



UNIVERSITI
MALAYA
KUALA LUMPUR

Renal Biopsy CPC
Singapore
11-12 August 2018

SLIDE SEMINAR CASE 77

Dr Cheah Phaik Leng & Dr. Looi Lai Meng
University of Malaya



Case 2

JDR, 72-year-old Indian female

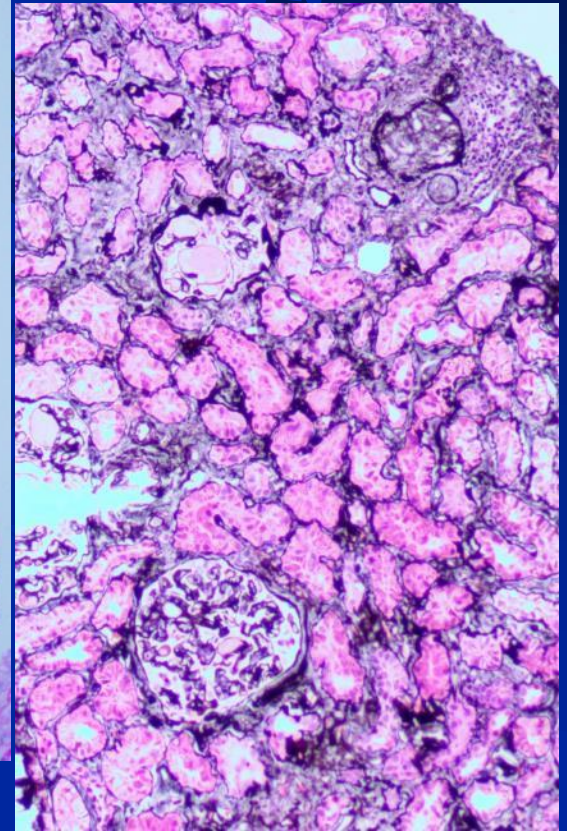
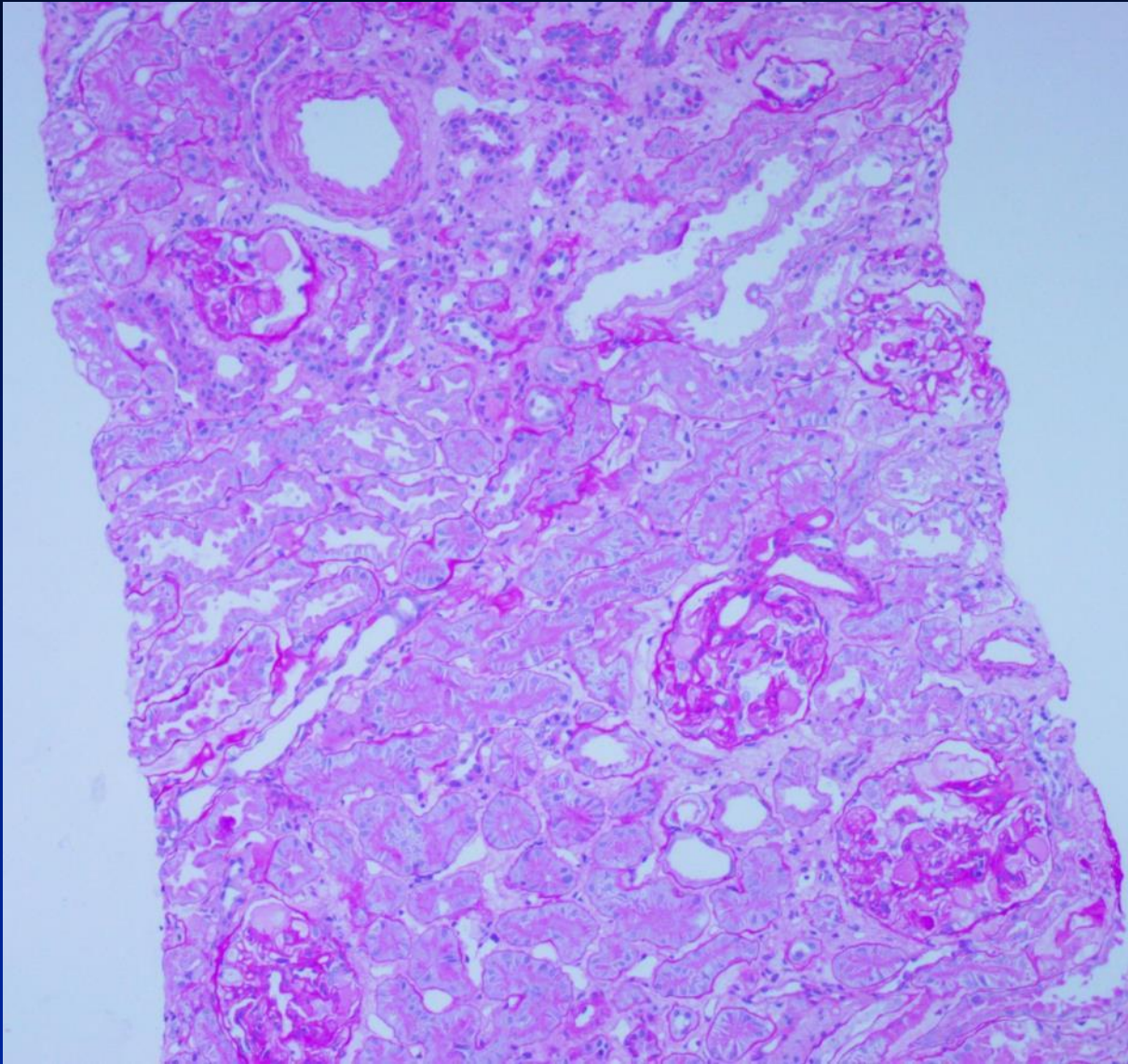
- Sudden onset severe leg swelling 1 month prior to biopsy
- Hypertensive; well-controlled DM
- Proteinuria 2g/24 hr. Urine RBC 5+
- S alb 29 g/L (L),
- Creat 95 umol/L. eGFR: 52
- ?Membranous/minimal change/FSGS/DM



Past history

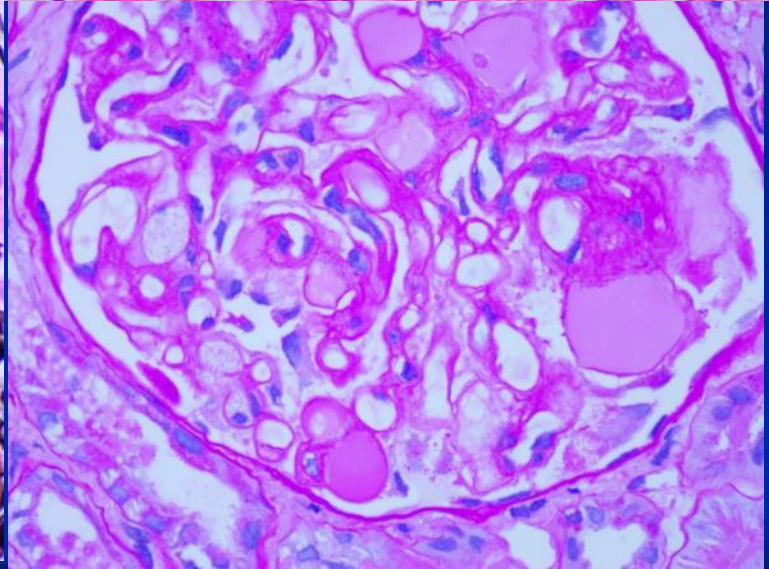
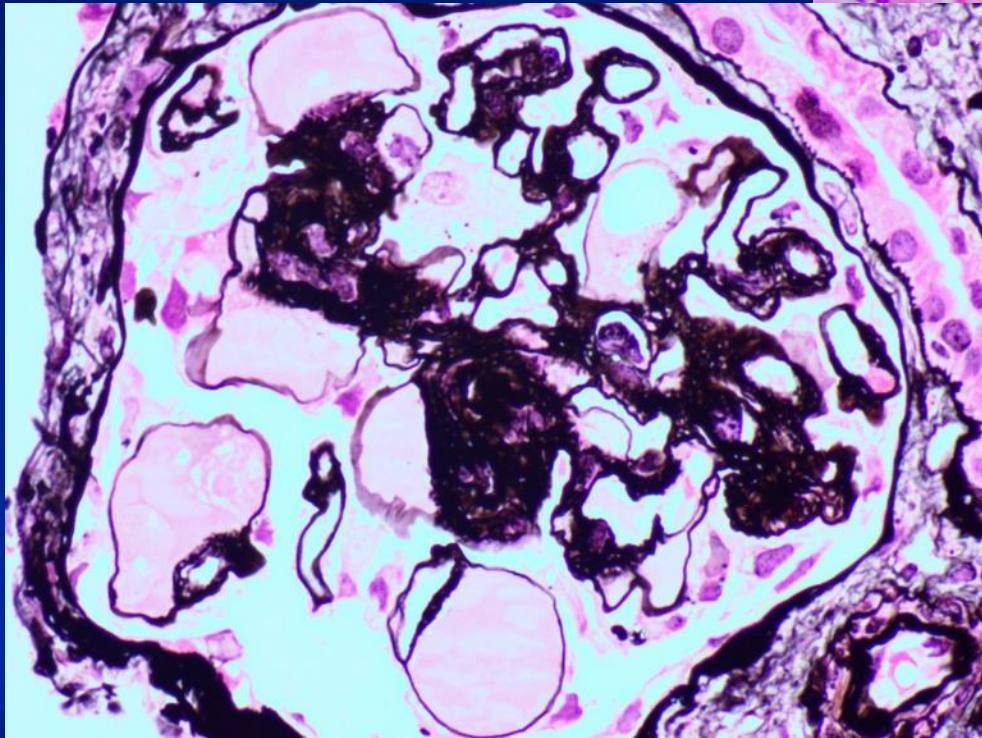
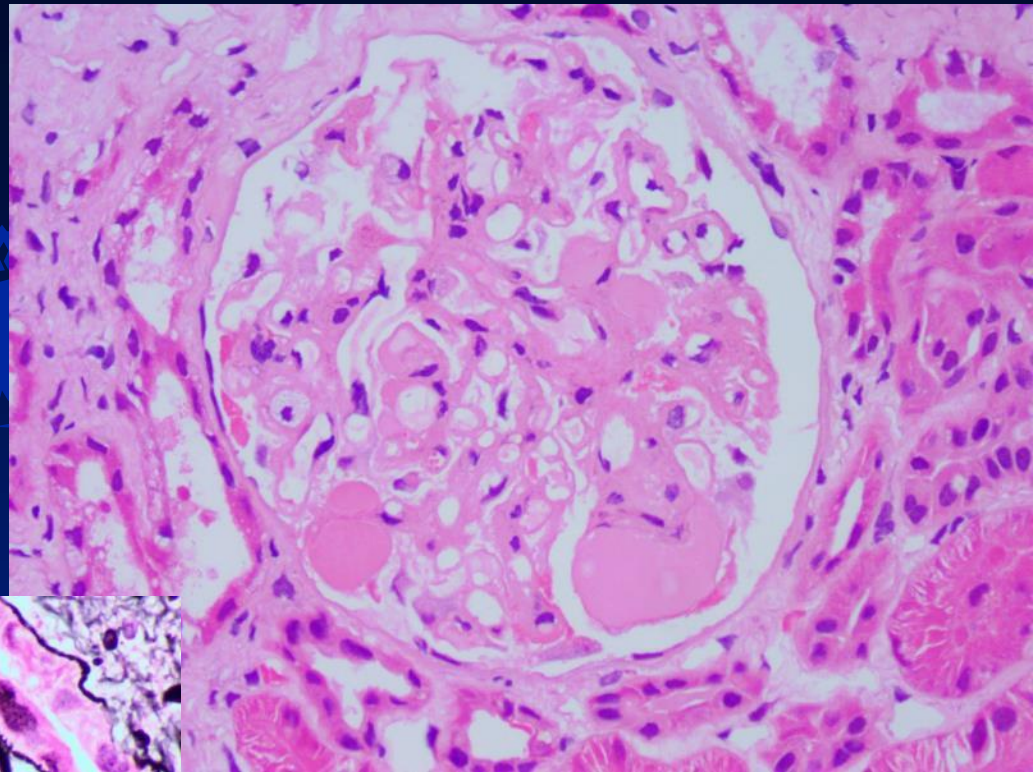
- Papillary serous adenocarcinoma endometrium, high grade
 - ◆ Stage T1aN2M0
- Treated with Avastin (bevacizumab)
 - ◆ Stopped 1 month prior to leg swelling

