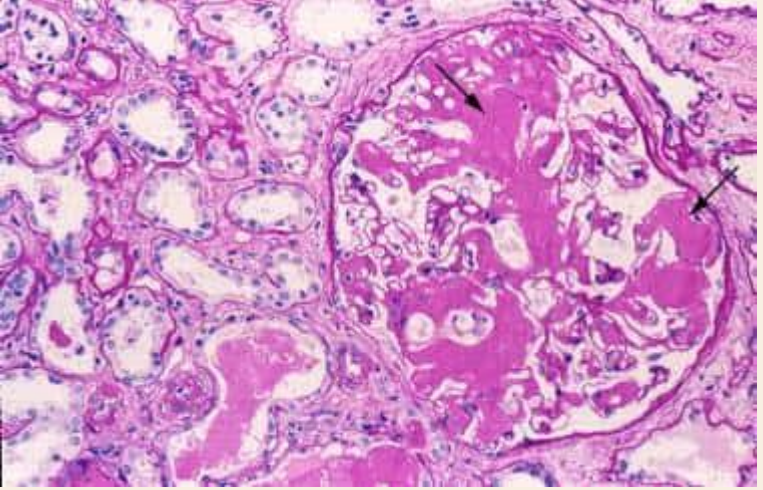
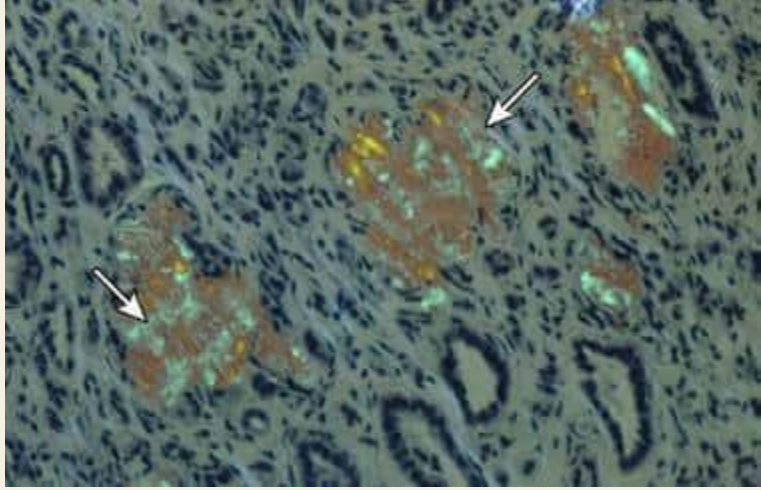
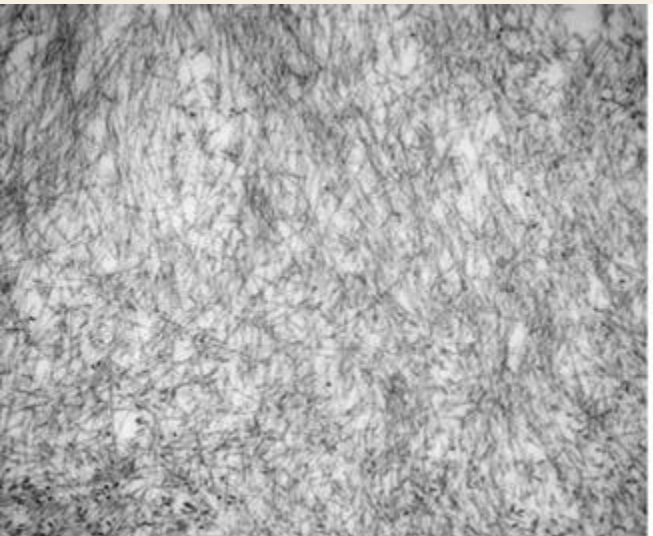


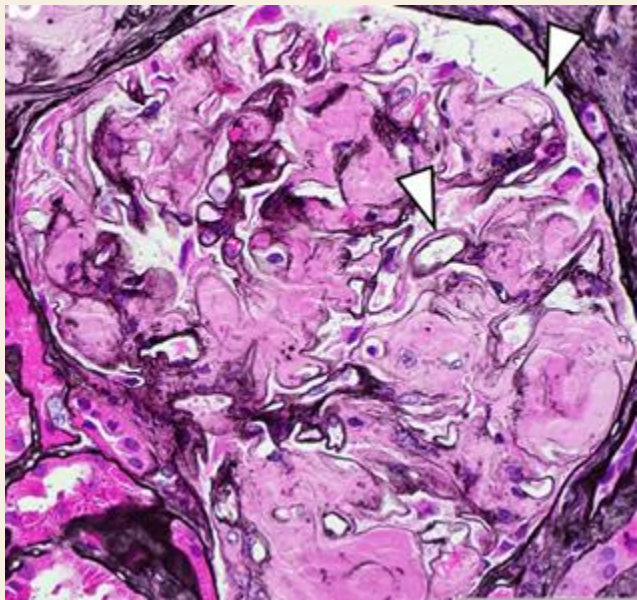


Updates in Amyloidosis



Shokoufeh Savaj

Professor of Iran University of Medical Sciences



Macroscopic :

The specimen consists of 3 pieces of gray soft tissue M:2.5cm. EMB:100%

Microscopic :

Multiple sections are prepared and stained for H&E (x3), PAS(x3) and jones' (x3) methods. The biopsy consists of 3 pieces of cortical tissue containing 39 glomeruli, o is globally sclerosed.

The glomeruli are enlarged, show mild increased mesangial matrix and cellularity. One glomerulus shows small cellular crescent. There is no segmental scar or adhesi to Bowman's capsule. Some hyaline globules are also present. The glomerular basement membrane shows no spike, holes but splitting in the area of segmental sca There is no crescent, endocapillary proliferation, or fibrinoid necrosis. Congo red s was negative.

The tubules show simplification of their lining with a few casts in their lumen associated with atrophic changes in about 5% of the tissue surface with proportiona fibrosis of the interstitium and lymphocytic infiltration in scarred area.

The arteriols and 4 interlobular arteries are unremarkable. Large artery is not sampled.

IMMUNOFLUORSCENC MICROSCOPY:

Frozen sections each containing 3 glomeruli, are stained with IgG, IgA, IgM, C1q, C4, C3, kappa, lambda, Fibrinogen, and polyvalent antisera. IgA shows 3+ mesangial granular deposits. C3 shows trace mesangial deposits. C1q shows 2+ mesangial deposition. Kappa shows 3+ and lambda shows 2+ mesangial deposition. Polyvalent is the same as IgA. All the other antisera are negative.

Kidney Biopsy:

IgA Nephropathy

Comment: All glomeruli show increased mesangial matrix and cellularity and IF study show mesangial deposits of IgA that is diagnostic of IgA nephropathy. There is no segmentally sclerotic lesions or adhesion to Bowman capsule. There is 5% tubular atrophy and interstitial fibrosis that are in favor of very mild chronicity of the disease. There is one small cellular crescent, in favour of very mild activity of the disease. There is also 2+ mesangial deposition of C1q that has been reported in an otherwise typical IgA nephropathy.

(Mesangial C1q deposition in the glomeruli is associated with a poor renal outcome and severe pathologic features in patients with IgAN. The deposition of C1q in IgAN could therefore serve as an indicator of a poor renal prognosis. Clin Nephrol. 2013 Aug;80(2):98-104)

But other secondary causes of IgA nephropathy such as Lupus Nephritis should be considered in differential diagnosis and in the follow up of the patient.

A 32 Yrs old man with nephrotic syndrome around 6 gram/day had biopsy in 1394/12
Treatment with cellcept 4 months and cyclosporin 300 mg after that. Patient did not continued prescription due to side effect and came back after two years.

Path.No : S-96-2258T

Specimen

Kidney needle biopsy.

Clinical Data:

A known case of IgA nephropathy since 2 years ago with proteinuria about 11 gr/day & hepatosplenomegaly.

Gross Examination

The specimen received in normal saline & composed of 2 cores of needle biopsy specimen measuring 1.7 cm & 1.5 cm in length & 0.1 cm in diameter. One of them was bisected & processed for IF studies & the remaining pieces were processed for LM studies.

Microscopic Examination

I.F. FINDINGS

Five glomeruli are present with the following immunofluorescent characteristics:

1:Total IgS: Negative.
2: IgA:Negative.
3: IgG:Negative.
4: IgM:Negative.
5: C1q:Negative.
6: C3c:Negative .
7: C4c:Negative.
8:Fibrinogen:Negative.
9:Kappa light chain:Negative.
10:Lambda light chain:Negative.

LM FINDINGS:

Serial sections stained by H&E,PAS,Trichrome Jone's & Congo-Red methods show renal cortical (60%) & medullary (50%) parenchyma with presence of about 12 glomeruli.Ten out of them are globally hyalinized .Two other glomeruli reveal mild segmental mesangial widening devoid of GBM thickening, spike , endocapiliary hypercellularity, inflammation &/or necrosis(All of the glomeruli reveal deposition of amyloid material) Some of the tubules reveal resorptive changes .Interstitial fibrosis & tubular atrophy in about 50-60% of the cortical area are found .Foci of mild patchy chronic interstitial inflammation are obvious .Amyloid depcsition along vascular wall is seen.

Diagnosis

Renal Biopsy :

-Amyloidosis with involvement of both glomeruli & vessels
-Global scar in 10 out of 12 glomeruli.
-IF/TA:50-60%.
-IHC staining for SAA,Kappa & Lambda light chain is positive indicating secondary amyloidosis.

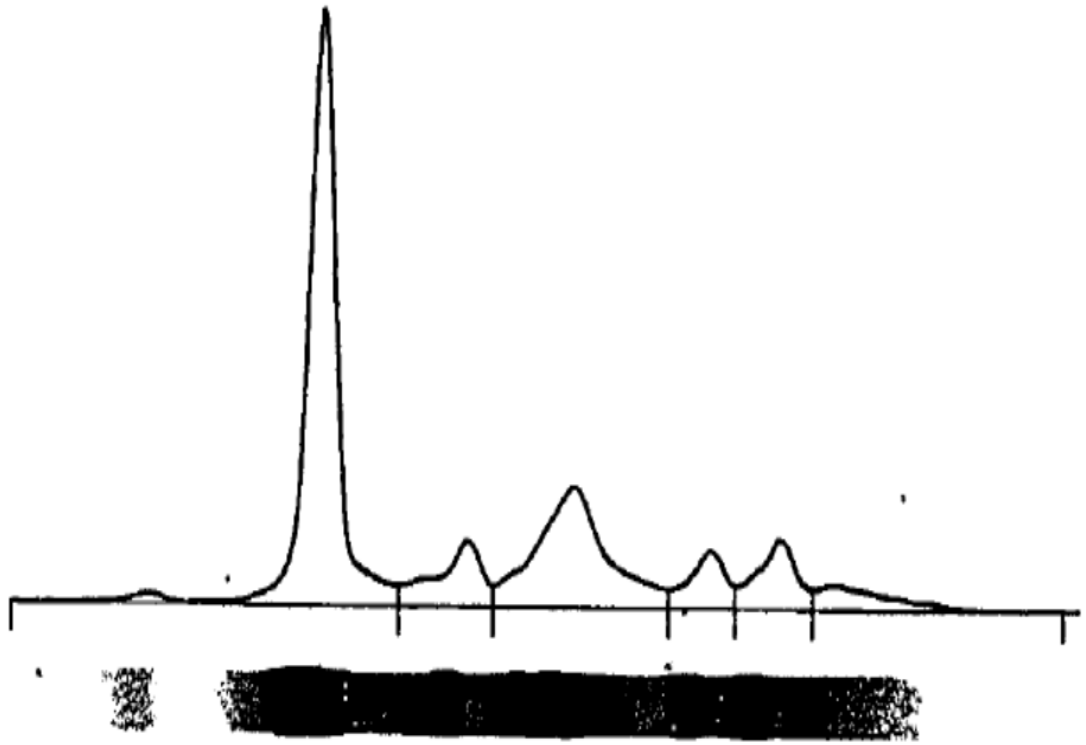
دکتر پیمان محمدی تربتی
MD AP-CP

دکتر محمود پروین
MD AP-CP

:25:16AM
996/06/19

جواب این آزمایش بدون مهر و امضای پاتولوژ

Serum Protein Capillary Zone Electrophoresis



Fractions	%	Ref. %	g/dl	Ref. g/dl
Albumin	49.5	55.8 - 66.1	2.03	4.00 - 4.80
Alpha 1	8.2	2.9 - 4.9	0.34	0.20 - 0.40
Alpha 2	23.8	7.1 - 11.8	0.98	0.50 - 0.90
Beta 1	5.8	4.7 - 7.2	0.24	0.30 - 0.50
Beta2	7.6	3.2 - 6.5	0.31	0.20 - 0.50
Gamma	5.1	11.1 - 18.8	0.21	0.80 - 1.40

MICROSCOPIC DESCRIPTION:

Bone Marrow Aspiration slides demonstrate cellular marrow revealing myeloid to erythroid ratio about 3 to 1, hematopoietic cells in different stages of maturation, no significant dyspoiesis in erythroids & granulocytic series, less than 3.5 % plasma cell series with several mature, some immature forms (plasma blasts with high nuclear:cytoplasmic ratio, deep blue cytoplasm, some with perinuclear hof, irregular nuclei, fine chromatin and one or two prominent nucleoli), too rare binucleated forms and no evidence of dysplastic changes almost 25 % lymphoid cells, mostly normal looking mature forms, no increase in immature/blastic population, 6 % eosinophilic series, and normal megakaryocytic maturation.

Bone Marrow Biopsy demonstrates a short piece of subcortical bone marrow (periosteal fibrous tissue, cortical bone, and small amounts of subcortical hypocellular marrow), in several deep examined sections, totally inadequate for assessment. Few hematopoietic cells with heterogeneous appearance are present. No evidence of granuloma, fibrosis or any lymphoid aggregate identified in several examined sections in this specimen.

No evidence of apple green" birefringence with Congo red stain and polarized light microscopy.

