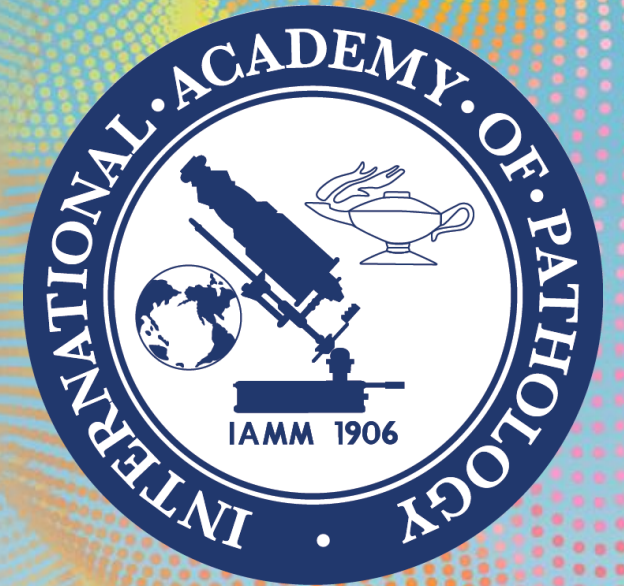


TKI INDUCED GLOMERULOPATHIES

- Dr. Mrudula Krishnaswamy
Anatomical pathology staff specialist
 - Dr. Uasim Harkus
Anatomical pathology trainee
- Concord Repatriation General Hospital/ NSW health pathology.



Disclosure of Relevant Financial Relationships

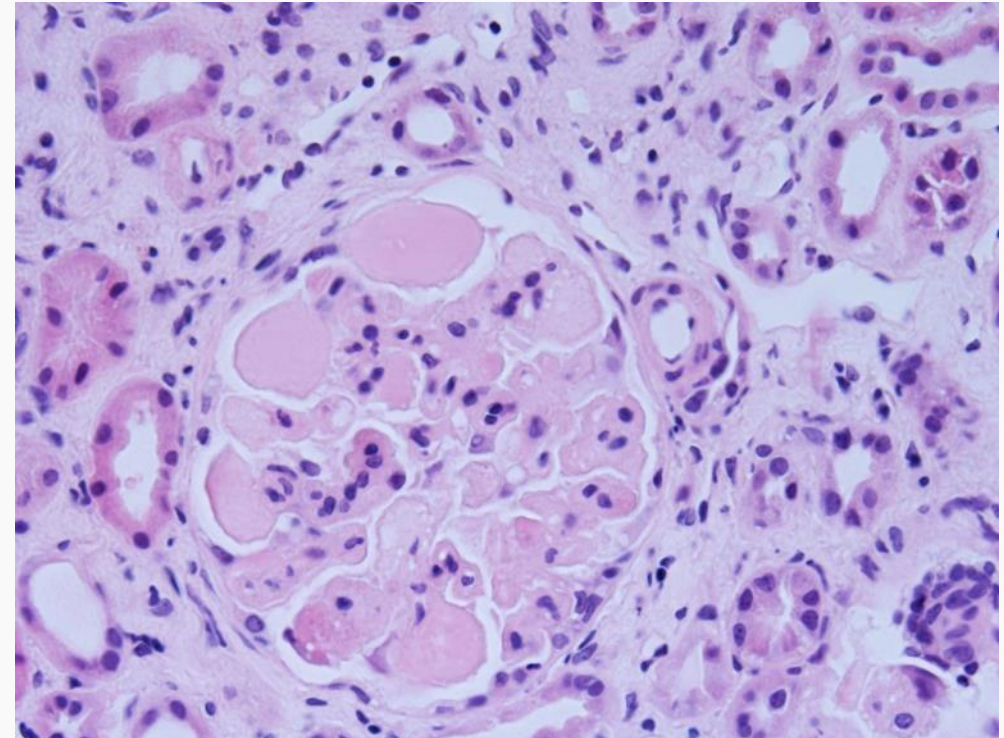
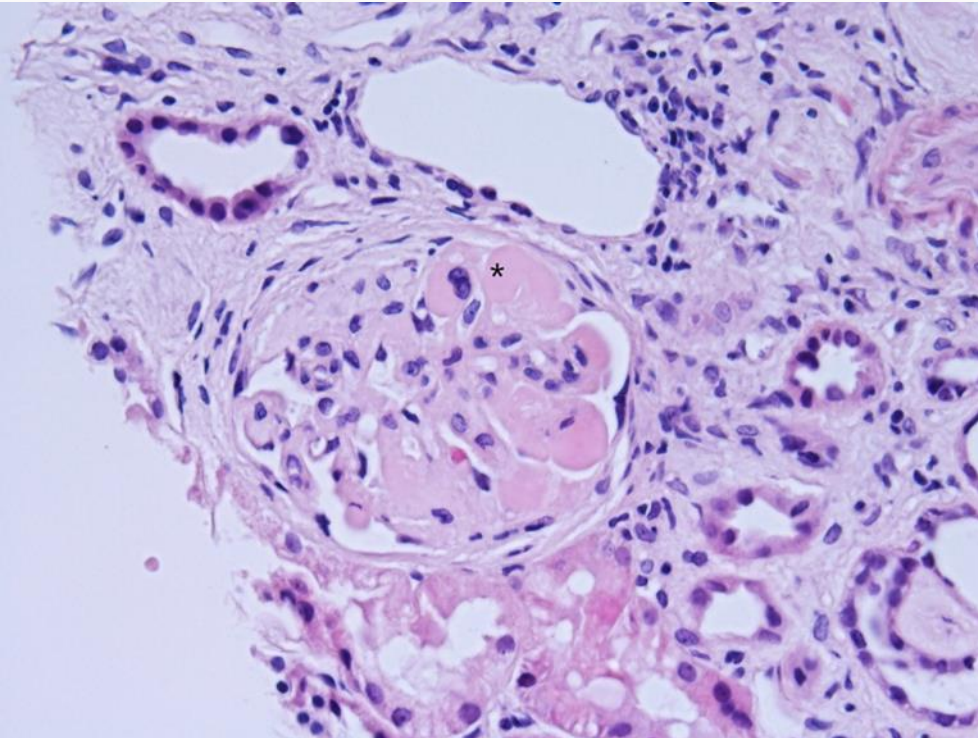
No relevant financial relationships.