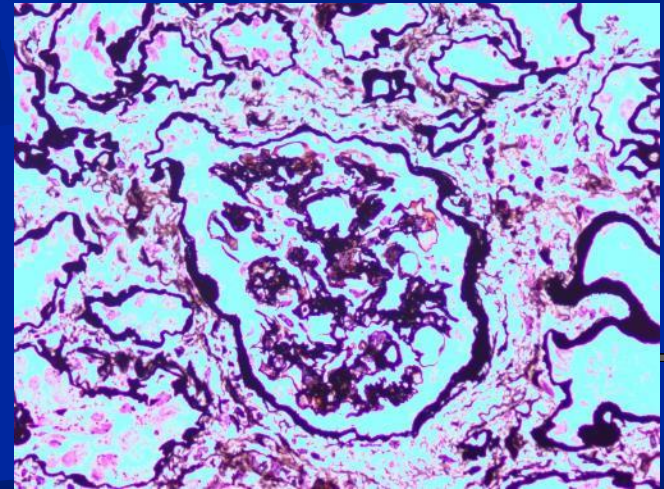
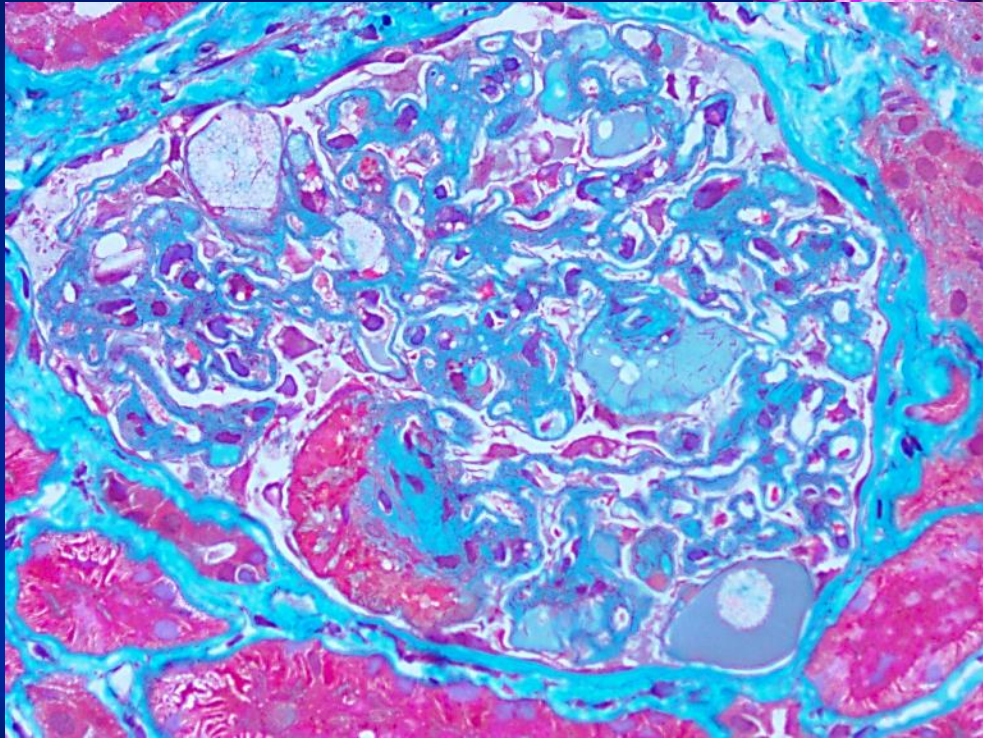
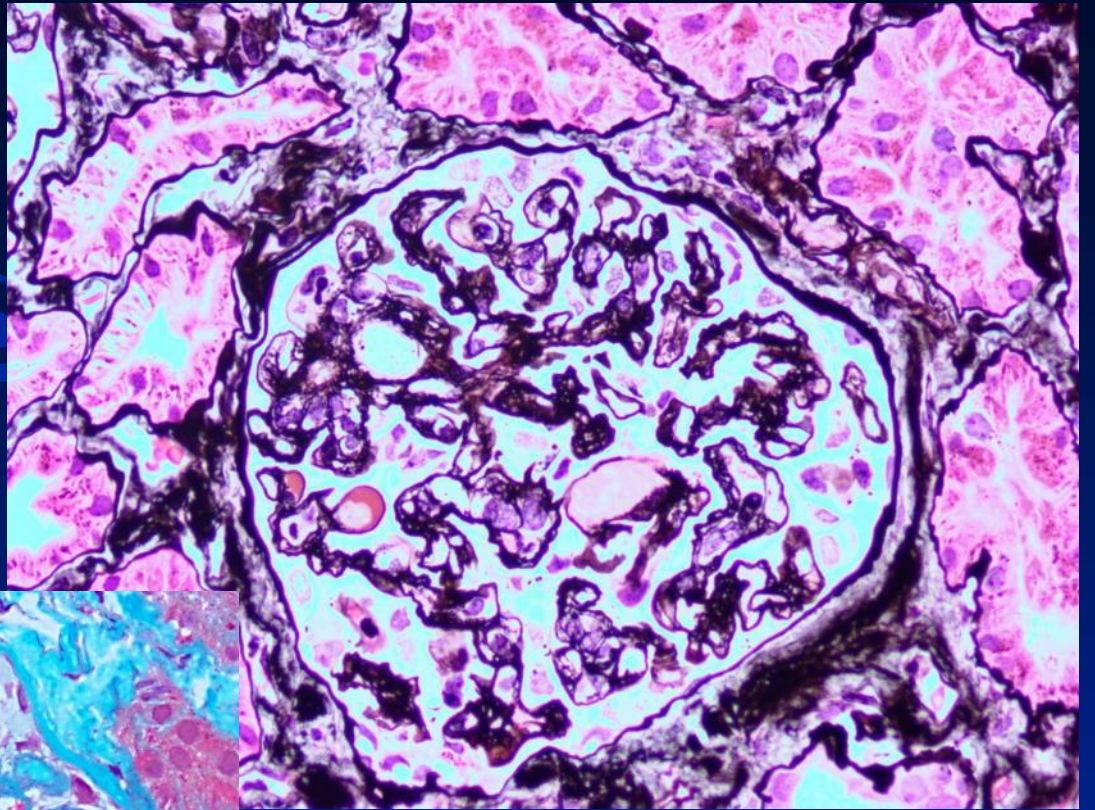