Immunohistochemistry study:

Kappa light chain: Negative (inadequate specimen for definite assessment)
Lambda light chain: Negative (inadequate specimen for definite assessment)

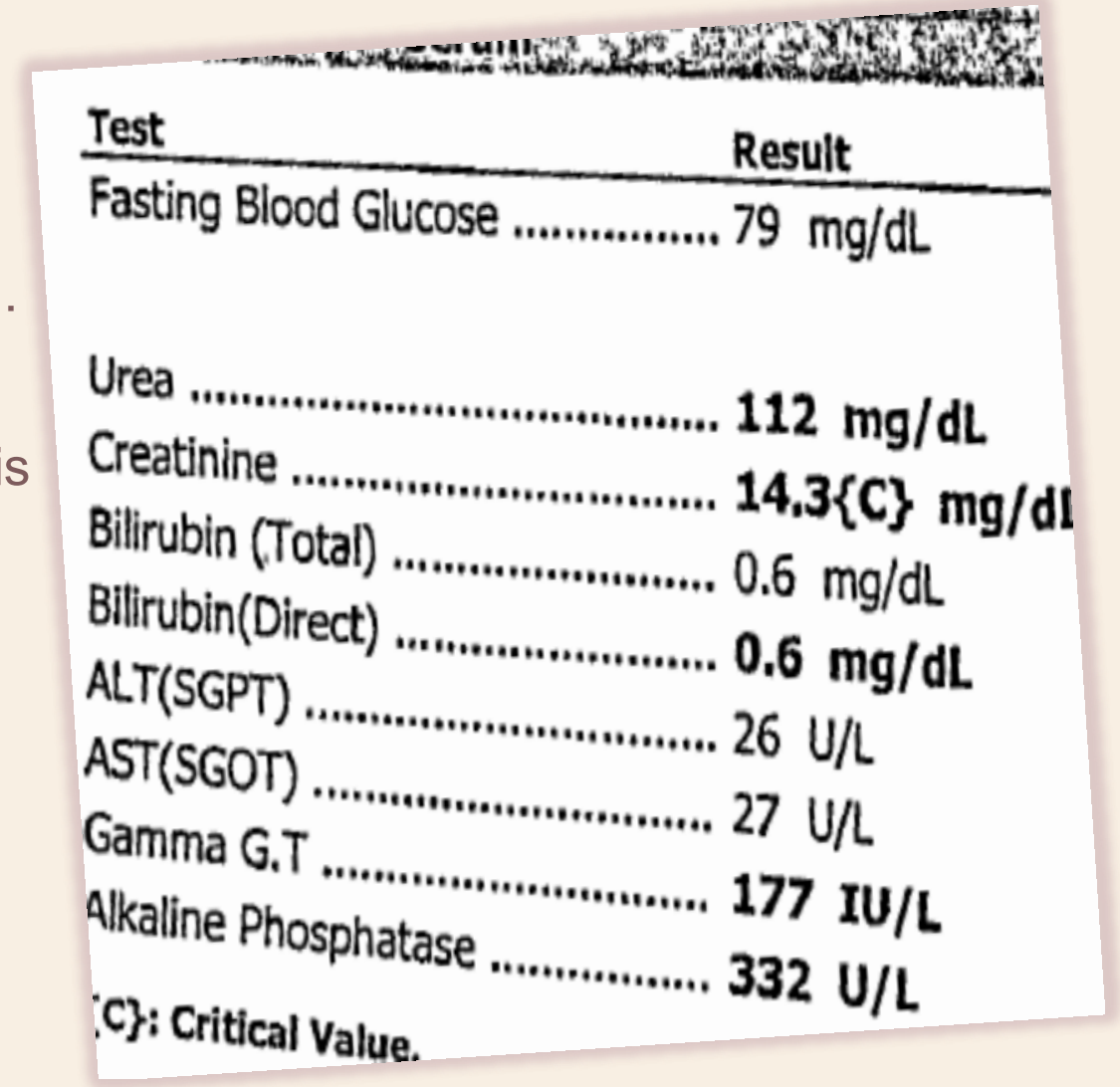
CLINICAL INFORMATION:

34 year old male, known case of under-treatment IgA nephropathy from two years ago, recently

Spiral Abdominopelvic CT Scan (without contrast):

Mild ascites is noted.
Mild splenomegaly and moderate hepatomegaly are seen.
There are multiple mesenteric lymph nodes (measuring up to 10mm in SAD) accompanied with engorgement of mesenteric vessels and mesenteric fat stranding and nodularity extends to the paraceliac trunk and SMA levels.
These finding could be due to panniculitis or vasculitis or ... .
Small to top normal size paraaortic adenopathy is depicted.
The rest grossly is recommended.
No accurate history is available so comparison and lab data test is recommended./f

- 97/6/27 Amyloidosis
- Severe ascites and edema, hypoalbuminemia, slightly elevated AST, ALT. Gamma GT and alkaline phosphatase is high. Serum Creatinine: 11.4 mg/ dl
- No periodic fever, addiction, arthritis, vasculitis and IBD and chronic infection
- Bone marrow flow cytometry: normal
- No cardiac involvement
- Normal ileocolonoscopy
- 97/5/7 dialysis began



Test	Result
Fasting Blood Glucose	79 mg/dL
Urea	**112 mg/dL**
Creatinine	**14.3{C} mg/dL**
Bilirubin (Total)	0.6 mg/dL
Bilirubin(Direct)	**0.6 mg/dL**
ALT(SGPT)	26 U/L
AST(SGOT)	27 U/L
Gamma G.T	**177 IU/L**
Alkaline Phosphatase	**332 U/L**

{C}: Critical Value.

Urine

Complete Urine Analysis

Macroscopic

Color	*Pale-Yellow*
Appearance	*Clear*
PH	7
Sp.Gravity	1021
Protein	*3+*
Blood	*Negative*
Glucose	*2+*
Ascorbic Acid	*Negative*
Urobilinogen	*Negative*
Bilirubin	*Negative*
Nitrite	*Negative*
Ketone	*Negative*

Microscopic

WBC	6-8
RBC	0-1
Epithelial	1-3
Bacteria	*Rare*
Mucus	*Rare*

Crystal

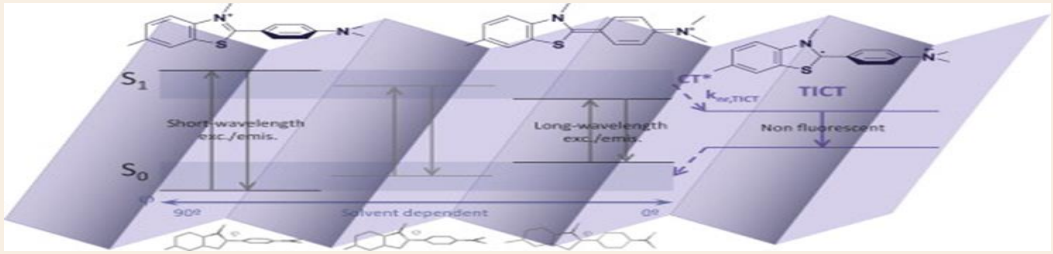
Cast

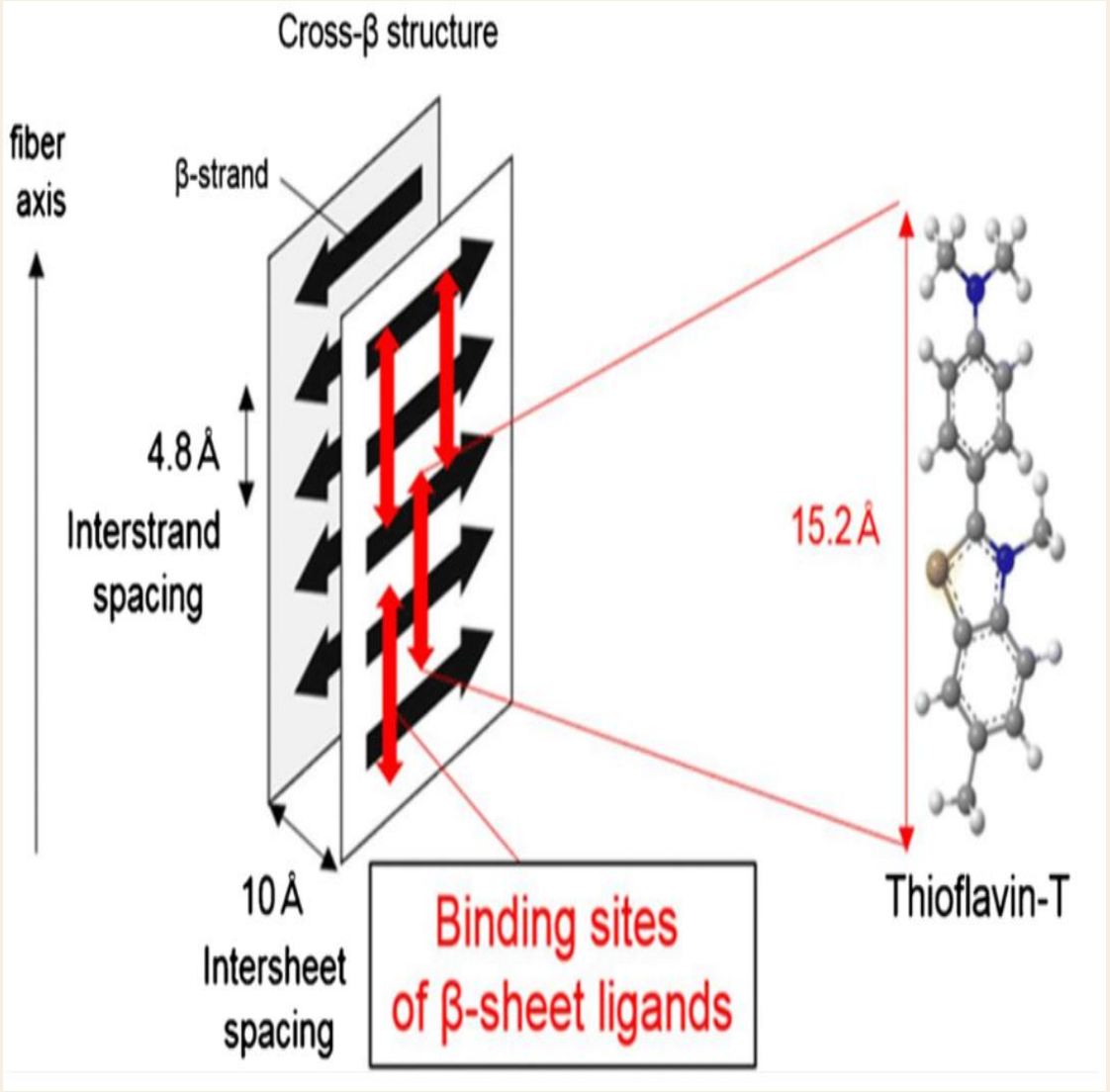
Granular	0-1
Hyaline	0-1

History

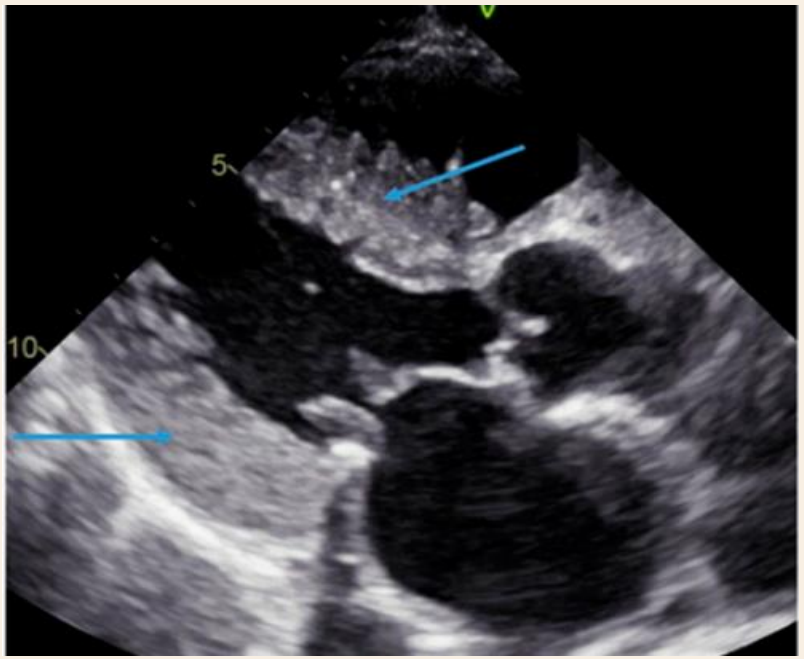
- First introduced by Schleiden in 1838 to describe plant starch.
- The word ‘amyloid’ was introduced by Rudolf Virchow in 1854 describing a pathologic substance initially believed to be related to cellulose or starch but soon shown to be of protein nature.
- At 1883 Congo red developed by Bottinger
- At 1920 polarized microscopy was used to demonstrate apple- green birefringence
- At 1950 Thioflavin T used showed yellow-green fluorescence.
- At 1959 unbranched fibrils 8-10 nm in width by electron microscopy
- Immunohistology (immunofluorescence or immunoenzymatic techniques), immunoelectron microscopy
- Developments by proteomics on fixed tissue using laser-capture microdissection and mass spectroscopy,

- Amyloidosis results from the predominantly extracellular tissue deposition of fibrils composed of low molecular weight subunits of a variety of proteins, typically in the range of 5 to 25 kD.
- Soluble precursors undergo conformational changes that lead to the adoption of a predominantly antiparallel beta-pleated sheet configuration in which state they auto-aggregate in highly ordered fibrils.
- 42 different human protein precursors of amyloid fibrils that causes 8 different types of systemic and 28 localized forms of amyloidosis.

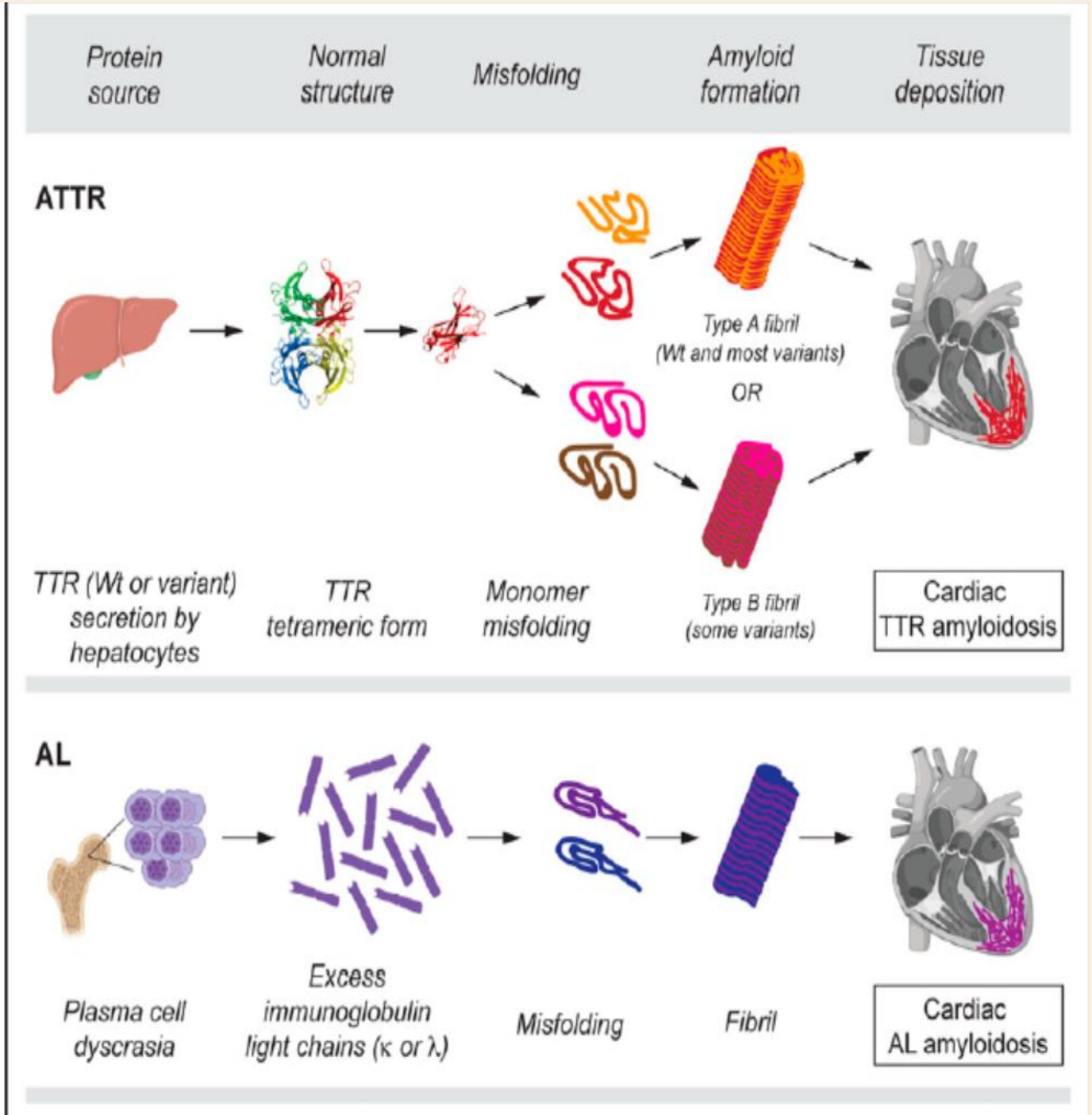




Amyloid molecular mechanisms and imaging characteristics. Source protein, misfolding, fibril formation, and deposition are depicted for cardiac ATTR and cardiac AL.



