UNIVERSITI MALAYA
KUALA LUMPUR

Renal Biopsy CPC
Singapore
11-12 August 2018

SLIDE SEMINAR
CASE 76

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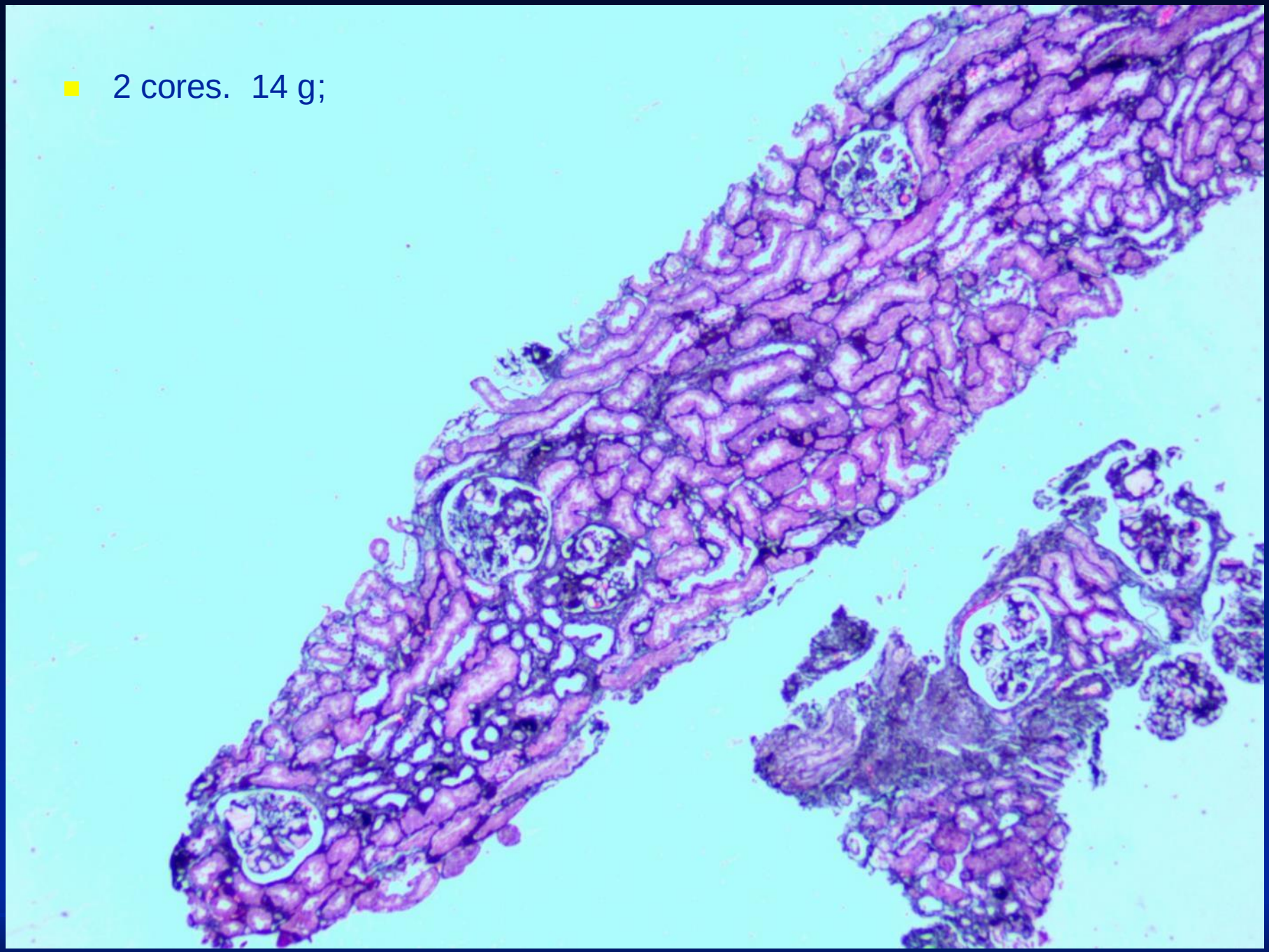
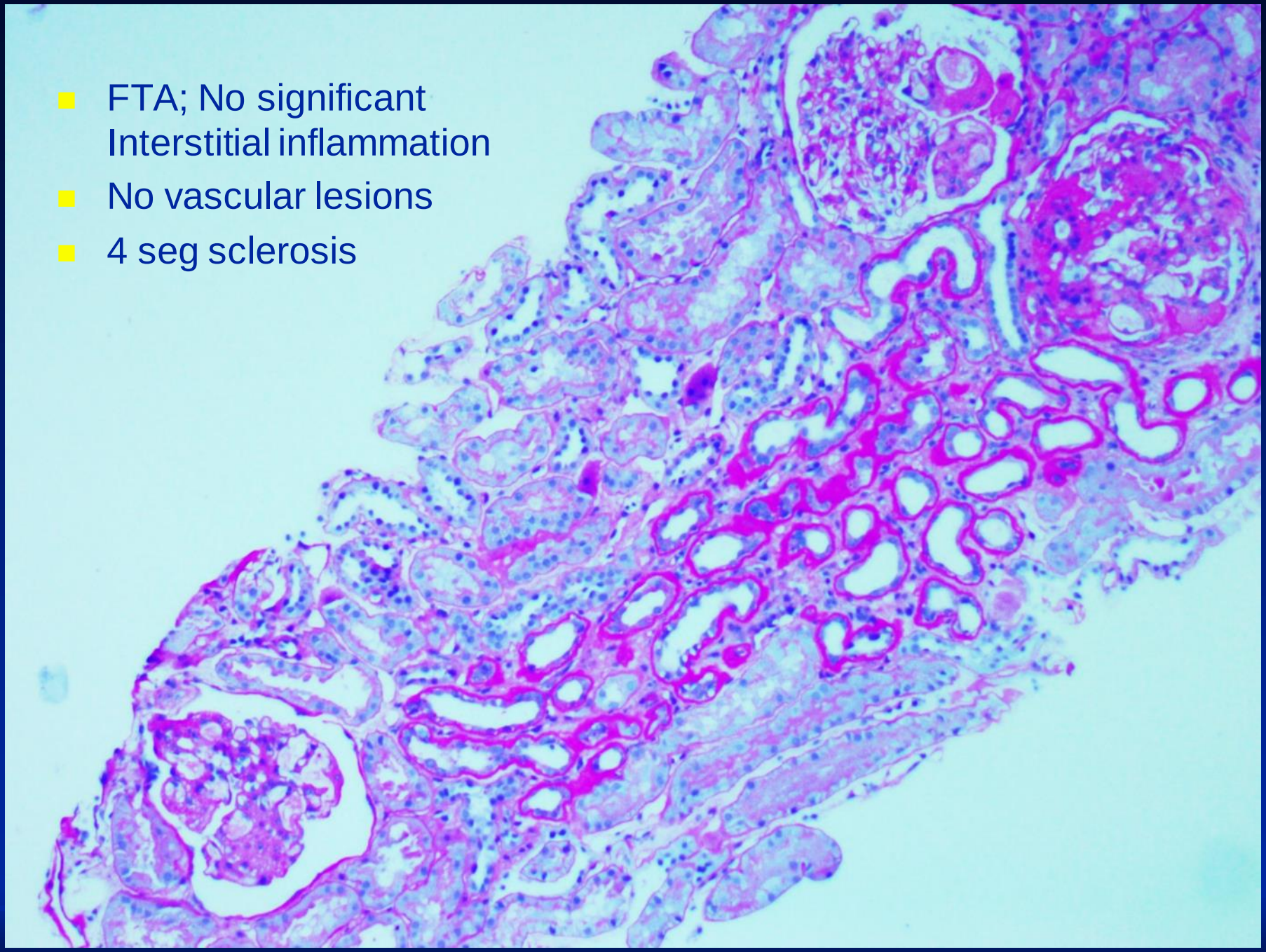
National Distinguished Professor
University of Malaya

