UPDATE of RENAL AMYLOIDOSIS

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MUI

DEFINATION:

- Amyloid is defined as the deposition of insoluble protein fibrils, forming histologically a homogeneous, extracellular eosinophilic mass.
- Congo Red +++
- Displays green birefringence under polarized light

Amyloidosis constitutes a heterogeneous group of distinct diseases which differ in their pathogenesis and clinical course.

INTRODUCTION

- Amyloidosis is a group of diseases characterized by extracellular deposition of betasheet fibrils.
- In the systemic forms, the amyloid causes progressive organ dysfunction, leading to death of the patients.

REVIEW

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Renal Amyloidosis: Presentation, Diagnosis, and Management

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ABSTRACT

More than 35 amyloid precursor proteins have been identified and many have tropism for the kidney. Renal amyloidosis is most commonly seen in AL and AA amyloidosis and the main clinical manifestations are proteinuria and progressive renal dysfunction. On renal pathology, hallmark findings of amyloidosis include Congo red positivity with apple-green birefringence and randomly arranged fibrils measuring 7-12 nm in diameter on ultrastructural examination. Management of renal amyloidosis typically combines therapy targeting the underlying amyloid process and supportive management. Patients with renal amyloidosis who progress to end-stage renal disease can be treated with dialysis, and in selected patients, with renal transplantation.

INTRODUCTION

The kidney is one of the most commonly affected organs in amyloidosis, and the associated kidney dysfunction contributes significantly to morbidity and mortality. Of the >35 structurally and functionally heterogeneous proteins known to have the predisposition to undergo misfolding and form amyloid fibrils, many have a predilection for the kidney. These include immunoglobulin light chain (AL) or heavy chain (AH) or both (AHL), serum amyloid A (AA), leukocyte chemotactic factor 2 (ALECT2), apolipoprotein (AApo) AIV, and mutant proteins in several hereditary forms of amyloidosis (transthyretin [ATTR], fibrinogen A-α chain [AFib], AApoAI and AII, AApoCII and CIII, gelsolin [AGel], and lysozyme [ALys])[1,2] (Table 1).

Table 1 Main Types of Amyloidosis with Kidney Involvement

Amyloid Type	Precursor Protein	Acquired or Hereditary	Affected Renal Compartment
AL/AH/AHL	Ig light or heavy chain	Acquired	Glomerulus, tubulointerstitium, vasculature
AA	Serum amyloid A	Acquired	Glomerulus, tubulointerstitium, vasculature
ATTR	Transthyretin, mutant type	Hereditary	Glomerulus, tubulointerstitium, vasculature (varies based on type of mutation)
ALECT2	Leukocyte chemotactic factor-2	Acquired	Tubulointerstitium, vasculature, and less commonly glomerulus
AApoAI	Apolipoprotein AI	Hereditary	Predominantly medullary tubulointerstitium
AApoAII	Apolipoprotein AII	Hereditary	Predominantly glomerulus
AApoAIV	Apolipoprotein AIV	Acquired	Medullary tubulointerstitium
AApoCII	Apolipoprotein CII	Hereditary	Predominantly glomerulus
AApoCIII	Apolipoprotein CIII	Hereditary	Glomerulus, tubulointerstitium, vasculature
AFib	Fibrinogen α chain	Hereditary	Predominantly glomerulus
AGel	Gelsolin	Hereditary	Predominantly glomerulus
Alys	Lysozyme	Hereditary	Glomerulus, medullary tubulointerstitium

Ig = immunoglobulin.

INTRODUCTION

- The overall prevalence of renal amyloidosis in native kidney biopsies is 1.6%. In the United States, AL is the most common cause of renal amyloidosis (81%-86%), followed by AA (7%), then ALECT2 (2.5%-2.7%).

INTRODUCTION

- In AL amyloidosis, the kidney is affected in up to 80% of patients.
- Renal dysfunction is the predominant manifestation in AA amyloidosis, with 97% of patients excreting >500 mg protein per day.

INTRODUCTION

- Although ATTR has been increasingly recognized, wild-type ATTR does not appear to be associated with renal amyloidosis and mutational ATTR is an uncommon cause of renal disease

CLINICAL FEATURES

- Clinical presentation of patients with renal amyloidosis is determined by the amyloid type, the location and amount of amyloid deposition within the kidney, and the extent of extrarenal involvement.

CLINICAL FEATURES

- The most common manifestation of renal amyloidosis is proteinuria, which ranges from minimal to massively nephrotic, depending on the degree of glomerular involvement.
- AL amyloidosis commonly affects the glomerulus, and patients with AL renal amyloidosis often present with a high degree of proteinuria, with >65% of patients afflicted with nephrotic syndrome.

CLINICAL FEATURES

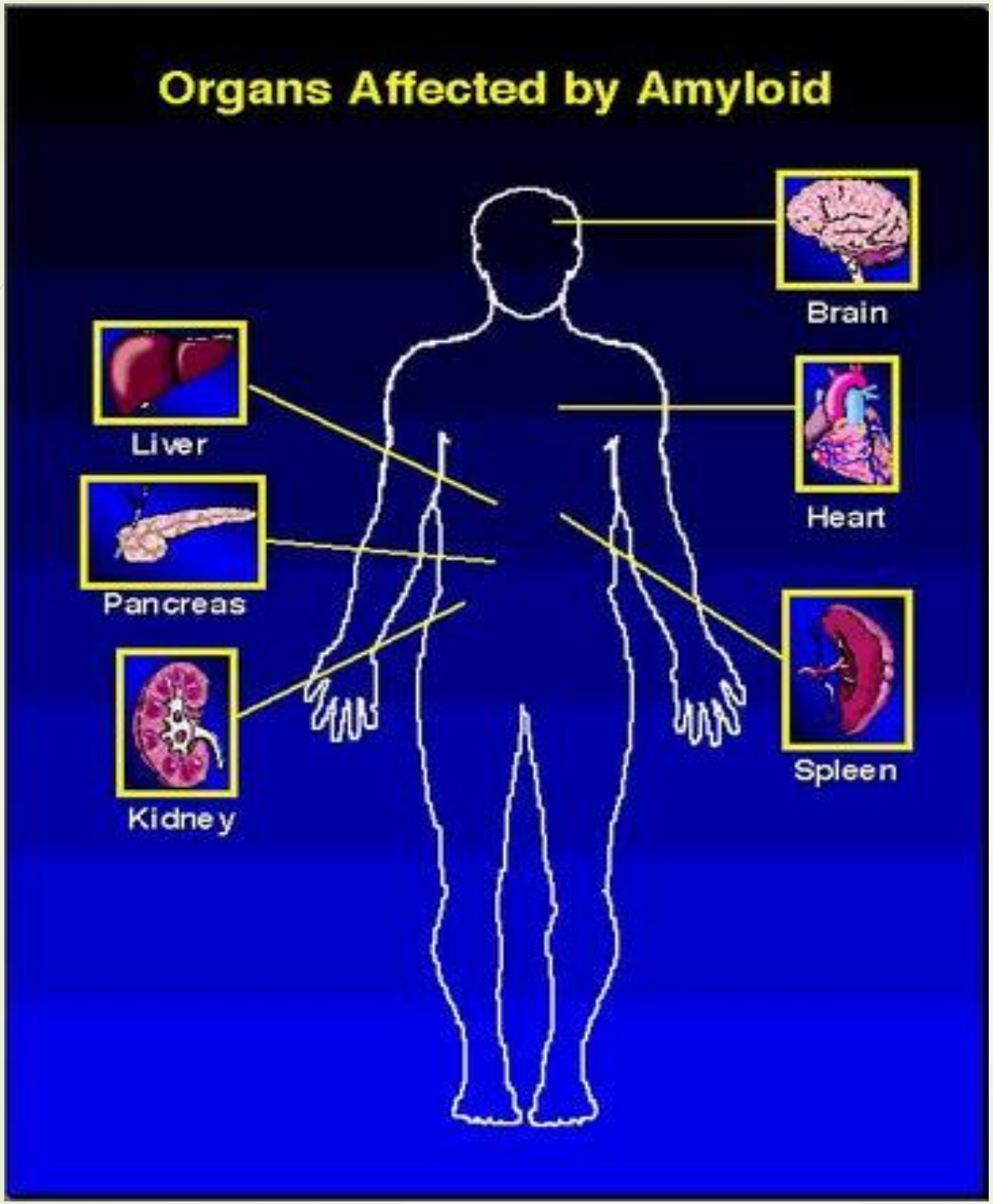
- When amyloid deposition predominantly affects the tubulointerstitium, such as in ALECT2 and AApoAI//IV, proteinuria is not a common feature and nephrotic syndrome is rare; in these patients, renal dysfunction tends to be the primary renal manifestation.

CLINICAL FEATURES

- Crescentic glomerulonephritis including anti-glomerular basement membrane disease has been reported in patients with AA amyloidosis.
- Rarely, tubular involvement by amyloid can lead to Fanconi syndrome or nephrogenic diabetes insipidus.

CLINICAL FEATURES

- Clinically, more than 75% of patients with renal amyloidosis present with peripheral edema; this is due to nephrotic syndrome, renal failure, heart failure, or a combination of these.
- Hypotension is commonly seen in patients with autonomic dysfunction or advanced heart failure and can contribute to progressive renal dysfunction.


Organs Affected by Amyloid
Brain
Liver
Heart
Pancreas
Spleen
Kidney

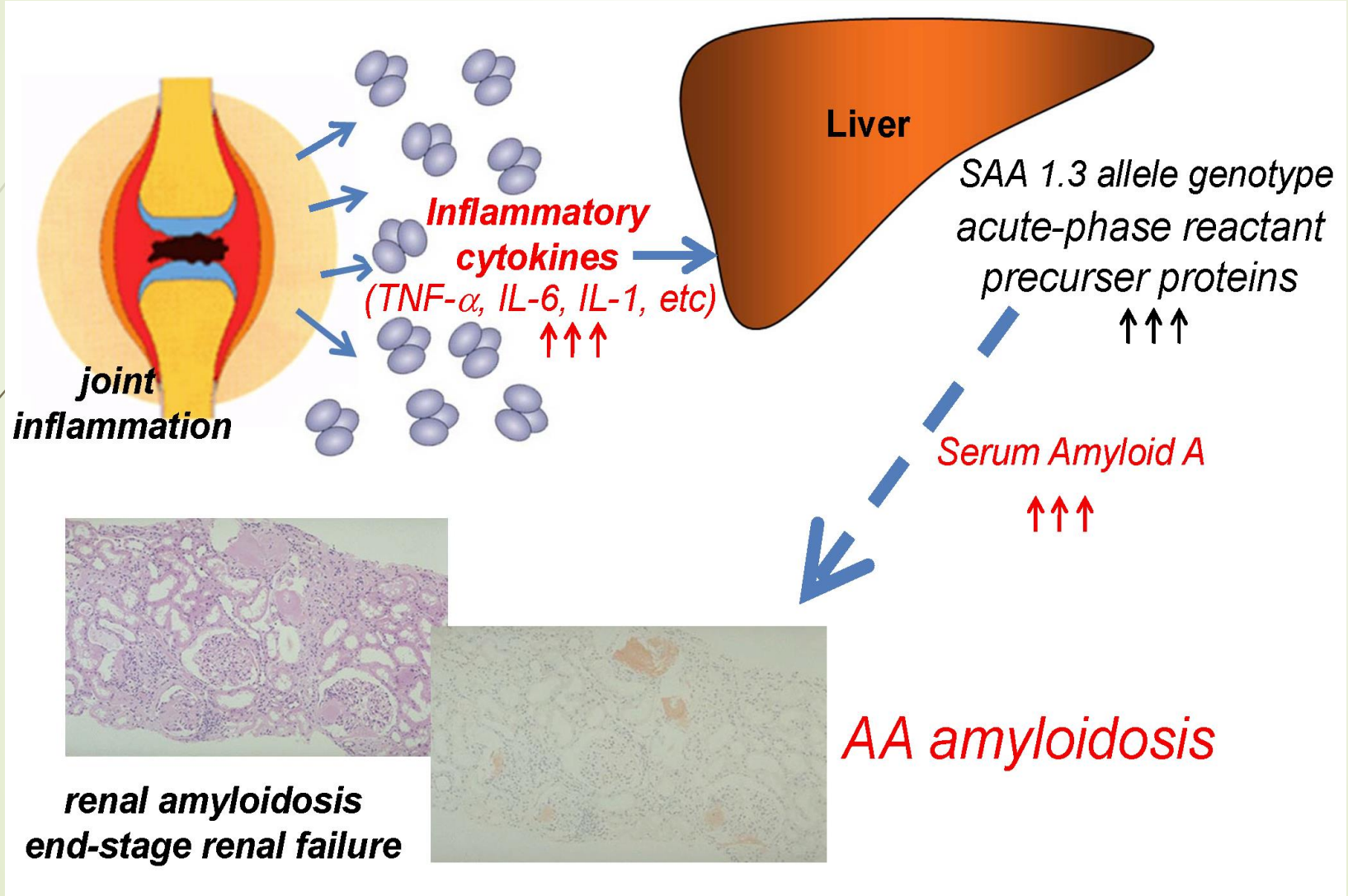
AL/AH AMYLOIDOSIS

- Precursor protein is Immunoglobulin light chain (AL) or a few times heavy chain (AH).
- Associated with hepatic, cardiac and GIT involvement.
- The most common clinical presentation is proteinuria with or without renal insufficiency

AA AMYLOIDOSIS (Formally Secondary Amyloidosis).