PATIENT A: HISTORY

- 93-year-old male
- Papillary thyroid cancer – 2011
- Radioactive iodine 2011-2017.
- Progression of disease 2019 - Commenced on Lenvatinib 20 mg daily.
- Other PMHx: HTN, CKD
- May 2022: Serum creatinine 165 $\mu\text{mol/L}$, eGFR 30 ml/min/1.73m²
- August 2022: Serum creatinine 220 $\mu\text{mol/L}$, eGFR 21 ml/min/1.73m², nephrotic-range proteinuria (urine albumin: creatinine (uA:Cr) 603mg/mmol), reduced serum albumin (23g/L from 32g/L) and increasing exogenous thyroid hormone requirements (TSH rose to 24mIU/L from 0.78mIU/L), and Anasarca.
- Lenvatinib was withheld and a kidney biopsy was performed:

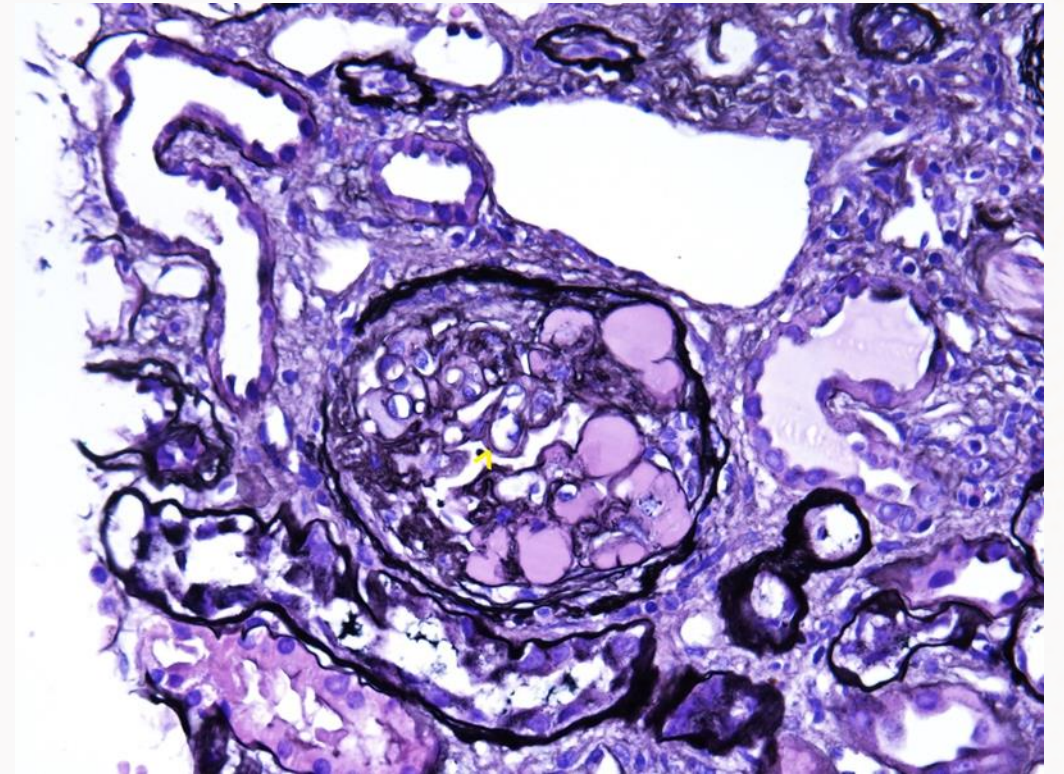
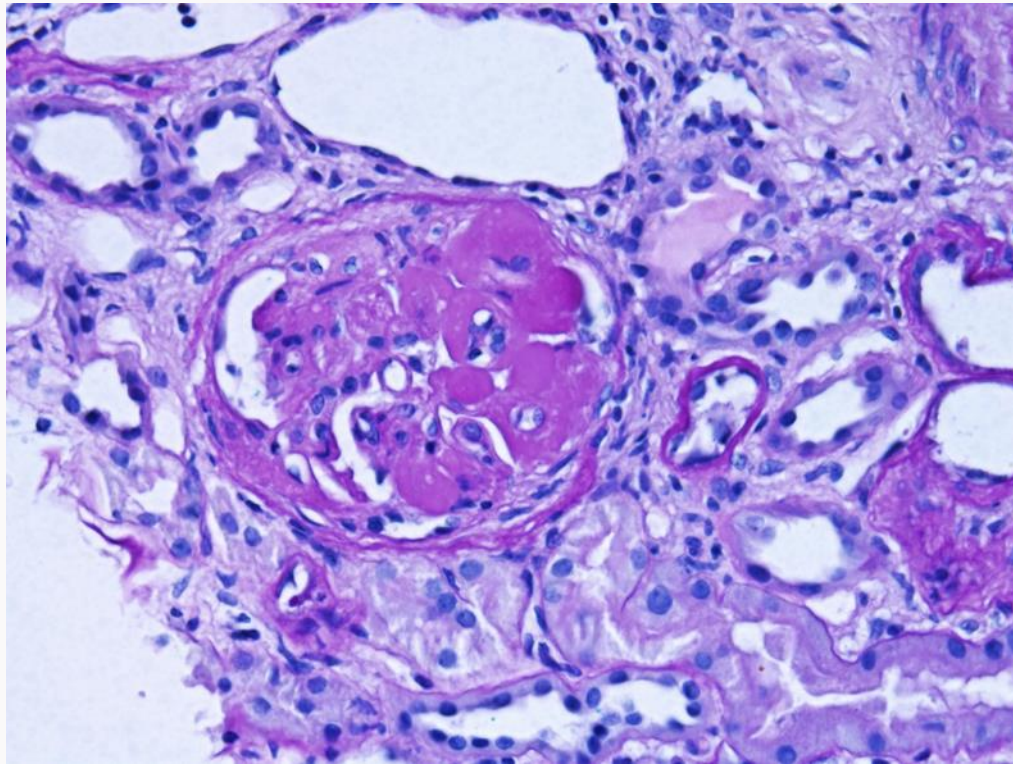
PATIENT A: KIDNEY BIOPSY - H&E

- Prominent hyaline globules formation with segmental sclerosing lesions.
- Glomerular capillary double contour formation.