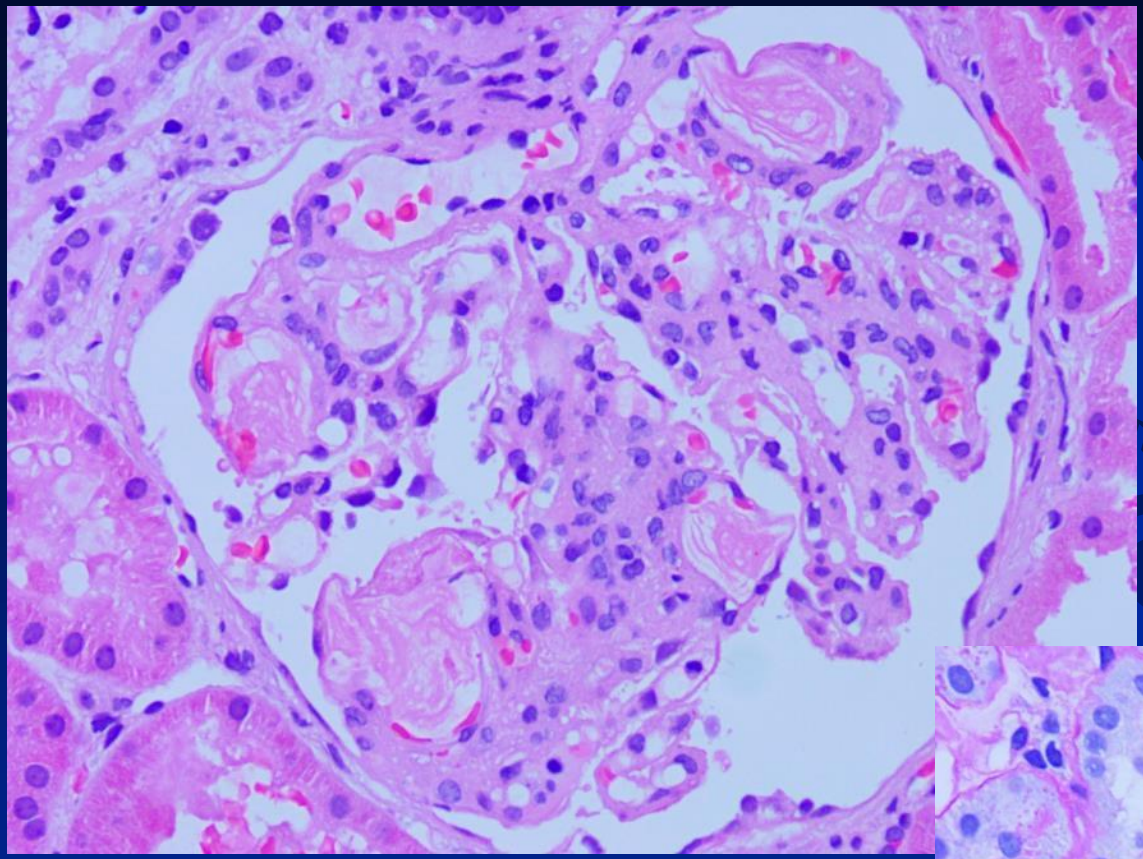
Case 1
RP, 18-year-old Indonesian male

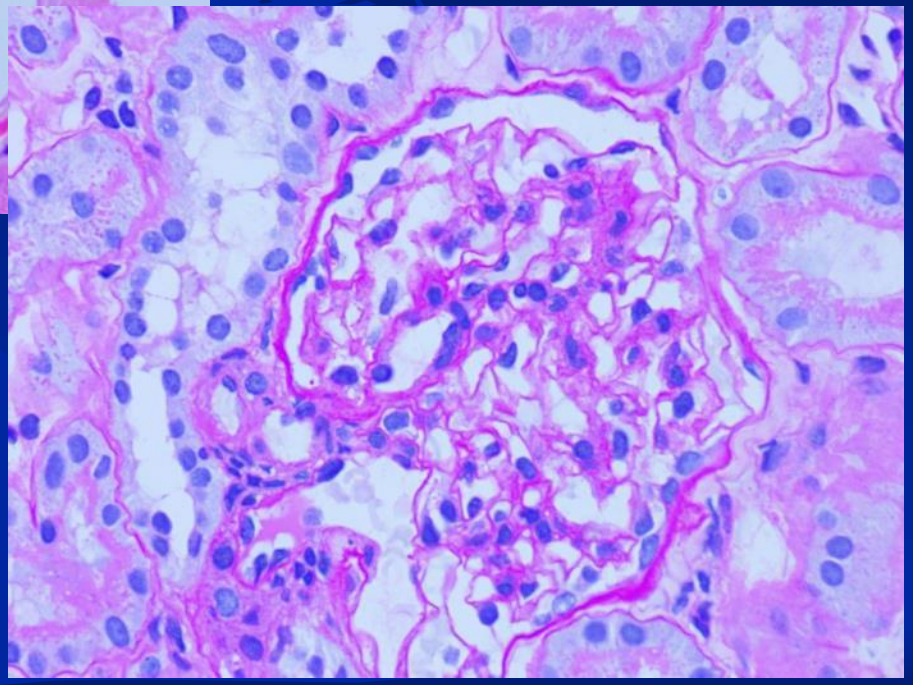
- Nephrotic syndrome developed 2 months prior to biopsy
- Hypertensive.
- Proteinuria 3994mg/24 hr. Urine RBC 32/hpf
- Total cholesterol 5.5 mmol/L (H). HDL 1 (L), LDL 3.2 (H), TG 2.8 (H)
- S alb 33 g/L (sl Low), A/G ratio: 1.9 (N)
- Normal renal function. Creat 71umol/L. eGFR: 131.8 (N)
- ?IgA nephropathy

- 2 cores. 14 g;



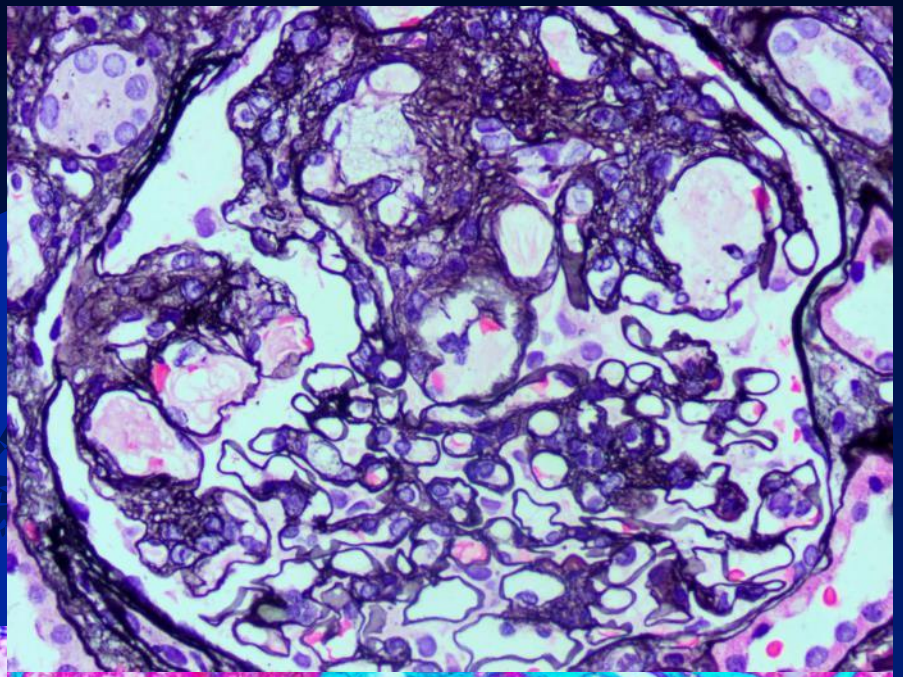

FTA; No significant Interstitial inflammation
No vascular lesions
4 seg sclerosis