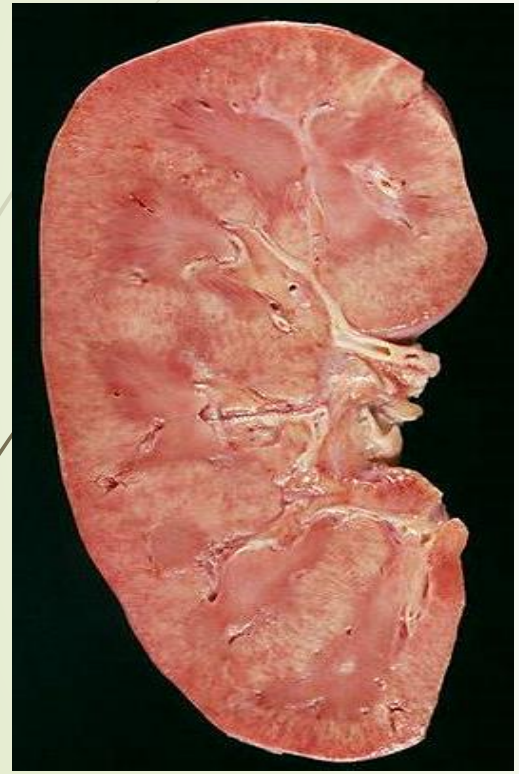
- AA amyloidosis arises in the context of an acute phase response seen in inflammatory arthritis, periodic fevers, chronic infections and malignancies.
- This protein is derived from acute phase reactant **Serum Amyloid A or SAA**

PATHOGENESIS:



RENAL MORPHOLOGY

GROSS PATHOLOGY

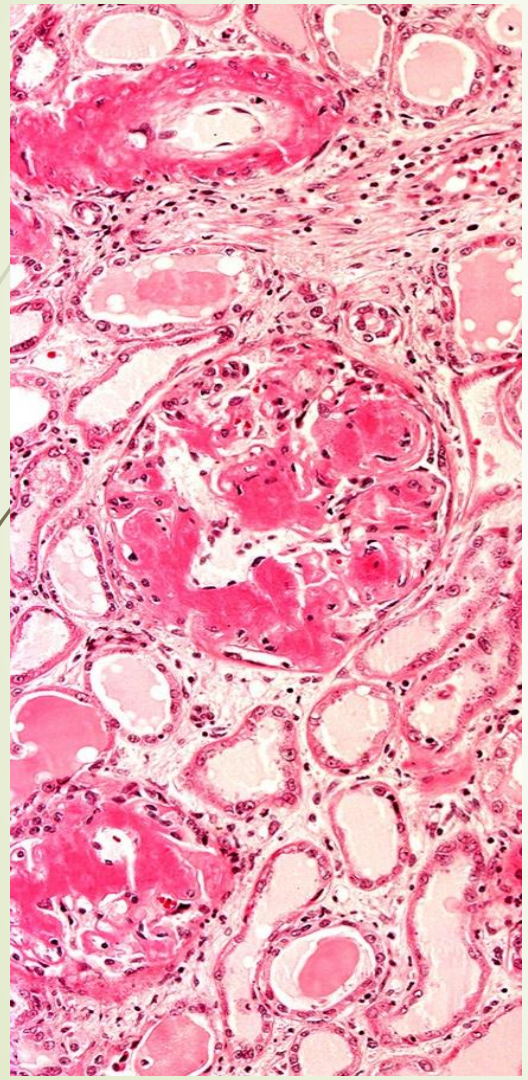


Enlarged kidneys

Pale, waxy appearing cut surfaces

Increase in the weight of kidney

LIGHT MICROSCOPY:



- Amyloid deposits can be found in any of the renal compartments.
- Glomerular amyloid formations begin in the mesangium.
- And then extends to the capillary walls.

In H/E sections, amyloid appears as eosinophilic, amorphous, hyaline material.

Continued..

Amyloid deposition in glomeruli may occur in following patterns:

- 1) Segmental.
- 2) Diffuse mesangial.
- 3) Nodular.
- 4) Pure basement membrane pattern

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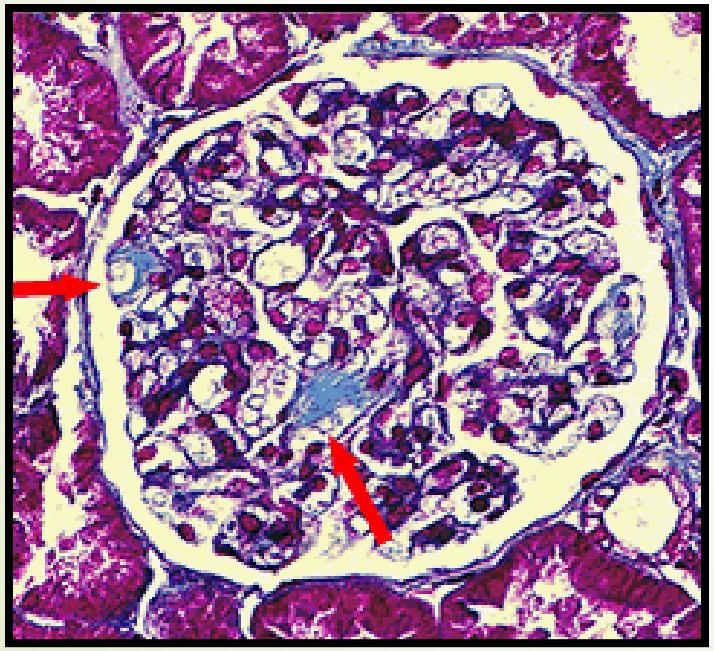
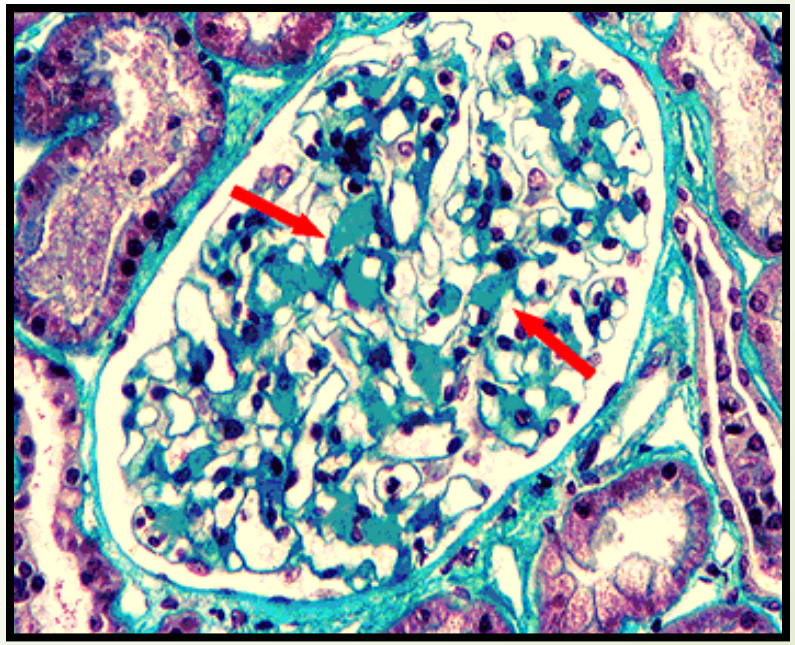
- Early segmental deposits are small and confined to mesangium without creating nodularity

- It is very easy to miss this early form





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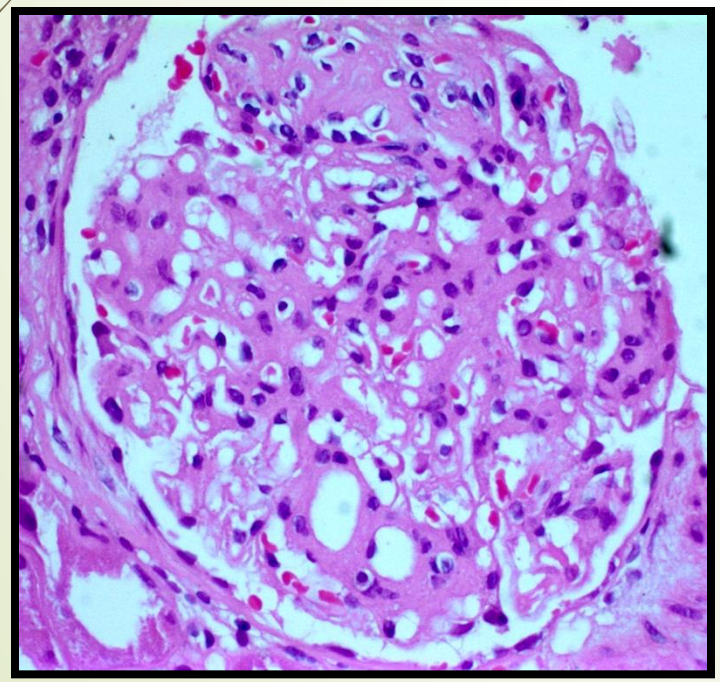
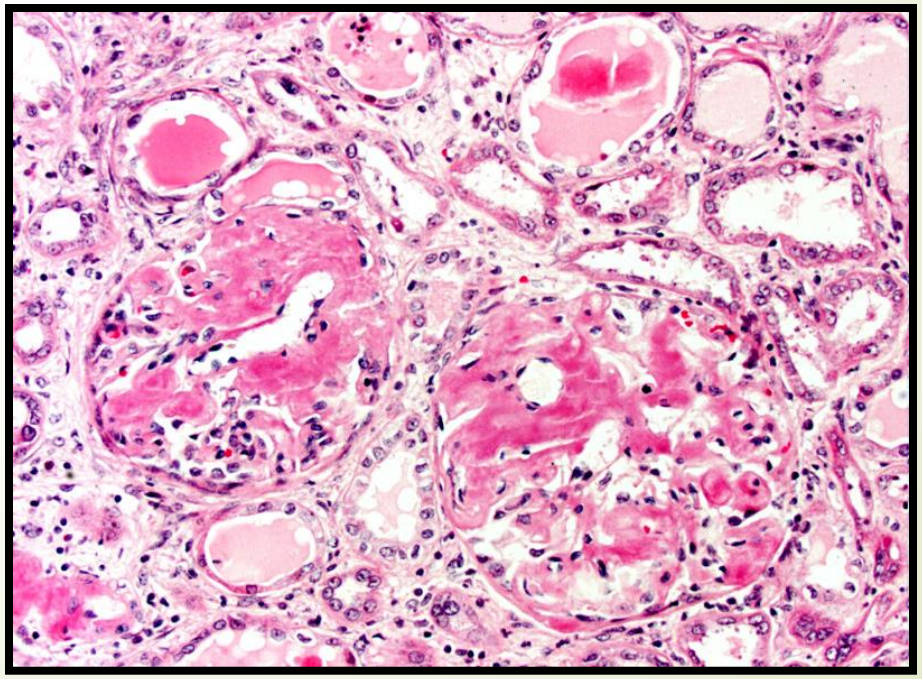
- In the diffuse form
- The mesangium is uniformly expanded by weakly PAS positive acelluar deposits.