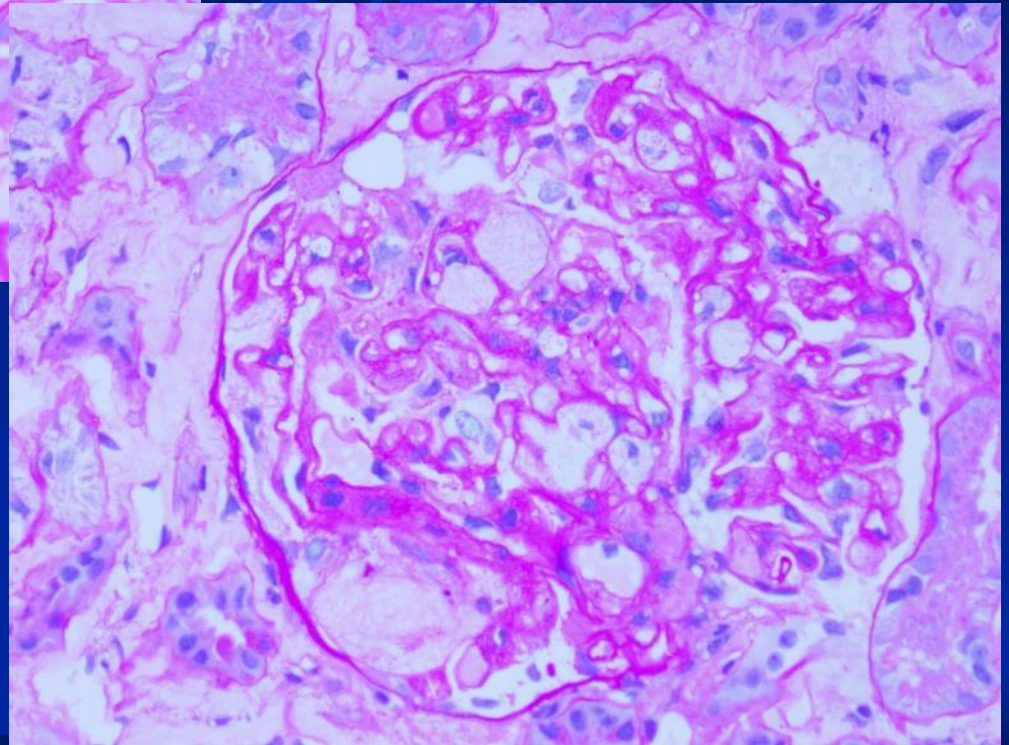
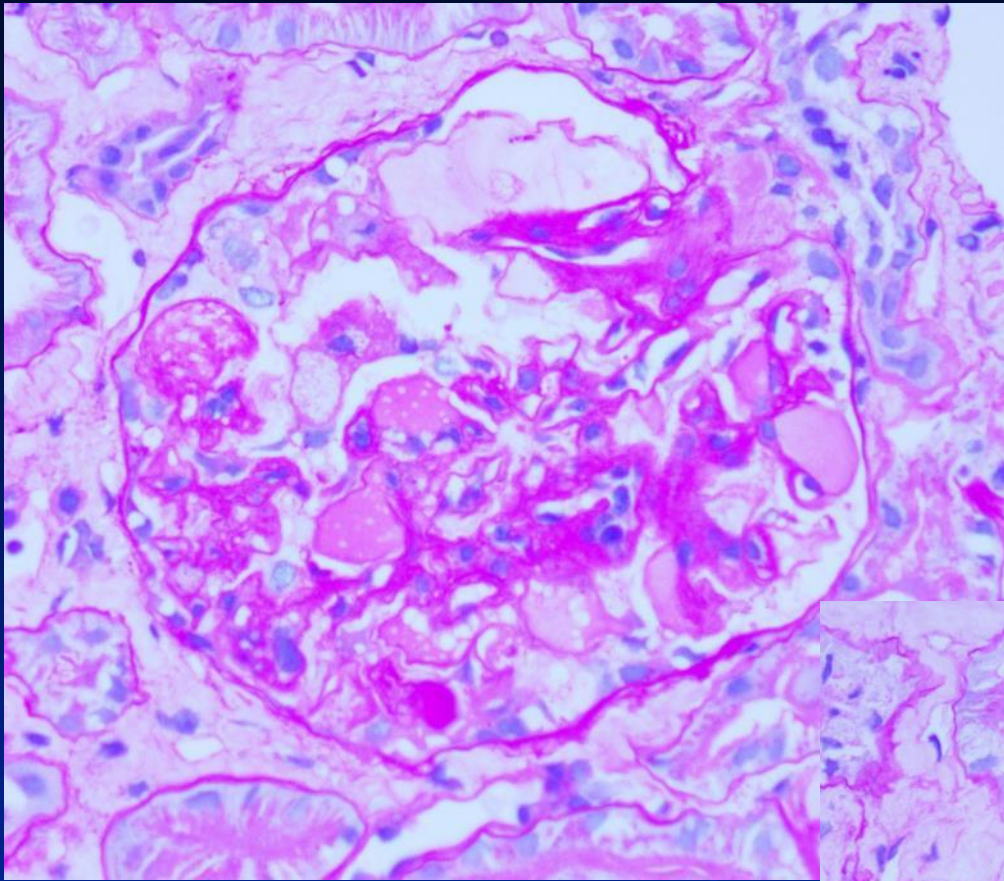


■ 5 cores. 28 g, 4 sclerosed

Intracapillary “deposits”



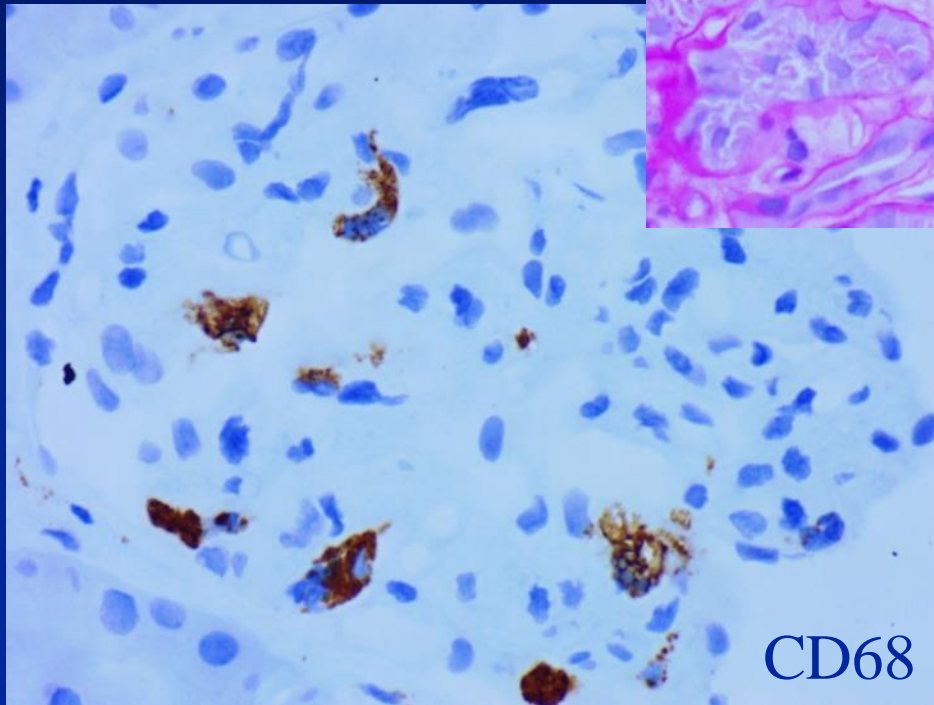
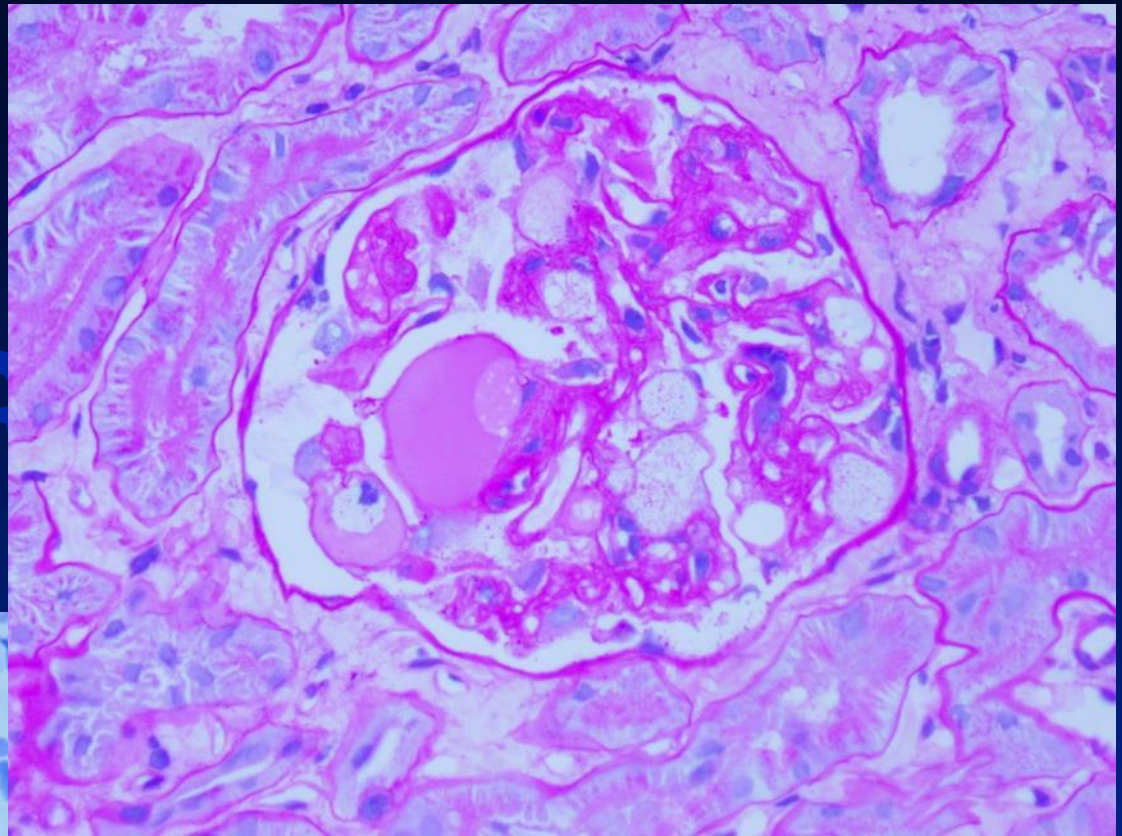