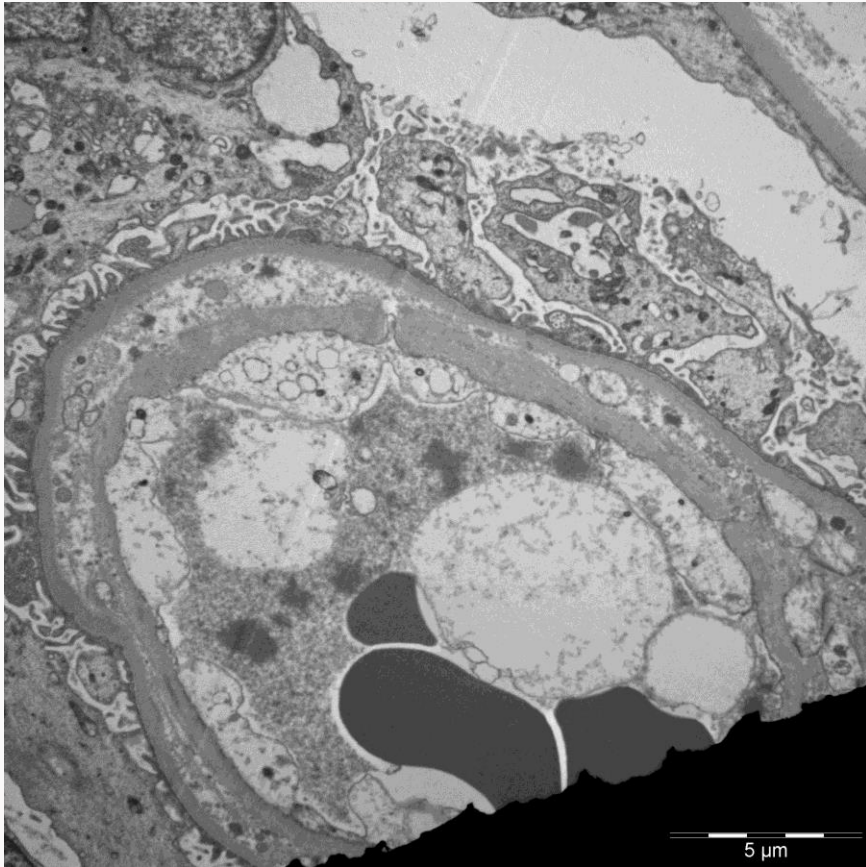
PATIENT A: KIDNEY BIOPSY ANCILLARY TESTING

- PAS + ve hyaline globules within capillary lumen and capillary loops.
- Glomerular capillary double contour formation- Methenamine silver stain.