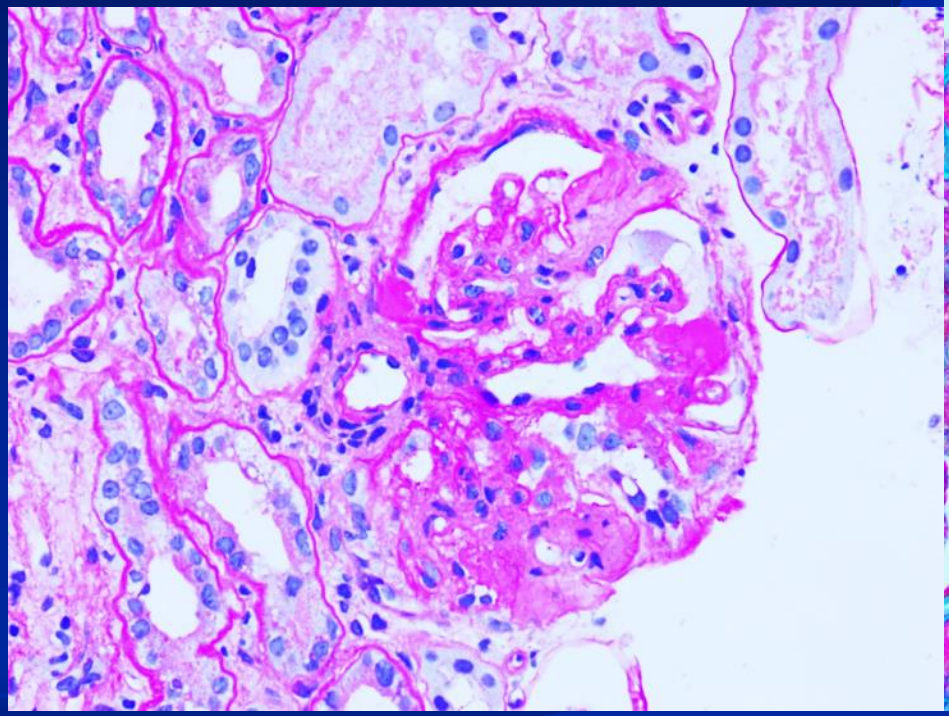


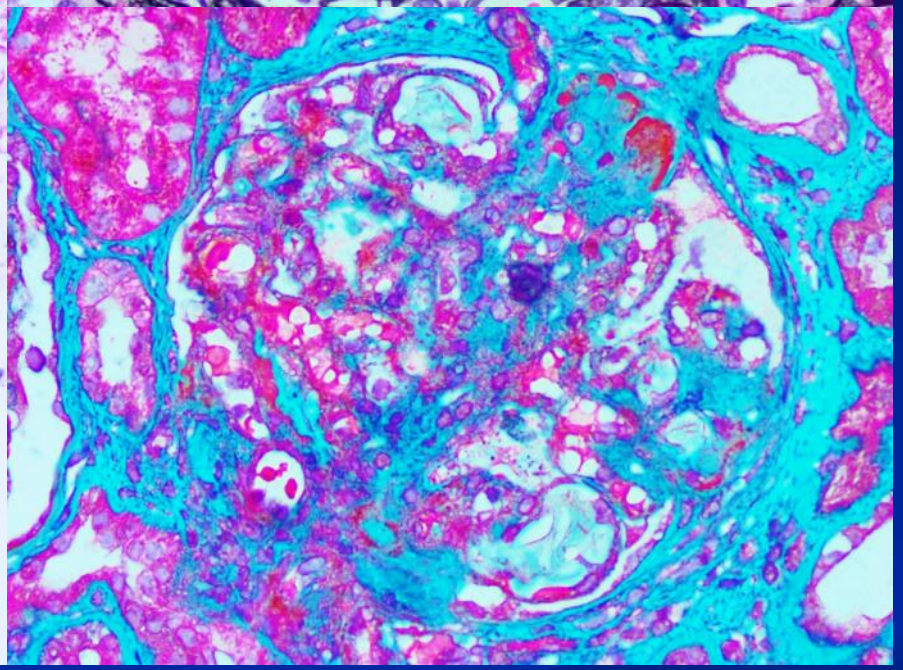


Increase in mesangial matrix and cellularity

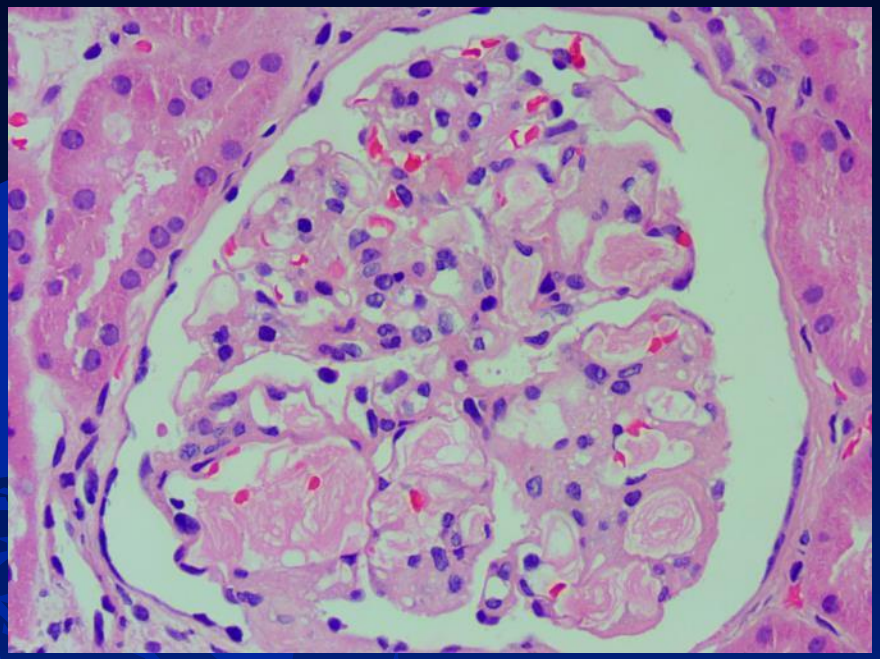
Segmental lesions

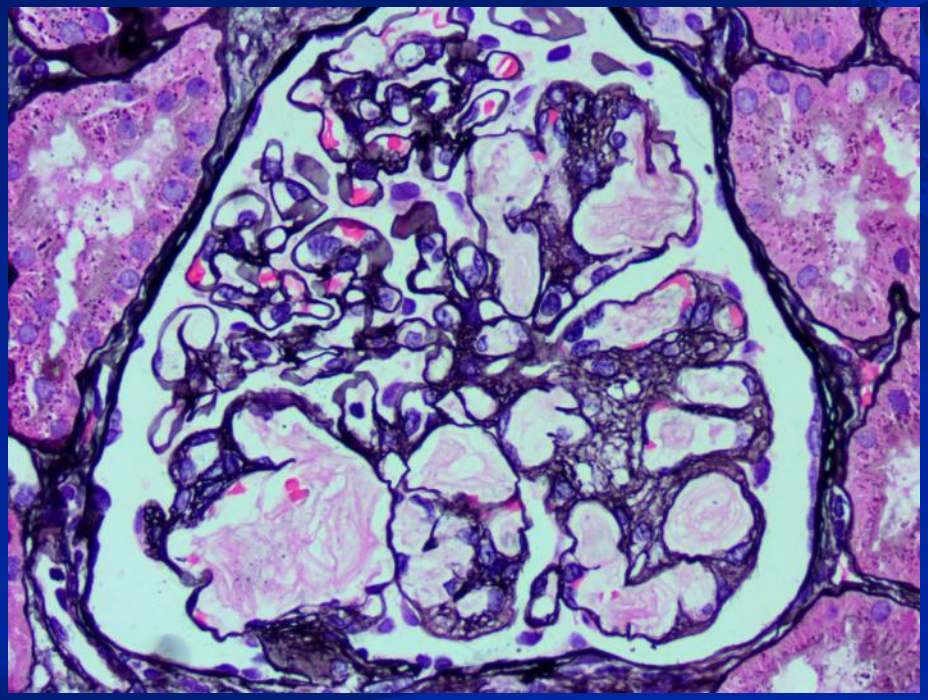


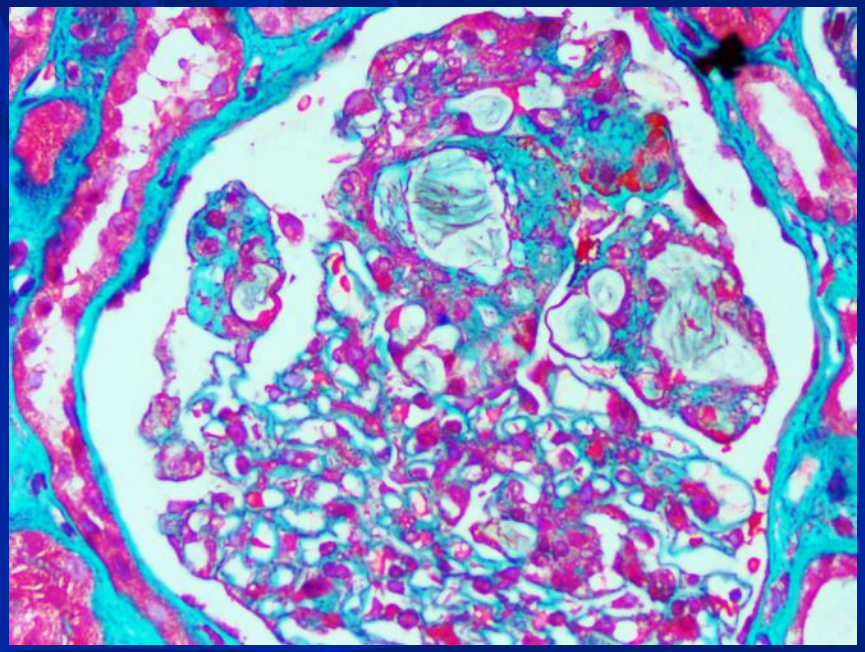