Mesangial cellularity
with mesangiolytic and
endotheliosis

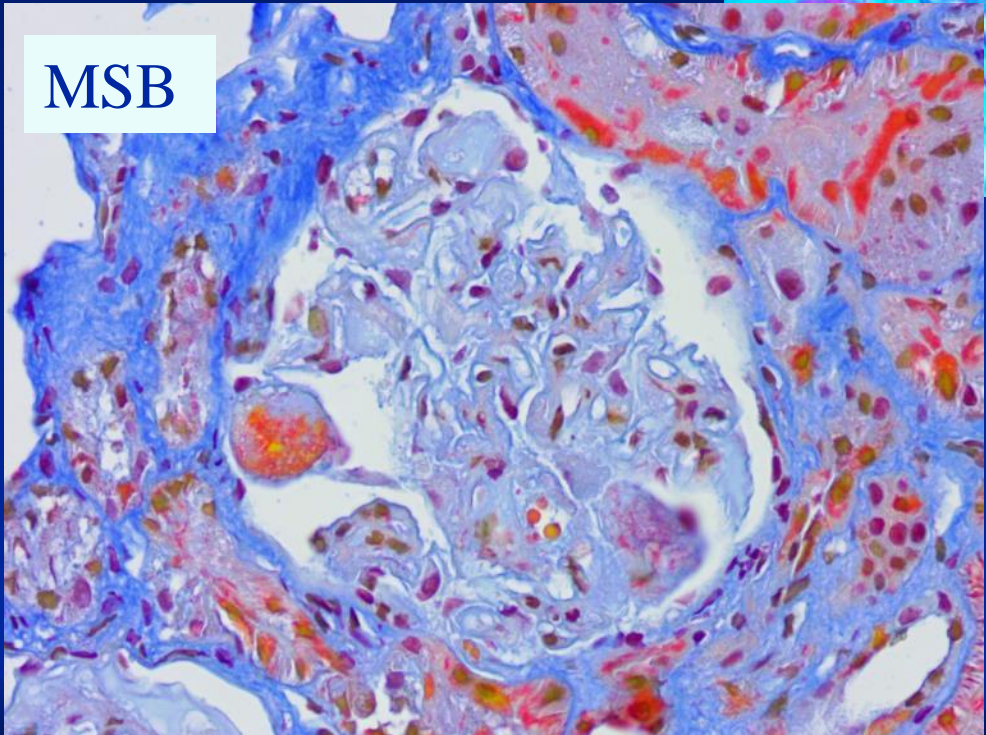
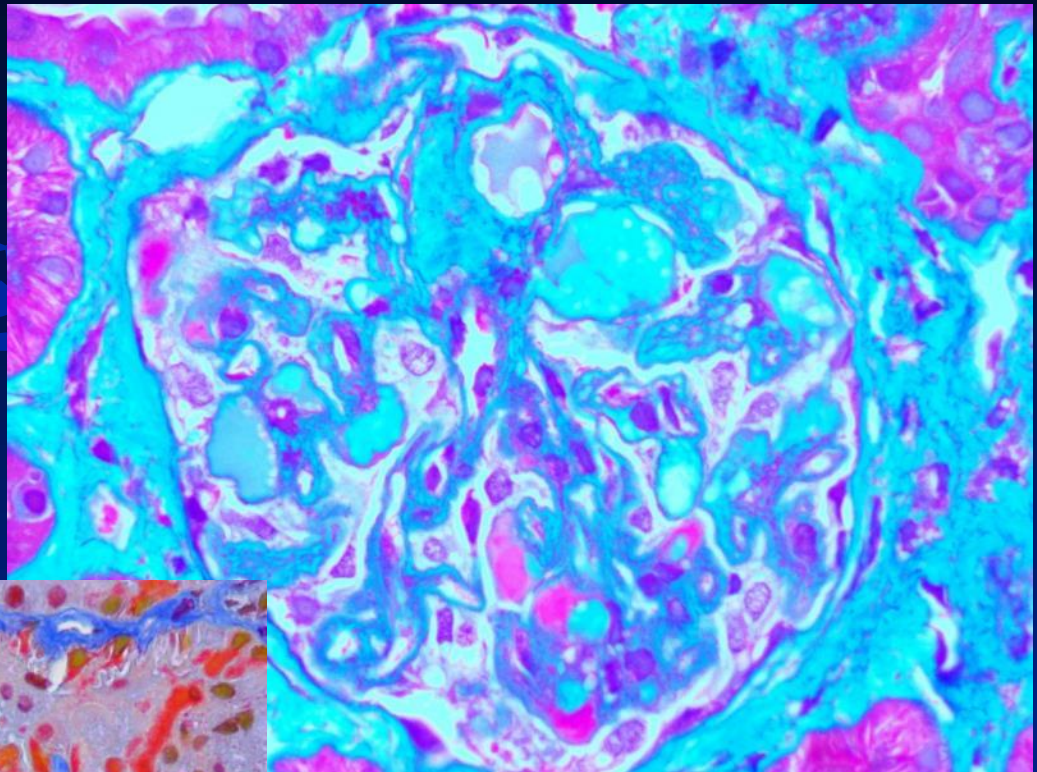
Foam cells

Foam cells

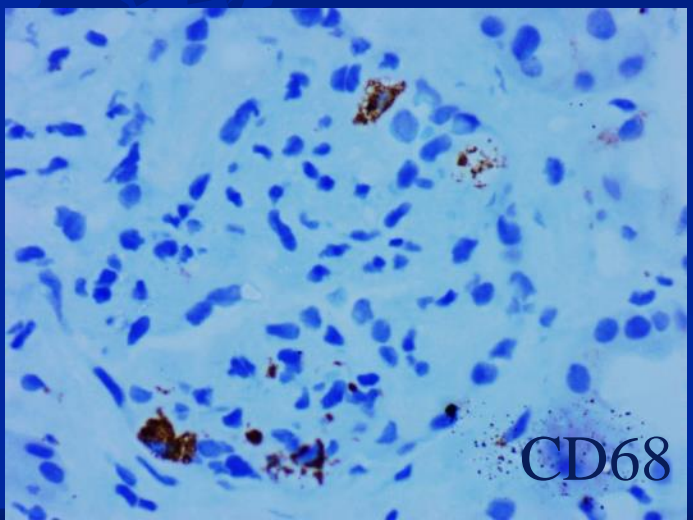


CD68

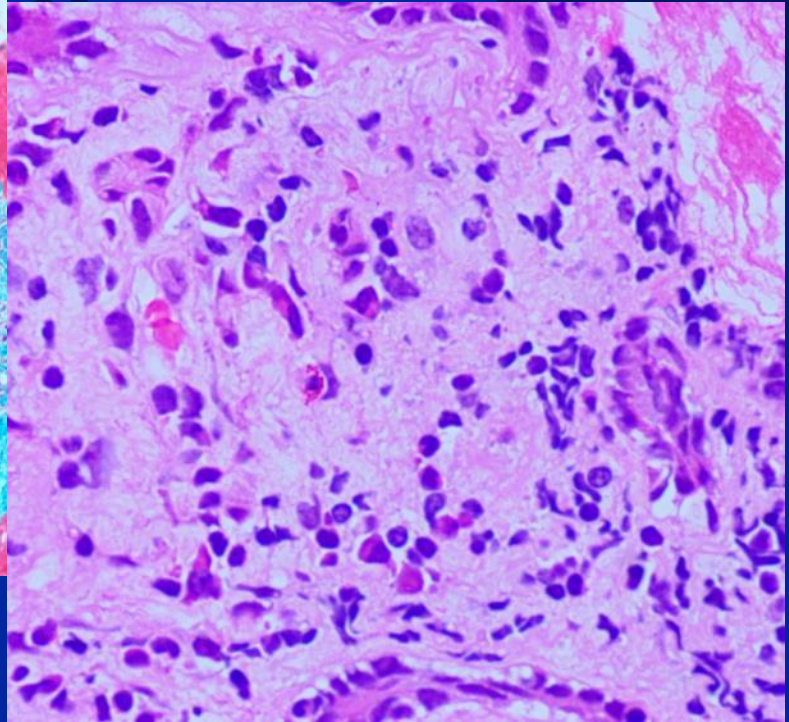
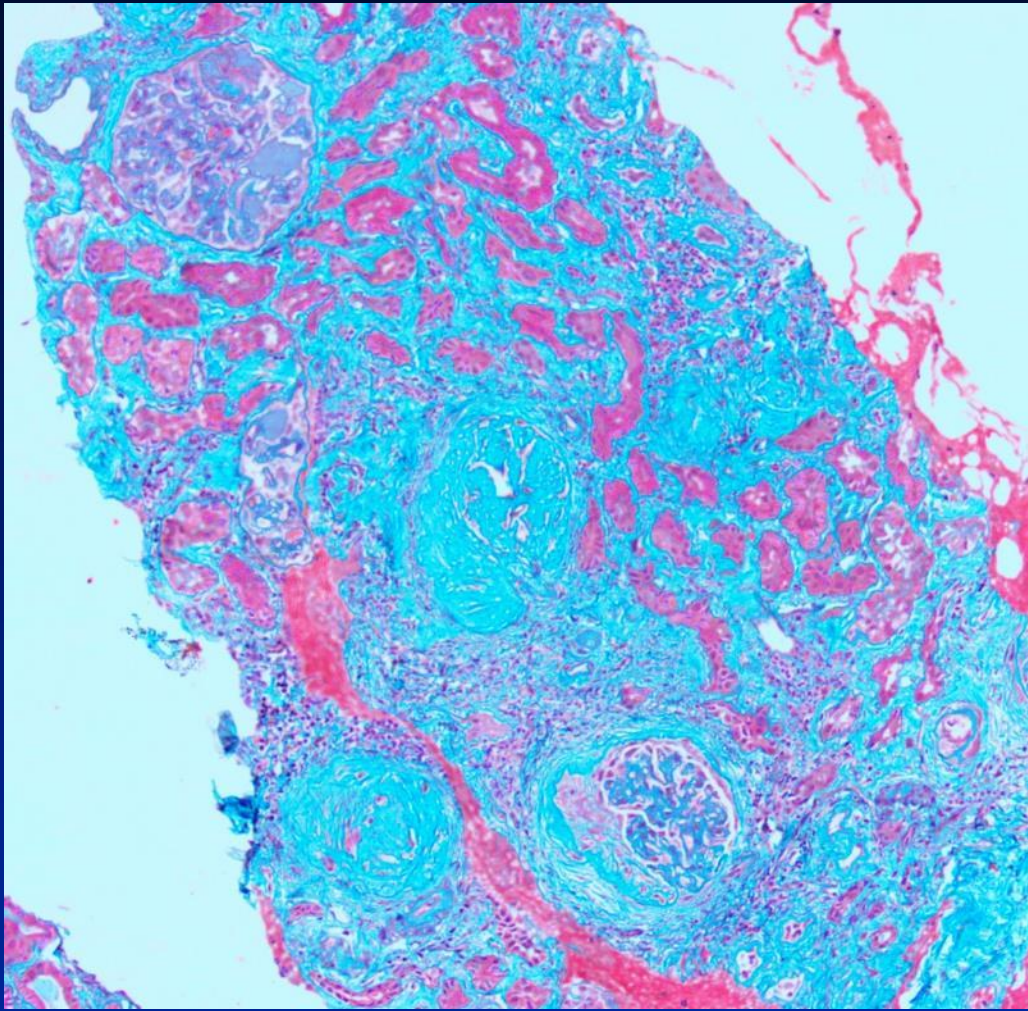