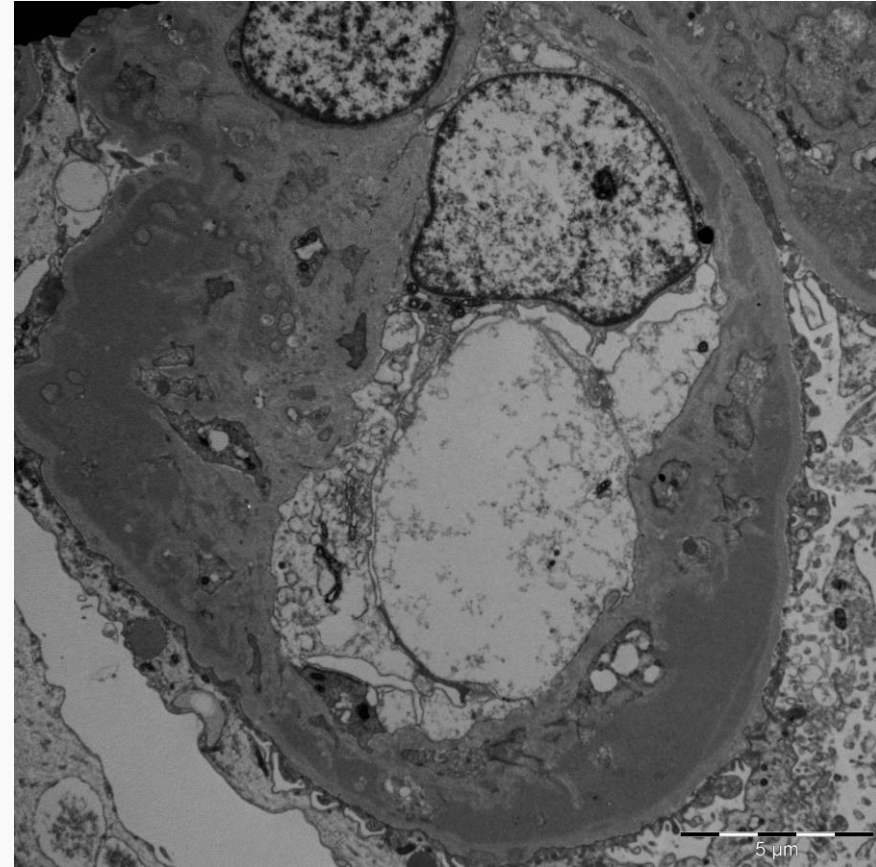


PATIENT A: KIDNEY BIOPSY - EM

- Double contour formation

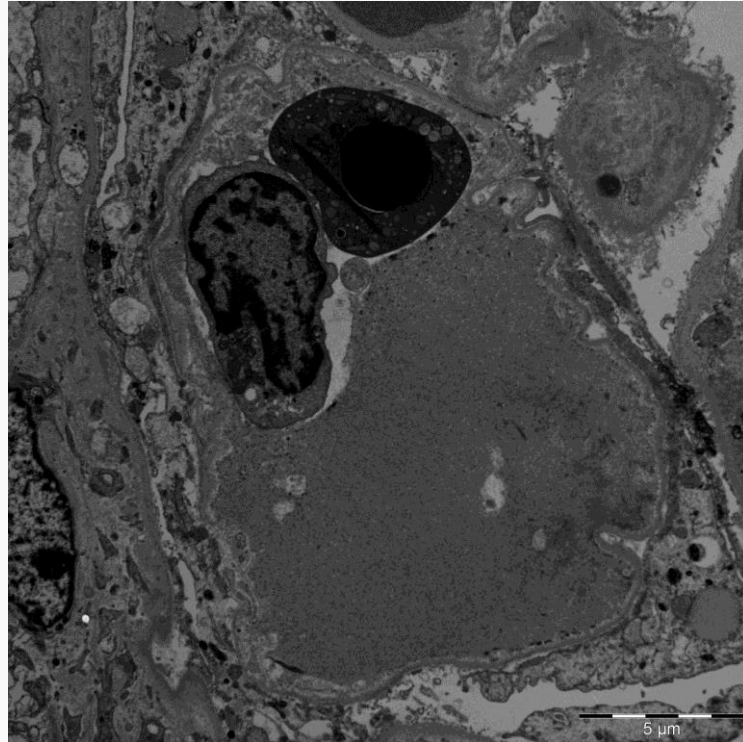


- Double contour with deposition of hyaline material



PATIENT A: KIDNEY BIOPSY - EM

- Within capillary lumen



- High power image of sub-structure

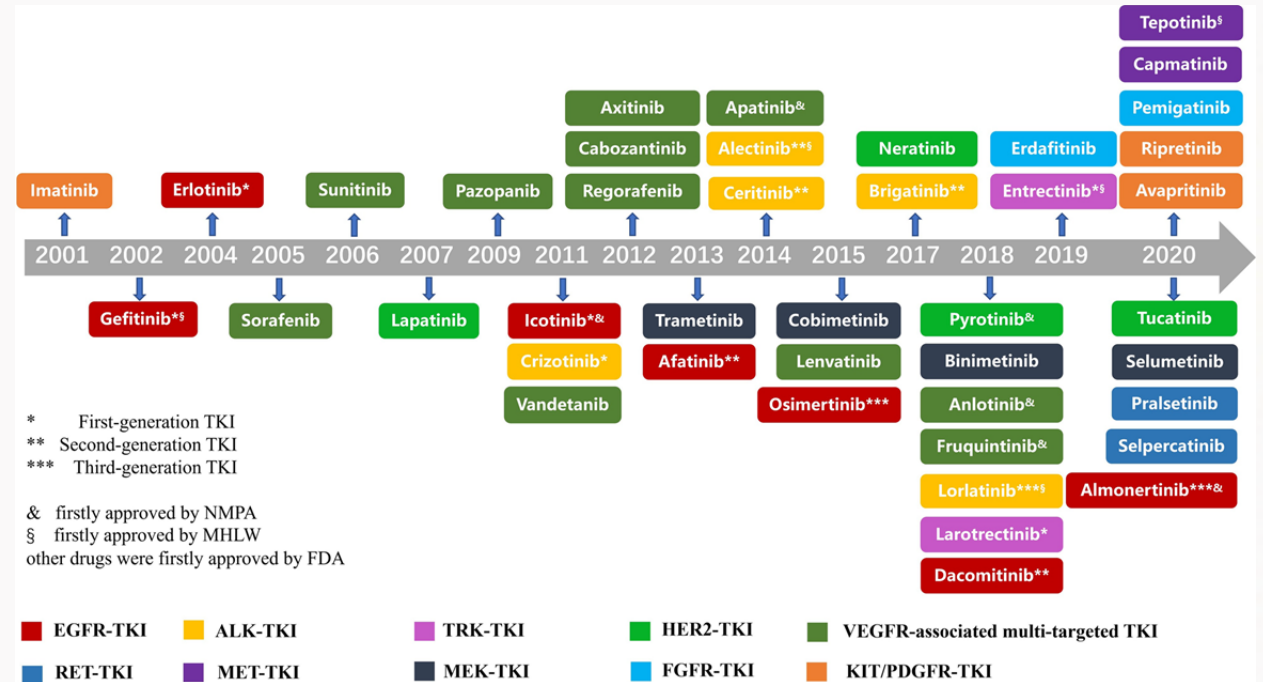


PATIENT A: PROGRESS

- Nephrotic syndrome resolved within two months of Lenvatinib cessation and supportive treatment with diuretics and renin-angiotensin system (RAS) blockers.
- Serum albumin rose to 39g/L with uA:Cr falling to 47mg/mmol.
- His kidney impairment peaked at a Cr of 350umol/L (eGFR 12ml/min/1.73m²) in January 2023 but subsequently settled to a new baseline of Cr 233umol/L (eGFR 20ml/min/1.73m²).