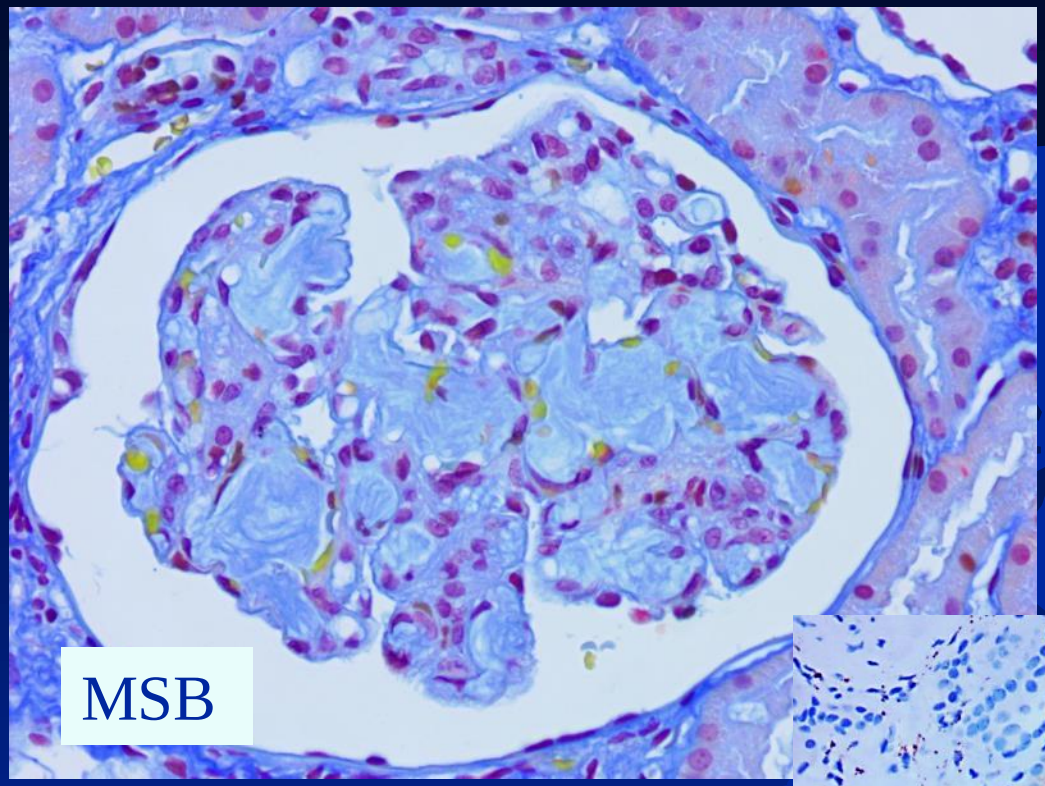


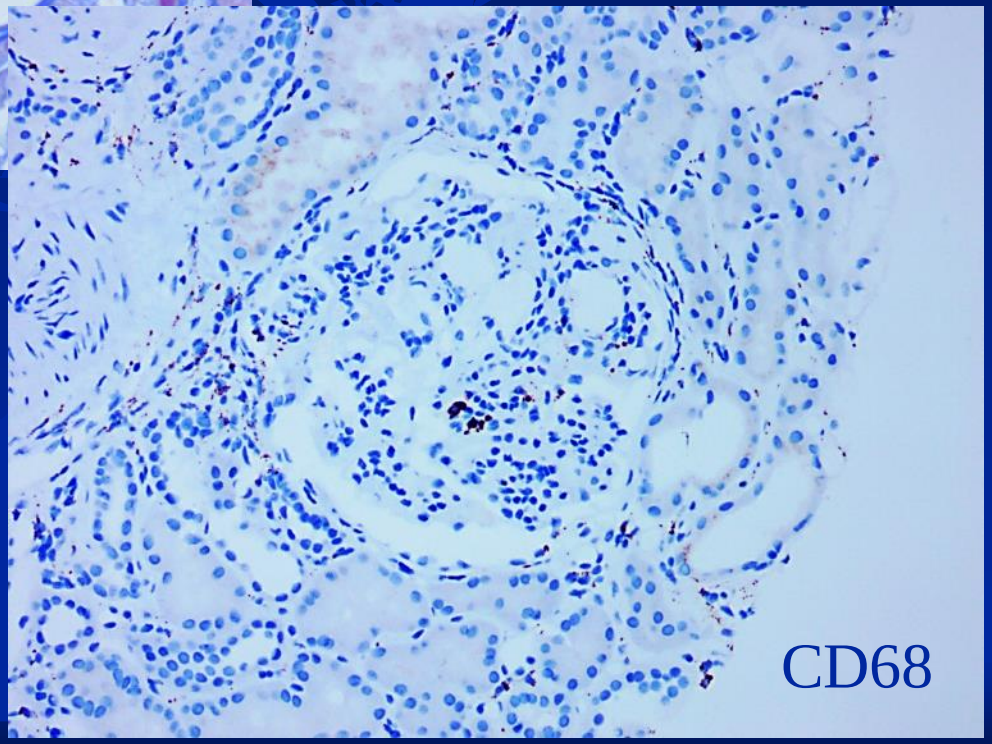
Intracapillary deposits

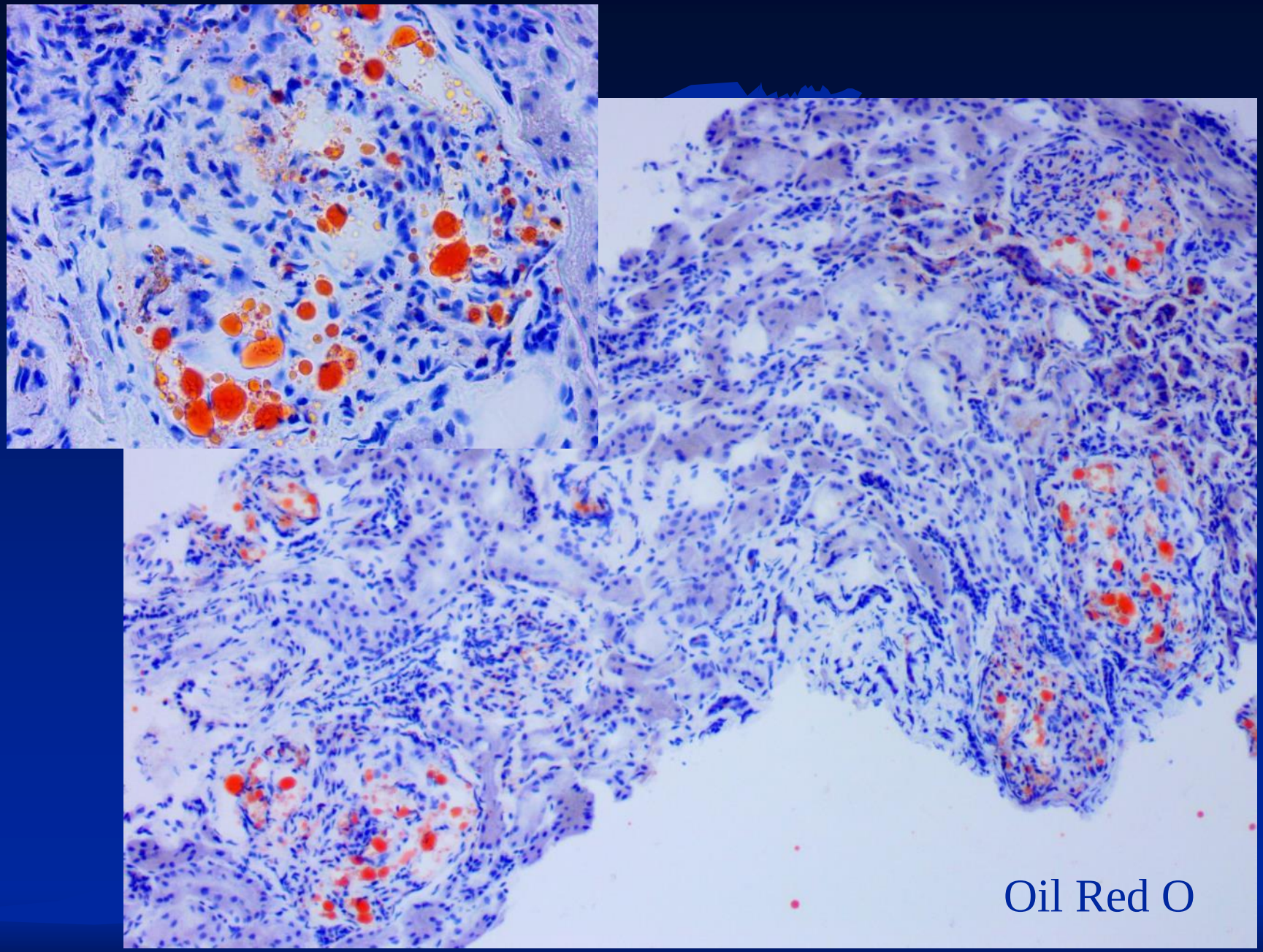






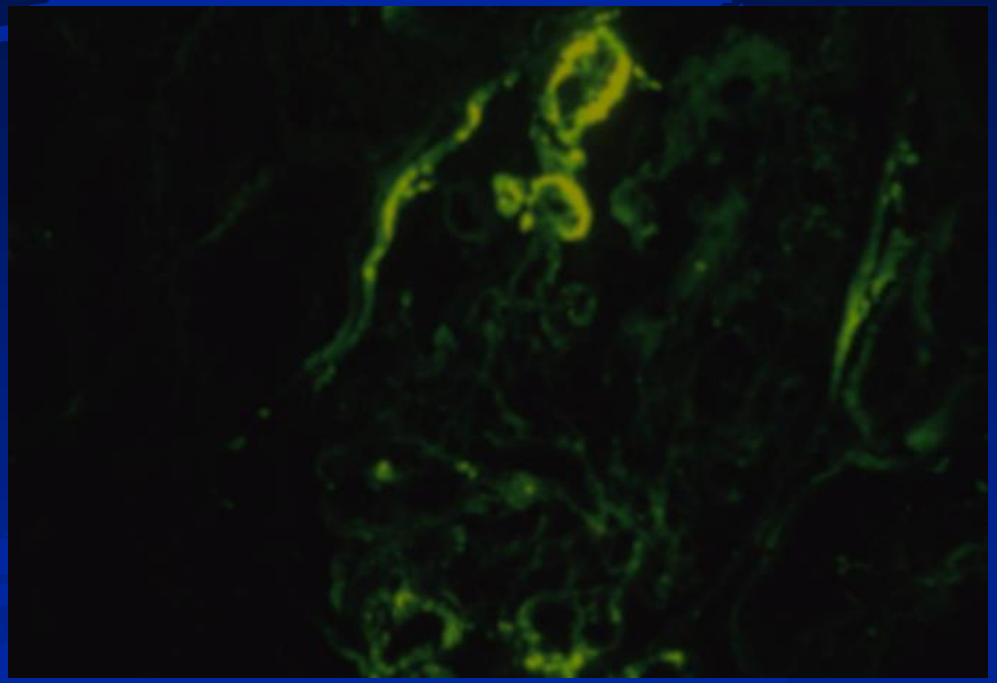

MSB


CD68


Oil Red O

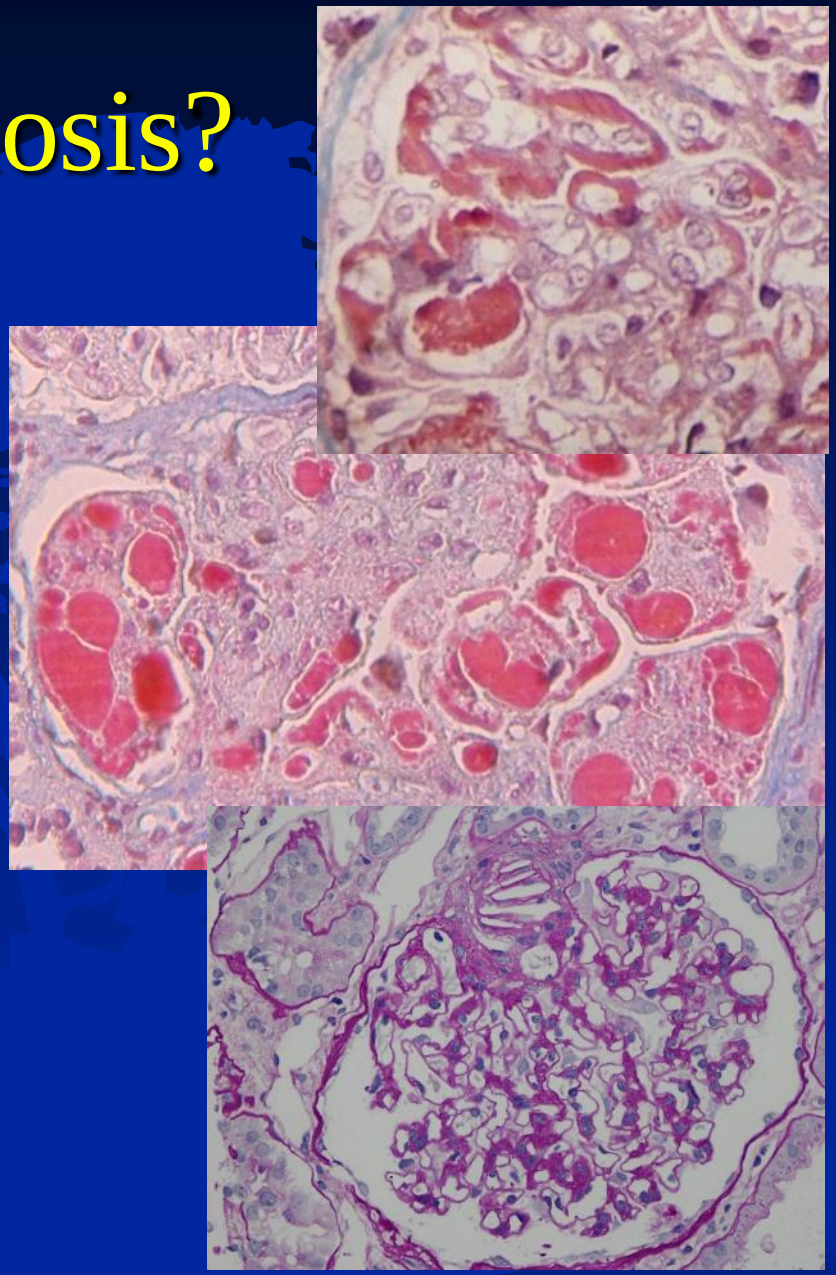
Immunofluorescence

- Non-specific globular C1q



Differential diagnosis?

- Lupus nephritis
- DIC
- Cholesterol embolism
- Fat embolism
- Hereditary renal lipidosis (Fabry, Gaucher, Nieman-Pick etc)



Lecithin–cholesterol acyltransferase (LCAT) deficiency?