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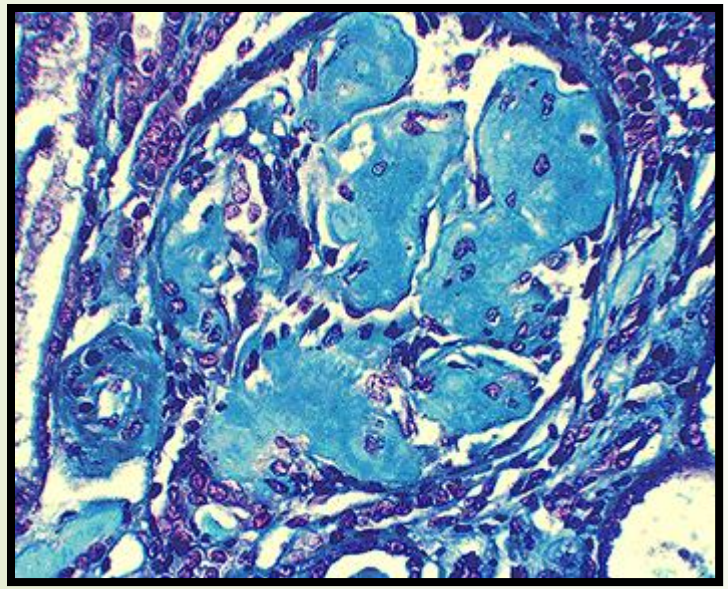
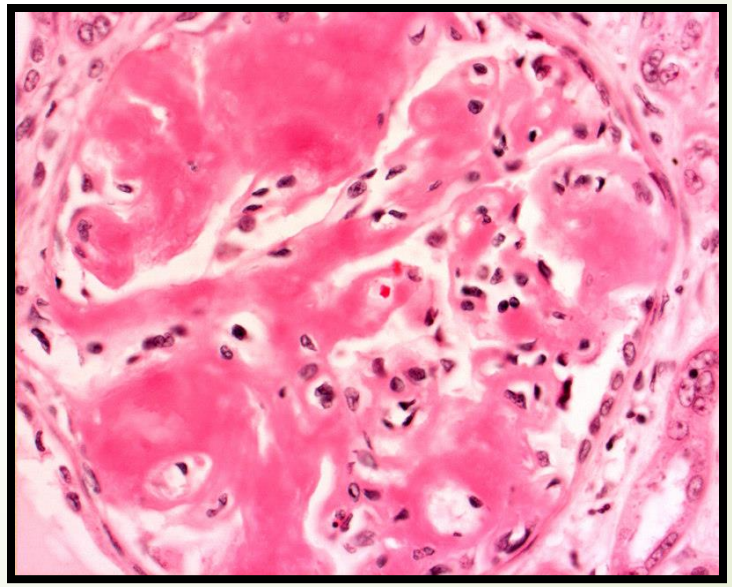
- In the nodular form
- Mesangium is asymmetrically expanded by large masses of amyloid that compress the capillary spaces.





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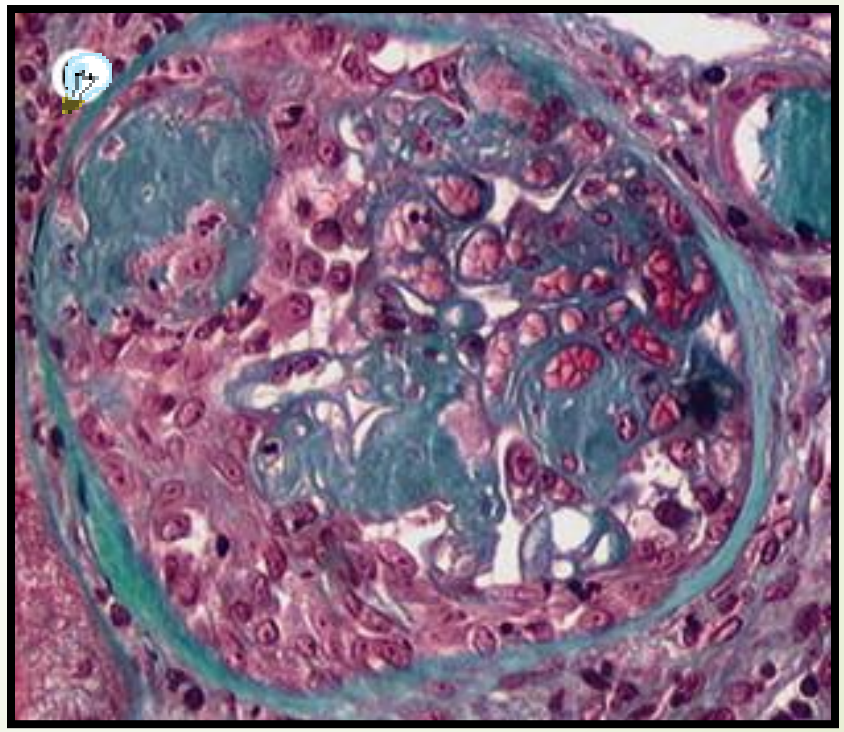
- Rarely cresents can be seen

Highlighting the fact that capillary wall rupture has occured



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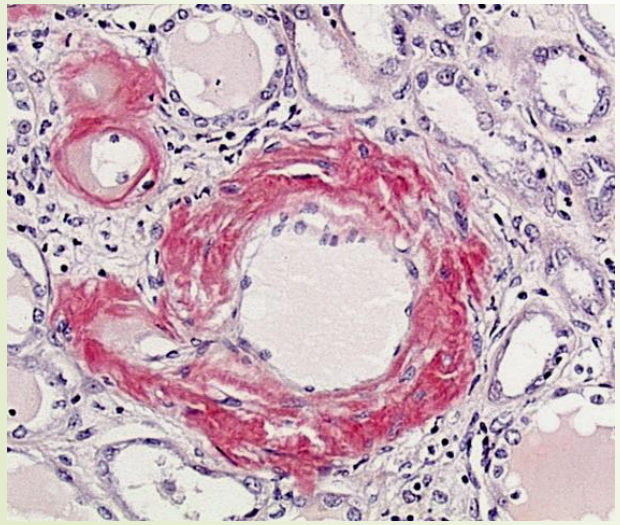
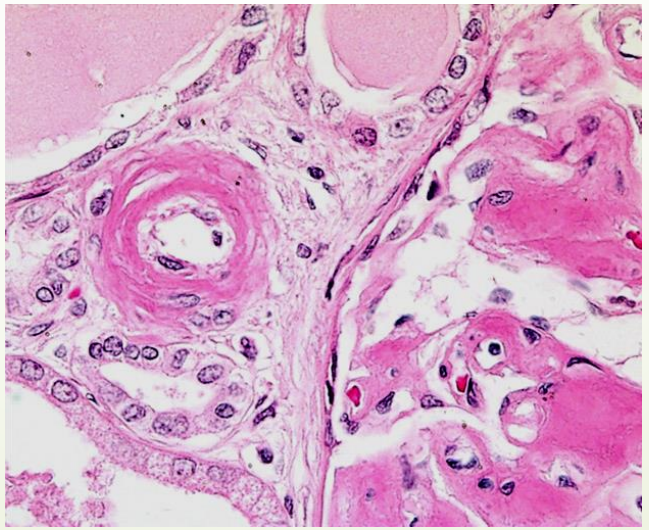
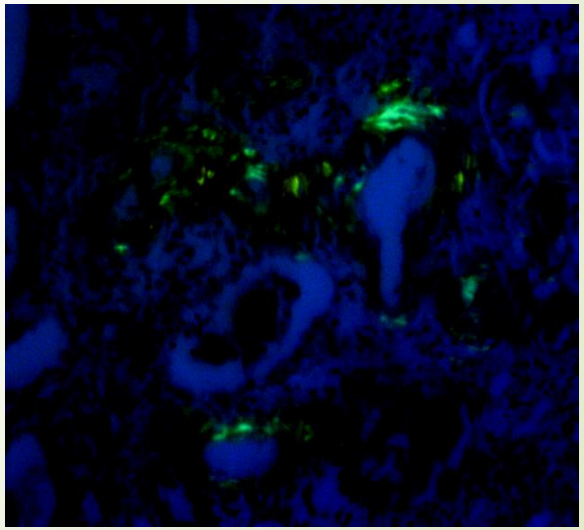
- Renal vessels are often involved with arteriolar deposits being most frequent followed by deposits in arteries, PTCs and veins.
- These deposits may be subtle or may replace the vessel wall completely, occluding the lumen.
- In rare cases vessels walls are the only site for amyliod deposition.







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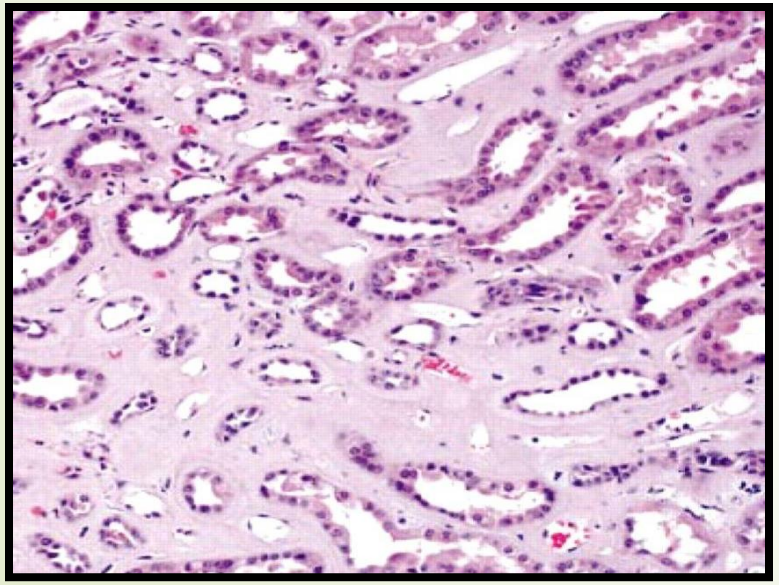
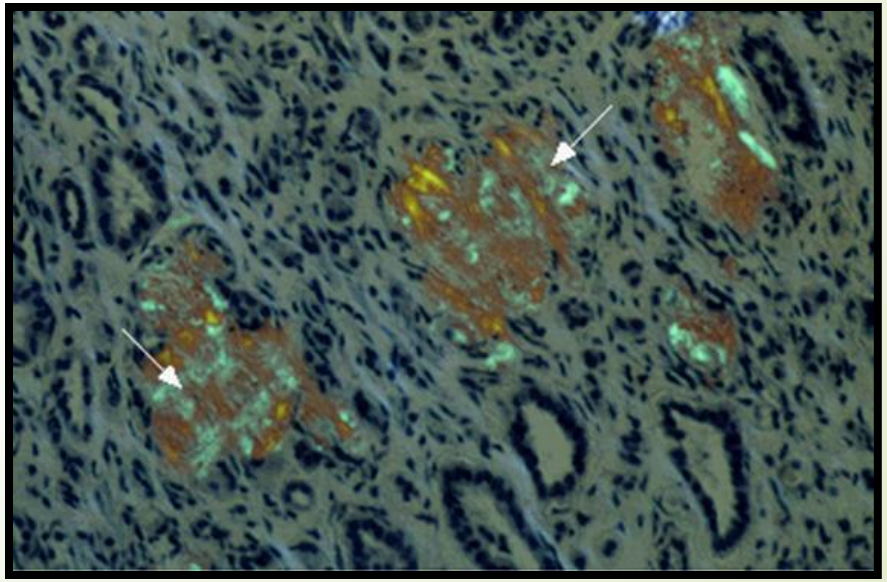
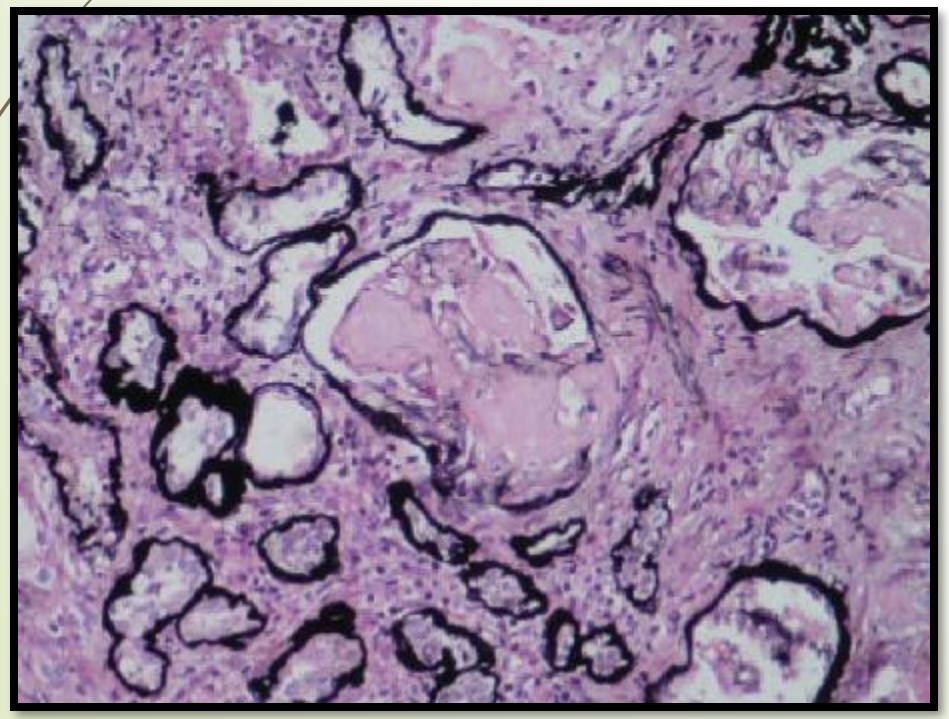
- The tubules may show non specific findings.
- Interstitial and peri-tubular amyloidosis is seen in 50 %of cases.
- Medullay amyloid deposits are more frequent.
- A multinucleated giant cell reaction may accompany amyloid deposits.