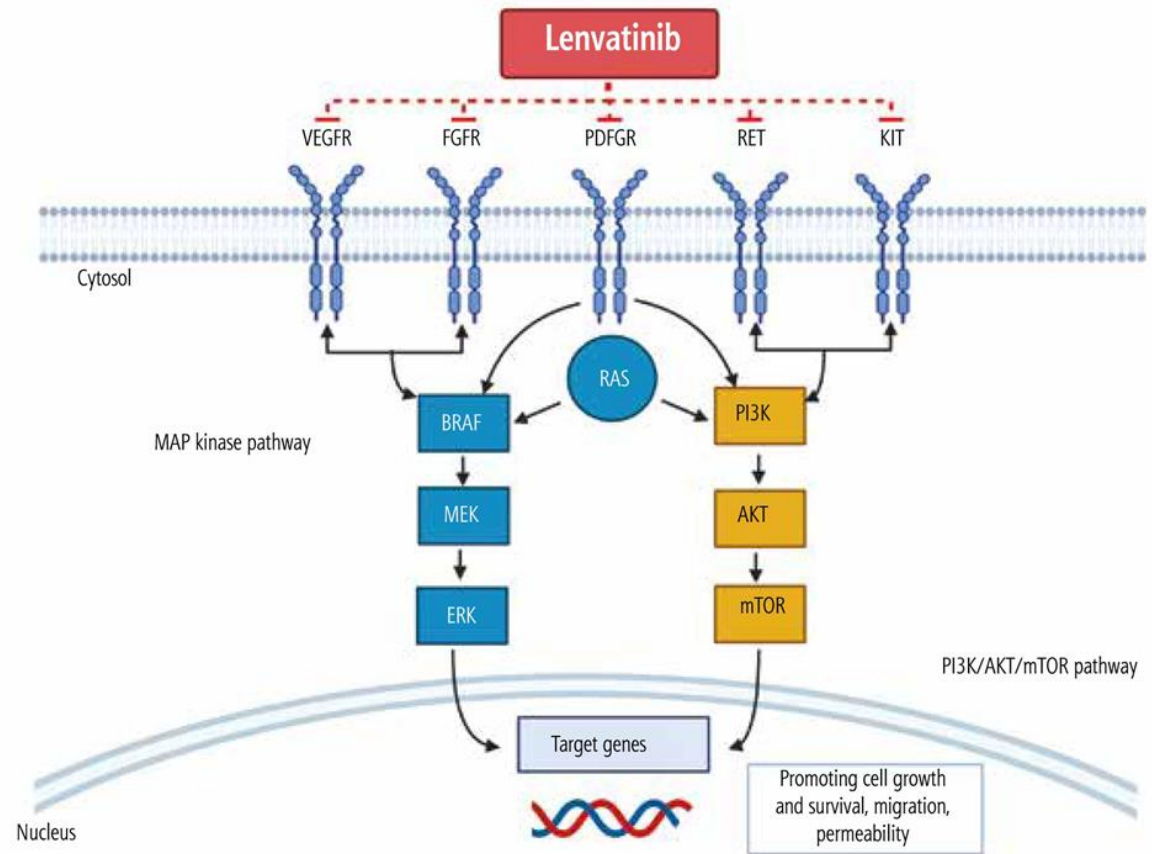
TKI IN CANCER TREATMENT

- Abnormal activation of tyrosine kinases is implicated in tumorigenesis, progression, invasion, and metastasis of malignancies.
- Wild-type tyrosine kinases can also function as critical nodes for pathway activation in cancer.
- TKI targets include EGFR, ALK, ROS1, HER2, NTRK, VEGFR, RET, MET, MEK, FGFR, PDGFR, and KIT.
- Some TKIs block a broader range of targets, such as VEGFR-associated multi-targeted TKIs.