Scott Jerome et al, JOURNAL OF NUCLEAR MEDICINE TECHNOLOGY, 2023



Fibril protein	Precursor protein	Systemic and/or localised	Acquired or hereditary	Target organs
AL	Immunoglobulin light chain	S, L	A, H	All organs, usually except CNS
AH	Immunoglobulin heavy chain	S, L	A	All organs except CNS
AA	(Apo) serum amyloid A	S	A	All organs except CNS
ATTR	Transthyretin, wild type	S	A	Heart mainly in males, lung, ligaments, tenosynovium
	Transthyretin, variants	S	H	PNS, ANS, heart, eye, leptomeninges
Aβ2M	β2-microglobulin, wild type	S	A	Musculoskeletal system
	β2-microglobulin, variants	S	H	ANS
AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C terminal variants), skin (C terminal variants)
AApoAII	Apolipoprotein A II, variants	S	H	Kidney
AApoAIV	Apolipoprotein A IV, wild type	S	A	Kidney medulla and systemic
AApoCII	Apolipoprotein C II, variants	S	H	Kidney
AApoCIII	Apolipoprotein C III, variants	S	H	Kidney
AGel	Gelsolin, variants	S	H	Kidney PNS, cornea
ALys	Lysozyme, variants	S	H	Kidney
ALECT2	Leukocyte chemotactic factor-2	S	A	Kidney, primarily
AFib	Fibrinogen α, variants	S	H	Kidney, primarily
ACys	Cystatin C, variants	S	H	CNS, PNS, skin
ABri	ABriPP, variants	S	H	CNS
ADan[b]	ADanPP, variants	L	H	CNS

Aβ	Aβ protein precursor, wild type	L	A	CNS
	Aβ protein precursor, variant	L	H	CNS
AαSyn	α-Synuclein	L	A	CNS
ATau	Tau	L	A	CNS
APrP	Prion protein, wild type	L	A	CJD, fatal insomnia
	Prion protein variants	L	H	CJD, GSS syndrome, fatal insomnia
	Prion protein variant	S	H	PNS
ACal	(Pro)calcitonin	L	A	C-cell thyroid tumours
		S	A	Kidney
AIAPP	Islet amyloid polypeptide[c]	L	A	Islets of Langerhans, insulinomas
AANF	Atrial natriuretic factor	L	A	Cardiac atria
APro	Prolactin	L	A	Pituitary prolactinomas, aging pituitary
AIns	Insulin	L	A	Iatrogenic, local injection
ASPC[d]	Lung surfactant protein	L	A	Lung
ACor	Corneodesmosin	L	A	Cornified epithelia, hair follicles
AMed	Lactadherin	L	A	Senile aortic, media
AKer	Kerato-epithelin	L	A	Cornea, hereditary
ALac	Lactoferrin	L	A	Cornea
AOAAP	Odontogenic ameloblast-associated protein	L	A	Odontogenic tumours
ASem1	Semenogelin 1	L	A	Vesicula seminalis
AEnf	Enfurvitide	L	A	Iatrogenic
ACatK[e]	Cathepsin K	L	A	Tumour associated
AEFEMP1[e]	EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1	L	A	Portal veins Aging associated

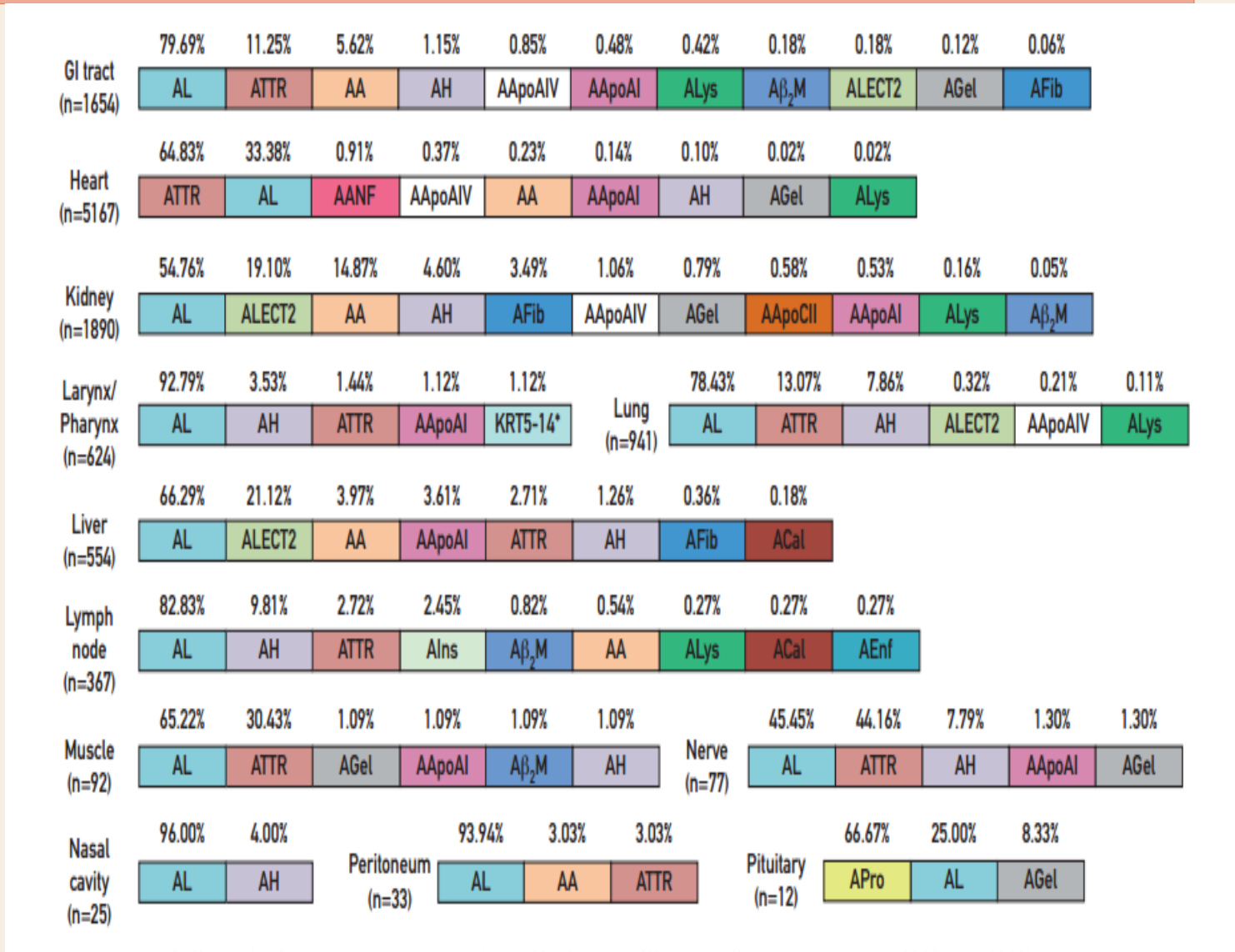
Prevalence

- A review of more than 11,000 patients seen at a single center from 1987 - 2019 showed that systemic AL amyloidosis accounted for 56%, ATTR 21 %, and AA 8 % of typed cases , a substantial increase in the recognition of systemic amyloid due to ATTR in major referral centers.
- The prevalence of renal amyloidosis in native kidney biopsies is approximately 2 % In a large biopsy series of 474 cases of renal amyloidosis, the most common type was immunoglobulin-associated (light chain [AL], heavy chain [AH], or both [AHL]) amyloidosis (86 %), followed by AA amyloidosis (7 %) and leukocyte cell-derived chemotaxin 2 (ALECT2) amyloidosis (3 %).

Said SM,Clin J Am Soc Nephrol 2013; 8:1515
Ravichandran S,N Engl J Med. 2020;382(16):1567

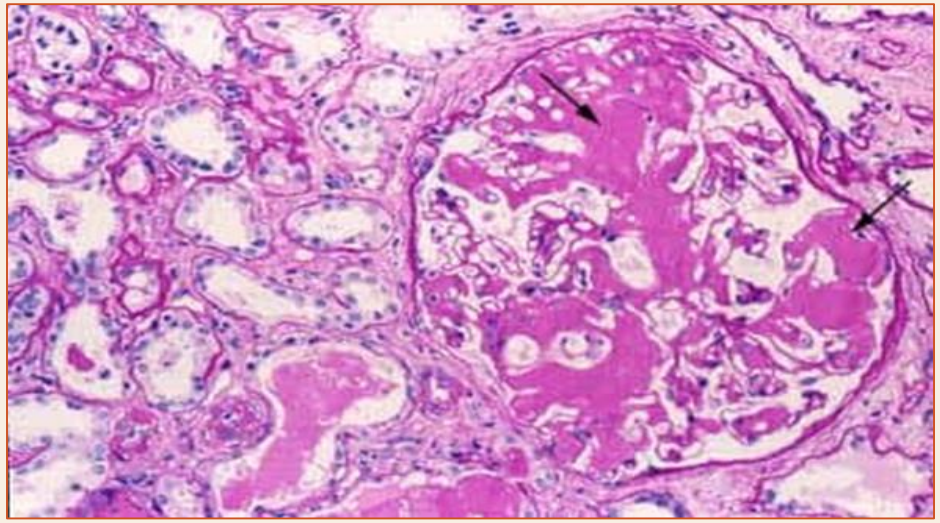
Map Of Amyloid Types By Organs

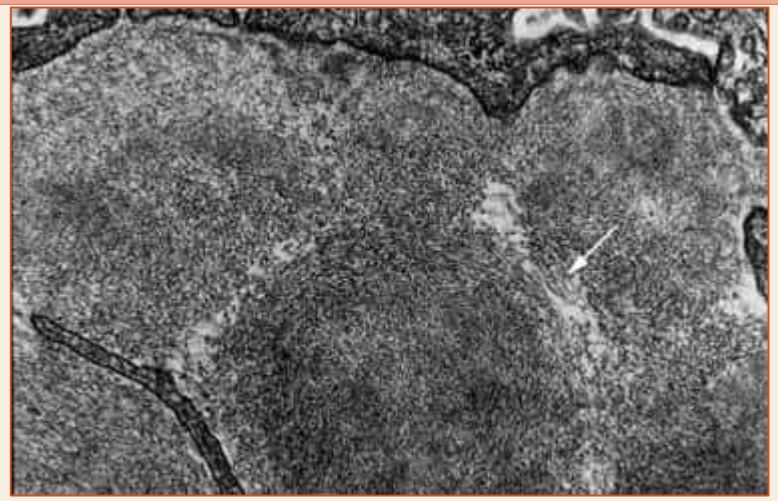
Amyloid Typing by Mass Spectrometry in Clinical Practice: a Comprehensive Review of 16,175 Samples.
They identified 21 established amyloid types from January 1, 2008, to December 31, 2018.

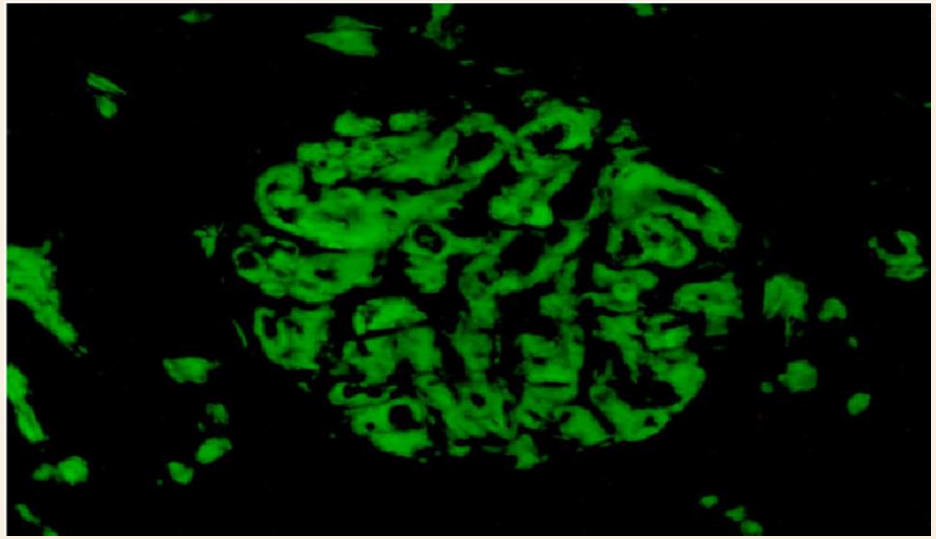


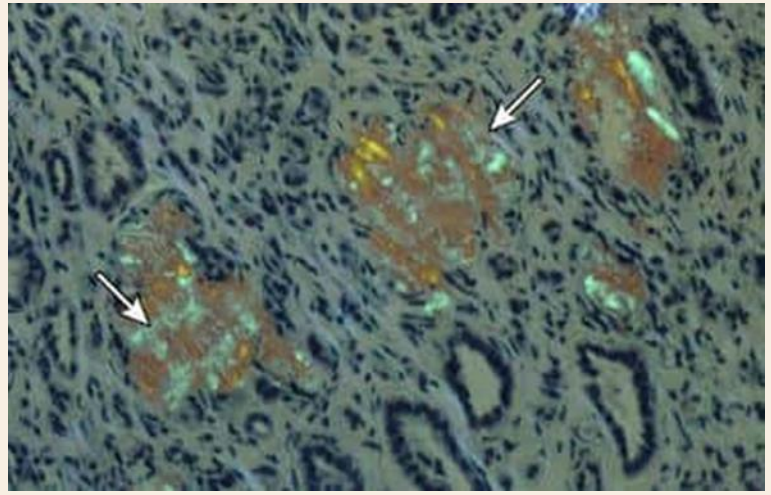
Dasari et al, Mayo Clin Proc. September 2020;95(9):1852-1864

Identifying amyloid: Kidney or liver biopsy is positive in over 90 percent of cases, abdominal fat pad aspirate (60 to 80 percent), rectal biopsy (50 to 70 percent), bone marrow biopsy (50 to 55 percent), or skin biopsy (50 percent).