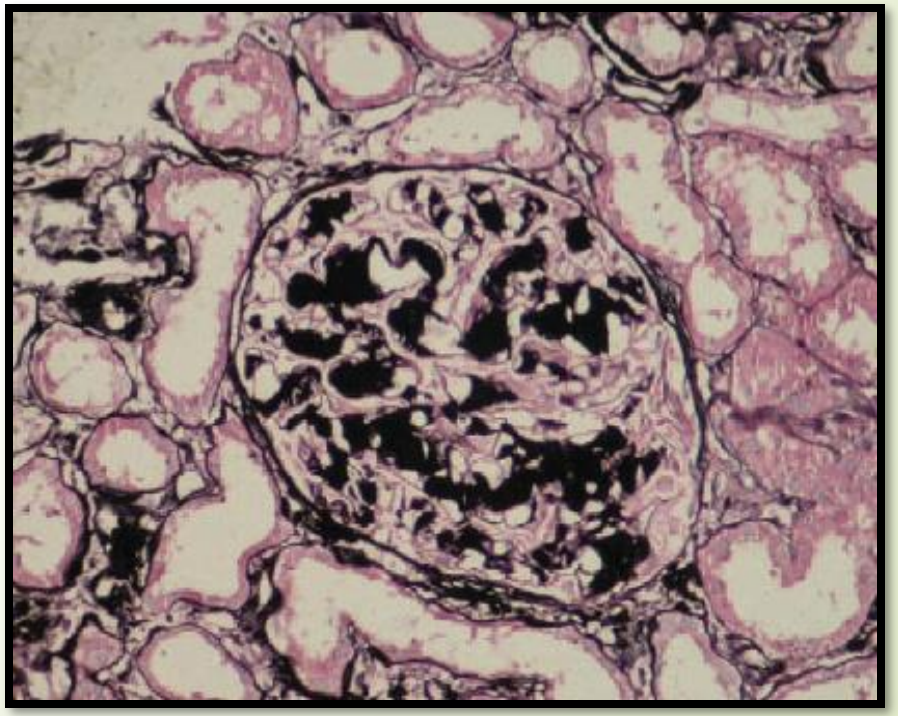




DETECTION OF AMYLOID:

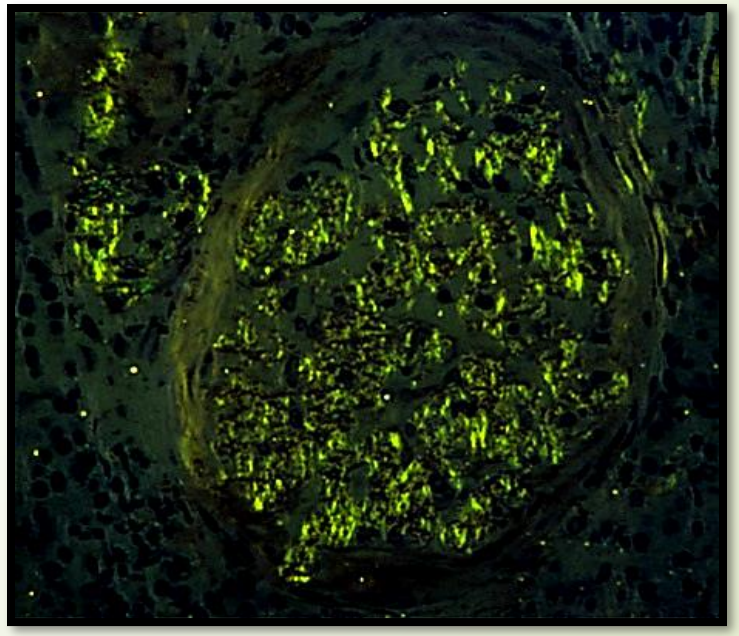
- **Amyloid do not stain by silver staining**
- **Occasionally may stain with silver stains and show spicules (Jones silver).**





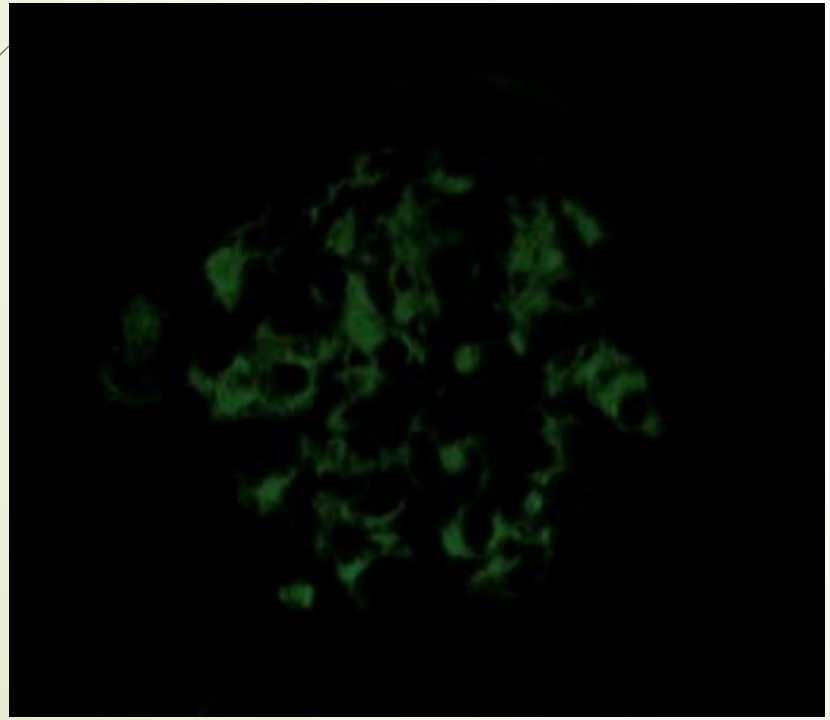
DETECTION OF AMYLOID

- **Congo red** is the gold standard procedure.
- Congo Red-Positive material must polarize and produce apple green birefringence to be considered diagnostic.
- To demonstrate small amount of amyloid, sections should be cut to a thickness of 9 to 10um.



DETECTION OF AMYLOID

- **Thioflavin fluorescence is more sensitive in detecting small amount of amyloid.**



TYPING OF AMYLOID DEPOSITS:

- Typing of amyloid deposits is important because of the difference in their treatment strategies.
- Typing of the amyloid deposits can be performed with various techniques.
- The most definitive method used is IF or IHC staining of tissue using antibodies that are directed against known amyloid proteins.

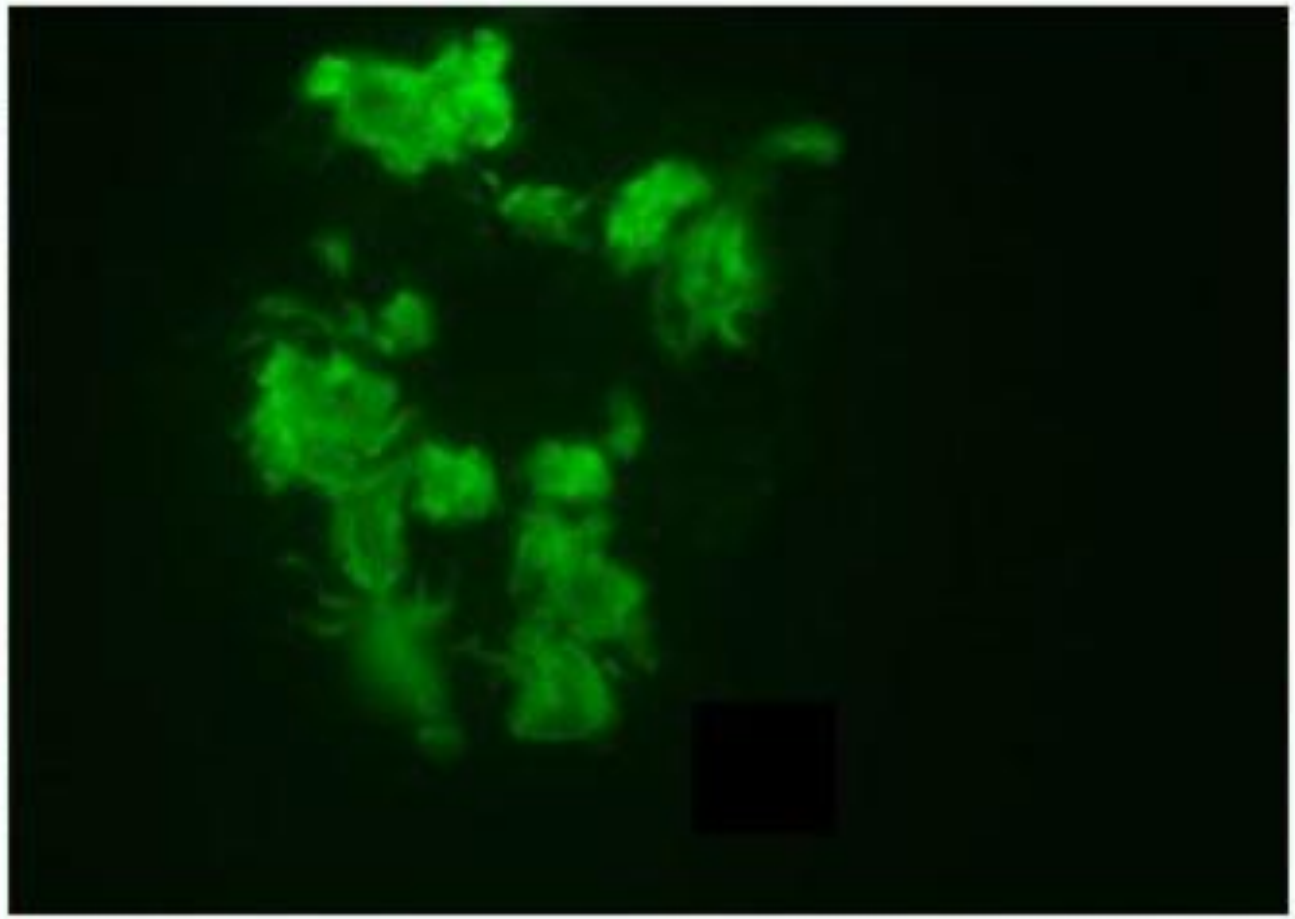
ANTIBODY PANEL:

- The typical antibody panel should include
- Amyloid P component
- Kappa & lambda Ig light chains
- Amyloid A protein
- Transthyretin
- Fibrinogen
- Beta-2 microglobulin

Stains for AA and Apolipoprotein AI , AII, may be included depending upon the differential diagnosis.

