INFLAMMATORY MYOPATHIES

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LEC.3

These are heterogeneous group of rare disorders characterized by **immune mediated muscle injury & inflammation.**

Under this heading are three disorders:-

1. Polymyositis.
2. Dermatomyositis.
3. Inclusion body myositis.

They may occur alone or with other autoimmune disease as systemic sclerosis.

Clinically, they present with symmetric muscle weakness initially affecting large muscles of the trunk, neck & limbs, with difficulty in getting up from a chair.

In dermatomyositis, there is associated skin rash that involves the upper eyelids together with periorbital edema.

Histologically, there is infiltration of lymphocytes with degeneration of muscle fibers.

Mixed connective tissue disease:

Patients present with multiple features suggestive of SLE, polymyositis & systemic sclerosis.

They also have high titer of antibodies to ribonucleoprotein antigen.

Two distinctive features of this disease:-

1. The kidneys are rarely involved.
2. An extremely good response to corticosteroids.

Polyarteritis nodosa (PAN):

It is a systemic disease characterized by inflammatory necrosis of the wall of small-& medium-sized arteries.

The clinical effects are the result of vessel occlusion leading to small areas of infarction.

The tissues most seriously affected are the kidneys, heart, alimentary tract, liver, CNS, peripheral nerves, skeletal muscle & skin. The cause of the disease is unknown, but it is likely to be immune-complex-mediated.

There is an association with chronic hepatitis B virus antigenemia.

Amyloidosis

Amyloidosis indicates an abnormal extracellular deposition of pathogenic proteins in various tissue and organs.

As the material accumulates, it produces pressure atrophy of the adjacent parenchymal cells.

Morphology

The diagnosis depends on identification by light microscopy of amyloid deposition in biopsy material.

H & E stain shows amyloid as an amorphous, eosinophilic hyaline extracellular substance.

Amyloid also takes up certain special stains; the most widely used of these is **Congo red stain**, which gives pink to red color under ordinary light microscopy but characteristically ***apple green birefringence under plarizing microscopy.***

Electron microscopy of amyloid shows that it is composed of fibrils in a ß- pleated sheet.

Effects

Progressive accumulation of amyloid causes pressure atrophy of the adjacent cells.

Composition

Amyloid is not a single chemical entity, three major & several minor biochemical forms could be found.

Physical nature of amyloid

The major component of amyloid (95%) is made up of nonbranching fibrils, each is 7.5-10 nm in width; these fibrils show characteristic crossed ß-pleated sheet conformation.

There is in addition a minor component (5%), which is nonfibrillar; it is made up of a pentagonal glycoprotein (P-component) as well as proteoglycans.

Chemical nature of amyloid:

1. **AL (amyloid light chain)** derived from plasma cell & contains Ig light chain. It is encountered with some forms of monoclonal B-cell proliferation.

2. AA (amyloid- associated) is derived from serum precursor protein synthesized by the liver (serum amyloid associated) (SAA).

It is non-immunoglobulin protein and deposited in the setting of chronic inflammatory states.

3. Aβ is found in the cerebral lesions of Alzheimer disease.

4. Transthyretin (TTR) is a normal serum protein that binds & transports thyroxin & retinol.

It is deposited in the heart of aged patients.

A mutant form of TTR is deposited in some genetic disorders leading to **familial amyloid polyneuropathies.**

5. $ß_2$ microglobulin is a Component of the MHC class 1 molecules, normal serum protein.

Amyloidosis is either systemic (generalized) or localized in distribution.

Systemic amyloidosis may be:

1. Primary, which is associated with immunocyte dyscrasia.
2. Secondary as a complication of chronic diseases.

Classification of amyloidosis

Clinicopathological category	Associated diseases (type of amyloid)
A. Systemic (generalized)	
1. Immunocyte dyscrasia (primary amyloidosis)	Multiple myeloma (AL)
2. Reactive systemic (secondary)	Chronic inflammatory disorder(AA)
3. Hemodialysis-associated	Chronic renal failure

4. Hereditary

Familial Mediterranean fever (AA)

Familial amyloidotic neuropathy (TTR)

5. Amyloid of aging Systemic senile amyloidosis (TTR)

B. Localized amyloidosis

1. Senile cerebral — Alzheimer disease Aβ
2. Endocrine

Thyroid	Medullary ca. thyroid
Pancreas (Islets of Langerhan)	Diabetes type 2

3. Heart — Isolated aterial amyloidosis

Systemic amyloidosis

1. **Primary amyloidosis of AL type** is usually systemic. Examples include:-
   amyloidosis associated with **multiple myeloma** (a malignant neoplasm of plasma cells).