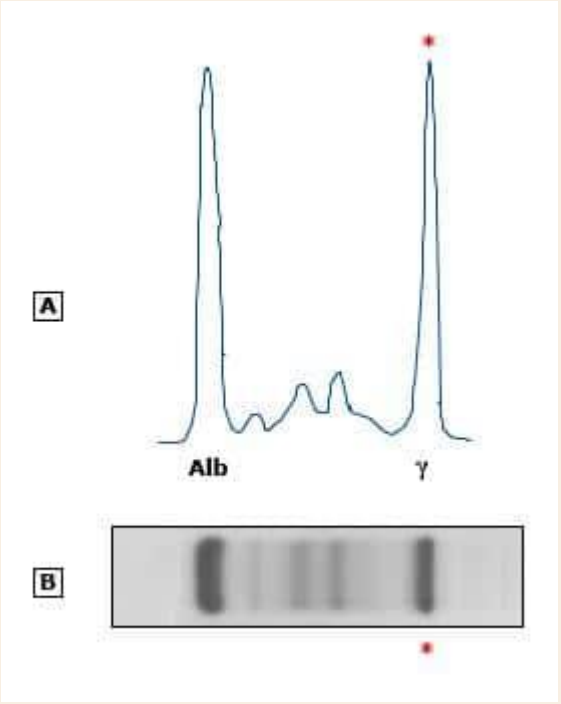








Evidence Of Monoclonal Plasma Cell Clone



Evaluation with serum and urine immunofixation plus a serum free light chain ratio analysis provides the most sensitive measure for this M protein.

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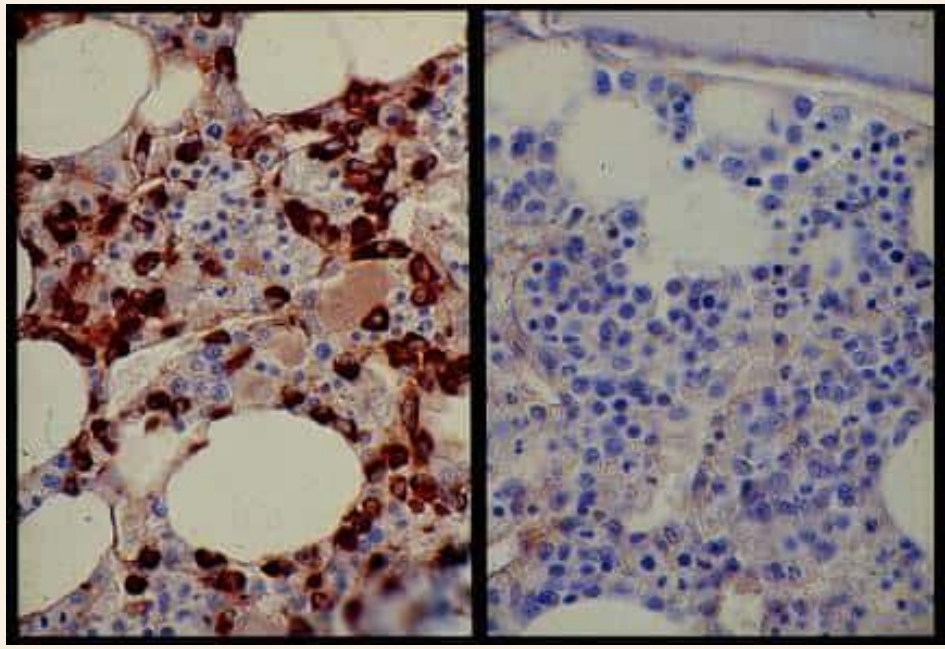
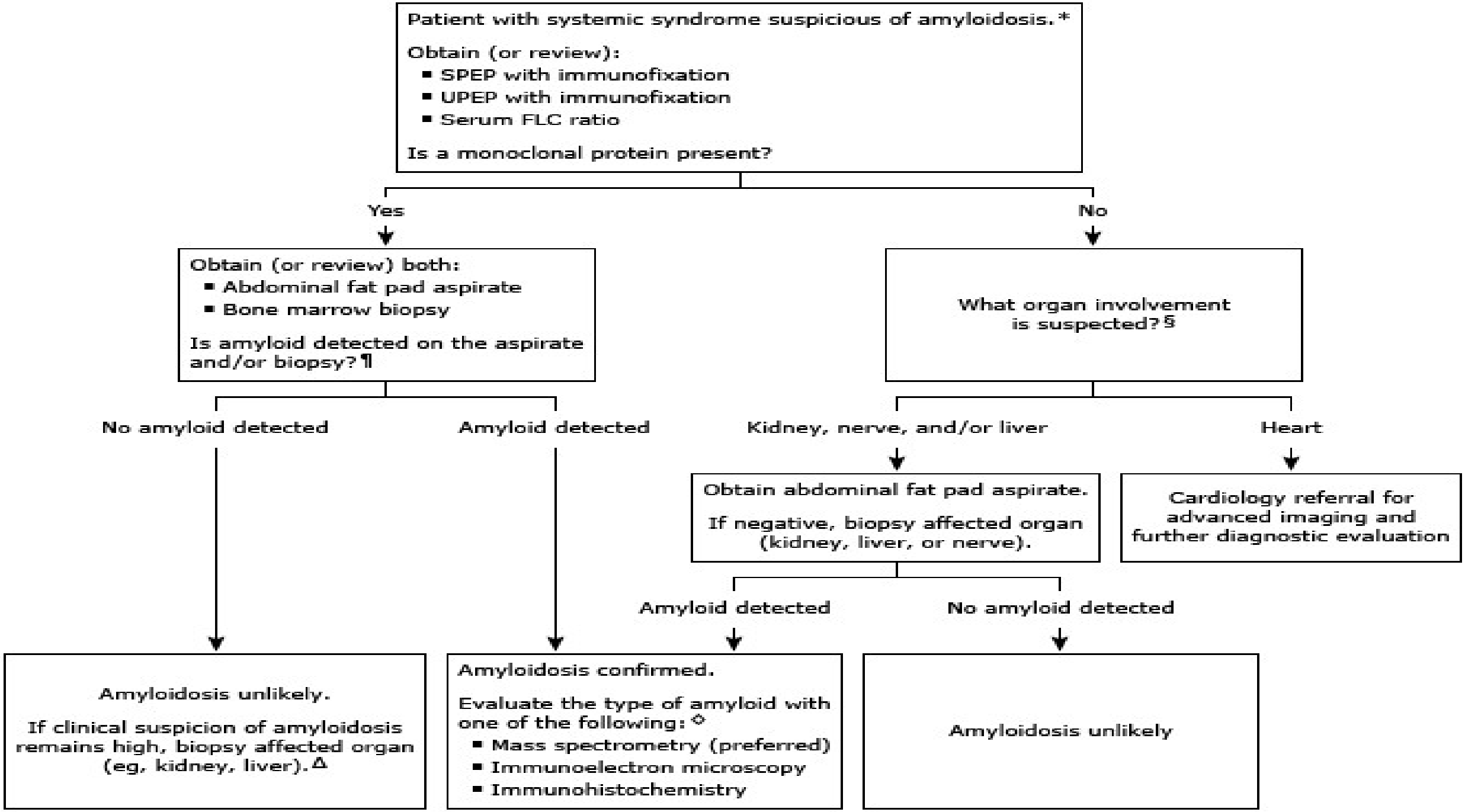
The M protein in AL amyloidosis is IgG in approximately 35 percent, IgA in 10 percent, IgM in 5 percent, IgD in 1 percent, and light chain (lambda or kappa) in the remaining patients.



Monoclonal plasma cell disease: intense staining for lambda light chains (left panel, 70%) with almost no staining for kappa light chains (right panel 30%).


Patient with systemic syndrome suspicious of amyloidosis.*
Obtain (or review):
SPEP with immunofixation
UPEP with immunofixation
Serum FLC ratio
Is a monoclonal protein present?
Yes
No
Obtain (or review) both:
Abdominal fat pad aspirate
Bone marrow biopsy
Is amyloid detected on the aspirate and/or biopsy?¶
What organ involvement is suspected?§
No amyloid detected
Amyloid detected
Kidney, nerve, and/or liver
Heart
Obtain abdominal fat pad aspirate.
If negative, biopsy affected organ (kidney, liver, or nerve).
Cardiology referral for advanced imaging and further diagnostic evaluation
Amyloid detected
No amyloid detected
Amyloidosis unlikely.
If clinical suspicion of amyloidosis remains high, biopsy affected organ (eg, kidney, liver).Δ
Amyloidosis confirmed.
Evaluate the type of amyloid with one of the following:◇
Mass spectrometry (preferred)
Immunoelectron microscopy
Immunohistochemistry
Amyloidosis unlikely

International Myeloma Working Group diagnostic criteria for systemic AL amyloidosis

Diagnosis of systemic AL amyloidosis requires all of the following:
▪ Presence of an amyloid-related systemic syndrome (eg, renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement)
▪ Positive amyloid staining by Congo red in any tissue (eg, fat aspirate, bone marrow, or organ biopsy)
▪ Evidence that amyloid is light-chain-related established by direct examination of the amyloid using mass spectrometry-based proteomic analysis, or immunoelectronmicroscopy, and
▪ Evidence of a monoclonal plasma cell proliferative disorder (serum or urine monoclonal protein, abnormal free light-chain ratio, or clonal plasma cells in the bone marrow)

Determining the type of amyloid

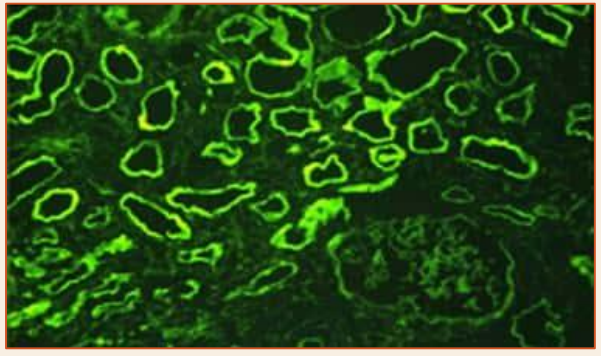
Mass spectrometry is the preferred method since immunohistochemistry and immunofluorescence have a greater risk of false positive and false negative results. Laser microdissection with mass spectrometry (MS)

100 percent specificity and sensitivity in the training set, not available.

Immunoelectron microscopy: highly sensitive and specific method for amyloid typing, which is, however, only available in few expert centers

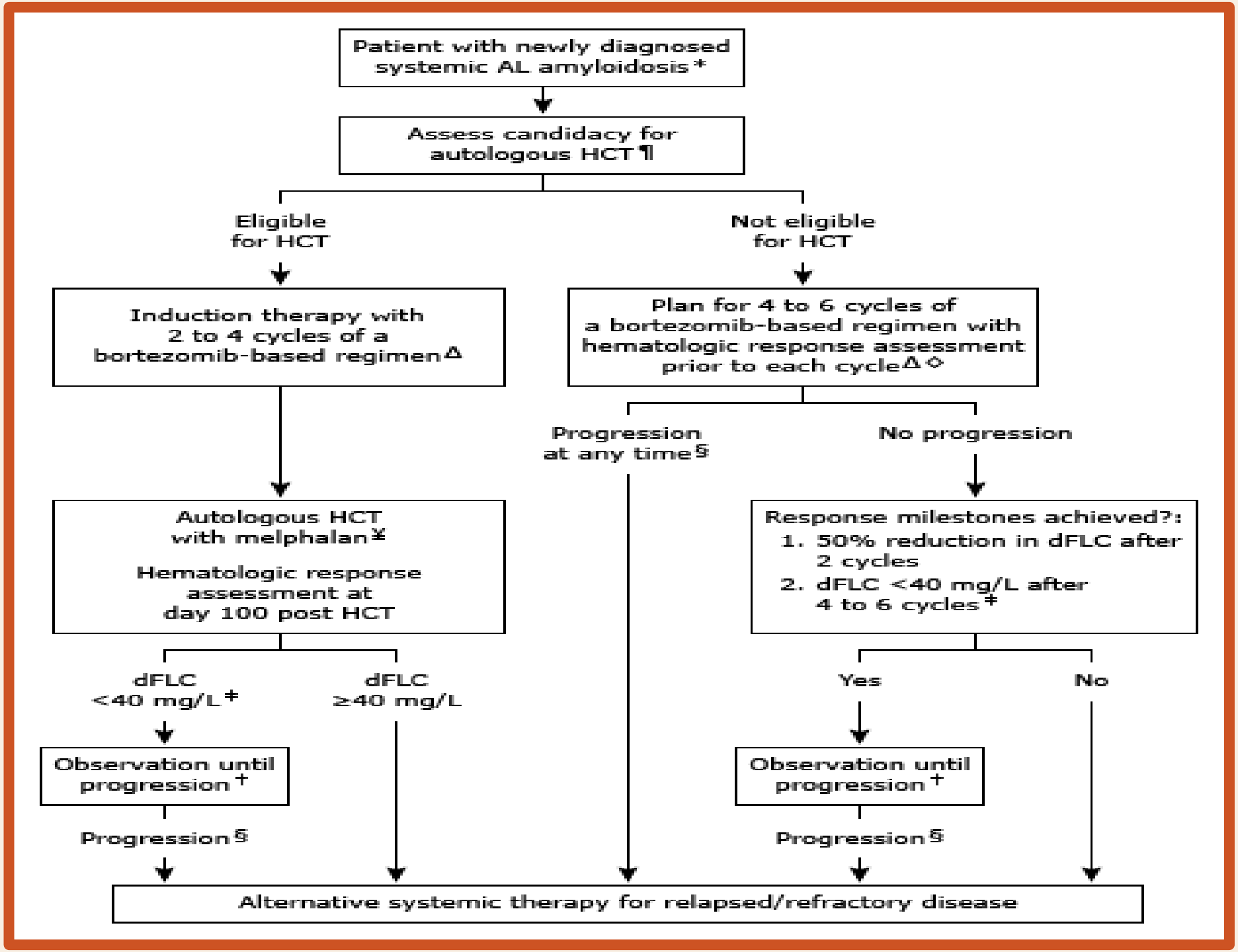
Immunohistochemical staining (eg, for kappa and lambda light chains, transthyretin, and serum amyloid A component) of the amyloid can determine the type of amyloidosis.

Anti-kappa light chain antibodies
along the tubular basement membranes



Criteria For Kidney Staging, Response And Progression

		Palladini et al. (2014) [36]	Kastritis et al. (2017) [37]	Basset et al. (2022) [38]
Staging	Stage I	eGFR > 50 mL/min and Proteinuria < 5 g/24 h	24h UPr/eGFR ratio < 30	eGFR > 50 mL/min and UACR < 3600 mg/g
	Stage II	eGFR < 50 mL/min or Proteinuria > 5 g/24 h	24h UPr/eGFR ratio 30–99	eGFR < 50 mL/min or UACR ≥ 3600 mg/g
	Stage III	eGFR < 50 mL/min and Proteinuria > 5 g/24 h	24h UPr/eGFR ratio ≥ 100	eGFR < 50 mL/min and UACR ≥ 3600 mg/g


Patient with newly diagnosed systemic AL amyloidosis*
Assess candidacy for autologous HCT¶
Eligible for HCT
Not eligible for HCT
Induction therapy with 2 to 4 cycles of a bortezomib-based regimen△
Plan for 4 to 6 cycles of a bortezomib-based regimen with hematologic response assessment prior to each cycle△◇
Progression at any time§
No progression
Autologous HCT with melphalan¥
Hematologic response assessment at day 100 post HCT
Response milestones achieved?:
1. 50% reduction in dFLC after 2 cycles
2. dFLC <40 mg/L after 4 to 6 cycles‡
dFLC <40 mg/L‡
dFLC ≥40 mg/L
Yes
No
Observation until progression†
Observation until progression†
Progression§
Progression§
Alternative systemic therapy for relapsed/refractory disease

AL Amyloidosis Treatment

Patients Should Meet All Of The Following Criteria for HCT !