- This panel allowed definitive typing of amyloid in 90% of kidney biopsies

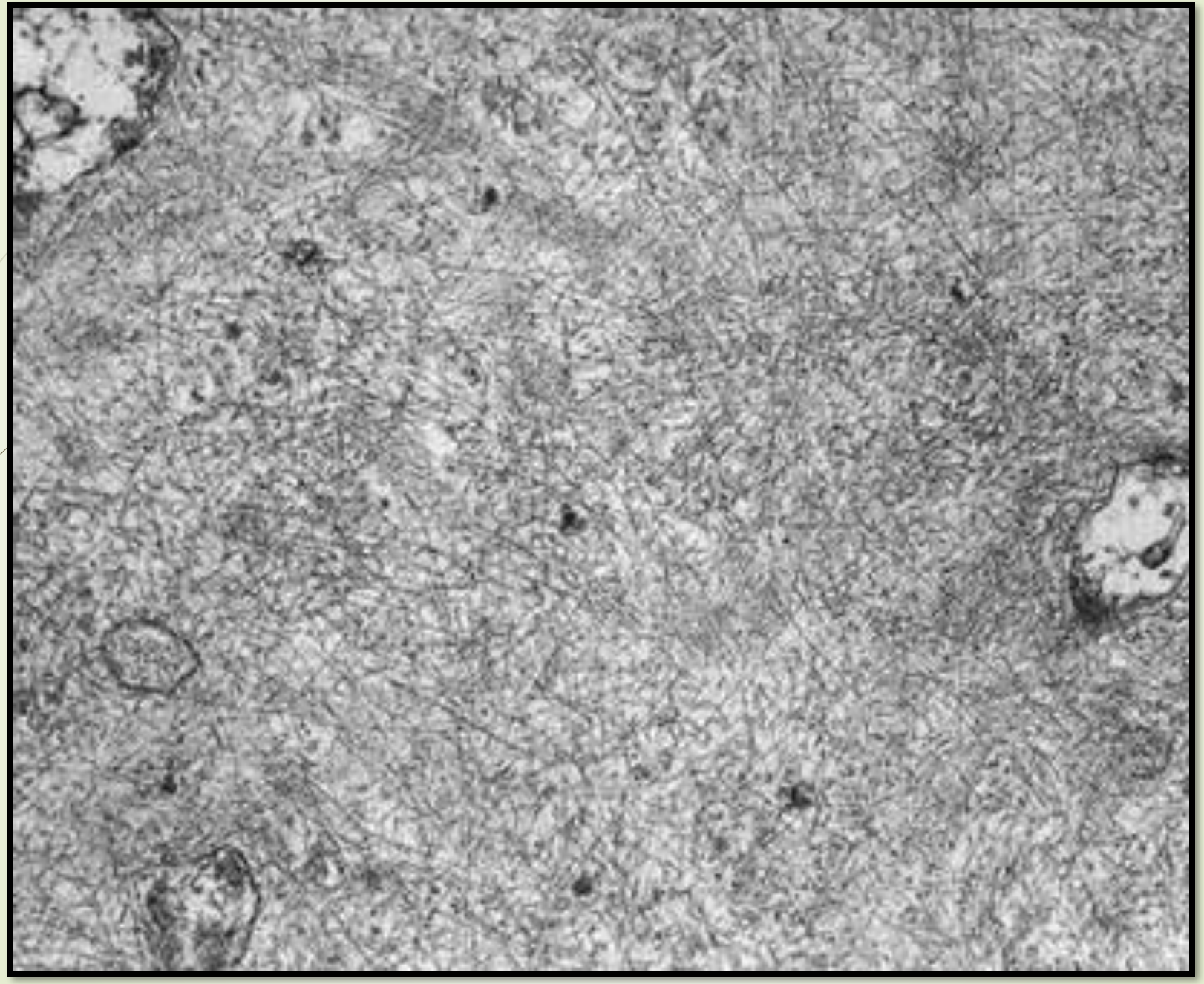
Immunofluoresence: α – serum amyloid A (SAA)

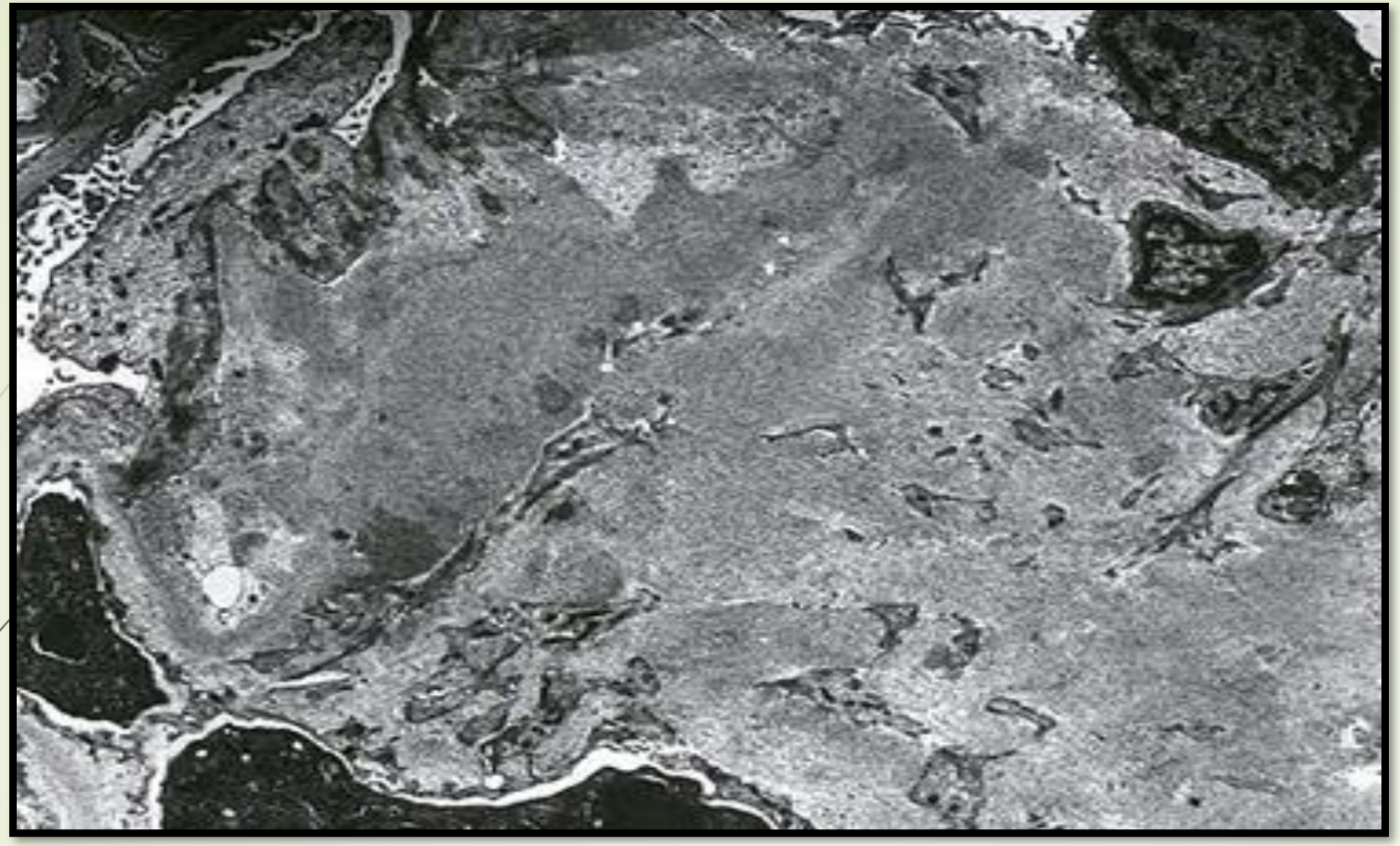


- **Commercial antibodies are raised against the constant regions of the Ig light chains.**

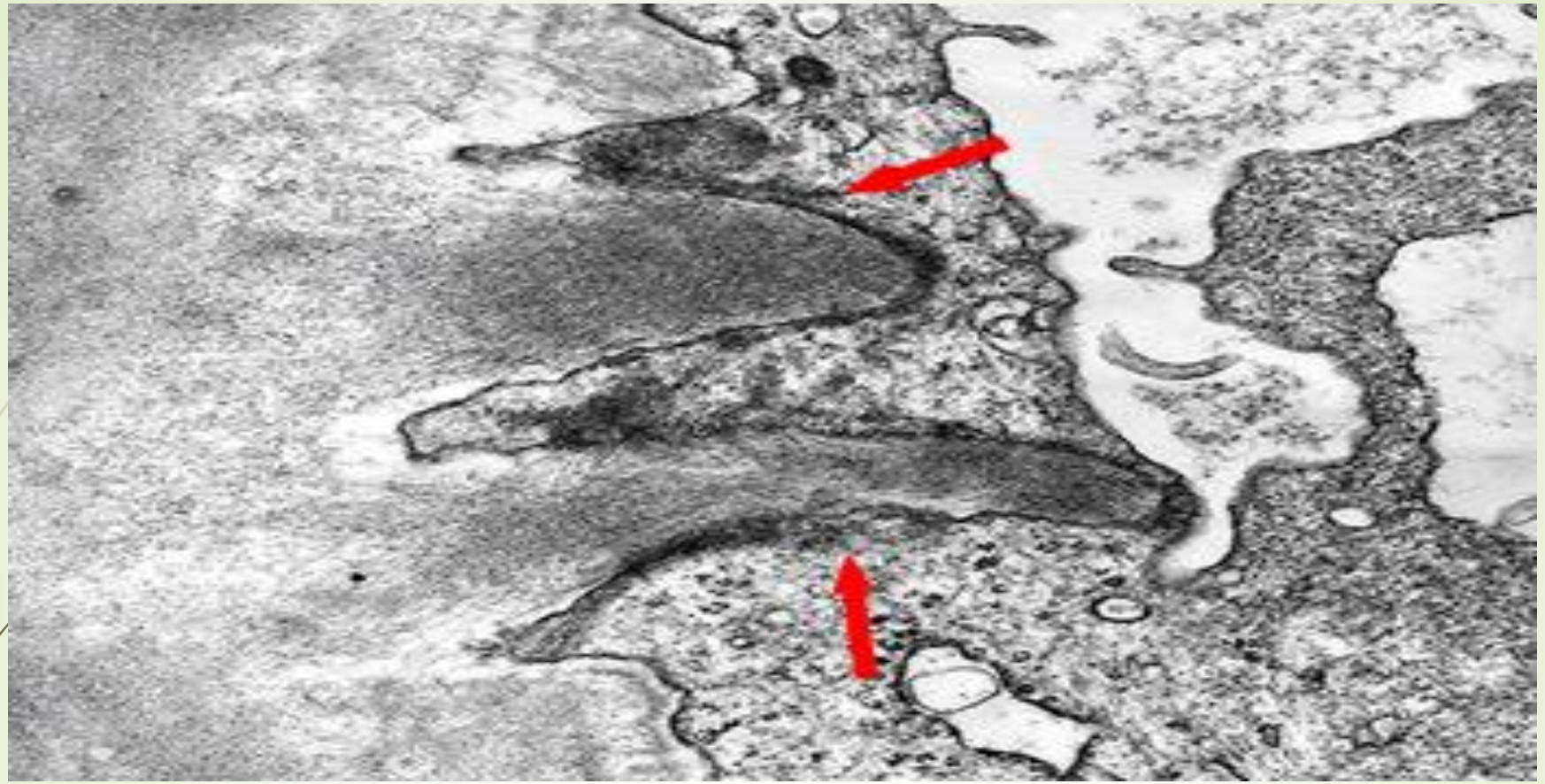
- **A subset of AL, in which amyloid fibrils are derived from a truncated light chain "containing only variable regions" will be nonreactive with commercial antibodies**