In this neoplasm two forms of proteins are synthesized:

a. Abnormal amount of specific immunoglobulin producing M (myeloma) protein spike on serum electrophoresis.

b. λ &κ light chains known as Bence Jones protein which is excreted in urine.

2. Reactive systemic amyloidosis (A A);

the distribution of the amyloid deposition in this pattern is systemic.

Previously this from was considered to be secondary because it is associated with chronic infectious diseases like TB, bronchiectasis and chronic osteomyelitis.

With the use of antibiotics to control such infections, currently it tends to be associated with chronic inflammation caused by autoimmune states such as rheumatoid arthritis and inflammatory bowel disease specifically Crohn's disease.

3. Heredofamilial amyloidosis; examples include Familial Mediterranean Fever, which is an autosomal recessive febrile illness of unknown cause.

It is associated with inflammation of serosal membranes such as the peritoneum, pleura & synovium.

The type of amyloid involved is AA protein , which suggests that chronic inflammation plays a vital rule.

4. Systemic senile amyloidosis (TTR)

usually occurs in the age group 70-80 years; the heart is predominantly involved.

Localized amyloidosis (AL)

which is limited to one organ or tissue.

Such a deposition may produce detectable nodular masses or be evident only through microscope examination.

Endocrine amyloid (TTR)

This form is found in medullary carcinoma of the thyroid, islet cell tumor of pancreas and pheochromocytoma.

Pathogenesis

Long standing tissue injury & inflammation cause macrophage activation & lead to elevated SAA levels through the influence of cytokines (IL_1, IL_6) on liver cells. Elevation of SAA levels alone does not lead to amyloidosis.

It is believed that SAA is normally degraded to soluble end products by the action of monocyte-derived enzymes.

So individuals who develop amyloidosis have an enzyme defect that results in the incomplete breakdown of SAA, thus generating insoluble AA molecules.

Morphological effects on various organs

Kidneys become large, pale, gray and firm. Amyloid is deposited in the glomeruli, peritubular tissue and in the wall of blood vessels.

Spleen becomes firm, enlarged, pale and waxy on cut section (Sago spleen).

Liver is enlarged, pale and waxy. The deposition occurs in the space of Disse and surrounding blood vessels.

Stomach and intestine; wide-spread deposition of amyloid leads to mucosal atrophy, diarrhea and malabsorption.

Clinical correlation

The clinical features depend on the site, amount & duration of amyloid deposition.

Weakness, fatigue & weight loss are the most common initial symptoms.

Later other manifestations may be apparent as ***renal disease*** (nephrotic syndrome), which is often the major cause of symptoms in reactive systemic amyloidosis.

Liver involvement is associated with hepatomegaly.

Heart involvement may lead to cardiomyopathy that is associated with arrhythmias.

