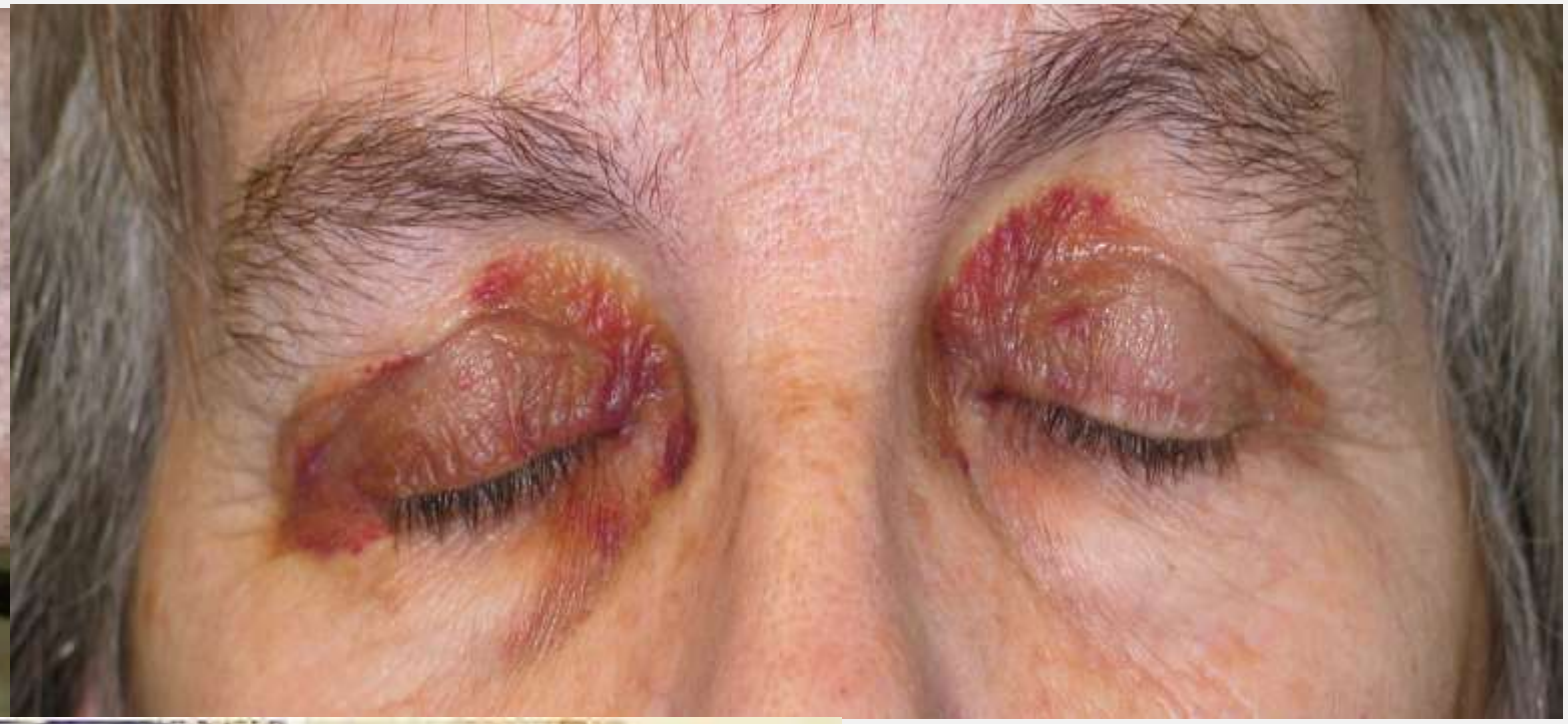
POEMS RX

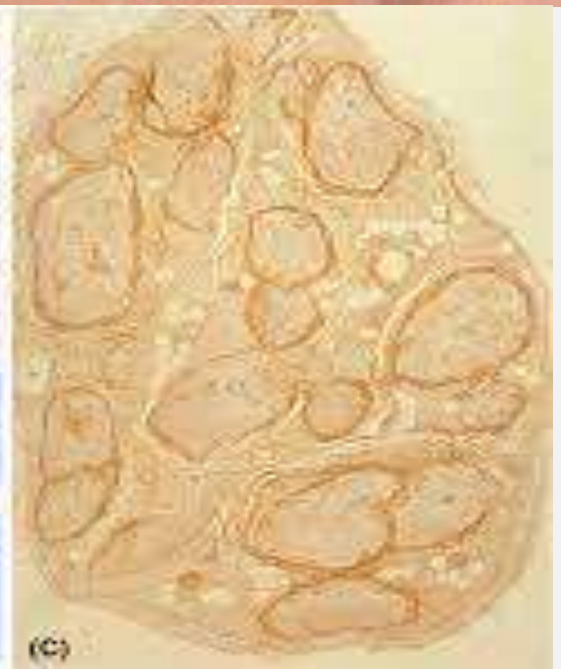
- Treatment:
- High-dose melphalan followed by autologous hematopoietic cell transplantation is an effective therapy.
- Immunomodulatory drugs, such as daratumumab, bortezomib, used for patients who are not candidates for hematopoietic cell transplantation.
- Lenalidomide (a derivative of thalidomide) has been shown to be a highly effective and safe therapy
- Anti-VEGF therapy bevacizumab shows consistent clinical benefit.
- Neurologic response can be delayed and incomplete and may take up to 6 to 36 months after completion of therapy.

AMYLOID LIGHT CHAIN NEUROPATHY

- AL amyloidosis is the most common form of systemic amyloidosis, with immunoglobulins with the potential for misfolding and deposition as amyloid fibrils in the peripheral nervous system.
- Peripheral neuropathy occurs in patients with AL amyloidosis. Presents with a length-dependent sensory predominant polyneuropathy with a predilection for small fibers.
- The lambda light chain is more common than the kappa light chain in AL amyloidosis.
- If left untreated, it has a poor prognosis with median survival less than 18 months from onset.