Physiologic age ≤70 years

Troponin T <0.06 ng/mL (or hs-Troponin T <75 ng/mL)

Systolic blood pressure ≥90 mmHg

Creatinine clearance ≥30 mL/min (unless on chronic stable dialysis)

Eastern Cooperative Oncology Group (ECOG) performance status ≤2

New York Heart Association (NYHA) functional status class I or II

No more than two organs significantly involved (liver, heart, kidney, or autonomic nerve)

No large pleural effusions

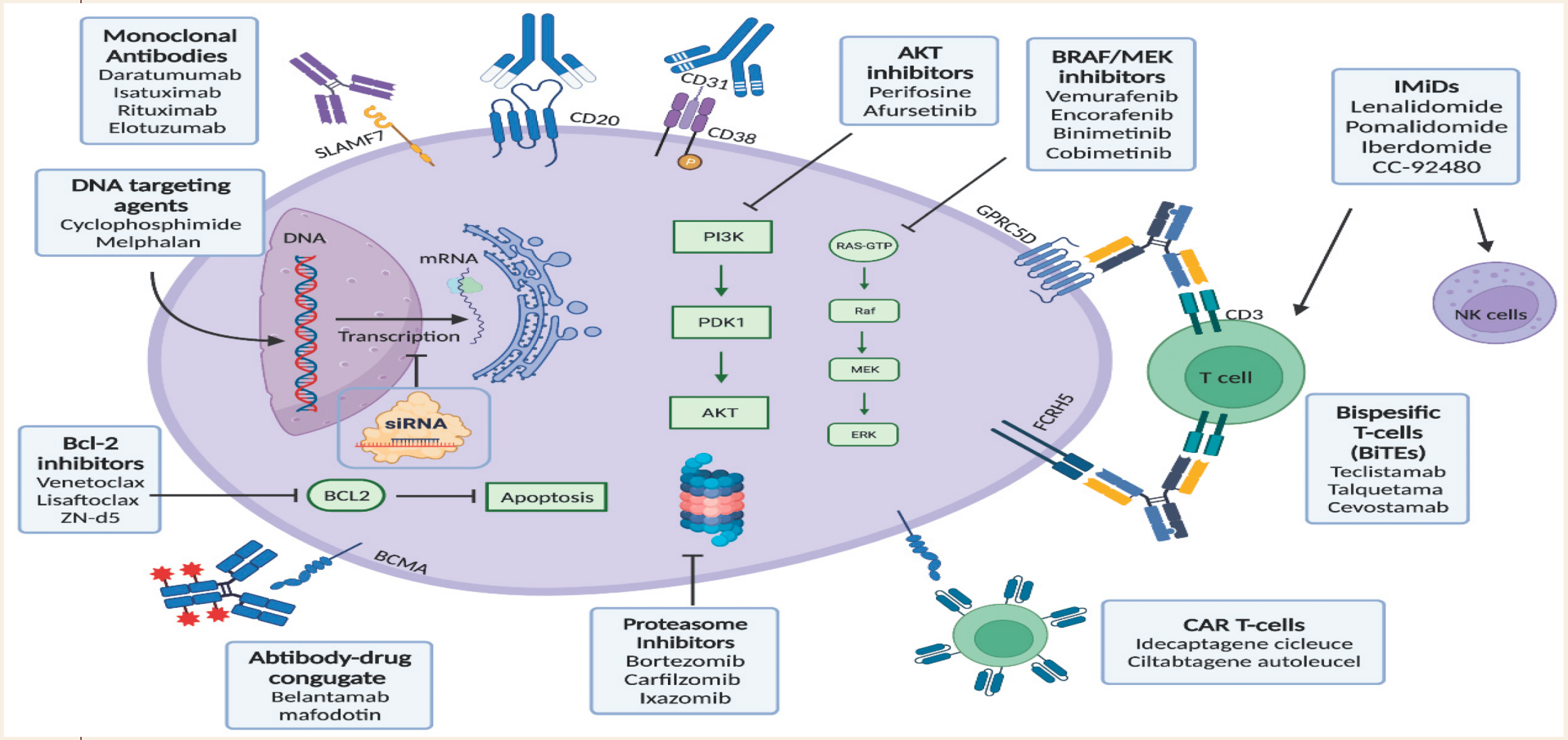
- Assessment of other organ involvement: heart, kidney, liver, lung, nerves, soft tissue
- No conventional treatment
- Careful management of cardiac complications
- Eligibility for autologous hematopoietic cell transplantation (HCT)

Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis

- Daratumumab is a human IgG- k monoclonal antibody that targets CD38, a glycoprotein uniformly expressed on human plasma cells. It has a direct antitumor and immunomodulatory mechanism with demonstrated efficacy as monontherapy or in combination with standard of care regimens for multiple myeloma.
- RCT in 399 patients, 11.4 months follow up , response rate 53.3 % vs 18.1%, RR: 2.9, P< 0.001.
- The addition of Daratumumab to bortezomib, cyclophosphamide, and dexamethasone was associated with higher frequencies of hematologic complete response and survival free from major organ deterioration or hematologic progression.

Kastris et al, NEJM, 2021

Actionable Cellular Molecules And Signaling Pathways To Target Plasma Cells In AL



Hematologic response assessment

Response	Criteria
Complete	Both criteria must be met: (1) Negative serum and urine immunofixation (2) Either a FLC ratio within the reference range or the uninvolved FLC concentration is greater than involved FLC concentration with or without an abnormal FLC ratio
VGPR	Reduction in the dFLC to <40 mg/L
Partial	>50% reduction in the dFLC
No response	Less than a PR
Progression	• From CR: any detectable M-protein or abnormal FLC ratio (light chain must double) • From PR: 50% increase in serum M protein to >0.5 g/dL or 50% increase in urine M protein to >200 mg/day (a visible peak must be present) • FLC increase of 50% to >100 mg/L

CR, complete response; FLC, free light chain; dFLC, difference between involved and uninvolved FLC; M-protein, monoclonal protein; PR, partial response; VGPR, very good partial response.

Graded Organ Response Criteria

Organ	Category	Criteria
Heart [45]	Cardiac complete response (CarCR)	Nadir NT-proBNP $\leq$ 350 pg/mL or BNP $\leq$ 80 pg/mL
	Cardiac very good partial response (CarVGPR)	>60% reduction in NT-proBNP/BNP from baseline level not meeting CarCR
	Cardiac partial response (CarPR)	31–60% reduction in NT-proBNP from baseline level not meeting CarCR
	Cardiac no response (CarNR)	$\leq$30% reduction in NT-proBNP from baseline level
Renal [46]	Renal complete response (RenCR)	Nadir proteinuria $\leq$ 200 mg/24-h
	Renal very good partial response (RenVGPR)	>60% reduction in proteinuria from baseline level not meeting RenCR
	Renal partial response (RenPR)	31–60% reduction in proteinuria from baseline level not meeting RenCR
	Renal no response (RenNR)	$\leq$30% reduction in proteinuria from baseline level

Chronic Inflammatory Conditions Associated With AA Amyloidosis

Periodic fevers

- Familial Mediterranean fever
- Cryopyrin-associated periodic syndrome (CAPS)
- TNF receptor-associated periodic syndrome (TRAPS)
- Mevalonate kinase deficiency (HIDS)
- Deficiency of adenosine deaminase 2 (DADA2)

Neoplasia

- Hodgkin disease
- Renal cell carcinoma
- Adenocarcinoma of the lung, gut, urogenital tract
- Basal cell carcinoma
- Hairy cell leukemia
- Castleman disease
- Hepatic adenoma
- Squamous cell carcinoma

Chronic inflammatory arthritides

- Rheumatoid arthritis
- Juvenile idiopathic arthritis
- Ankylosing spondylitis
- Psoriatic arthropathy
- Reactive arthritis
- Adult-onset Still's disease
- Systemic lupus erythematosus
- Gout
- Caplan's syndrome

Vasculitides

- Polyarteritis nodosa
- Takayasu arteritis
- Behçet syndrome
- Giant cell arteritis/polymyalgia rheumatica
- Sweet syndrome

Inflammatory bowel disease

- Crohn disease
- Ulcerative colitis

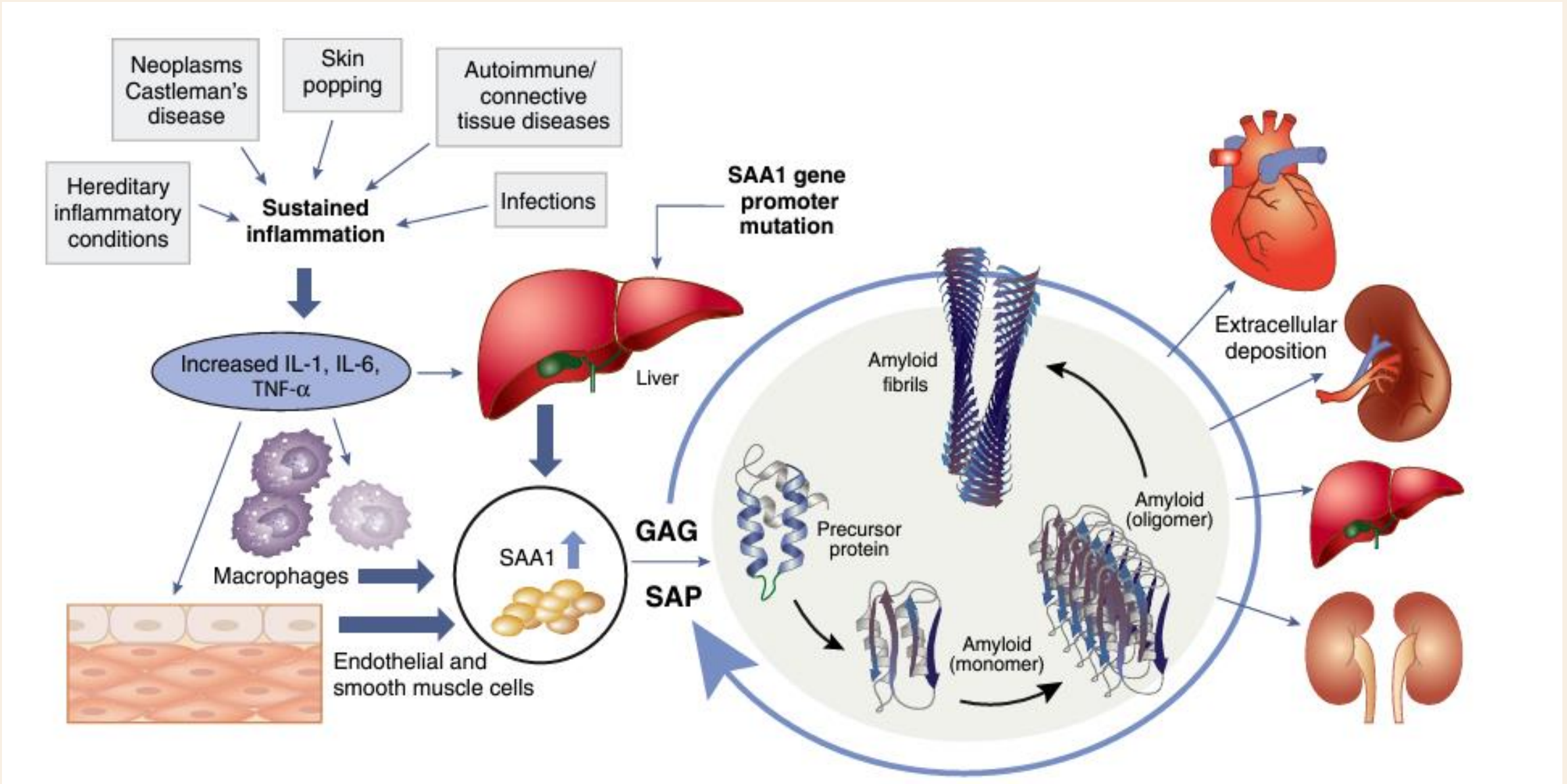
Chronic infections

- Bronchiectasis
- Chronic cutaneous ulcers
- Chronic pyelonephritis
- Chronic osteomyelitis
- Subacute bacterial endocarditis
- Leprosy
- Tuberculosis
- Whipple's disease
- Chronic brucellosis
- HIV 1/2 infection
- Brucellosis

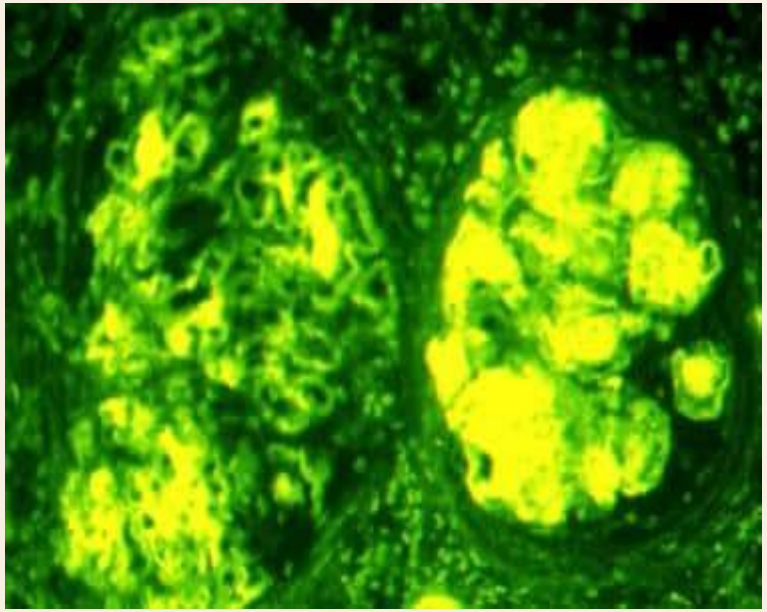
Other

- IV and subcutaneous drug misuse
- Cystic fibrosis
- Hidradenitis suppurativa
- Kartagener's syndrome
- Epidermolysis bullosa
- Hypogammaglobulinemia
- Cyclic neutropenia
- Common variable immunodeficiency
- Hyperimmunoglobulin M syndrome
- SAPHO syndrome
- Obesity
- IgG4-related disease
- Sickle cell disease
- Fabry disease