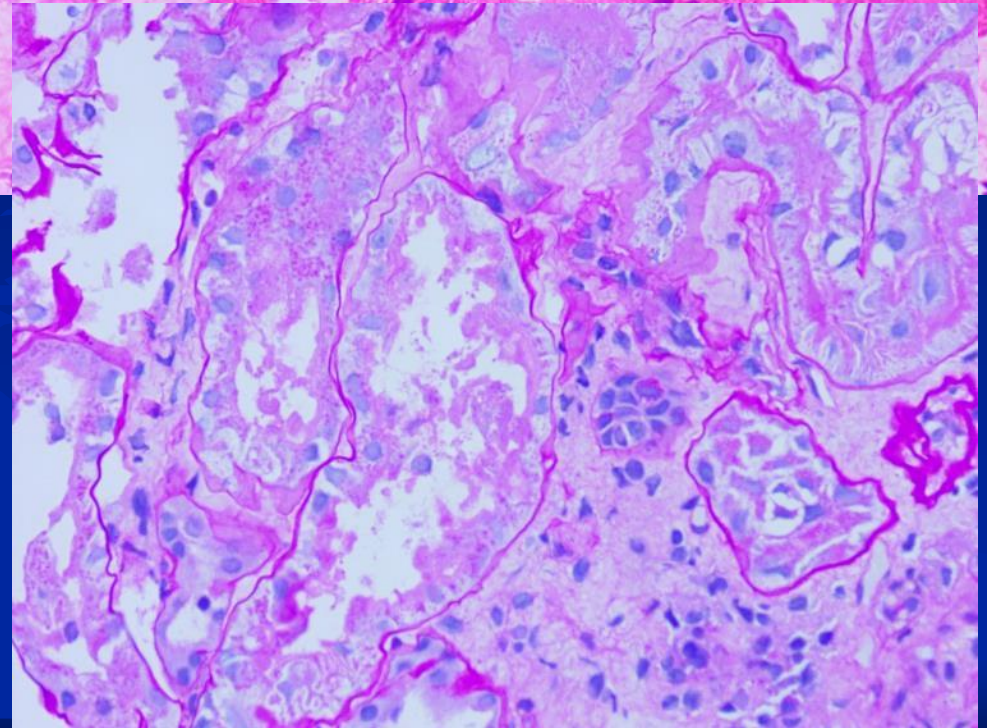
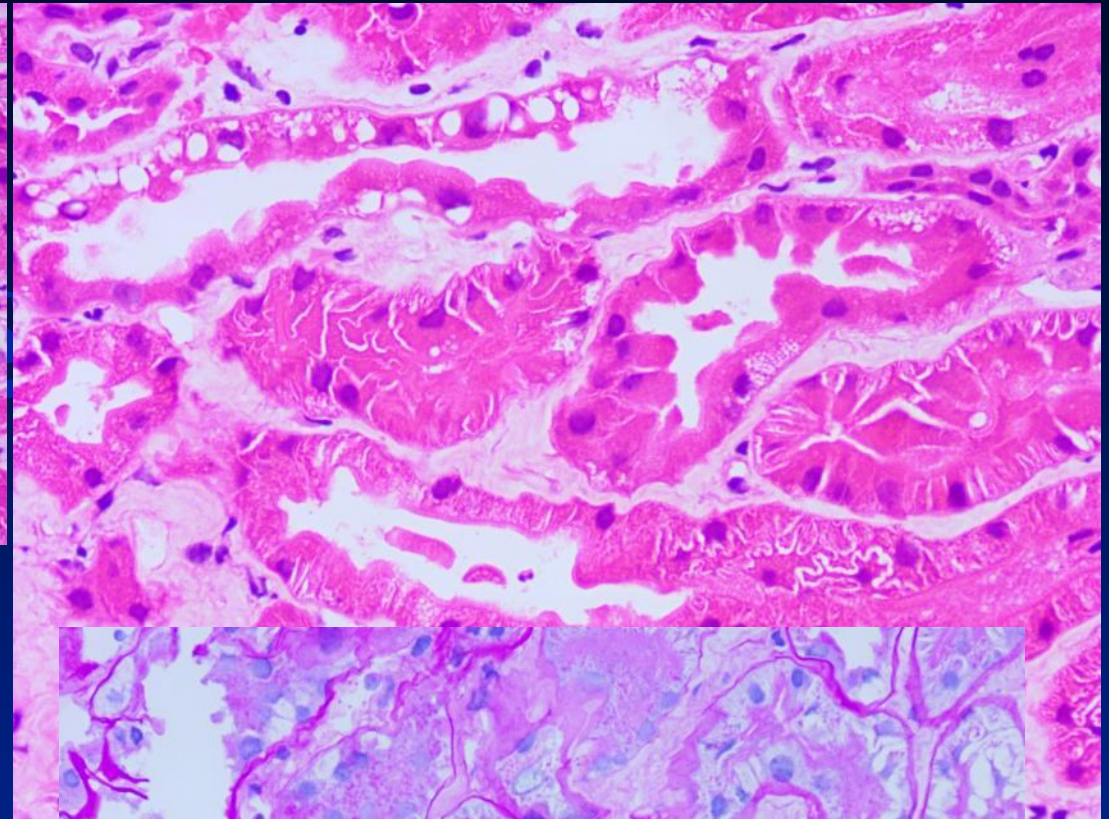
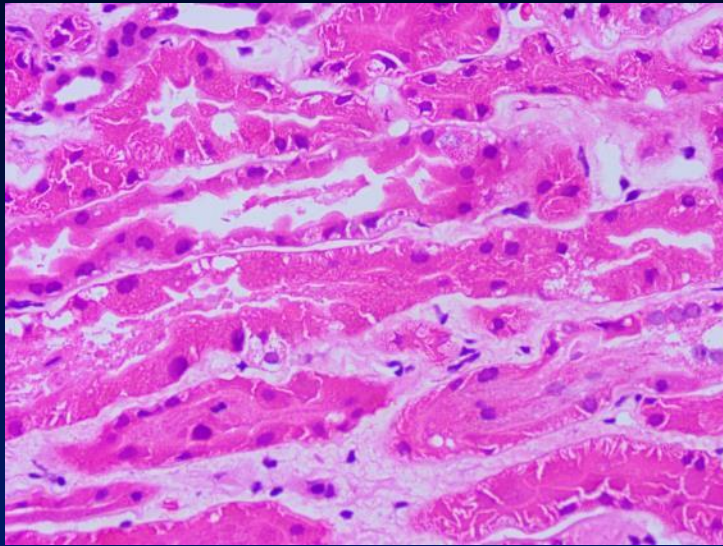
MSB