- LCAT deficiency is caused by loss-of-function mutations in both alleles of the *LCAT* gene
- Impaired esterification of free cholesterol in the plasma, leading to accumulation of phospholipids, including lecithin, in the organs of the body
- Clinical features: corneal opacities ("fish eye"), normochromic anaemia, premature atherosclerosis, low HDL and α-lipoprotein levels, and elevated LDL
- Glomeruli reveal foam cells, and thickening of capillary walls with bubbly, vacuolated or honeycomb appearance, some double-contour

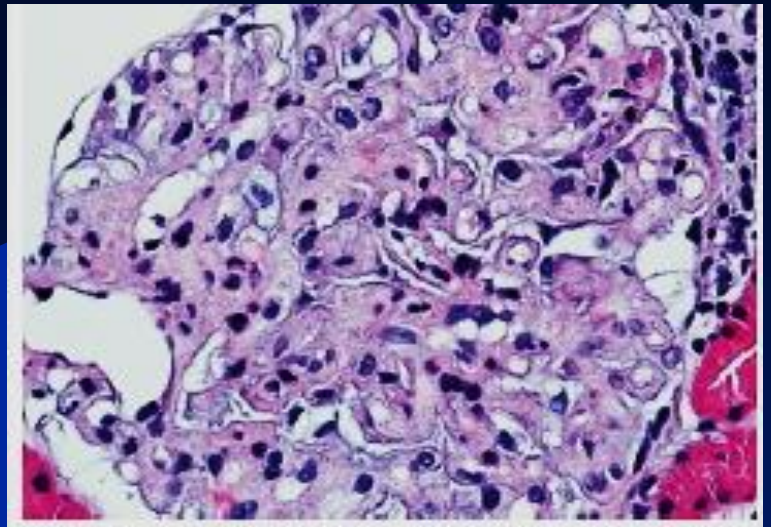
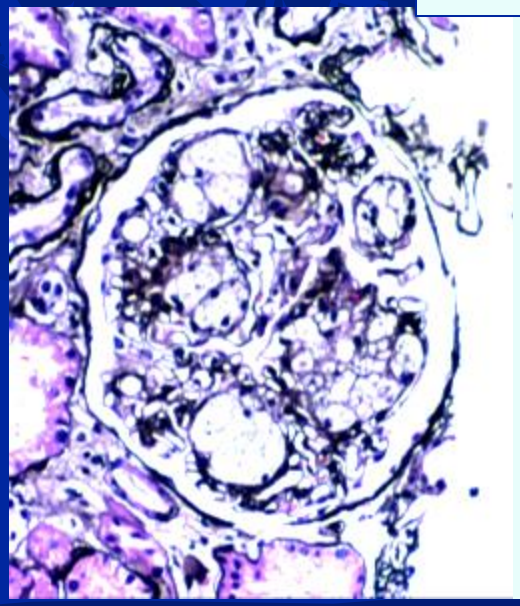


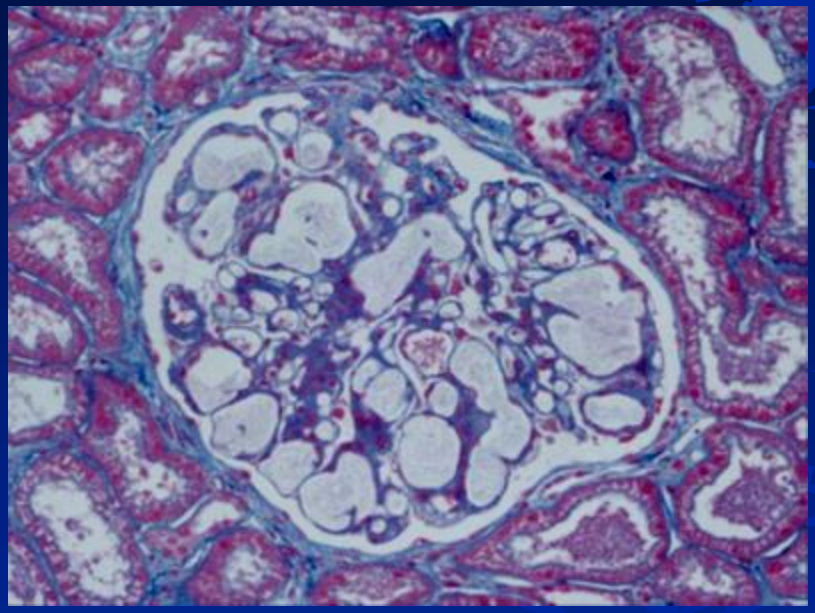
Figura 2b – Glomerulus with vacuolated mesangial matrix and thickened capillary walls; the GBM has a "bubbly" aspect and, in some of the capillary loops, exhibits a double contour appearance (light microscopy, haematoxylin and eosin stain; 400x).

Source: AJKD Atlas of Renal Pathology 2017.



The markedly expanded capillary loops filled with foam cells are evident in this case of LCAT deficiency.
Source: AJKD Atlas of Renal Pathology 2001. Agnes Fogo

Lipoprotein glomerulopathy?



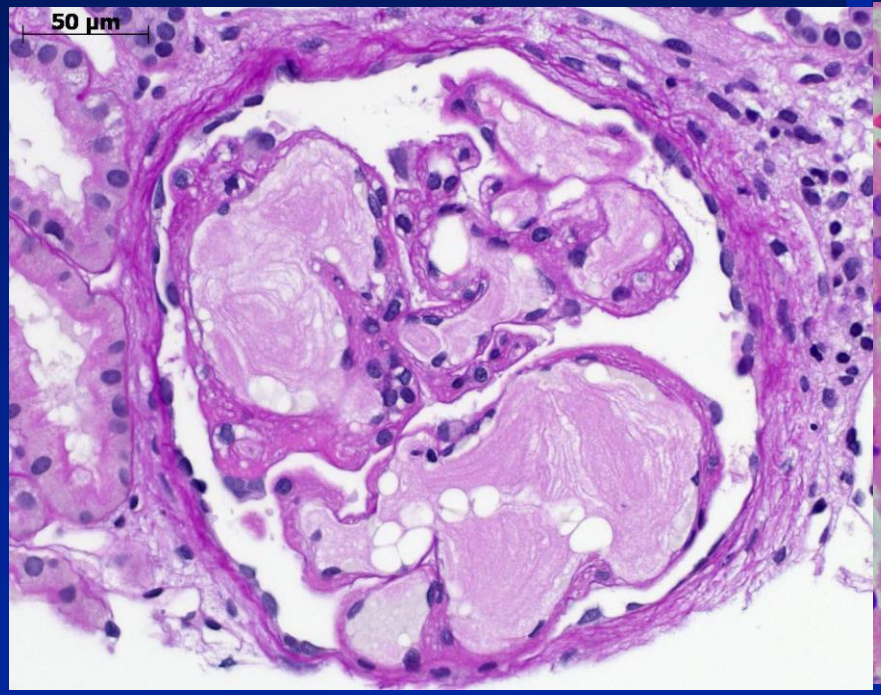
Glomerulus with lipoprotein thrombi. Capillary lumina are enlarged with pale-stained and mesh-like substances (Azan-Mallory stain, 3300).

Kidney International, Vol. 55, Suppl. 71 (1999), pp. S-37–S-41

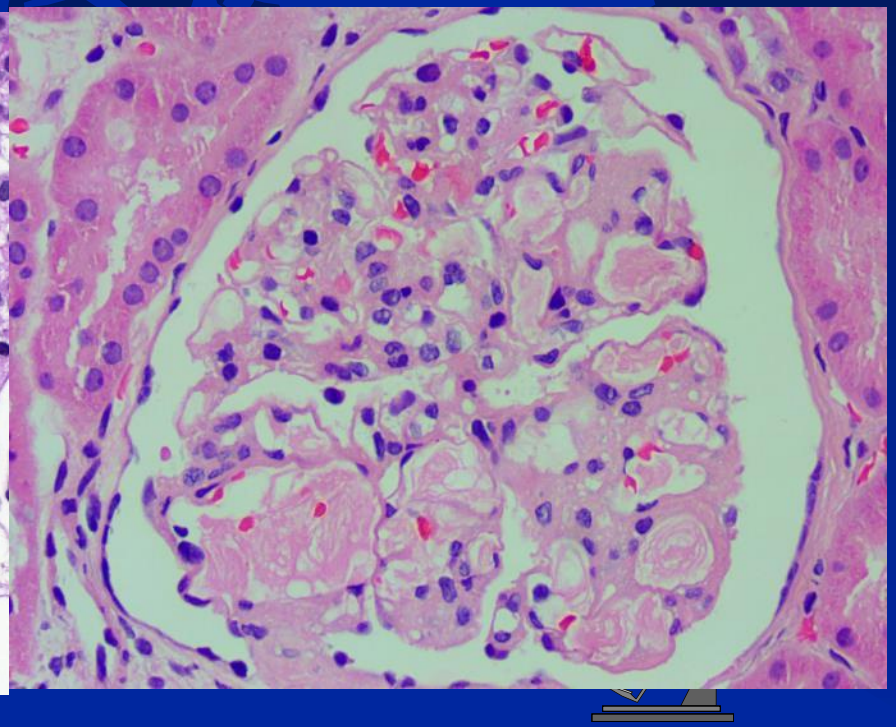
- Ballooning of glomerular capillaries with "lipoprotein thrombi"
- Pale, laminated
- Oil red O positive
- Variable mesangial proliferation
- Progressive glomerulosclerosis