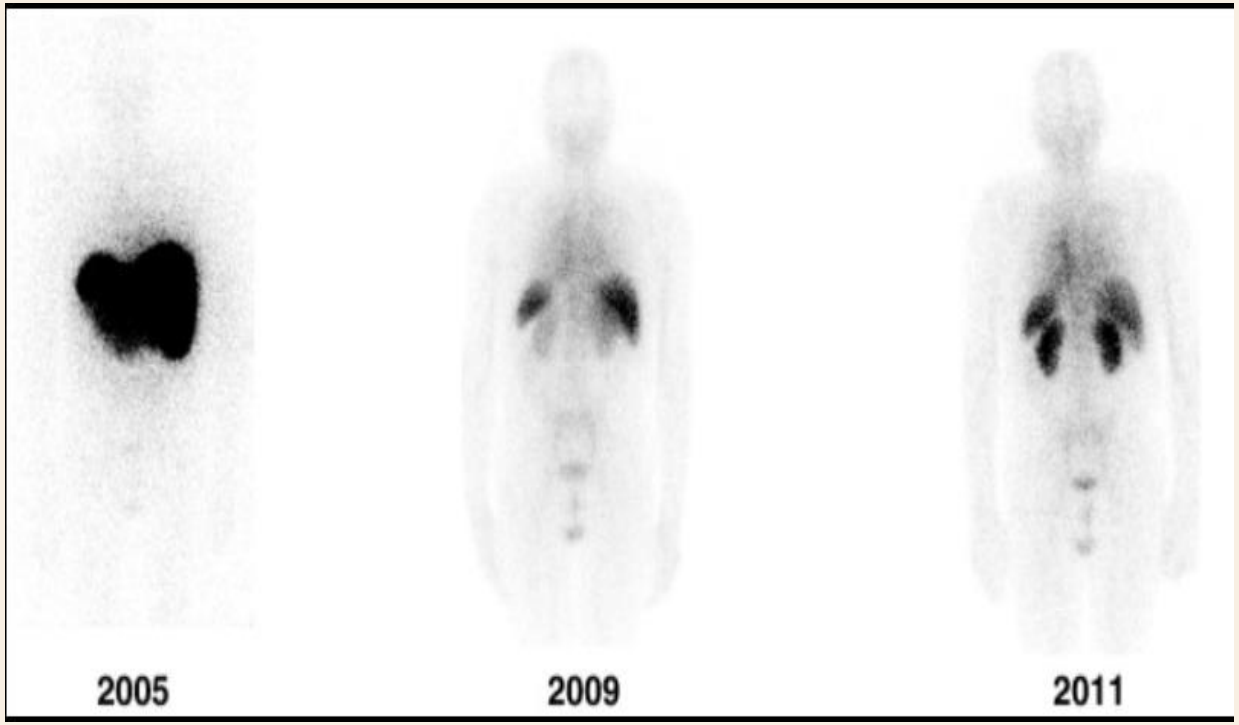
Pathogenesis of amyloid A (AA) amyloidosis



Diagnosis of AA Amyloidosis



- Positive immunohistochemical staining of amyloid deposits with monospecific anti-AA protein antiserum is highly specific for AA amyloidosis when performed in expert centers.
- Serum amyloid P component (SAP) scintigraphy is a radiolabeled variant of the SAP found in all method of measuring the extent of amyloid involvement by using a amyloid deposits.
- This test is more accurate in secondary amyloidosis and may be positive even when tissue biopsy has been negative.



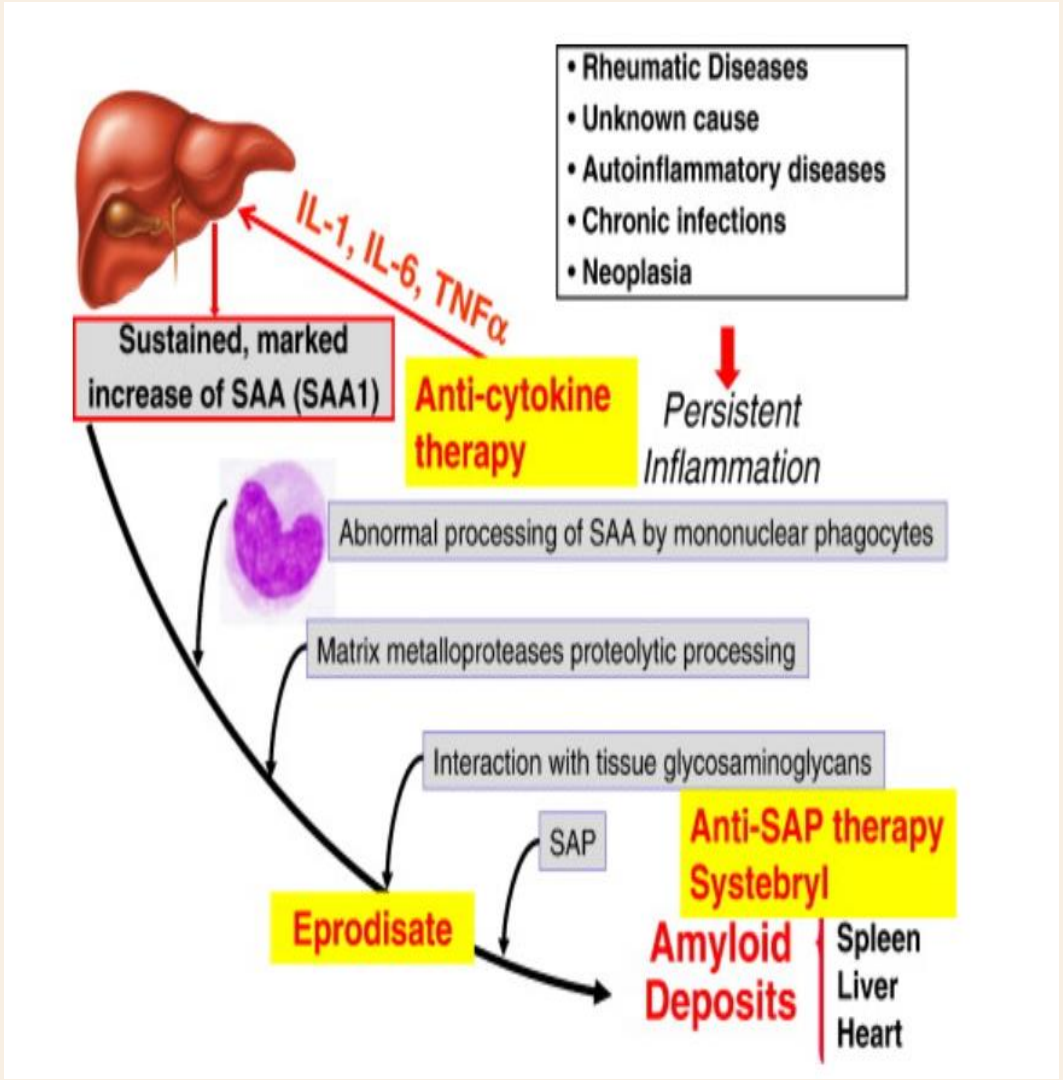
Goals in treatment

- Improvement In Renal Function
- Reduction In Protein Excretion
- Partial Resolution Of Amyloid Deposits.

The preferred therapy of AA amyloid is control of the underlying inflammatory disease

Treatment of AA (secondary) Amyloidosis

- Colchicine
- Anti TNF: Etanercept, Infliximab, Adalimumab, certolizumab pegol and Golimumab
- IL-1 receptor antagonist (IL-1ra): Anakinra (short acting) and Canakinumab (long acting)
- Anti-IL-6 receptor antibody: Tocilizumab, Tofacitinib
- Binding to cofactors and peptidic inhibitors: Eprodisate
- Clearance of amyloid deposits from tissue : bis (proline) compound (CPHPC), Monoclonal anti-AA antibodies



Conclusion

- Reduction of the SAA protein is presently the most effective treatment strategy for AA amyloidosis.
- This is often achieved using IL-1, IL-6, and TNF-a inhibitors as opposed to traditional therapies, such as colchicine used for FMF.
- Clinical trials are needed to identify the most appropriate agent.

TRANSTYRINE

- Multiple variants have been identified among patients with TTR amyloidosis.
- The gene for transthyretin (TTR or prealbumin), a protein involved in the transport of thyroxine and retinol (hence, TTR), is located on chromosome 18. Until now, at least 138 TTR variants have been described.
- Phenotypes: Peripheral and autonomic neuropathy and central nervous system disease, Cardiomyopathy, Vitreous amyloid
- Kidney disease may complicate other organ system involvement or be due to deposition of TTR amyloid in the kidney. The latter has been reported for 15 different TTR variants.

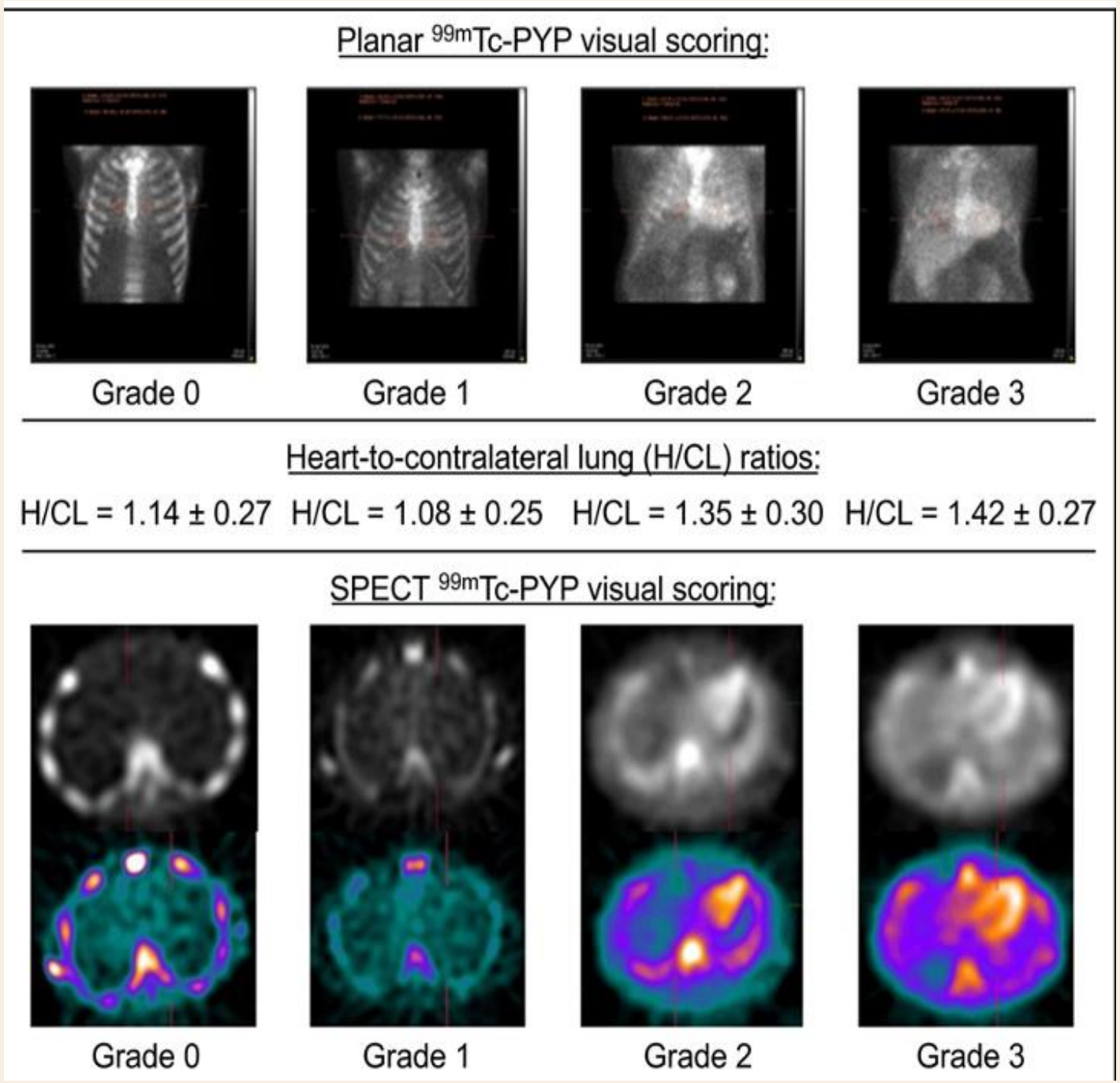
- Transthyretin amyloid cardiomyopathy is a late onset disease; symptoms are predominately manifested in male patients 60 years of age or older.
- The condition can be inherited as an AD caused by pathogenic mutations in the transthyretin gene TTR (ATTRm) or by the deposition of wild-type transthyretin protein (ATTRwt), previously called senile systemic amyloidosis.
- Ongoing ATTR amyloid deposition in the heart drives the progression of infiltrative cardiomyopathy, leading to worsening heart failure, arrhythmias, and conduction disease.
- Median survival in cardiac involvement is 2-6 years and 4-17 years for polyneuropathy.

Cardiac amyloidosis: Three radiotracers have been used in cardiac amyloidosis Imaging and staging

1-^{99m} Tc-3,3-diphosphono-1,2-propanodicarboxylic acid

2-^{99m} Tc-pyrophosphate

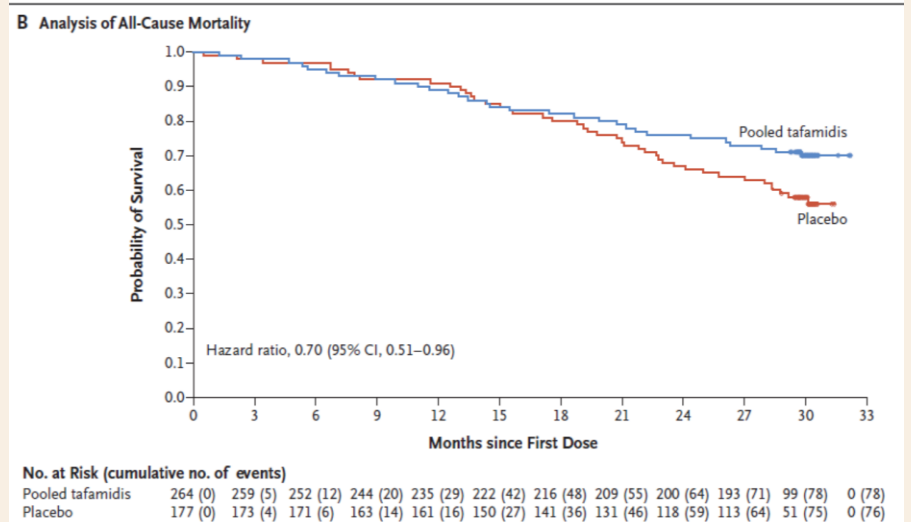
3-^{99m} Tc-hydroxymethylene diphosphonate