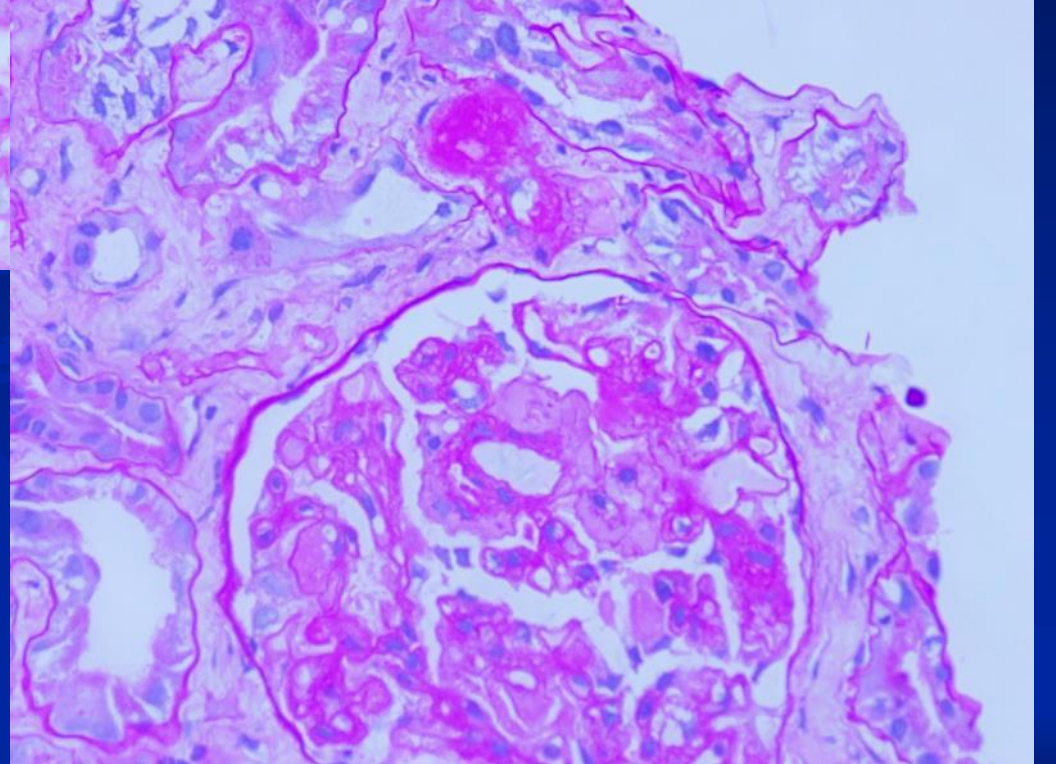
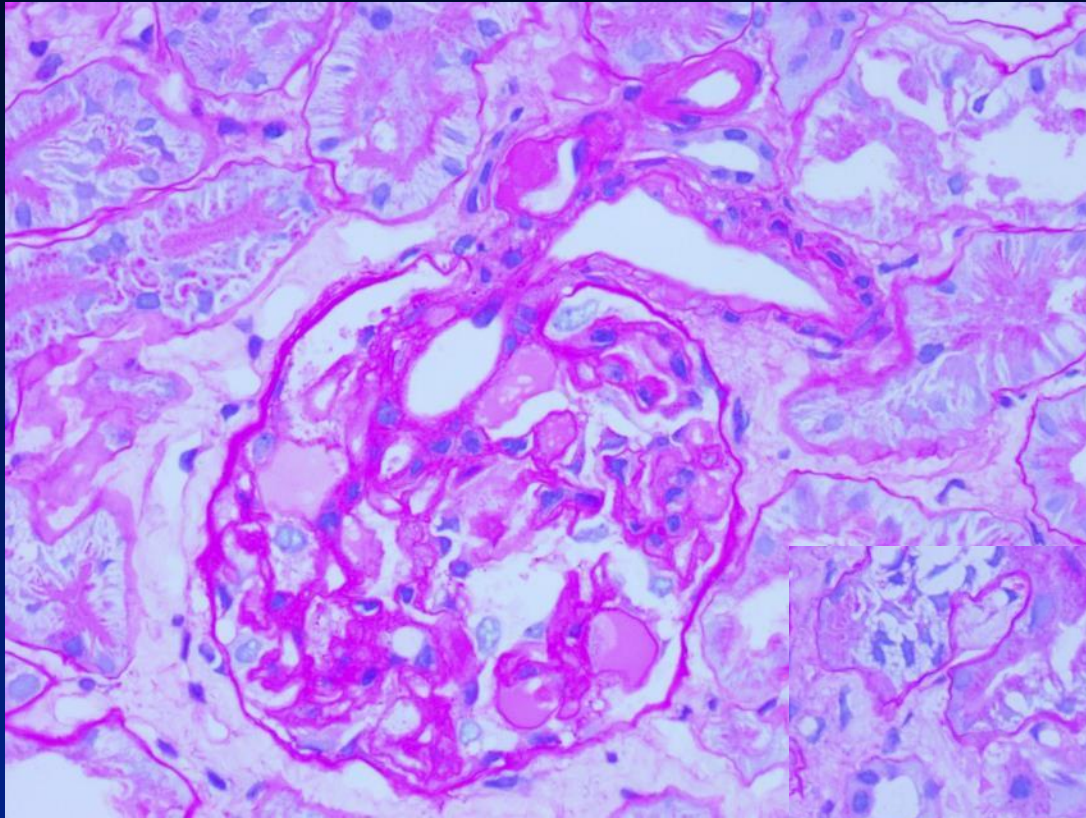
CD68