- **Therefore, negative light chain staining does not rule out AL amyloidosis.**

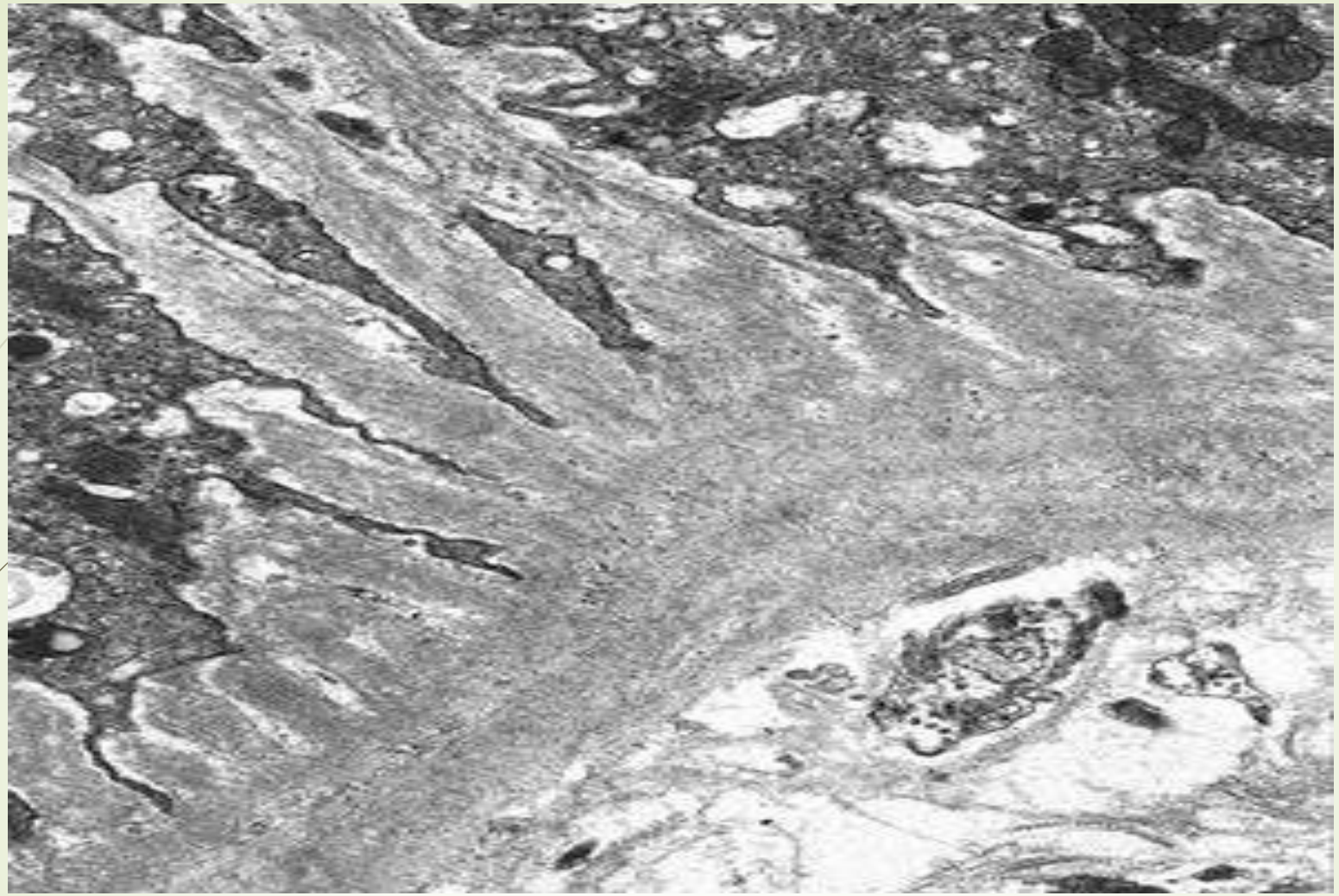




- **Massive expansion of the mesangium by fibrillar deposits.**



- Subepithelial spikes due to amyloid deposition.



- Amyloid infiltration through the basement membrane with resulting feathery spikes with basement membrane material and delicate amyloid fibrils are shown in this case.

A proposed histopathologic classification

Table 2. Histopathologic Classification of Renal Amyloidosis Based on Glomerular Involvement

Class	Definition
0	No amyloid deposition
I	Minimal amyloid deposition
II	Mesangial minimal amyloid deposition
III	Focal mesangiocapillary amyloid deposition (including nodular amyloidosis)
IV	Diffuse mesangiocapillary amyloid deposition
V	Membranous amyloid deposition (observed generally in non–AA amyloidosis, especially AL amyloidosis)
VI	Advanced renal amyloidosis

Renal amyloidosis was divided into 6 classes
Similar to the classification of SLE

MANAGEMENT

- Without treatment, renal amyloidosis will ultimately lead to end-stage renal disease (ESRD) or death in the majority of patients. Therapy of renal amyloidosis varies with the type of amyloid.

MANAGEMENT

- Optimal management usually combines therapy targeting the underlying amyloid formation process and The goal of treatment is to reduce amyloid burden, limit further renal injury, and maintain or improve renal function.
- Renal response is measured by change in renal function (serum creatinine, estimated glomerular filtration rate) and proteinuria.

General Supportive Management

- Renal function, proteinuria (if present), blood pressure, and volume status should be monitored closely in patients with renal amyloidosis.

Table 2 General Supportive Management in Renal Amyloidosis

Problem	Management	Comments
Fluid overload Nephrotic syndrome	Loop diuretics: Furosemide Torsemide Bumetanide Ethacrynic acid Thiazide diuretics: Hydrochlorothiazide Chlorthalidone Metolazone Indapamide Potassium-sparing diuretics: Amiloride Triamterene Mineralocorticoid receptor antagonists (MRAs) Dietary sodium restriction to <2 g/d or <90 mmol/d (dietary sodium chloride <5 g/d)	• Diuretic resistance is common in nephrotic syndrome (especially with presence of marked hypoalbuminemia) and advanced renal dysfunction. ○ Higher doses of loop diuretics frequently needed ○ Twice a day dosing preferred if able ○ Change furosemide to torsemide or bumetanide if oral bioavailability is a concern ○ Consider intravenous diuretics for severe edema ○ Add thiazide diuretic to block distal reabsorption of sodium ○ Potassium-sparing diuretics are weak diuretics but can enhance natriuretic effect when used with loop diuretic, especially in heart failure; can also limit urinary potassium loss • Monitor electrolytes and acid-base status. Correct hypokalemia and hypomagnesemia • Monitor blood pressure (hypotension common in cardiac amyloidosis) and renal function (avoid excessive reduction of effective circulating volume)

Proteinuria	Angiotensin-converting enzyme inhibitor (ACEi) or Angiotensin receptor blocker (ARB)	• Do not use combination of ACEi and ARB. • Monitor kidney function closely, especially in those with severe nephrotic syndrome (risk for acute kidney injury). • Monitor serum potassium level. • Monitor blood pressure closely. • Caution in patients with autonomic dysfunction and cardiac amyloidosis due to high risk for hypotension. • Addition of MRA can further reduce proteinuria. Monitor closely due to increased risk of hyperkalemia.
Hypertension	• Goal BP <125-130/<80 mm Hg for those with proteinuria or chronic kidney disease • Use ACEi or ARB as first-line therapy (for both blood pressure and proteinuria). • Non-dihydropyridine calcium channel blockers have beneficial effects on proteinuria but are contraindicated in cardiac amyloidosis due to excessive negative inotropic effect.	

Hypotension, autonomic dysfunction	• Midodrine: Alpha-1-adrenergic agonist. Caution in supine hypertension • Droxidopa: Prodrug to norepinephrine Alpha/Beta agonist • Fludrocortisone: Synthetic mineralocorticoid. Monitor closely for development of volume overload, supine hypertension, and exacerbation of heart failure • Compression stockings: Increase venous return. Contraindicated with leg ischemia or presence of skin wounds
Hyperlipidemia	• Lipid abnormalities improve with resolution of nephrotic syndrome/treatment of amyloidosis. • Pharmacologic lipid-lowering therapy (such as statin) may be indicated based on risk for cardiovascular disease and duration of nephrotic syndrome.
Thromboembolic risk due to nephrotic syndrome	• Optimal management is unclear due to lack of high-quality data. • Prophylactic anticoagulation might be considered if serum albumin is <2.5 g/dL but bleeding risk needs to be assessed. • If anticoagulation-associated bleeding risk is too high, consider antiplatelet therapy instead.

Review

Kidney Medicine

Serum Amyloid A Protein–Associated Kidney Disease: Presentation, Diagnosis, and Management

Jordan Thorne, David Clark, Laurette Geldenhuys, Keigan More, Amanda Vinson, and Karthik Tennankore

Serum amyloid A protein (AA) amyloidosis, also known as secondary amyloidosis, is a known consequence of chronic inflammation and results from several conditions including inflammatory arthritis, periodic fever syndromes, and chronic infection. AA amyloidosis can lead to multiorgan dysfunction, including changes in glomerular filtration rate and proteinuria. Definitive diagnosis requires tissue biopsy, and management of AA amyloid kidney disease is primarily focused on treating the underlying inflammatory condition to stabilize glomerular filtration rate, reduce proteinuria, and slow potential progression to kidney failure. In this narrative review, we describe the causes, pathophysiology, presentation, and pathologic diagnosis of AA amyloid kidney disease using an illustrative case of biopsy-proven AA amyloid kidney disease in a patient with long-standing rheumatoid arthritis who had a favorable response to interleukin 6 inhibition. We conclude the review with a description of established and more novel therapies for AA amyloidosis including published cases of use of tocilizumab (an interleukin 6 inhibitor) in biopsy-proven AA amyloid kidney disease.

Complete author and article information provided before references.

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General Approach

- The management of AA amyloid kidney disease involves suppression of systemic inflammation, in addition to pharmacologic treatment generally aimed at treating proteinuric kidney disease.
- Although formal studies are lacking, intuitively, the latter would include reninangiotensin-aldosterone system inhibitors, and sodium/glucose cotransporter 2 inhibition.

General Approach

- Furthermore, management of hyperlipidemia and edema may be required if the patient has high-grade proteinuria.
- Therapies targetedto decrease inflammation (and serum AA levels) should be tailored to a patient's underlying disease process.

Disease Specific-Approach

Rheumatoid and Inflammatory Arthritis

- As the European Alliance of Associations for Rheumatology guidelines adopted anti-TNF agents as first-line therapy for rheumatoid arthritis, anticytokine therapy as a treatment for AA amyloidosis was studied.

Rheumatoid and Inflammatory Arthritis

- When compared directly, etanercept was shown to be superior to cyclophosphamide in both preservation of eGFR and reduction in proteinuria.

Rheumatoid and Inflammatory Arthritis

- In addition to etanercept, both infliximab and adalimumab have been used to treat AA amyloidosis, although there have been no head-to-head comparisons of anti-TNF agents.

Rheumatoid and Inflammatory Arthritis

- Beyond rheumatoid arthritis, anti-TNF agents have also been shown to be effective and well-tolerated during long-term follow-up in both inflammatory bowel disease and other inflammatory arthropathies as well.

Familial Mediterranean Fever

- As the mainstay of treatment, colchicine's impact on AA amyloid kidney disease secondary to underlying familial Mediterranean fever has been well documented.

Familial Mediterranean Fever

- Colchicine has been shown to reduce proteinuria and preserve kidney function.
- In one study, this effect did appear to be contingent on reaching a therapeutic dose of >1.5 mg per day and beginning treatment in patients with serum creatinine <1.5 mg/dL.

Familial Mediterranean Fever

- The presumed mechanism of action for colchicine's impact on amyloid deposition and subsequent kidney disease is suppression of cytokines involved in serum AA production that are also targeted by other therapies.
- Colchicine inhibits neutrophil production, and therefore production of IL-1 and IL-8.
- In addition, it reduces the protein expression of TNF.

Emerging Therapies Tocilizumab

- The management of AA amyloidosis continues to evolve as alternative cytokines involved in serum AA production are targeted.
- IL-6 is a proinflammatory cytokine that induces serum AA production via interaction with the signal transducer and activator of transcription protein.

Emerging Therapies
Tocilizumab

- Tocilizumab is a recombinant monoclonal antibody that blocks IL-6 signal transduction by targeting IL-6 receptor complex formation and has been shown clinically and in vitro to decrease AA production.