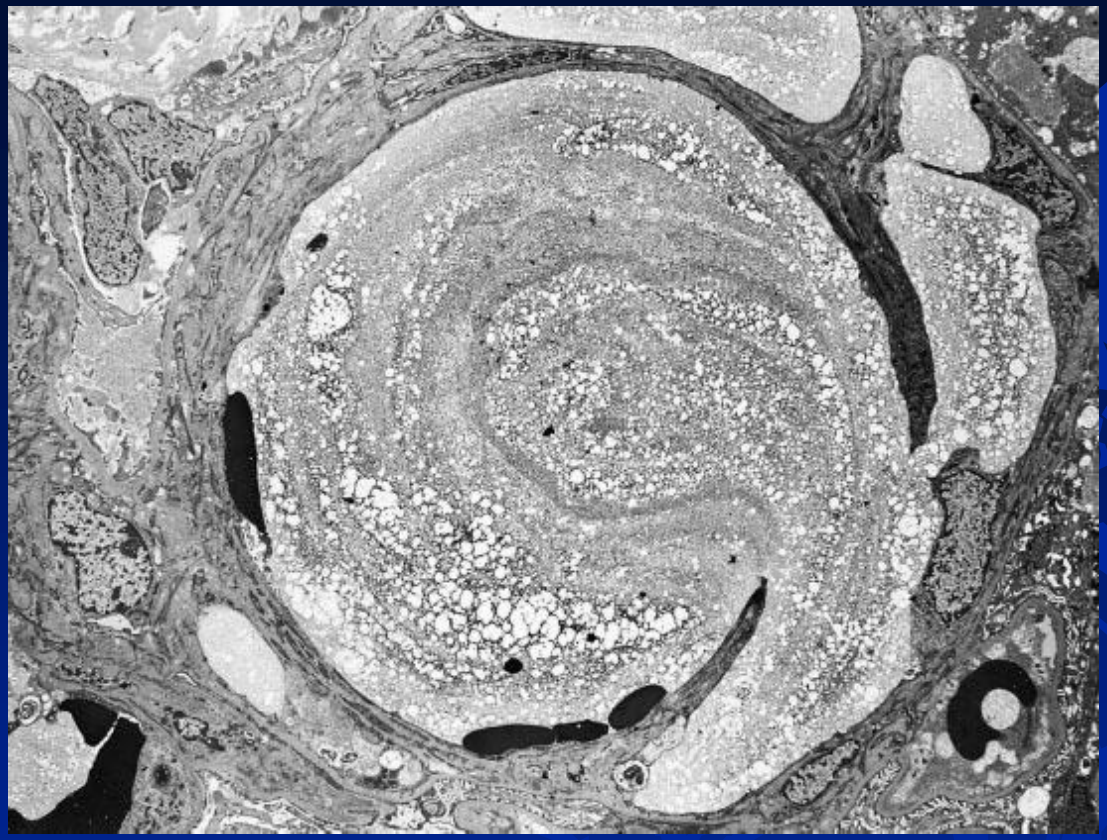
Lipoprotein glomerulopathy?

- Reported case



- Our case





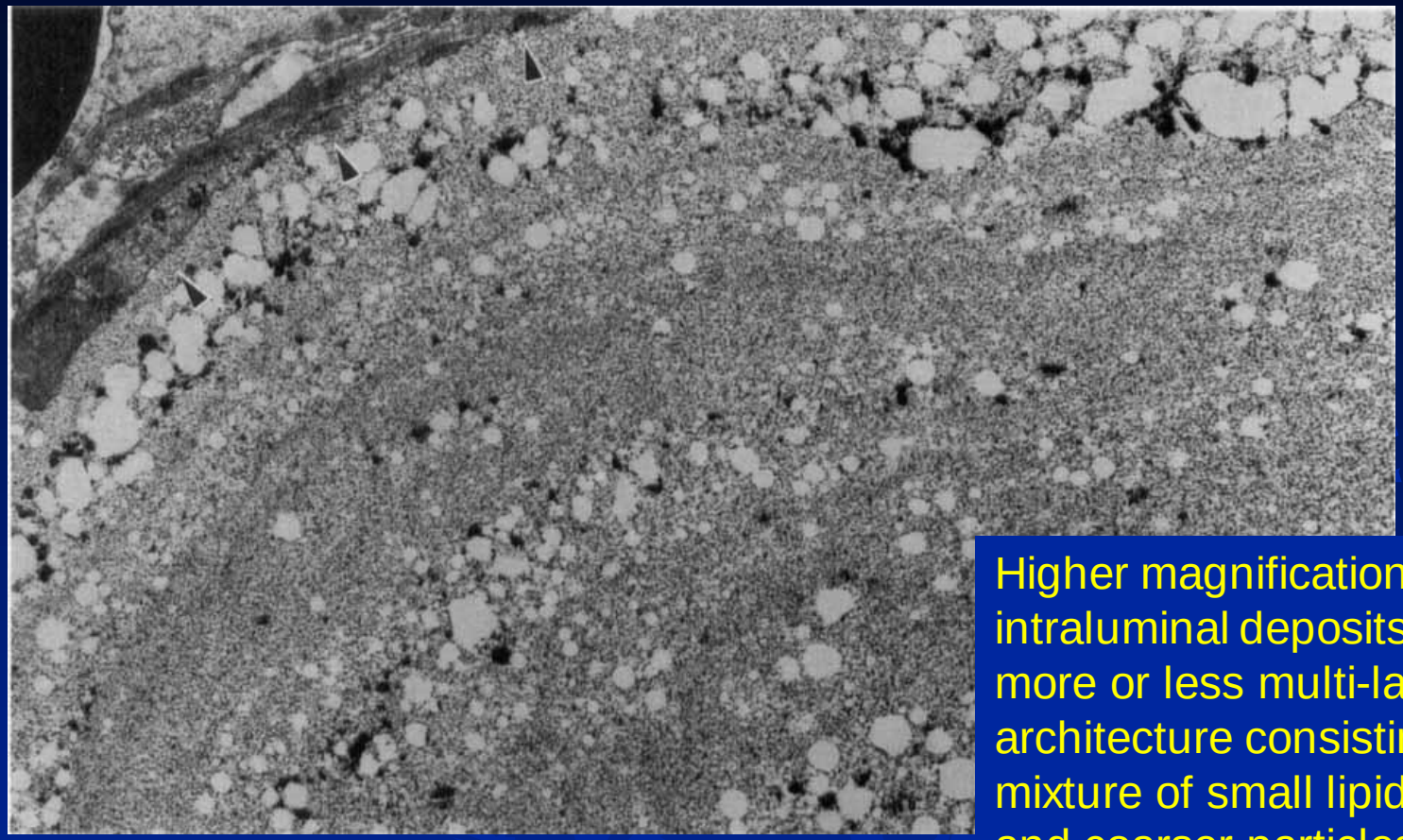
Electron micrograph of glomerulus:

A layered structure resembling a fingerprint is composed of granules and vacuoles in the capillary lumen (33000).

Lipoprotein glomerulopathy: Significance of lipoprotein and ultrastructural features

Kidney International, Vol. 55, Suppl. 71 (1999), pp. S-37–S-41

Takao Saito, Shinichi Oikawa, Hiroshi Sato, Toshinobu Sato, Sadayoshi Ito, and Jun Sasaki



A Case of Lipoprotein Glomerulopathy

Light and Electron Microscopic Observations of the Glomerulus

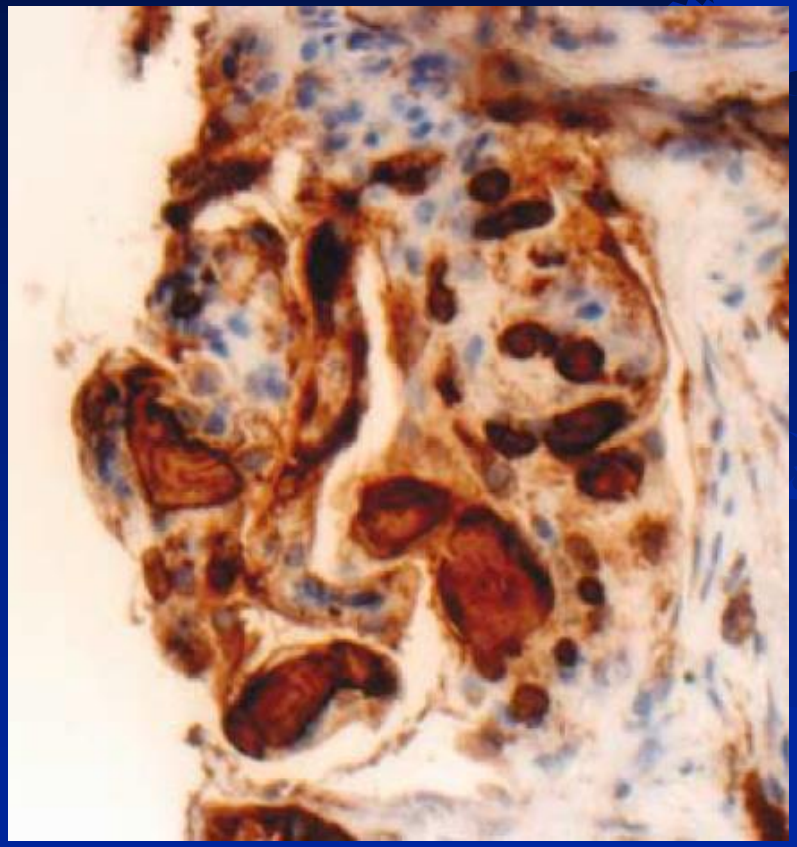
Toshikatsu Shibata[1], Naoe Kaneko[1], Yoshihito Hara[2],
Takao Saito[3], and Hiroshi Sakaguchi[4]