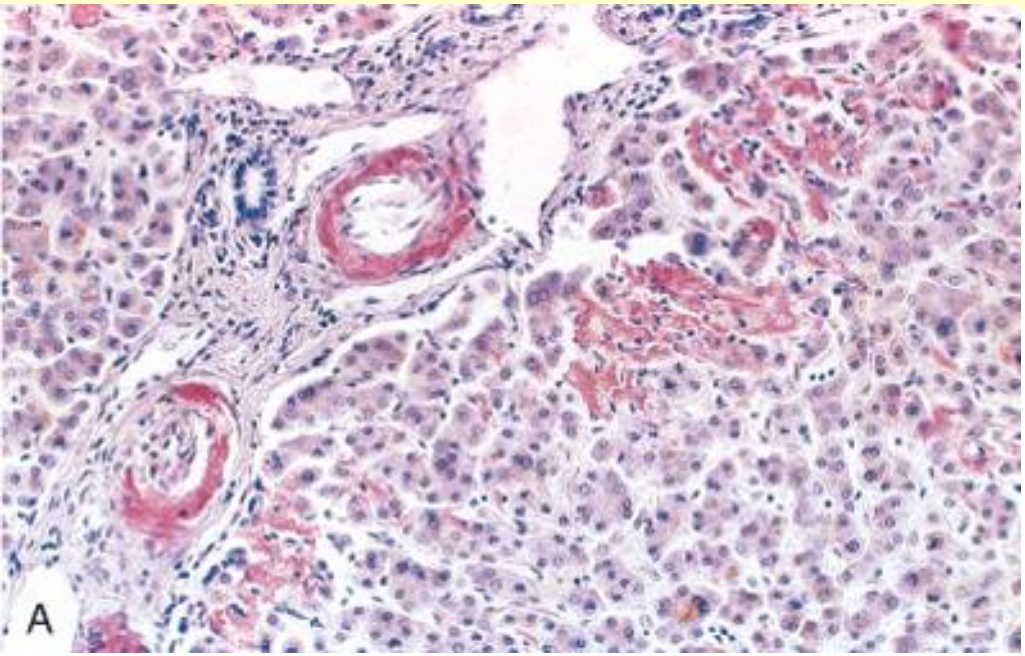
The prognosis is poor in systemic amyloidosis fallowing B -cell dyscrasias (the median survival after diagnosis is 14 months).

A better outlook in reactive amyloidosis depends on the ability to control the underlying condition.

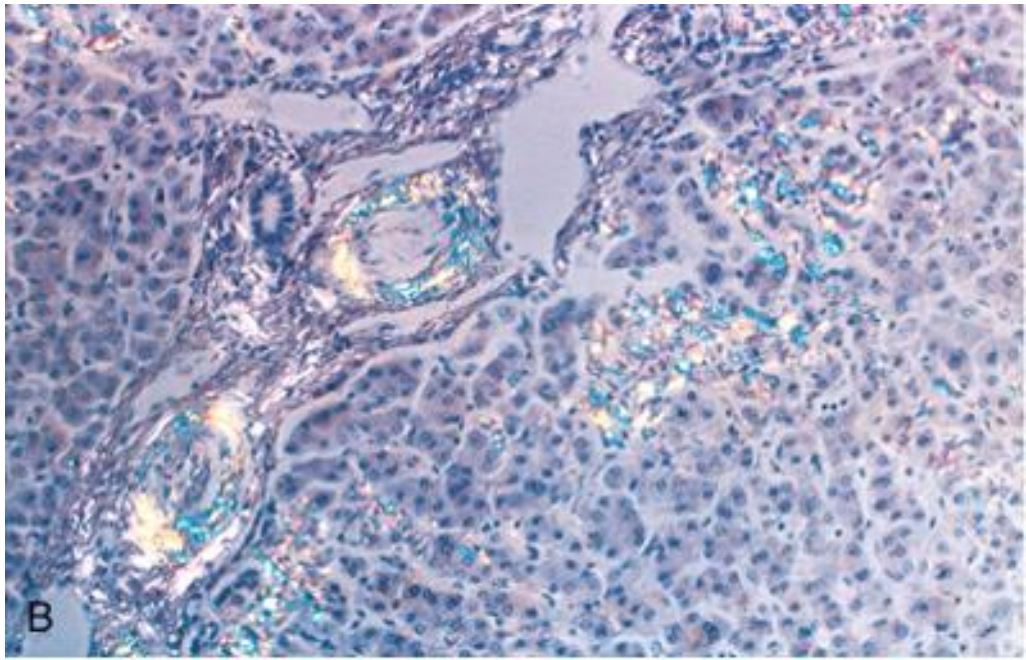
Favored biopsy sites for the diagnosis of amyloidosis include

a. Rectal or gingival biopsy in systemic amyloidosis.
b. Abdominal fat pad biopsy or aspirates.
c. Kidney biopsy, when renal manifestations are present.

Amyloidosis liver



A, A section of the liver stained with Congo red reveals pink-red deposits of amyloid in the walls of blood vessels and along sinusoids. B, Note the yellow-green birefringence of the deposits when observed by polarizing microscope.



Electron micrograph of 7.5-10 nm amyloid fibrils