Emerging Therapies
Tocilizumab

- IL-6 inhibitors have gradually become more widely used in the treatment of inflammatory arthropathies and as a result have been used in the treatment of AA amyloid kidney disease with a goal of reducing proteinuria and stabilizing kidney function.

Emerging Therapies
Tocilizumab

- Outcomes of these cases vary; however, tocilizumab has been shown to decrease serum AA, as well as improve proteinuria and GFR, most notably in AA amyloidosis associated with inflammatory arthritis.

Emerging Therapies
Tocilizumab

- The earliest reports of tocilizumab for systemic AA amyloidosis appear to date back to 2006, when Okuda et al reported improvements in serum AA amyloid levels, improvements in proteinuria, and histologic improvement in a 26-year-old woman with juvenile idiopathic arthritis.

Emerging Therapies
Tocilizumab

- However, it was not until 2011 that case reports of biopsy-proven AA amyloid kidney disease responding to tocilizumab were published.
- The first involved a patient presenting with nephrotic syndrome that was found to have biopsy-proven AA amyloid kidney disease in addition to underlying latent tuberculosis.

Emerging Therapies
Tocilizumab

- Subsequent treatment with tocilizumab lead to rapid improvement in proteinuria over a 9-week follow-up period; however, the patient experienced GFR decline because of gastrointestinal illness, ultimately leading to the need for hemodialysis.

Emerging Therapies
Tocilizumab

- Since then, there have been several case reports regarding the efficacy of tocilizumab in chronic diseases, including Behcet disease, polyarteritis nodosa, psoriatic arthritis, and rheumatoid arthritis. Specific to rheumatologic disease,

Emerging Therapies
Tocilizumab

- Okuda et al compared the effectiveness of tocilizumab to anti-TNF agents in 42 patients with AA amyloidosis.
- Patients in the tocilizumab group showed greater reduction in serum AA protein levels as well as improvements in kidney function and clinical disease activity.

Emerging Therapies
Tocilizumab

- Notably, all patients had biopsy-proven gastrointestinal AA amyloid involvement, whereas only 3 patients in the study had biopsy diagnosed AA amyloid kidney disease.

Emerging Therapies
Tocilizumab

- Shortly after, a 2015 series of 6 cases of biopsy-proven AA amyloid kidney disease also demonstrated the efficacy of tocilizumab in stabilizing GFR, reducing proteinuria, and improving inflammatory markers.

Emerging Therapies
Tocilizumab

- Additional case series have focused on amyloid load measured with serum amyloid P scintigraphy in addition to patient quality of life and have demonstrated rapid reduction in amyloid deposition within 10 days that was sustained over almost 2 years of follow-up.

Emerging Therapies
Tocilizumab

- Tocilizumab has also shown benefit in treating AA amyloidosis in a variety of other underlying conditions, including familial Mediterranean fever, multicentric Castleman disease and viral hepatitis.

Other Treatments

- Eprodisate, thought to prevent amyloid deposition by directly targeting glycosaminoglycan-amyloid fibril complexes, 61 initially showed promise after demonstrating superiority to placebo in AA-amyloid kidney disease in a composite outcome of kidney function and/or death.
- Unfortunately, a follow-up phase 3 clinical trial did not meet its primary outcome of preserved kidney function, and further studies targeting this pathway areongoing.

Other Treatments

- In addition, efforts to target amyloidogenic precursor proteins (specifically their interaction with glycosaminoglycans) are also in development.
- These treatments are not yet approved for use outside clinical trials.

Other Treatments

- Anti-AA amyloid-specific monoclonal antibodies have also been developed and have been shown to be effective in specifically targeting amyloid deposition in small animal studies.
- Although the hope is that fibril-specific monoclonal antibodies can remove pathologic amyloid deposits, this has yet to be demonstrated clinically.

Other Treatments

- The role of IL-6 in systemic inflammation and AA amyloidosis has been targeted via a different route, namely an IL-6 binding protein that has shown sustained antagonism of the receptor in vivo.
- Similar binding proteins have been used in ongoing studies for patients with hereditary amyloidosis as potential therapeutic options.

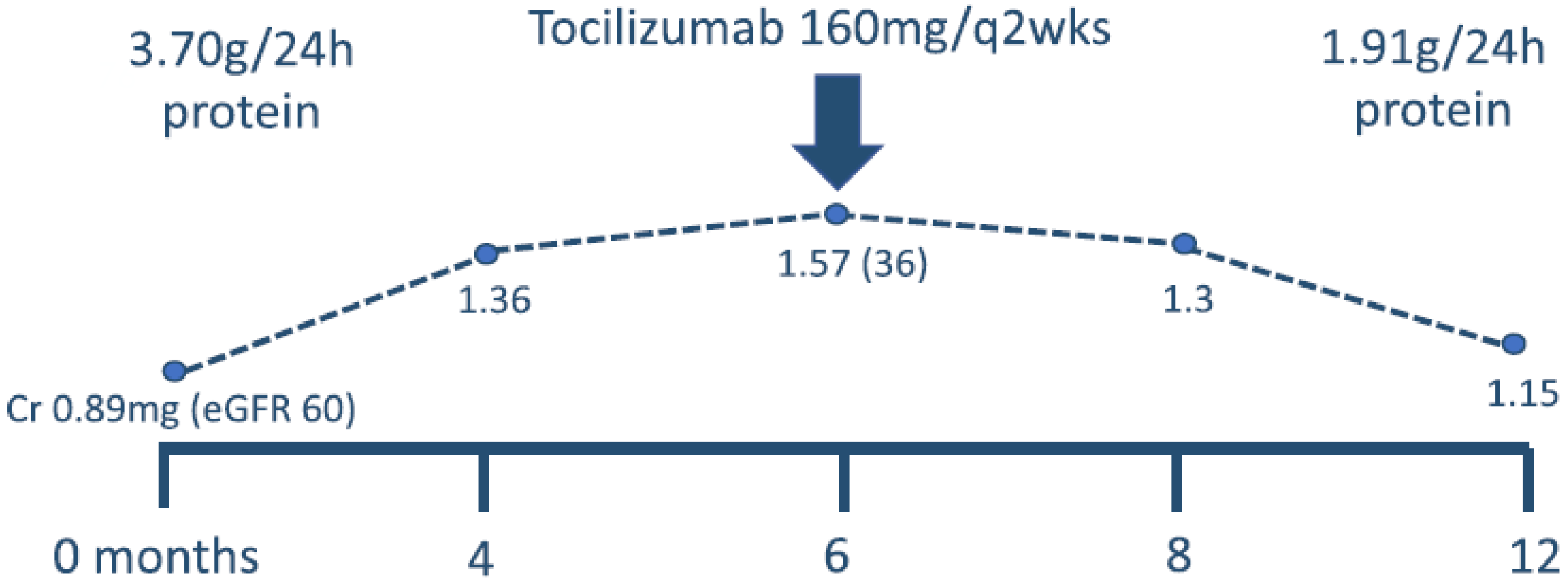


Figure 2. Treatment of biopsy-proven AA-amyloid kidney disease in a patient with rheumatoid arthritis using tocilizumab and subsequent response.

Neuromuscular

OPEN ACCESS

Review

Novel approaches to diagnosis and management of hereditary transthyretin amyloidosis

Antonia Carroll ,[1] P James Dyck ,[2] Mamede de Carvalho,[3,4] Marina Kennerson,[5] Mary M Reilly,[6] Matthew C Kiernan ,[7,8] Steve Vucic [9]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2021-327909).

For numbered affiliations see end of article.

ABSTRACT

Hereditary transthyretin amyloidosis (ATTRv) is a severe, adult-onset autosomal dominant inherited systemic disease predominantly affecting the peripheral and autonomic nervous system, heart, kidney and the eyes. ATTRv is caused by mutations of the transthyretin (TTR) gene, leading to extracellular deposition of amyloid fibrils in multiple organs including the peripheral (ATTRv-PN)), hereditary transthyretin amyloidosis–cardiomyopathy (ATTRv-CM), and renal and ocular involvement. Hereditary transthyretin leptomeningeal amyloidosis (ATTRv-LA) is a rare neurological phenotype. ATTRv has been regarded as a rare endemic disorder; however, advances in diagnostic techniques have indicated that ATTRv is more frequent than previously recognised.[1] Wild-

INTRODUCTION

- Transthyretin (TTR) is a human 56 kDa non-glycosylated amyloidogenic protein.
- Hereditary transthyretin amyloidosis (ATTRv) is caused by the deposition of variant TTR protein.

INTRODUCTION

- The main ATTRv phenotypes include polyneuropathy (hereditary transthyretin amyloidosis–polyneuropathy (ATTRv-PN)), hereditary transthyretin amyloidosis–cardiomyopathy (ATTRv-CM), and renal and ocular involvement.
- Hereditary transthyretin leptomeningeal amyloidosis (ATTRv-LA) is a rare neurological phenotype.

INTRODUCTION

- ATTRv has been regarded as a rare endemic disorder; however, advances in diagnostic techniques have indicated that ATTRv is more frequent than previously recognised.

INTRODUCTION

- Wild-type transthyretin amyloidosis (ATTRwt) manifests later and is increasingly recognized as the cause of amyloid cardiomyopathy, although it can also rarely cause peripheral neuropathy.

INTRODUCTION

- Advances in understanding of ATTRv pathogenesis has led to development of novel and therapeutic strategies.
- Aside from liver transplantation, alternative therapeutic options have including TTR tetramer stabilisers, genomic approaches using antisense oligonucleotide and small interfering RNA (siRNA) technologies, as well as novel TTR protein stabilisers and fibril removers.

A

Leptomeningeal Amyloidosis (LA)
- Headaches
- Stroke-like episodes
- Amyloid spells/Seizures
- Ataxia
- Spasticity
- Cerebral haemorrhage
- Dementia

Ocular disease
- Vitreous Deposits
- Glaucoma
- Abnormal conjunctival vessels
- Pupillary abnormalities

Amyloid Cardiomyopathy (ATTR-CM)
- Heart Failure with preserved ejection fraction
- Arrythmia
- Conduction block

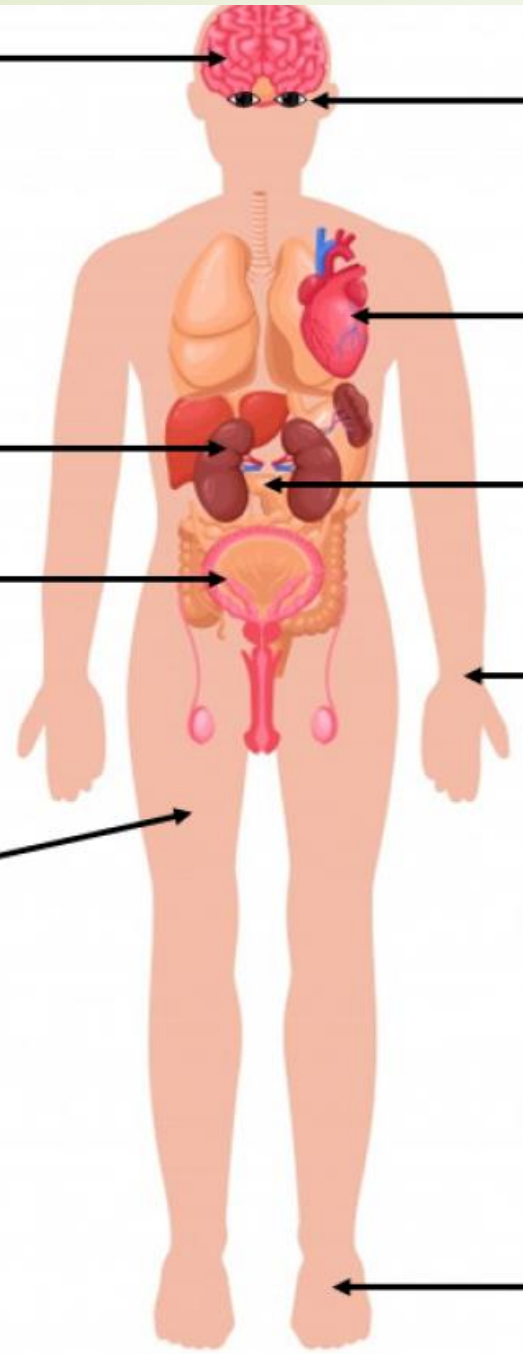
Renal
- Nephrotic syndrome
- Nephritic syndrome
- Renal failure