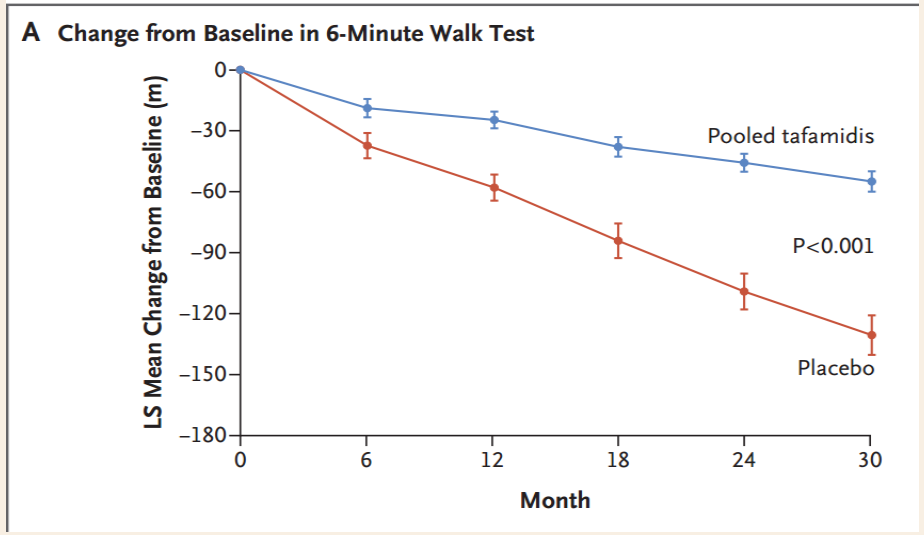


Scott Jerome et al, JOURNAL OF NUCLEAR MEDICINE TECHNOLOGY, 2023

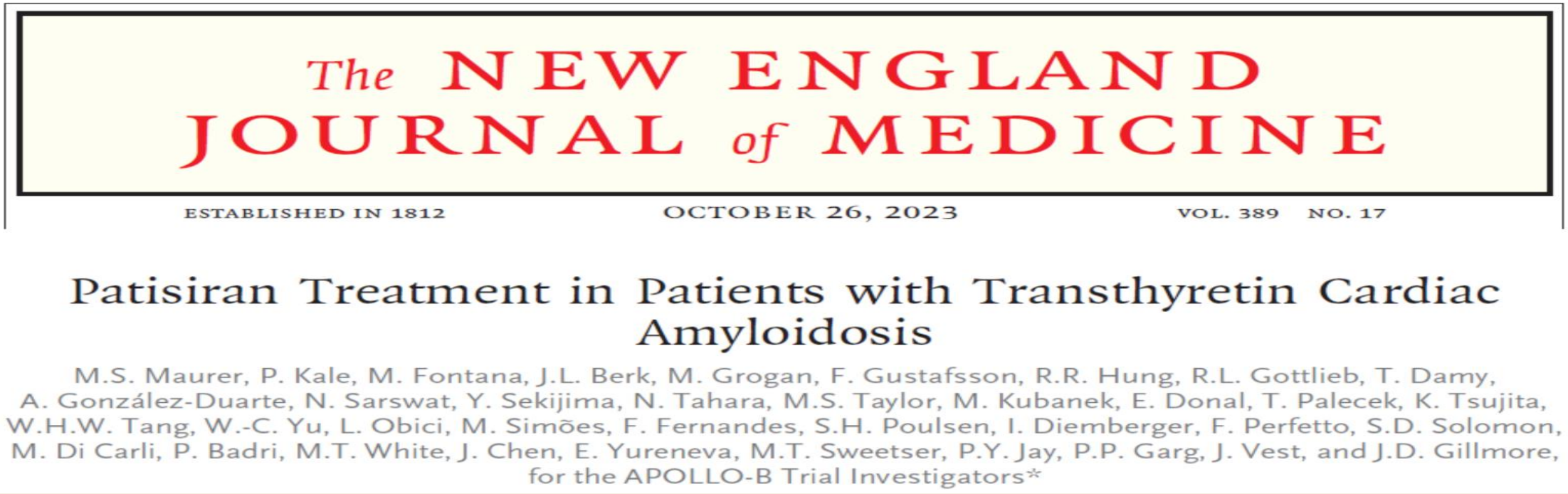
Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

- Tafamidis binds to transthyretin, preventing tetramer dissociation and stabilize protein which causes amyloidogenesis.
- In 441 patients, multicenter, international, double-blind, placebo-controlled, phase 3 trial, 2:1:2, 80 mg of tafamidis, 20 mg of tafamidis, or placebo for 30 months.
- Patients with heart failure due to transthyretin amyloid cardiomyopathy, treatment with tafamidis reduced all-cause mortality and cardiovascular-related hospitalizations as compared with placebo.





Maurer et al., NEJM 2018



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 26, 2023 VOL. 389 NO. 17

Patisiran Treatment in Patients with Transthyretin Cardiac Amyloidosis

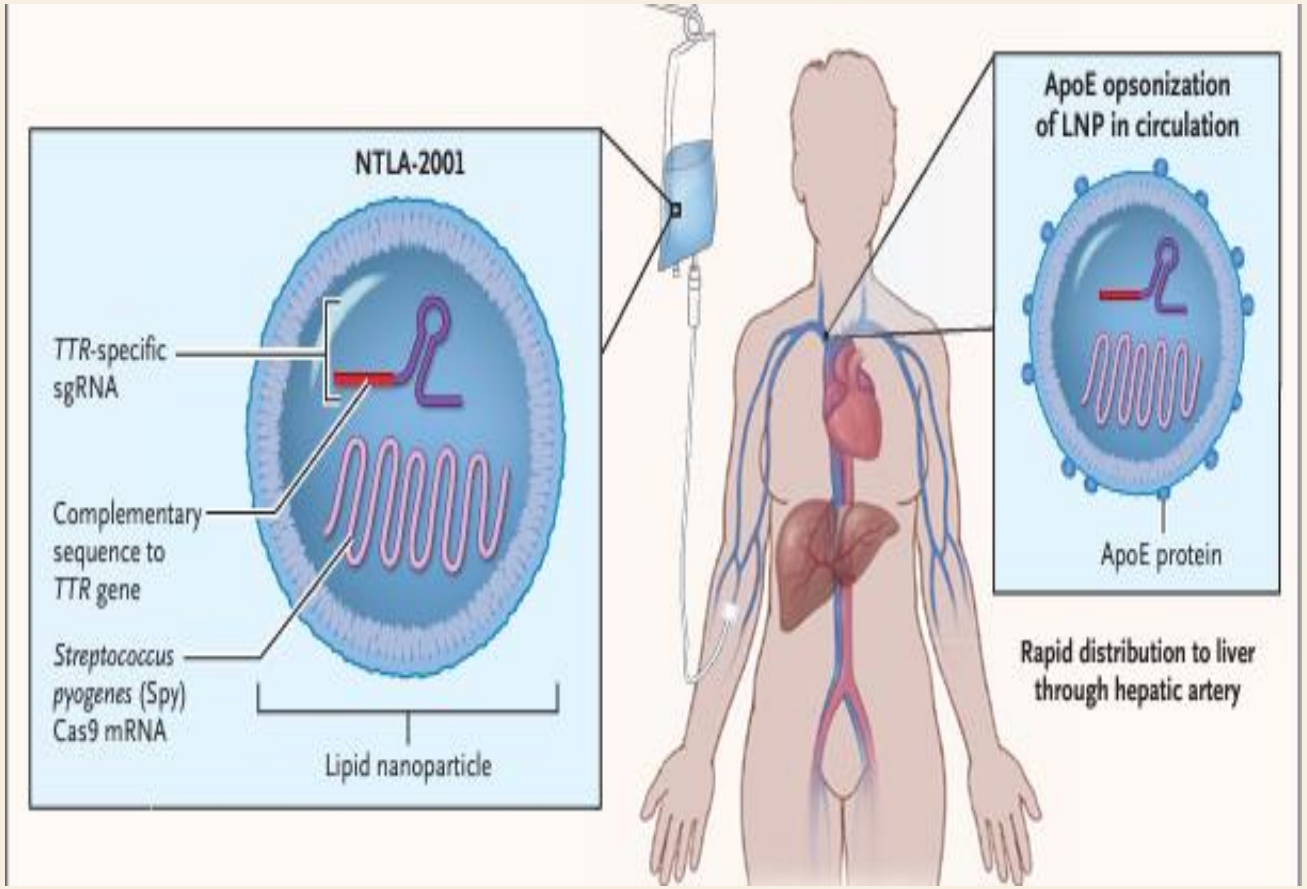
M.S. Maurer, P. Kale, M. Fontana, J.L. Berk, M. Grogan, F. Gustafsson, R.R. Hung, R.L. Gottlieb, T. Damy, A. González-Duarte, N. Sarswat, Y. Sekijima, N. Tahara, M.S. Taylor, M. Kubanek, E. Donal, T. Palecek, K. Tsujita, W.H.W. Tang, W.-C. Yu, L. Obici, M. Simões, F. Fernandes, S.H. Poulsen, I. Diemberger, F. Perfetto, S.D. Solomon, M. Di Carli, P. Badri, M.T. White, J. Chen, E. Yureneva, M.T. Sweetser, P.Y. Jay, P.P. Garg, J. Vest, and J.D. Gillmore, for the APOLLO-B Trial Investigators*

- RNA interference which inhibits production of Transthyretin in liver.
- In 1:1, RCT, double blind , 0.3 mg/kg every three months for 12 months.
- This drug preserved cardiac function, quality of life and health status in patients with transthyretin cardiac amyloidosis.

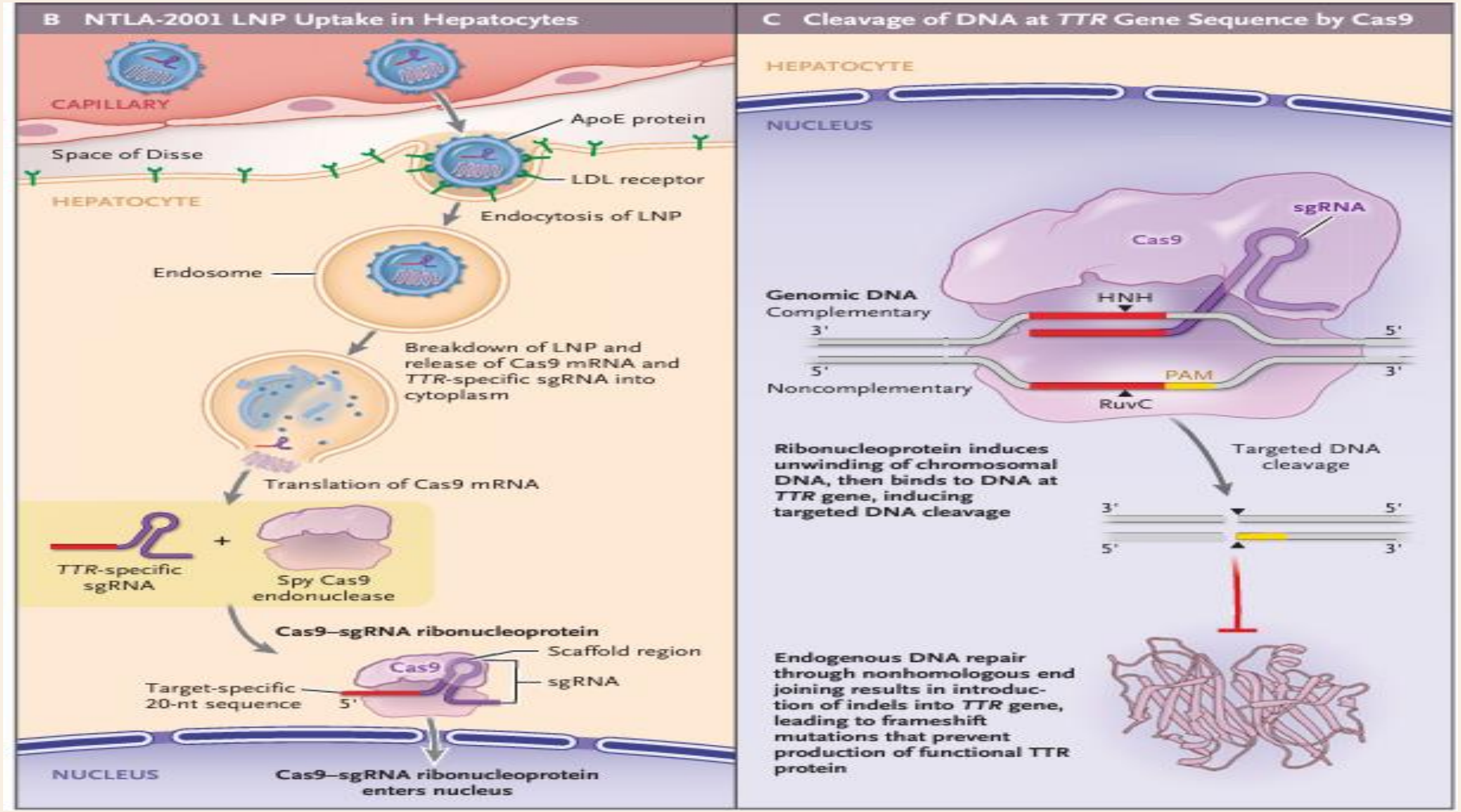
CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

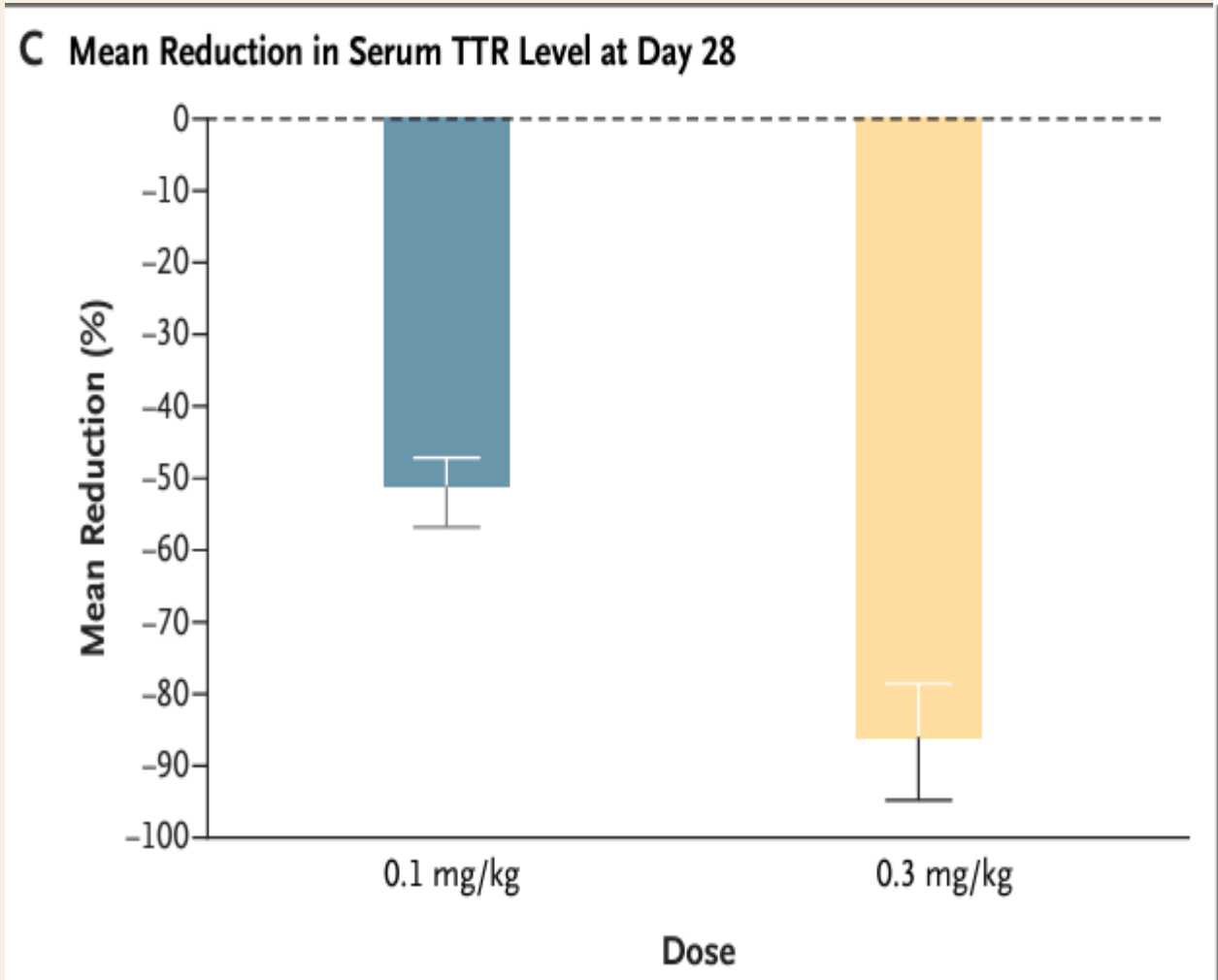
Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., Ph.D., Adam Amaral, B.A., Adam P. Boyd, Ph.D., Jeffrey E. Cehelsky, M.B.A., Mark D. McKee, M.D., Andrew Schiermeier, Ph.D., Olivier Harari, M.B., B.Chir., Ph.D., Andrew Murphy, Ph.D., Christos A. Kyratsous, Ph.D., Brian Zambrowicz, Ph.D., Randy Soltys, Ph.D., David E. Gutstein, M.D., John Leonard, M.D., Laura Sepp-Lorenzino, Ph.D., and David Lebwohl, M.D.