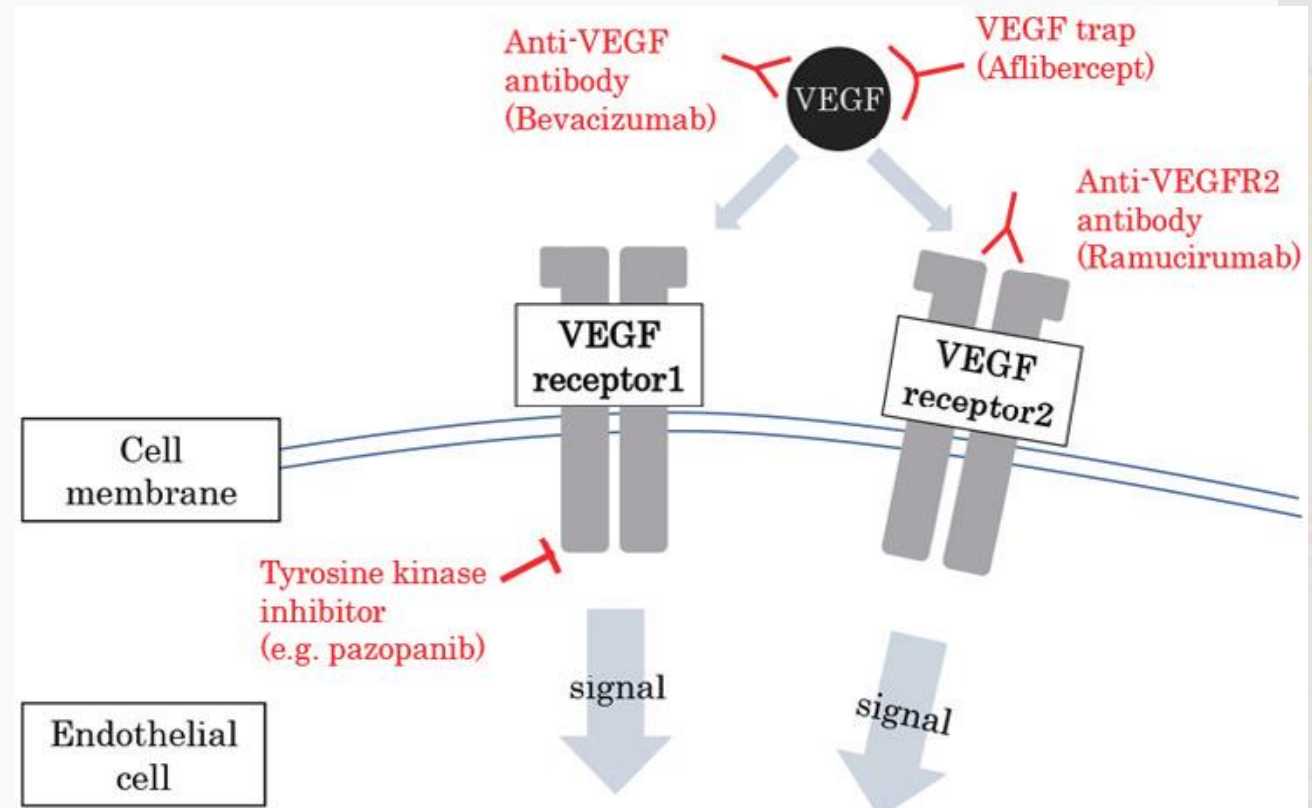
TKI EFFECT ON KIDNEYS

- Imatinib - Decline in GFR and new-onset CKD in 22% of patients.
- Bosutinib - Renal toxicity in <10% of patients.
- Lenvatinib - minimal change nephrotic syndrome/ focal segmental glomerulosclerosis-like lesions (cFSG), thrombotic microangiopathy (TMA), podocytopathy and renal tubule damage.



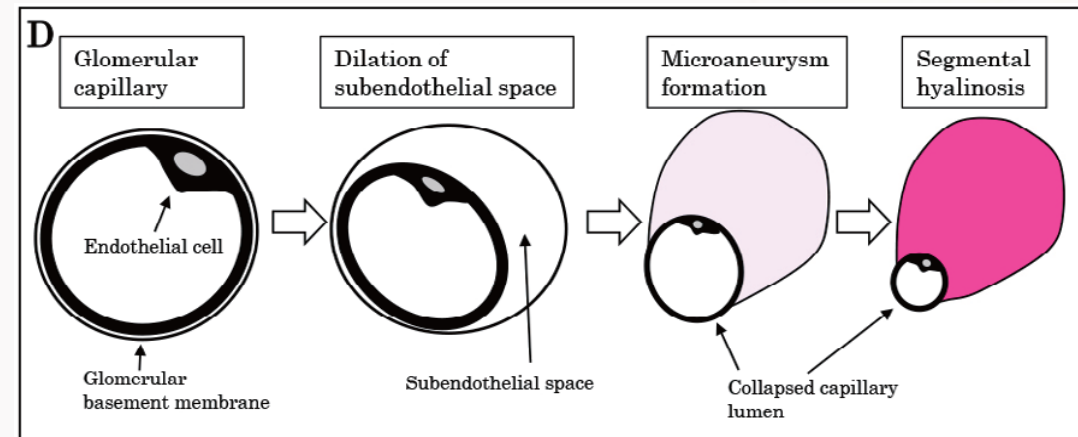
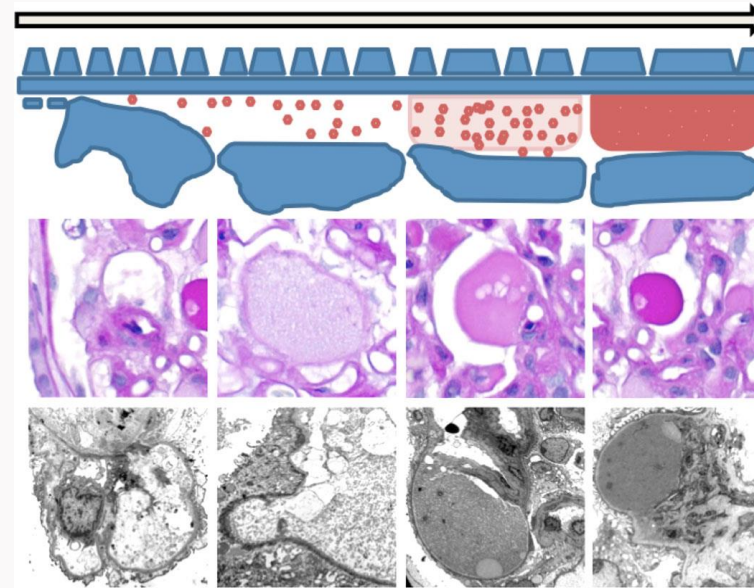
VEGF ROLE IN KIDNEY PHYSIOLOGY