DIAGNOSIS AMYLOID LIGHT CHAIN NEUROPATHY

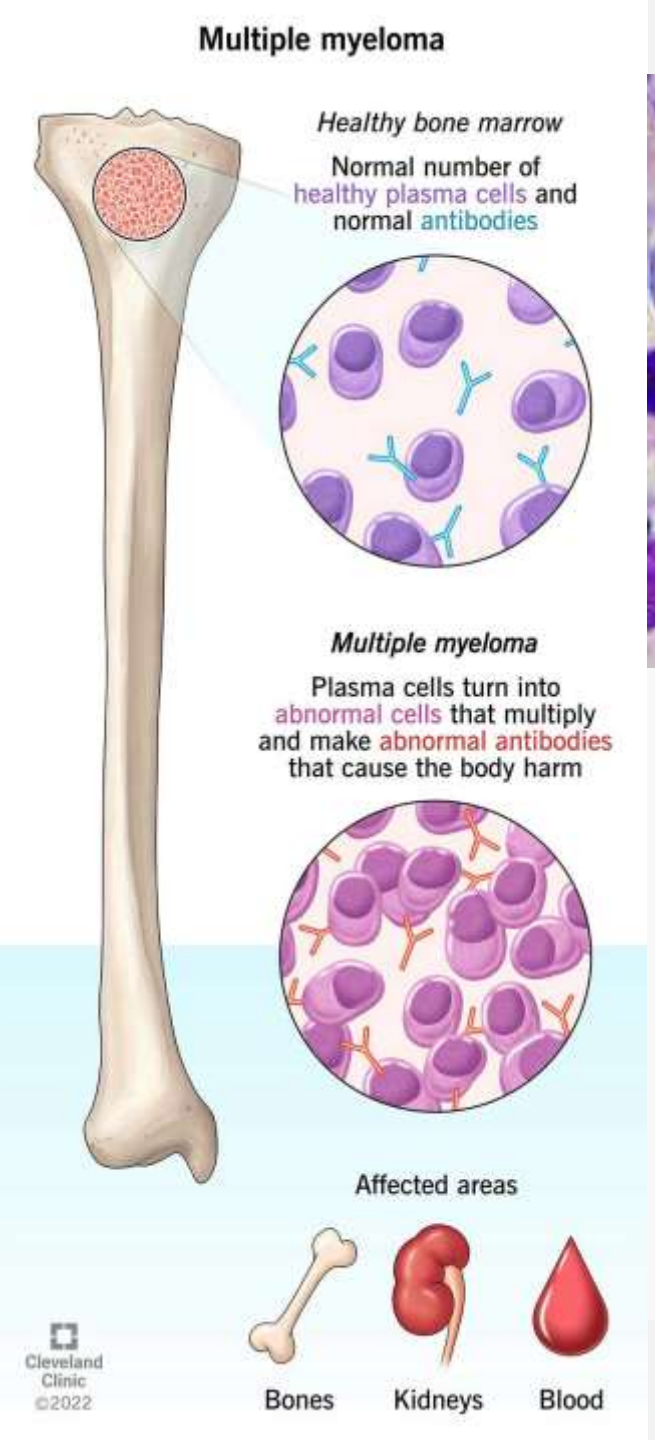
- Begins with Autonomic symptoms, include orthostatic hypotension, sweating, postprandial fullness, diarrhea, constipation, and erectile dysfunction,
- Clinical findings include periorbital purpura, hepatomegaly, macroglossia.
- Nerve conduction studies show length-dependent sensorimotor axonal neuropathy, with demyelinating findings such as prolonged distal motor latencies, severely reduced nerve conduction velocities, abnormal temporal dispersion, prolonged F-wave latencies
- Serum and urine protein immunofixation electrophoresis and serum free light chains assays should be obtained in all patients suspected of amyloid neuropathy.
- Histopathology demonstrating amyloid deposition in tissue is required for definite diagnosis.