Gastrointestinal
- Weight loss
- Diarrhea, or alternating diarrhoea and constipation
- Early satiety, nausea and vomiting, regurgitation
- Faecal incontinence

Autonomic neuropathy
- Postural hypotension
- Bladder paresis (hypotonia)
- Nocturia
- Incontinence
- Urinary retention
- Erectile dysfunction
- Abnormal sweating

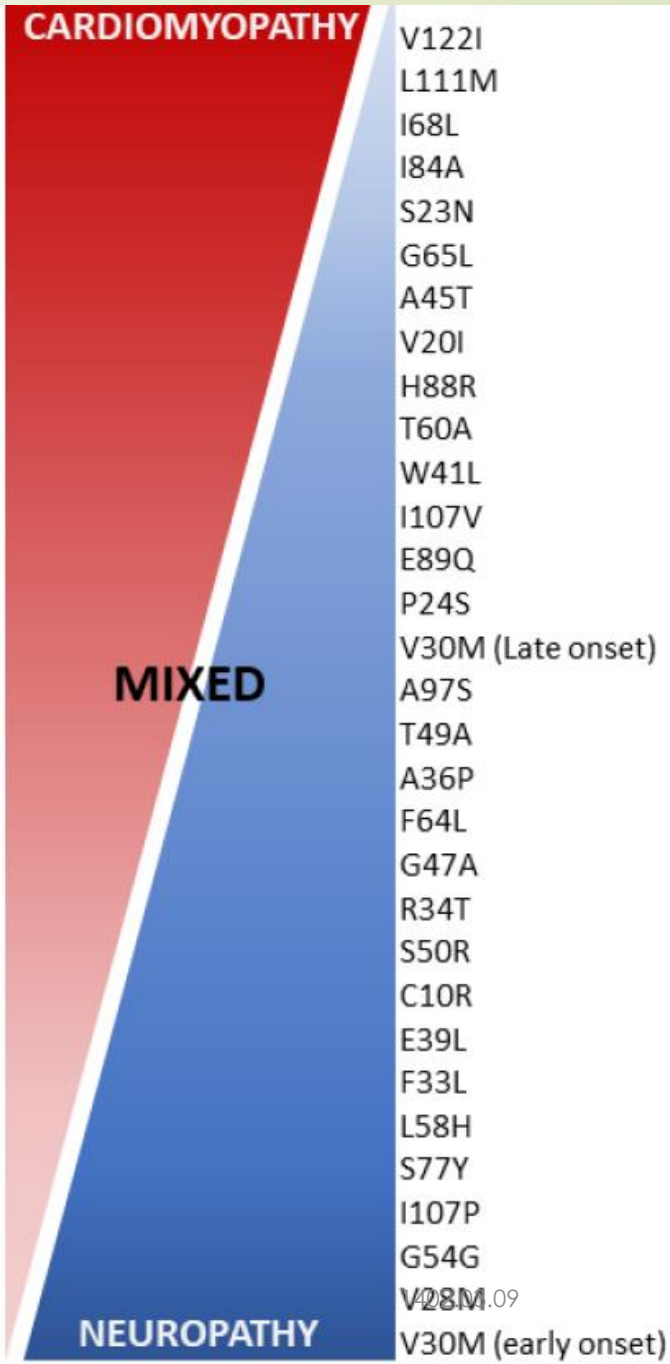
Tenosynovial deposition
- Carpal tunnel syndrome
- Tendon rupture

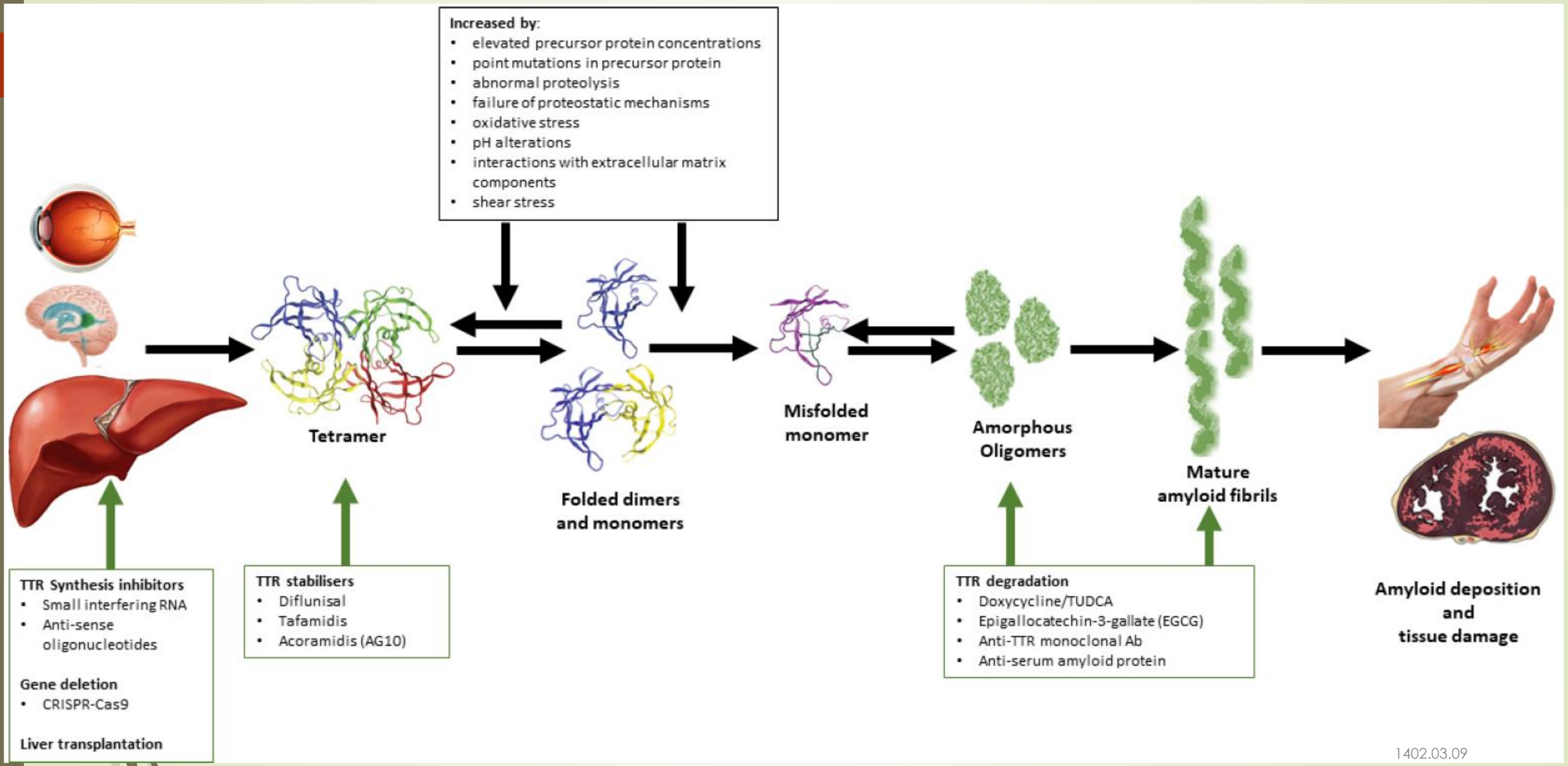
Myopathy



Amyloid Polyneuropathy (ATTR-PN)
- Small fibre neuropathy
- Large fibre sensory or sensorimotor neuropathy
- Autonomic neuropathy (see above)

B




Increased by:
elevated precursor protein concentrations
point mutations in precursor protein
abnormal proteolysis
failure of proteostatic mechanisms
oxidative stress
pH alterations
interactions with extracellular matrix components
shear stress
Tetramer
Folded dimers and monomers
Misfolded monomer
Amorphous Oligomers
Mature amyloid fibrils
Amyloid deposition and tissue damage
TTR Synthesis inhibitors
Small interfering RNA
Anti-sense oligonucleotides
Gene deletion
CRISPR-Cas9
Liver transplantation
TTR stabilisers
Diflunisal
Tafamidis
Acoramidis (AG10)
TTR degradation
Doxycycline/TUDCA
Epigallocatechin-3-gallate (EGCG)
Anti-TTR monoclonal Ab
Anti-serum amyloid protein

AL AMYLOIDOSIS

- Amyloidogenic light chains induce phenotypic changes that resemble a macrophage in the mesangial cell.
- Other intrinsic properties of the light chain may also influence fibril formation. lambda light chains may be more amyloidogenic than kappa light chains.

blood®
Review Article

Management of AL amyloidosis in 2020

Giovanni Palladini, Paolo Milani, and Giampaolo Merlini

Amyloidosis Research and Treatment Center, Foundation "Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo," and Department of Molecular Medicine, University of Pavia, Pavia, Italy

Table 1. Staging systems for AL amyloidosis

Staging system	Markers and thresholds	Stages	Outcomes*
Cardiac (NT-proBNP based)	NT-proBNP >332 ng/L cTnT >0.035 ng/mL (or cTnI >0.01 ng/mL)	I. No markers above the cutoff II. One marker above the cutoff IIIa. Both markers above the cutoff and NT-proBNP <8500 ng/L IIIb. Both markers above the cutoff and NT-proBNP ≥8500 ng/L	I. Median survival not reached, 57% with 10-y survival II. Median survival 67 mo IIIa. Median survival 15 mo IIIb. Median survival 4 mo
Cardiac (BNP based)	BNP >81 ng/L cTnI >0.1 ng/mL	I. No markers above the cutoff II. One marker above the cutoff IIIa. Both markers above the cutoff and BNP <700 ng/L IIIb. Both markers above the cutoff and BNP ≥700 ng/L	I. Median survival 151 mo, 57% with 10-y survival II. Median survival 53 mo III. Median survival 13 mo IV. Median survival 4 mo
Revised Mayo Clinic	NT-proBNP >1800 ng/L cTnT >0.025 ng/mL dFLC >180 mg/L	I. 0 markers above the cutoff II. 1 marker above the cutoff III. 2 markers above the cutoff IV. 3 markers above the cutoff	I. Median survival not reached, 57% with 10-y survival II. Median survival 69 mo III. Median survival 16 mo IV. Median survival 6 mo
Renal	eGFR <50 mL/min per 1.73 m^2 proteinuria >5 g per 24 h	I. Both eGFR above and proteinuria below the cutoffs II. Either eGFR below or proteinuria above the cutoffs III. Both eGFR below and proteinuria above the cutoffs	I. 1% risk of dialysis at 2 y II. 12% risk of dialysis at 2 y III. 48% risk of dialysis at 2 y

dFLC, difference between involved (amyloidogenic) and uninvolved circulating free light chain.

*Observed in 1378 patients with AL amyloidosis newly diagnosed at the Pavia Amyloidosis Research and Treatment Center from 2004 through 2018.

FDA Approves First and Only Treatment for AL Amyloidosis

Roxanne Nelson, RN, BSN

January 20, 2021

The first and only treatment for a rare and often fatal blood cell disorder has been approved in the United States.

The new indication is newly diagnosed light-chain (AL) amyloidosis, which affects about 4500 people in the United States each year. It occurs when blood the bone marrow produce amyloid deposits, which may then build up in vital organs (notably, the heart, kidneys, and liver) and eventually cause organ det Diagnoses are often delayed, and approximately 30% of patients die within the first year of diagnosis.

The new approval is for subcutaneous daratumumab (Darzalex Faspro), to be used in combination with bortezomib, cyclophosphamide, and dexamethas combination of drugs is often used in the treatment of multiple myeloma.

The US Food and Drug Administration granted an accelerated approval for daratumumab for use in AL amyloidosis on the basis of the hematologic compl rate from the phase 3 ANDROMEDA study.

This "milestone is an important step for patients diagnosed with this rare disease," said Isabelle Lousada, founder and CEO, Amyloidosis Research Conso statement. "Sadly, most patients with AL amyloidosis are diagnosed more than one year after their initial symptoms present, at a time when they may alrea experiencing organ deterioration or failure.

"I believe this approval will increase awareness of and education around this life-threatening disease and offer new hope for people with AL amyloidosis a caregivers," she said.


THANK YOU