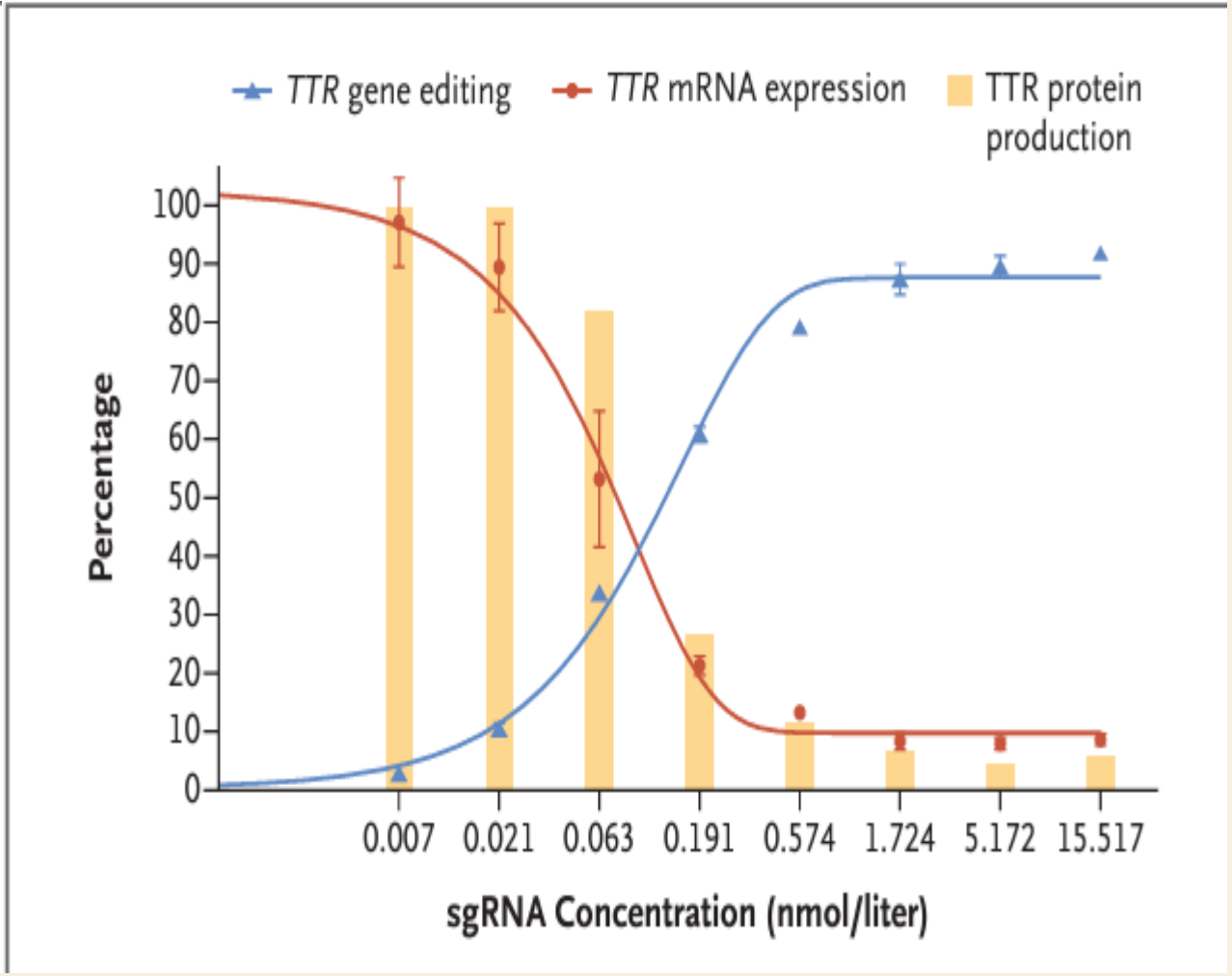
- NTLA-2001 is a new CRISPR-Cas9–based in vivo gene-editing therapy, administered by intravenous infusion, that is intended to edit TTR in hepatocytes, leading to a decrease in the production of both wild-type and mutant TTR after a single administration.
- NTLA-2001 consists of a proprietary lipid nanoparticle (LNP) delivery system with liver tropism, carrying a single guide RNA (sgRNA) that targets human TTR and a human-codon optimized



NEJM, 5 August 2021


B NTLA-2001 LNP Uptake in Hepatocytes
CAPILLARY
ApoE protein
Space of Disse
LDL receptor
HEPATOCYTE
Endocytosis of LNP
Endosome
Breakdown of LNP and release of Cas9 mRNA and TTR-specific sgRNA into cytoplasm
Translation of Cas9 mRNA
TTR-specific sgRNA
+
Spy Cas9 endonuclease
Cas9–sgRNA ribonucleoprotein
Scaffold region
Cas9
sgRNA
Target-specific 20-nt sequence
5'
NUCLEUS
Cas9–sgRNA ribonucleoprotein enters nucleus
C Cleavage of DNA at TTR Gene Sequence by Cas9
HEPATOCYTE
NUCLEUS
sgRNA
Cas9
HNH
Genomic DNA
Complementary
3'
5'
5'
3'
Noncomplementary
PAM
RuvC
Ribonucleoprotein induces unwinding of chromosomal DNA, then binds to DNA at TTR gene, inducing targeted DNA cleavage
Targeted DNA cleavage
3'
5'
5'
3'
Endogenous DNA repair through nonhomologous end joining results in introduction of indels into TTR gene, leading to frameshift mutations that prevent production of functional TTR protein





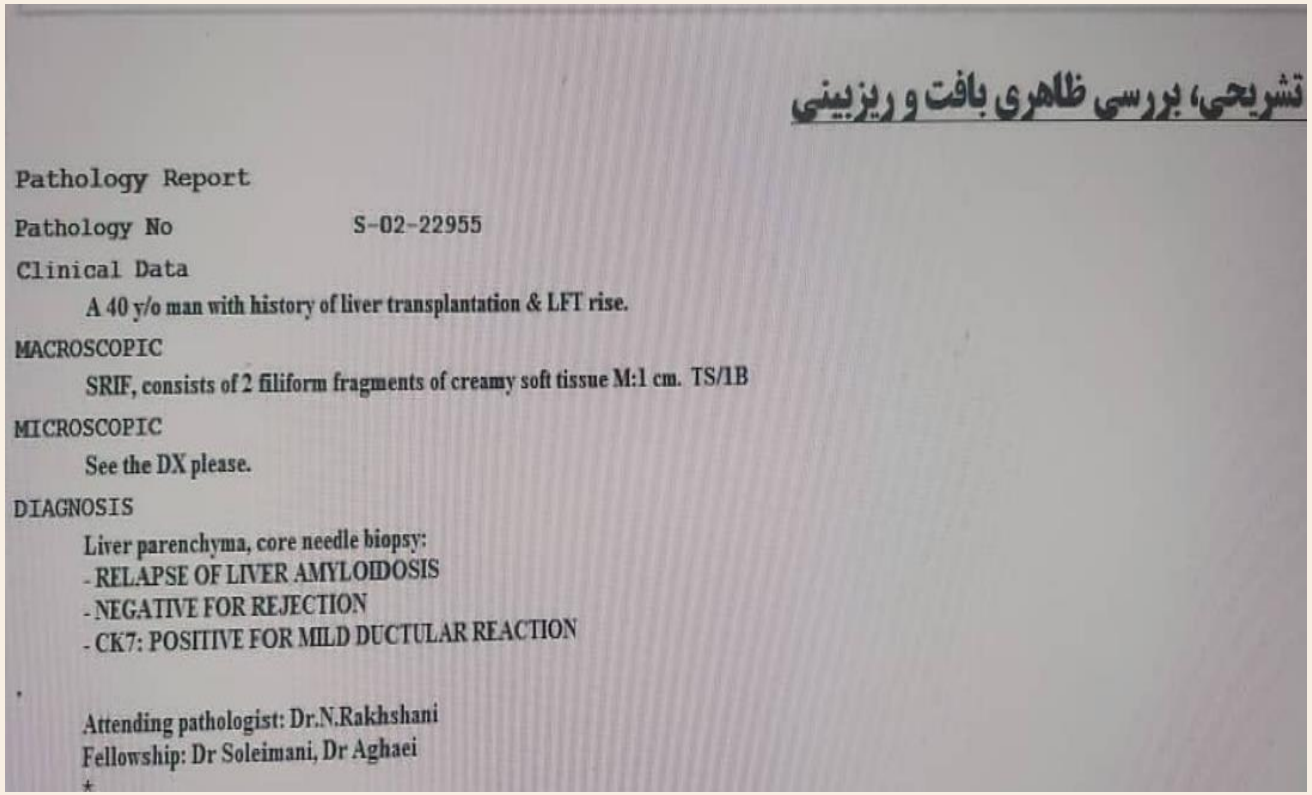
The CRISPR-Cas9 approach used for NTLA-2001 is modular and has the capacity to be adapted to treat other diseases with simple replacement of the sgRNA.

Data from the initial groups of 6 patients in this study provide clinical proof of concept for in vivo CRISPR-Cas9–mediated gene editing as a therapeutic strategy.

ALECT2 amyloidosis

- Leukocyte cell-derived chemotaxin 2 (ALECT2)-associated amyloidosis is a systemic form of amyloidosis with predominantly kidney and liver involvement.
- In one study of renal amyloidosis among Egyptians, ALECT2 amyloidosis was the second most common form of renal amyloidosis behind AA and ahead of AL amyloidosis.
- ALECT2 amyloidosis have better overall survival than those with AL or AA amyloidosis, possibly due to the absence or rare occurrence of cardiac involvement.
- Presentation: subnephrotic proteinuria, CKD and rare cardiac involvement.
- kidney survival is relatively poor, with up to 39 percent of patients progressing to ESKD.
- No specific therapies for ALECT2 amyloidosis.

- 98/6 liver and kidney transplant
- Last visit: No proteinuria, stable serum Creatinine around 1.5- 1.7 mg /dl, Increased liver enzymes (2 fold)



تشریحی، بررسی ظاهری بافت و ریزبینی

Pathology Report

Pathology No S-02-22955

Clinical Data

A 40 y/o man with history of liver transplantation & LFT rise.

MACROSCOPIC

SRIF, consists of 2 filiform fragments of creamy soft tissue M:1 cm. TS/1B

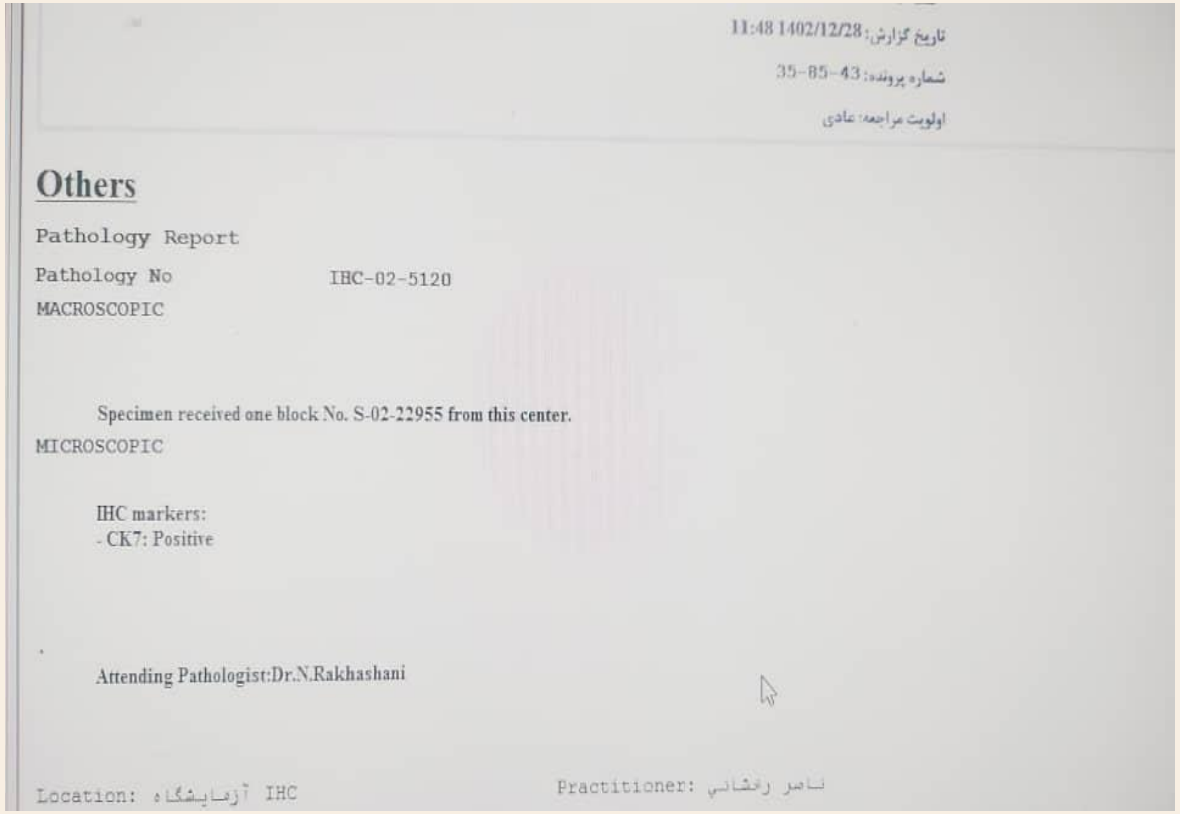
MICROSCOPIC

See the DX please.

DIAGNOSIS

Liver parenchyma, core needle biopsy:
- RELAPSE OF LIVER AMYLOIDOSIS
- NEGATIVE FOR REJECTION
- CK7: POSITIVE FOR MILD DUCTULAR REACTION

Attending pathologist: Dr.N.Rakhshani
Fellowship: Dr Soleimani, Dr Aghaei



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شماره پرونده: 43-85-35

اولویت مراجعه: عادی

Others

Pathology Report

Pathology No IHC-02-5120

MACROSCOPIC

Specimen received one block No. S-02-22955 from this center.

MICROSCOPIC

IHC markers:
- CK7: Positive

Attending Pathologist:Dr.N.Rakhashani

Location: آزمایشگاه IHC

Practitioner: ناصر رخشانی