Higher magnification of the intraluminal deposits reveals a more or less multi-layered architecture consisting of a mixture of small lipid droplets and coarser particles with high electron density, and dense sheet of fine sand-like granules.

Acta Pathologica Japonica 40 (6) : 1990

Focal segmental glomerulosclerosis with intraglomerular deposition suggestive of lipoprotein glomerulopathy

Needs confirmation



ApoE IHC. Source: Kidney Int 73:1097-1098,2008

- Apolipoprotein profile
- Mutational analysis of APOE gene
- Electron microscopy

Lipoprotein glomerulopathy

- First discussed in Japanese Society of Nephrology (5 cases) in 1988
  - Followed by publications in 1989 by Saito *et al* and Watanabe *et al*
- Rare kidney disease characterized by proteinuria, progressive kidney failure, and distinctive lipoprotein thrombi in glomerular capillaries
  - Variable mesangial proliferation
  - Dysbetalipoproteinaemia

Mutations in the gene that encodes apolipoprotein E (APOE; 107741)

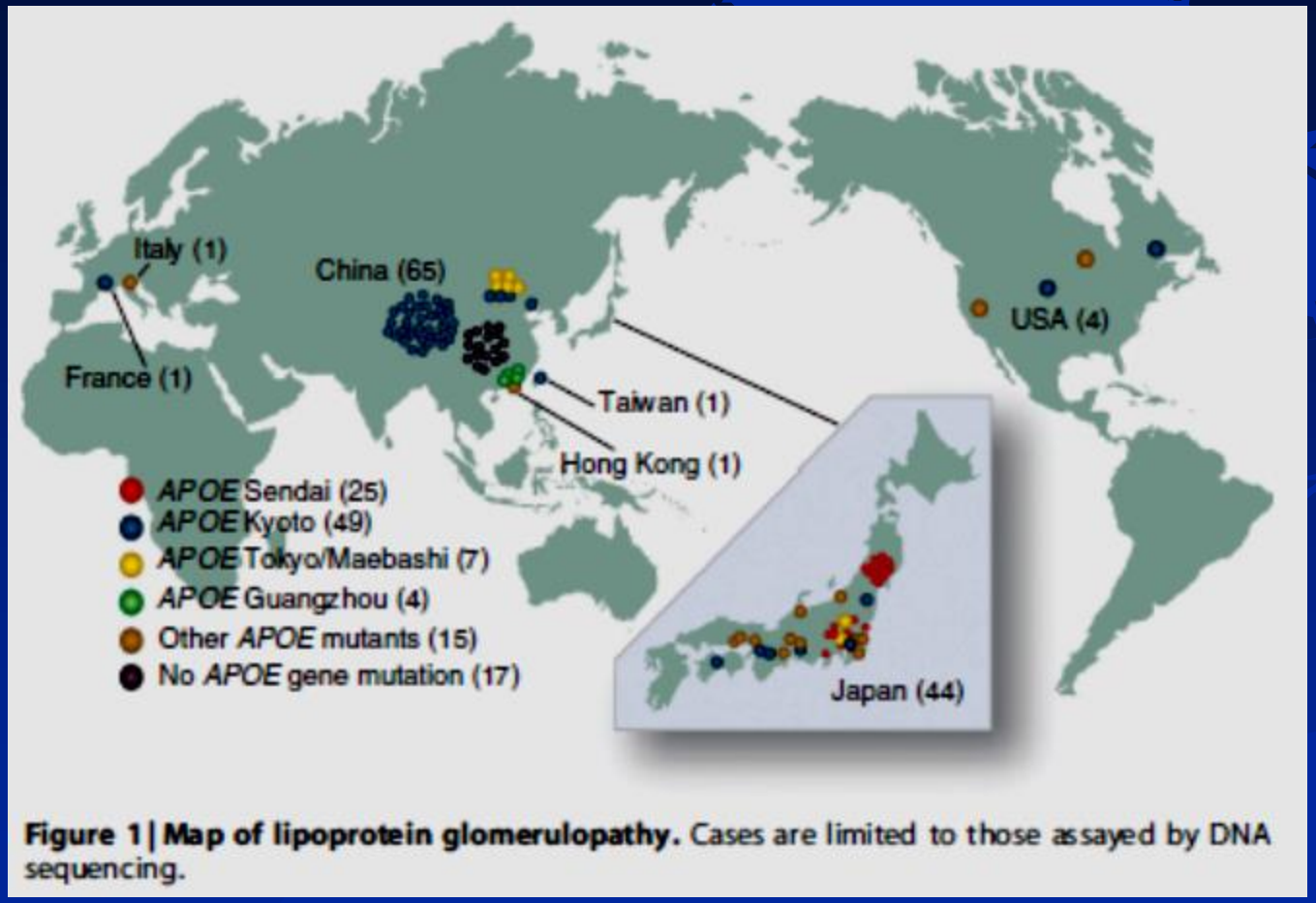


Figure 1 | Map of lipoprotein glomerulopathy. Cases are limited to those assayed by DNA sequencing.

Mainly Japanese and Chinese

Incomplete penetrance

?Epigenetics

Lipoprotein glomerulopathy may provide a key to unlock the puzzles of renal lipidosis

Takao Saito[1] and Akira Matsunaga[2]

Kidney International (2014) **85,** 243–245. doi:10.1038/ki.2013.404

Table 1 Crossroads between lipoprotein glomerulopathy and type III hyperlipidemia

	Lipoprotein glomerulopathy	Type III hyperlipidemia
Dyslipidemia	Of moderate severity, mild or even absent	Severe
Cutaneous xanthomas	Absent	Usually present
Atherosclerosis	Absent	Severe
Renal involvement	Always present	Extremely rare
Renal histology	Intraglomerular lipoprotein thrombi	Mesangial and interstitial foam cell accumulation
Genetics	Heterozygosity for rare apoE mutations	ApoE2 homozygosity, rarely heterozygosity for dominant apoE variants
Penetrance	Incomplete	Incomplete

Lipoprotein glomerulopathy

Vasilis Tsimihodimos and Moses Elisaf

Current Opinion in Lipidology 2011, 22:262–269

- Mutations in ApoE proteins
  - Structural changes
  - Lipoprotein aggregation
  - Glomerular "thrombi" deposition

Other factors

- Reduced receptor affinity
- Macrophage impairment

Key points

- Lipoprotein glomerulopathy is a rare disorder characterized clinically by proteinuria and increased serum concentrations of apoE and remnant lipoproteins.
- The histological hallmark of the disease is the presence of laminated, lipoprotein-containing thrombi within glomerular capillaries, whereas all the affected individuals carry rare apoE gene mutations in a heterozygous form.
- Lipoprotein glomerulopathy is a dominant inherited disease with incomplete penetrance.
- Disease progression usually results in overt nephrotic syndrome and end-stage renal disease.
- Lipid-lowering medications, mostly fibrates, have shown encouraging results in some case studies.
- LDL-apheresis using the HELP system or immunoadsorption onto staphylococcal protein A may have a role in refractory cases.
- Renal transplantation is not a therapeutic option for patients with lipid glomerulopathy since disease recurrence in the transplanted kidney is the rule.

Follow-up

- Proteinuria improved after starting Lipitor 10mg nocte
- Currently on Diltiazem, CoApproval, Lipitor and low dose Prednisolone 5mg daily
- ? Agreeable for mutational studies