- VEGF preserves the integrity of glomerular capillaries in the kidneys.
- VEGF, produced by podocytes, binds to VEGFRs on endothelial cells
- VEGF elicits an autocrine effect on podocytes.
- Anti-VEGF effect - impair the function of glomerular capillary walls by blocking communication between endothelial cells and podocyte.



VEGF ANTAGONISM EFFECT

- Microaneurysms with detached, collapsed endothelial cells filled with pale material and segmental capillary hyalinoses.
- Fibrin thrombus formation and fragmented erythrocytes are relatively infrequent findings.
- Inhibition of VEGF–VEGFR crosstalk - chronic glomerular TMA
- Endothelial leakage, formation of microaneurysms filled with proteinaceous fluid, that solidify to segmental hyalinoses.
- Formation of GBM double contours.
- Podocytic changes and segmental glomerulosclerosis might evolve secondarily .



CONCLUSION

- Renal dysfunction has been associated with TKI therapy.
- Variable changes including minimal change nephrotic syndrome/ focal segmental glomerulosclerosis-like lesions (cFSG), thrombotic microangiopathy (TMA) like changes, podocytopathy and renal tubule damage have been reported.
- Inhibition of the VEGF receptor can lead to endothelial damage/leakage, causing chronic glomerular TMA with specific morphological changes including the formation of PAS +ve hyaline globules and capillary double contour formation .
- Cessation of the causative agent can improve kidney function.

REFERENCES

- Nakashima, S., Sekine, A., Sawa, N., Kawamura, Y., Kono, K., Kinowaki, K., Kawada, M., Hasegawa, E., Akuta, N., Suzuki, Y., Ohashi, K., Takaichi, K., Ubara, Y., & Hoshino, J. (2022). Thrombotic microangiopathy, podocytopathy, and damage to the renal tubules with severe proteinuria and acute renal dysfunction induced by lenvatinib. *Internal Medicine*, *61*(20), 3083–3088. <https://doi.org/10.2169/internalmedicine.8365-21>
- Huang, L., Jiang, S. & Shi, Y. Tyrosine kinase inhibitors for solid tumors in the past 20 years (2001–2020). *J Hematol Oncol* **13**, 143 (2020). <https://doi.org/10.1186/s13045-020-00977-0>
- Rehman O, Jaferi U, Padda I, et al. Overview of lenvatinib as a targeted therapy for advanced hepatocellular carcinoma. *Clinical and Experimental Hepatology*. 2021;7(3):249-257. doi:10.5114/ceh.2021.109312.
- Shyam Sunder, S., Sharma, U.C. & Pokharel, S. Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. *Sig Transduct Target Ther* **8**, 262 (2023). <https://doi.org/10.1038/s41392-023-01469-6>
- Pfister F, Amann K, Daniel C, et al. Characteristic morphological changes in anti-VEGF therapy-induced glomerular microangiopathy. *Histopathology*. 2018;[73](https://doi.org/10.1111/his.13716)(6):990–1001. doi: 10.1111/his.13716
- Ozawa M, Ohtani H, Komatsuda A, Wakui H, Takahashi N. VEGF-VEGFR2 inhibitor-associated hyaline occlusive glomerular microangiopathy: a Japanese single-center experience. *Clin Exp Nephrol*. 2021 Nov;25(11):1193-1202. doi: 10.1007/s10157-021-02090-z. Epub 2021 Jun 11. PMID: 34115234.

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THANK YOU!