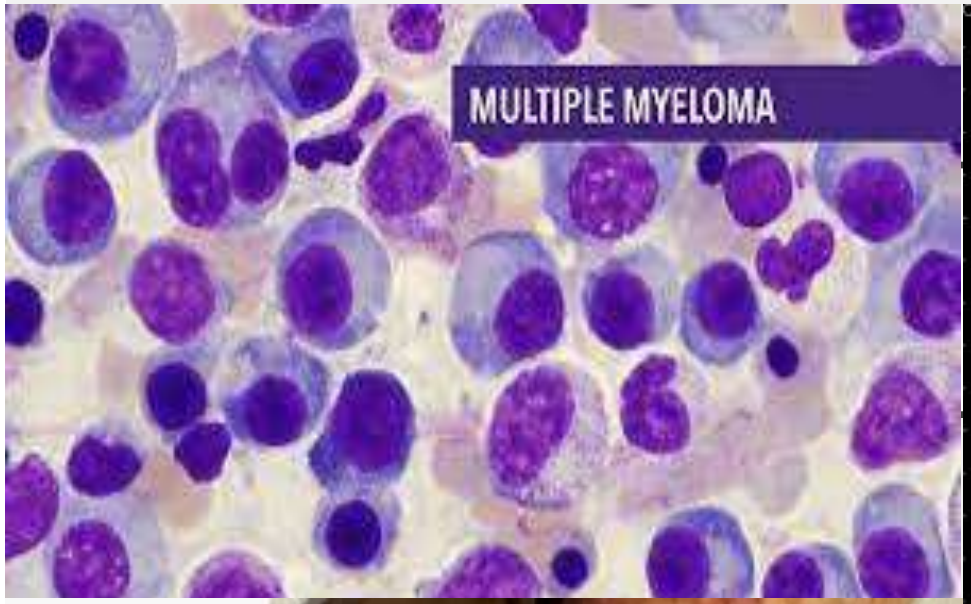
TREATMENT

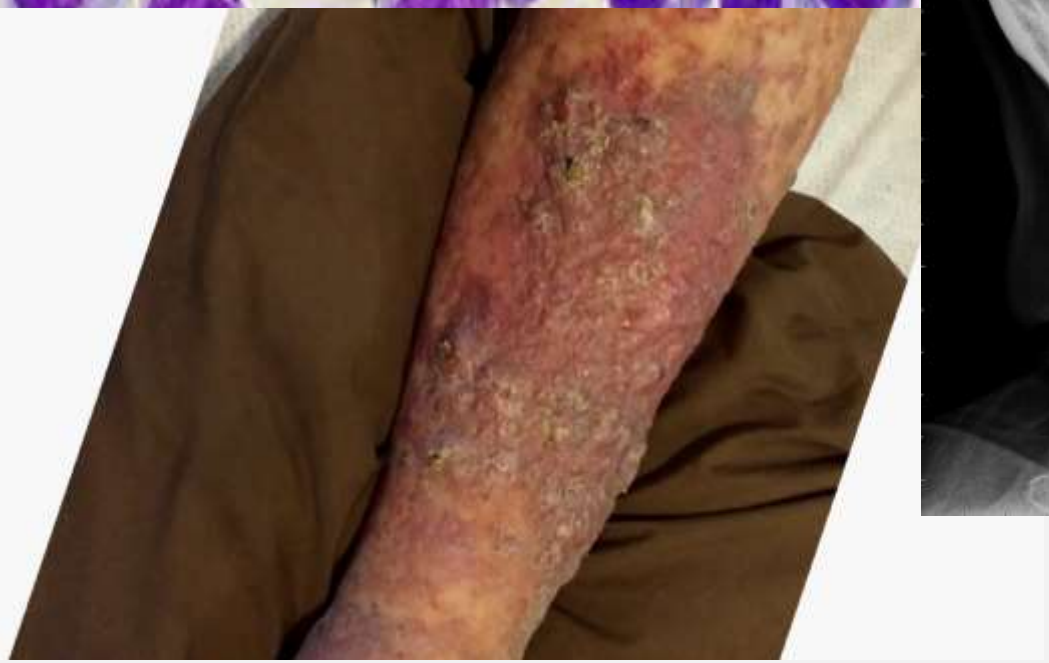
- Amyloidosis progress rapidly hence early intervention is crucial.
- High-dose chemotherapy followed by stem cell transplantation in eligible patients. Combinations of daratumumab with bortezomib, cyclophosphamide, and dexamethasone are options for transplant-ineligible patients with AL amyloidosis.
- However, bortezomib should be avoided in patients with peripheral neuropathy.