- FTA; Focal interstitial fibrosis and inflammation



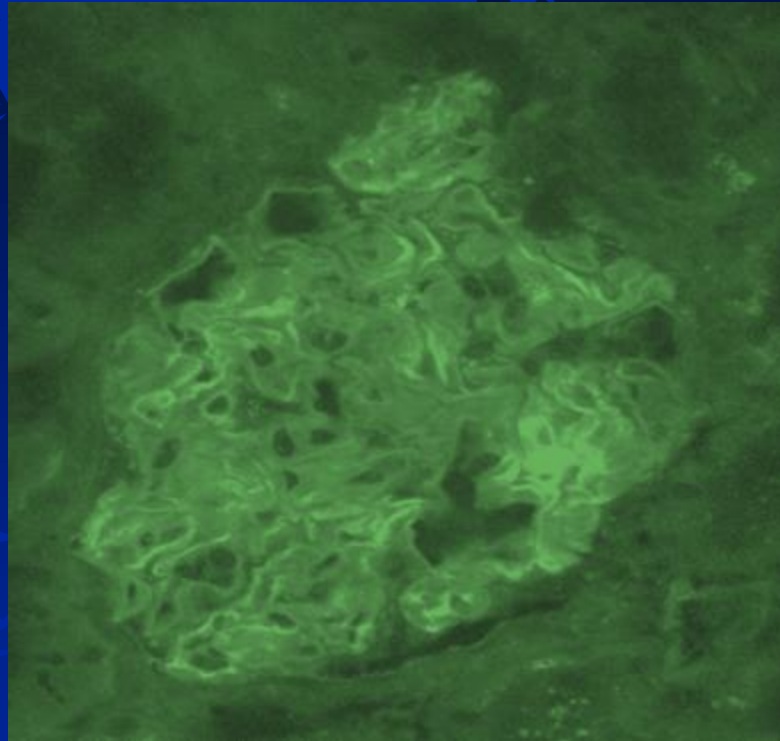
Acute tubular
injury, mild and
focal

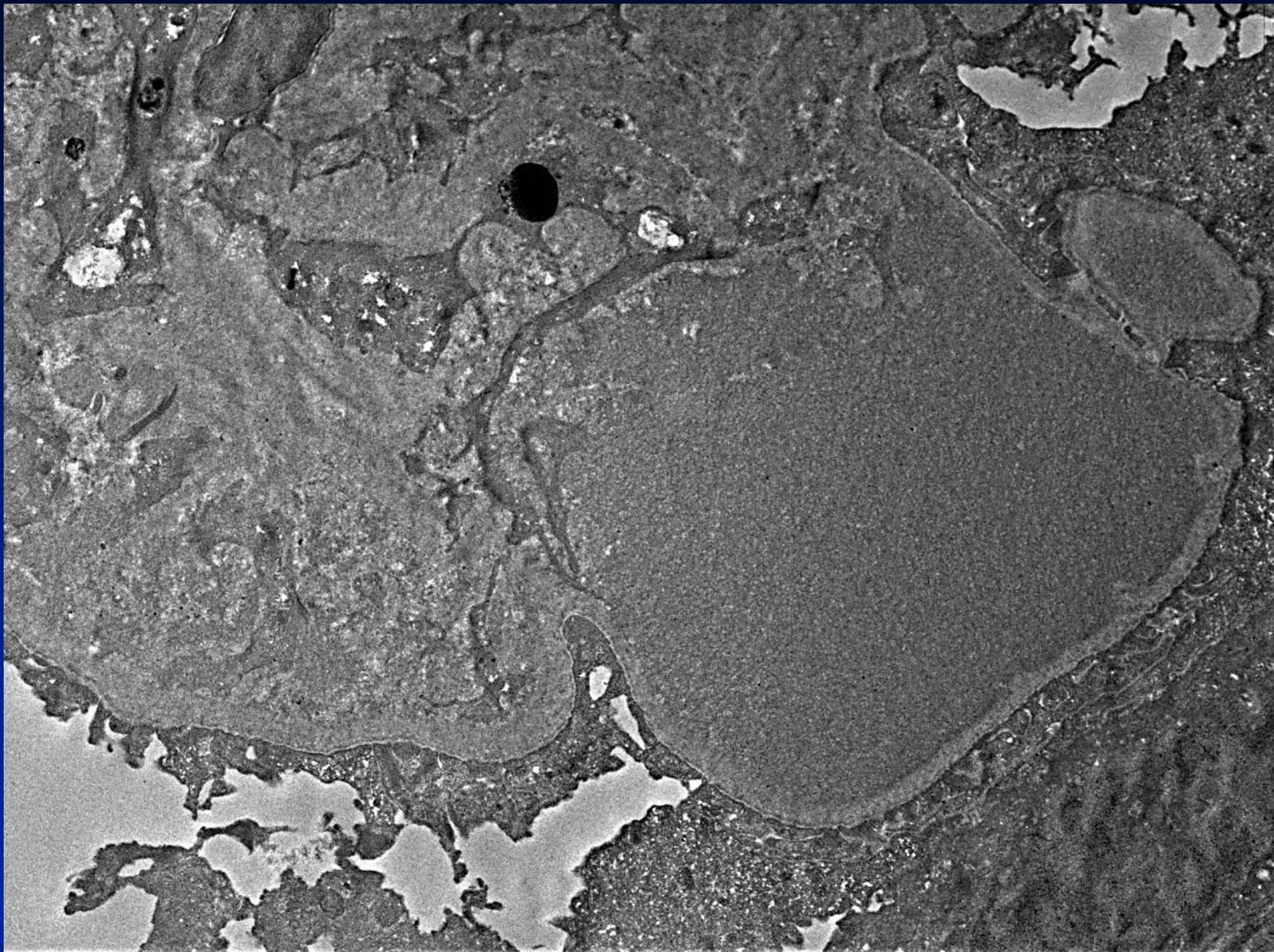


**Hyaline
arteriosclerosis**

Immunofluorescence

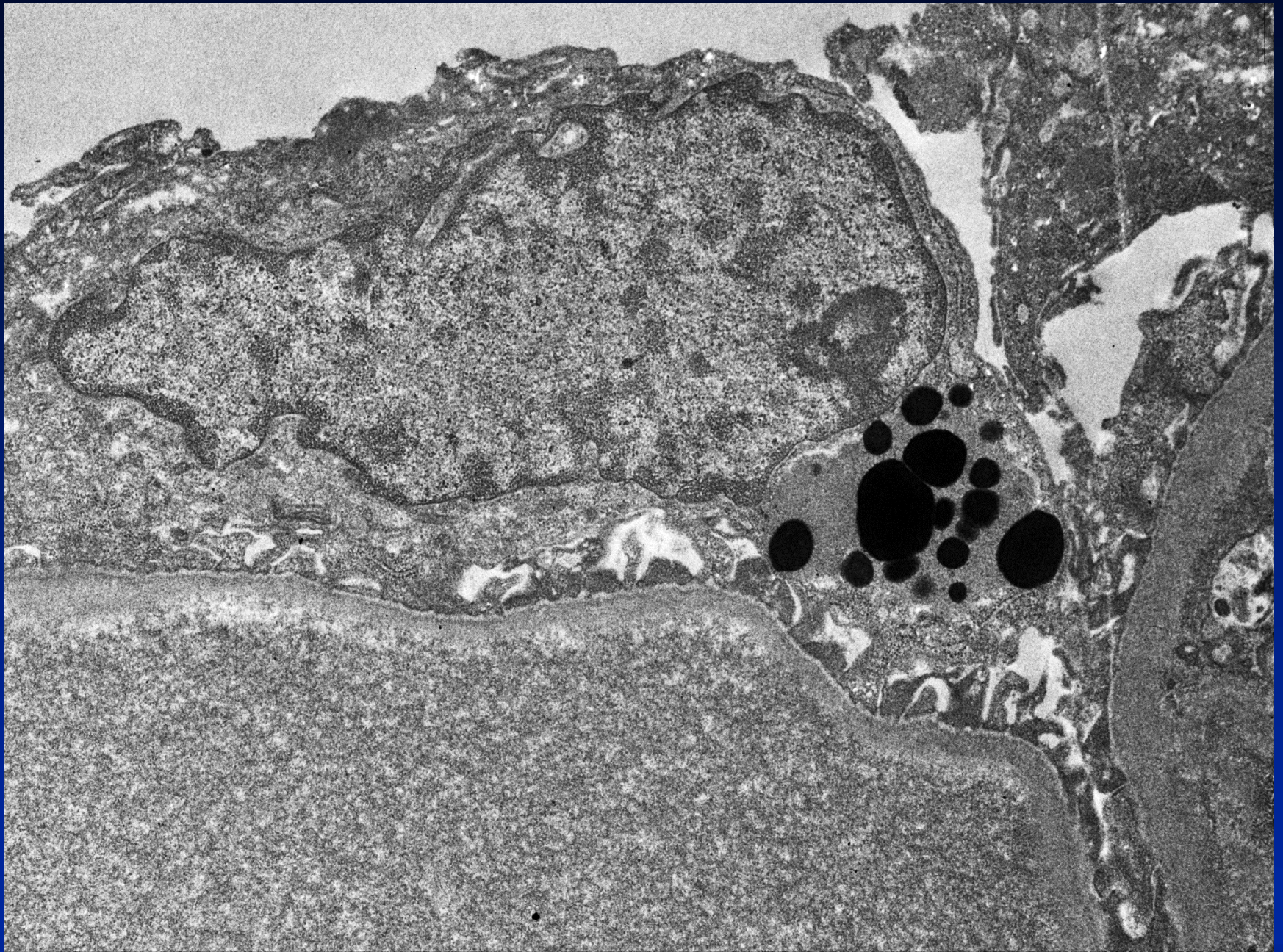
- No immune deposits

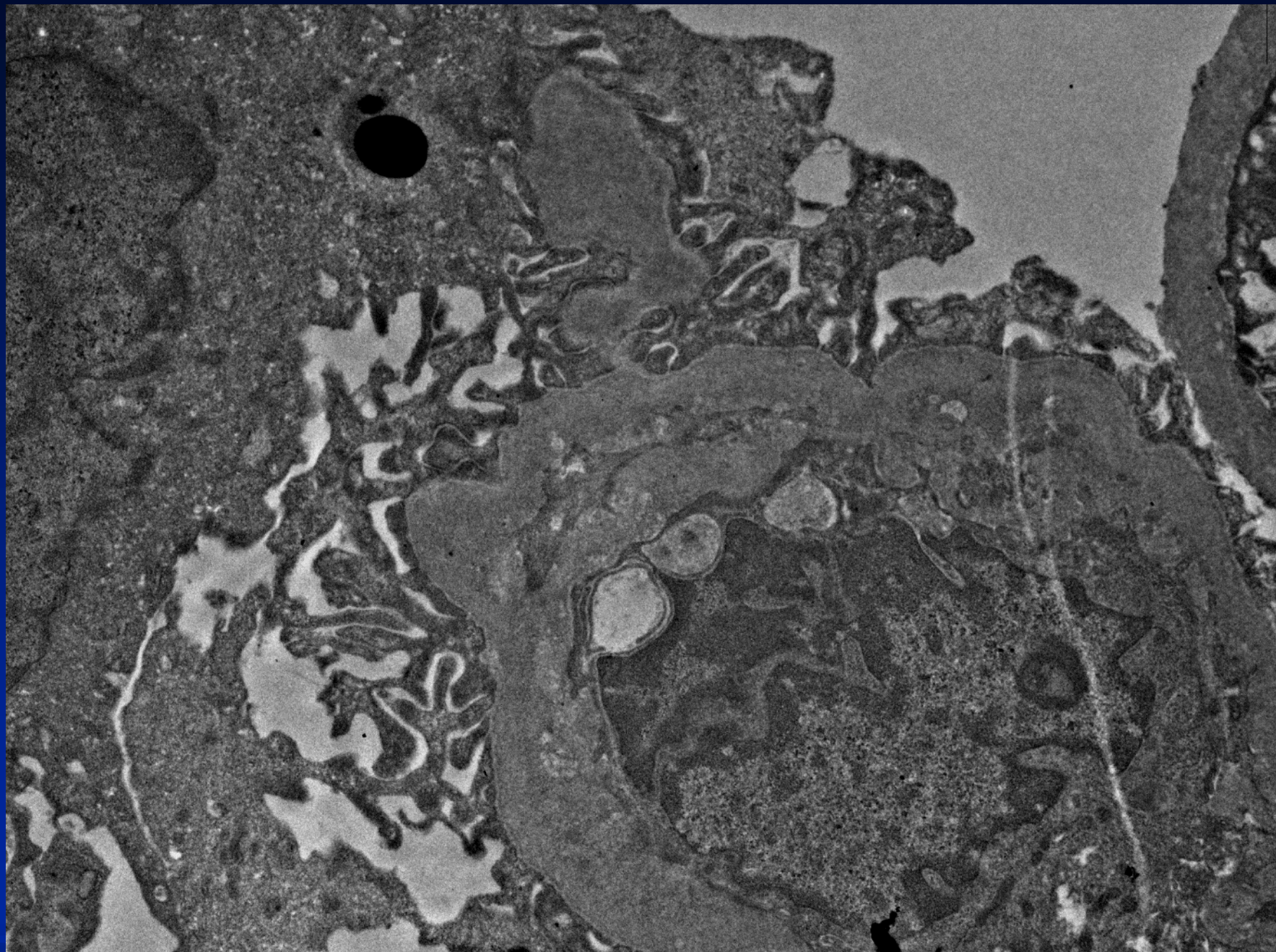




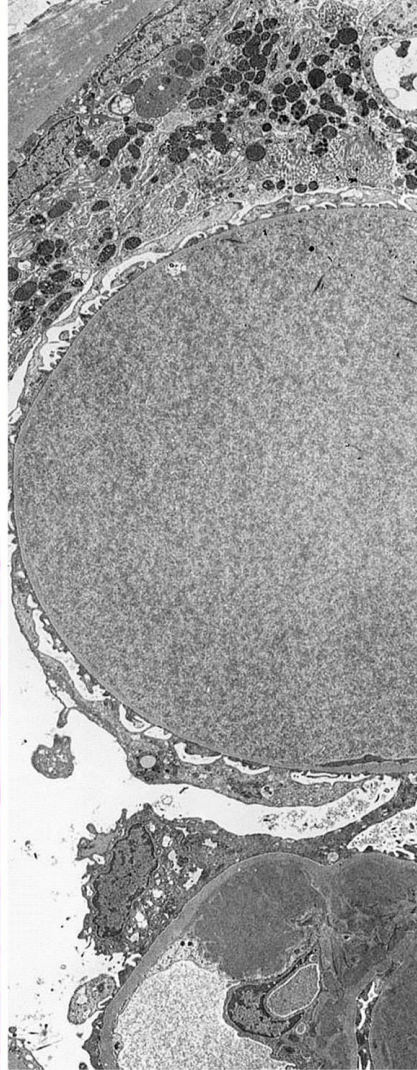
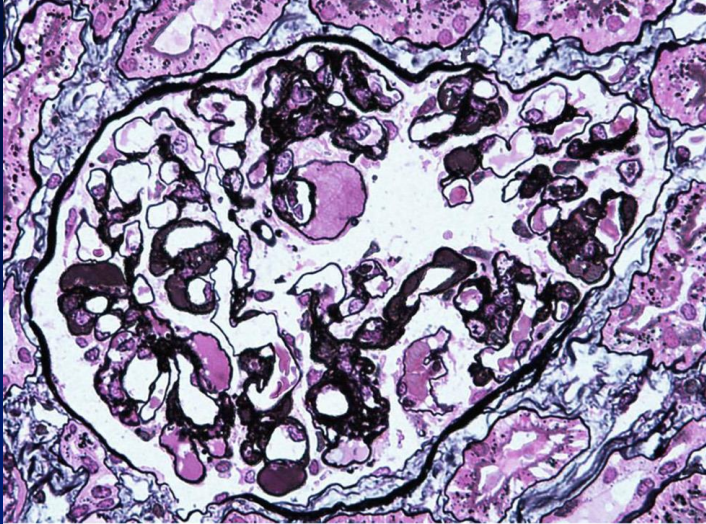
x3.0k Zoom-1 HC-1 80.0kV 2018/06/28 12:16:02
Hi-Tech Instruments App Lab