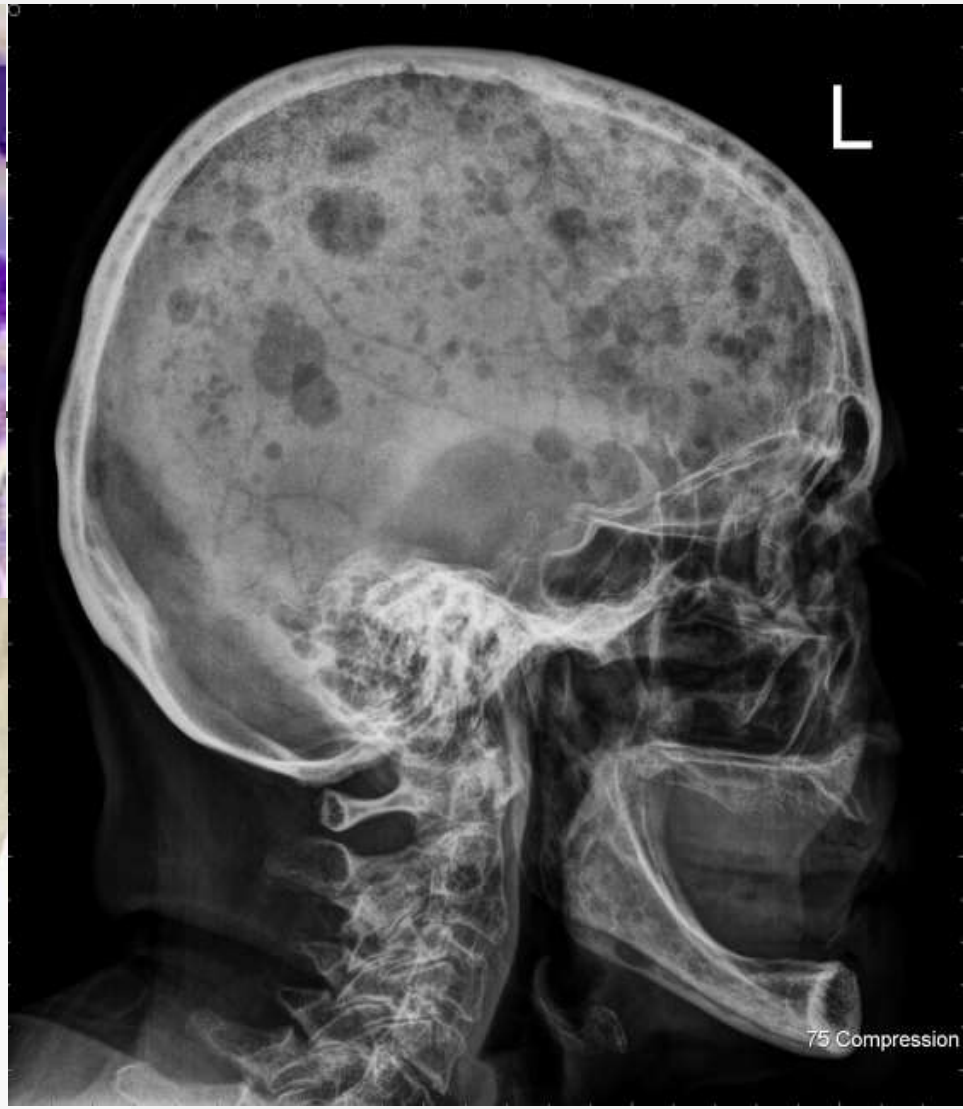
MULTIPLE MYELOMA–ASSOCIATED PERIPHERAL NEUROPATHY

- Multiple myeloma is a malignant non-IgM plasma cell disorder (IgG more frequently than IgA) that accounts for due to hematologic malignancies.
- Peripheral neuropathy is a common complication of multiple myeloma.
- Multiple myeloma is associated peripheral neuropathy usually presents with slowly progressive, painless, length-dependent sensory or sensorimotor polyneuropathy.
- Treatment is targeted to the underlying plasma cell dyscrasia.
- Neurotoxicity is a common side effect of multiple myeloma therapy, with usage of thalidomide and bortezomib.
- Second-generation proteasome inhibitors and immunomodulatory drugs, such as carfilzomib and pomalidomide.


Multiple myeloma
Healthy bone marrow
Normal number of healthy plasma cells and normal antibodies
Multiple myeloma
Plasma cells turn into abnormal cells that multiply and make abnormal antibodies that cause the body harm
Affected areas
Bones
Kidneys
Blood
Cleveland Clinic ©2022


MULTIPLE MYELOMA




L
75 Compression

IGA AND IGG PARAPROTEINEMIC NEUROPATHIES

- Monoclonal gammopathies can result in neuropathies with non-IgM monoclonal proteins and peripheral neuropathy mostly IgG- and IgA-associated.
- Seen in patients with POEMS syndrome or AL amyloidosis.
- CIDP is labelled as CIDP with a coincidental paraprotein.
- Patients have better response to conventional CIDP therapy.

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- Paraproteinemic Neuropathies Said R. Beydoun, MD, FAAN; Leila Darki, MD Peripheral Nerve and Motor Neuron Disorders p. 1492-1513 October 2023, Vol.29, No.5 doi: 10.1212/CON.0000000000001294

THANK YOU