5.0µm

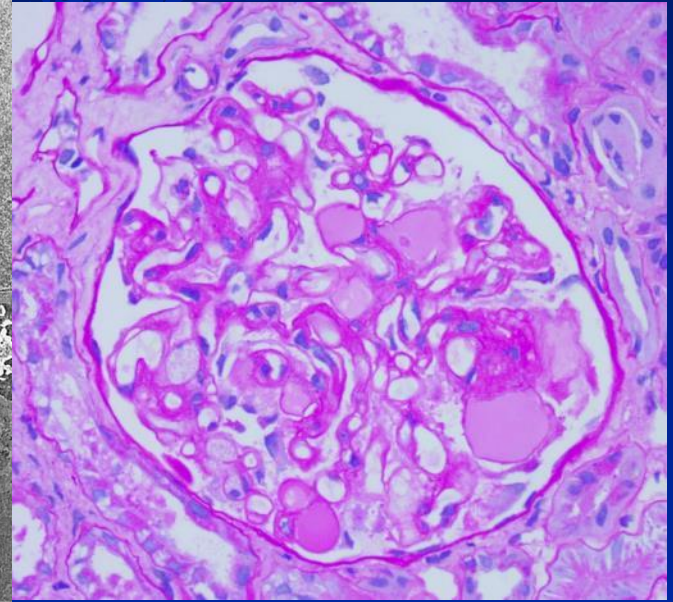
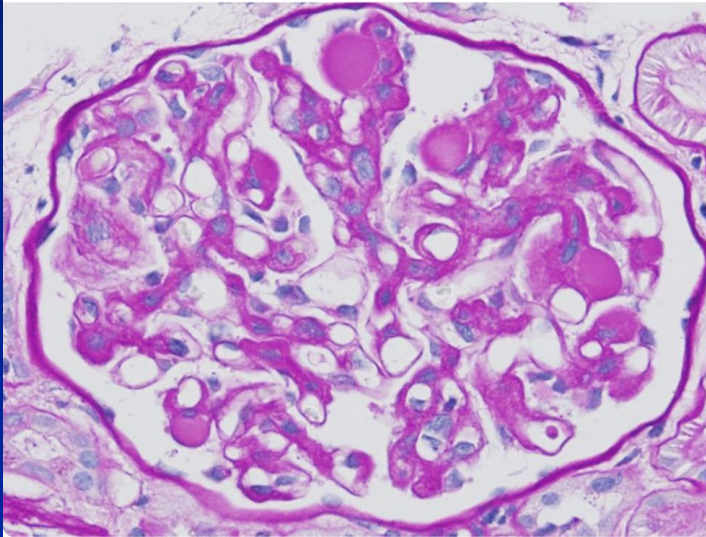




Bevacizumab induced nephropathy?



■ Our case



Reported case: Yahata et al. BMC Research Notes 2013, 6:450

Bevacizumab induced nephropathy

- Thrombotic microangiopathy
- Acute tubular injury



Bevacizumab

- A blocking humanized monoclonal antibody directed against (neutralizes) vascular endothelial growth factor (VEGF)
- Tumor angiogenesis mediated by VEGF plays a critical role in tumour progression
- Targeting the VEGF signaling pathway is an important current approach in cancer therapy.
- Bevacizumab (Avastin) has been approved for the treatment of many advanced cancers, including colorectal cancer, non–small cell lung cancer, breast cancer, renal cell carcinoma and glioblastoma multiforme.



Bevacizumab Increases Risk for Severe Proteinuria in Cancer Patients

[Shenhong Wu](#),^{✉*} [Christi Kim](#),^{*} [Lea Baer](#),[†] and [Xiaolei Zhu](#)[‡]

- Systematic review and meta-analysis of RCTs
- 16 studies, 12,268 patients with variety of tumours
 - ◆ Bevacizumab 6482; Control 5786
- Incidence of high grade (3 & 4) proteinuria: 2.2-4.3%
- Bevacizumab combined with chemotherapy vs chemotherapy significantly increased risk (4.79 fold)
- Dose dependent ($p=0.009$)
- Renal cell carcinoma has highest risk (incidence 10%)
- No difference between platinum and non-platinum based chemotherapy ($p=0.39$)



Proteinuria is a class effect of VEGF inhibitors

- Also recognised with axitinib, VEGF Trap, sorafenib, sunitinib
- Proteinuria risk is included in product insert (Bevacizumab):
 - ◆ Discontinue in nephrotic syndrome
 - ◆ Suspend if proteinuria $\geq 2\text{g}/24\text{hr}$
 - ◆ Resume when proteinuria $< 2\text{g}/24\text{ hr}$
- Other patterns of nephropathy reported
 - ◆ Membranous, IgA



Multiple VEGF dependent pathways

■ VEGF is produced by podocytes

- ◆ Activates VEGF receptor 2 on glomerular endothelial cells (transmembrane communication)

■ Inhibition of VEGF leads to

- ◆ loss of endothelial fenestration, proliferation & integrity
- ◆ Glomerular aneurysmal change & mesangiolysis
- ◆ Subacute thrombotic microangiopathy
 - Endotheliosis; membranoproliferative changes
- ◆ Hypertension



Keep in mind a combination of pathways

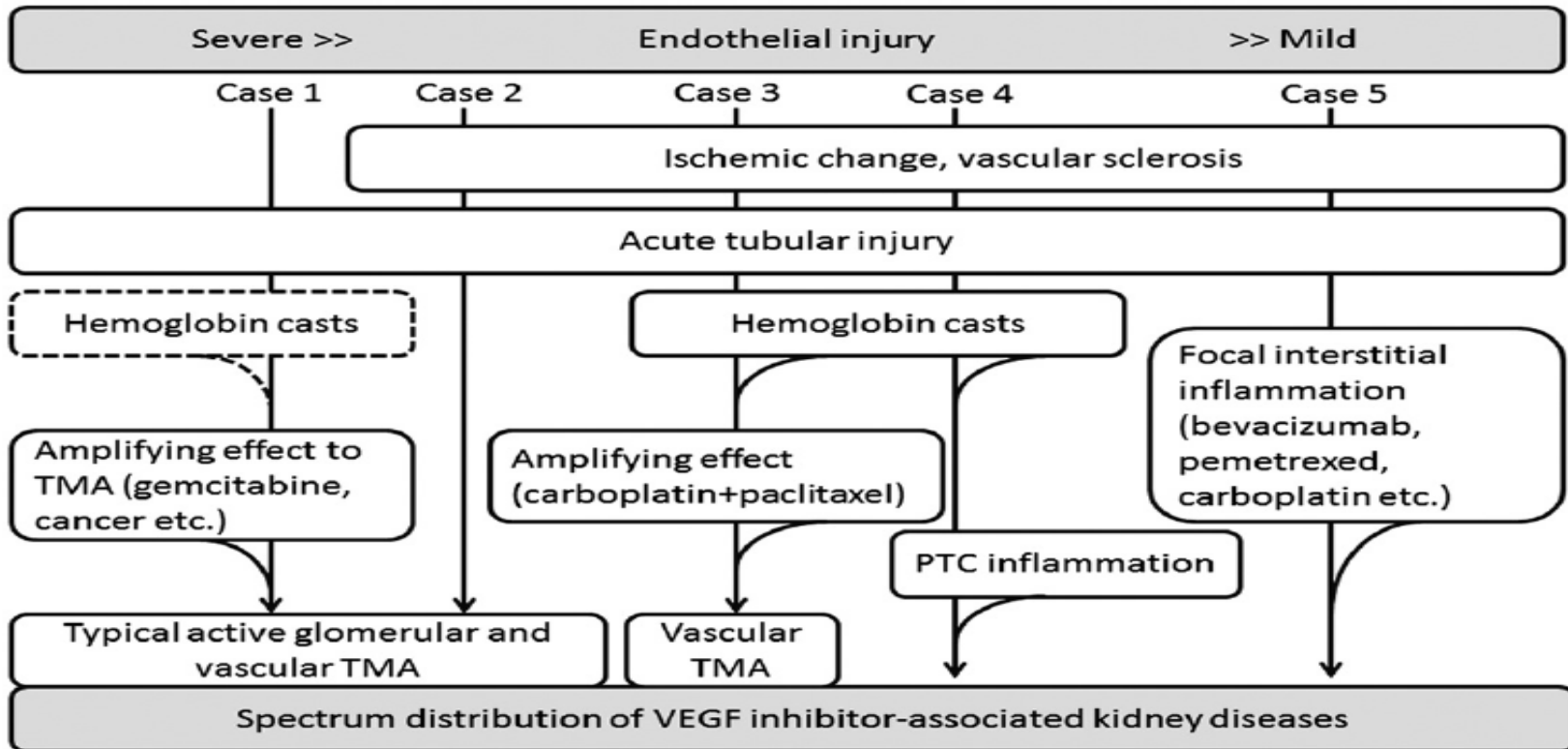


Fig. 4 Spectrum of renal pathological findings in present cases. Abbreviation: PTC; peritubular capillary.

Clinicopathological spectrum of kidney diseases in cancer patients treated with vascular endothelial growth factor inhibitors: a report of 5 cases and review of literature[☆]

Joichi Usui MD, PhD^{a,b}, Ilya G. Glezerman MD^c, Steven P. Salvatore MD^a, Chandra B. Chandran MD^d, Carlos D. Flombaum MD^c, Surya V. Seshan MD^{a,*}

Human Pathology (2014) 45, 1918–1927



Follow-up

- Stopped Avastin
- Current: Not nephrotic clinically
- Latest: Hb 12.7, creat 85 $\mu\text{mol/l}$, serum albumin 41 g/L, HbA1c 6.4%

