Between The Rock and The Kidney

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Disclosure of Relevant Financial Relationships

This case is courtesy of Dr. Jing Jing Li

Staff Specialist, Liverpool Hospital AP.

No relevant financial relationship.

History

- 69 years, Female.
- Advanced ovarian cancer (diagnosed March 2021)
- Chemotherapy history: carboplatin, paclitaxel, bevacizumab and gemcitabine
- Refractory hypertension.
- Elevated Kappa Serum free light chain (600mg/ml).
- Elevated protein/creat ratio: 310.5 mg/mmol cr.
- Elevated microalbumin/creat ratio: 262.1 mg/mmol cr
- No paraproteins in urine.
- Past history of IgA diagnosed 20 years ago….

History

- Renal function deteriorates slowly over 8 months.
- Creatinine: H 210 micro mol/L,
- Urea: H 21.5 mmol/L.
- Estimated GFR: L 25 mL/min/1.73m^2

Medications

Hypertension medications: furosemide 40mg BD, telmisartan 80mg nocte , prazosin 1mg TDS, hydrochlorothiazide 12.5mg, Spironolactone 12.5mg, amlodipine 20mg.

Maintenance Chemotherapy: gemcitabine and bevacizumab.

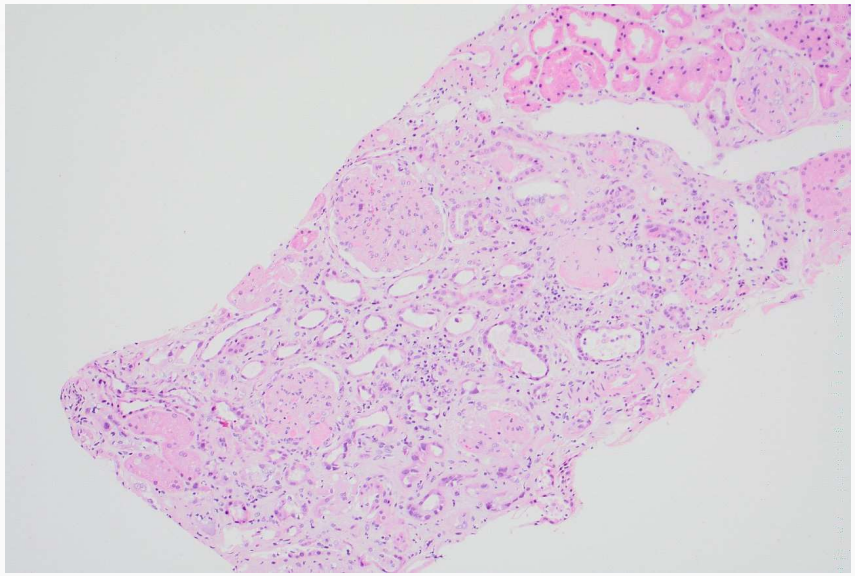
- The patient’s hypertension was not responding to multiple medications with increased tiredness and headaches.
- Breaks of the maintenance chemotherapy was applied to try to control the blood pressure.
- Systolic pressure 190.

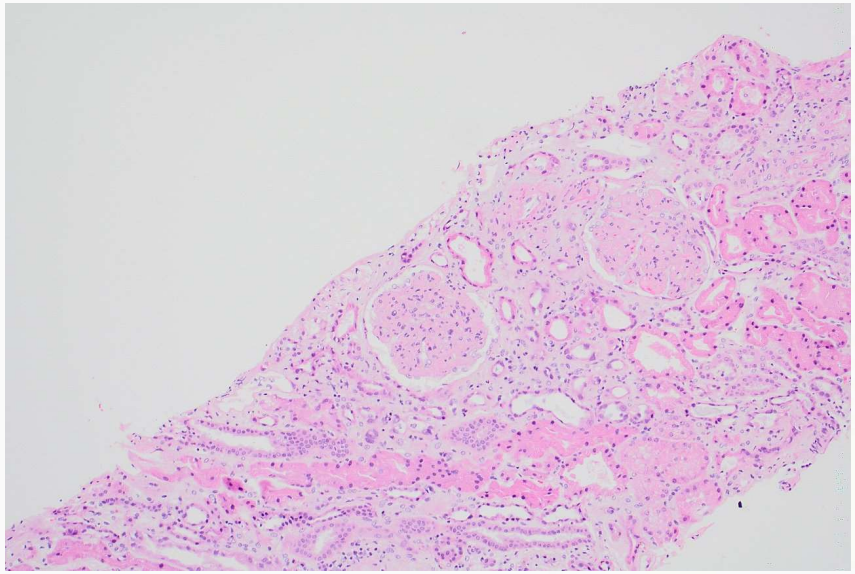
Clinical question

? Amyloid or light chain disease, ? Immunotherapy related GN

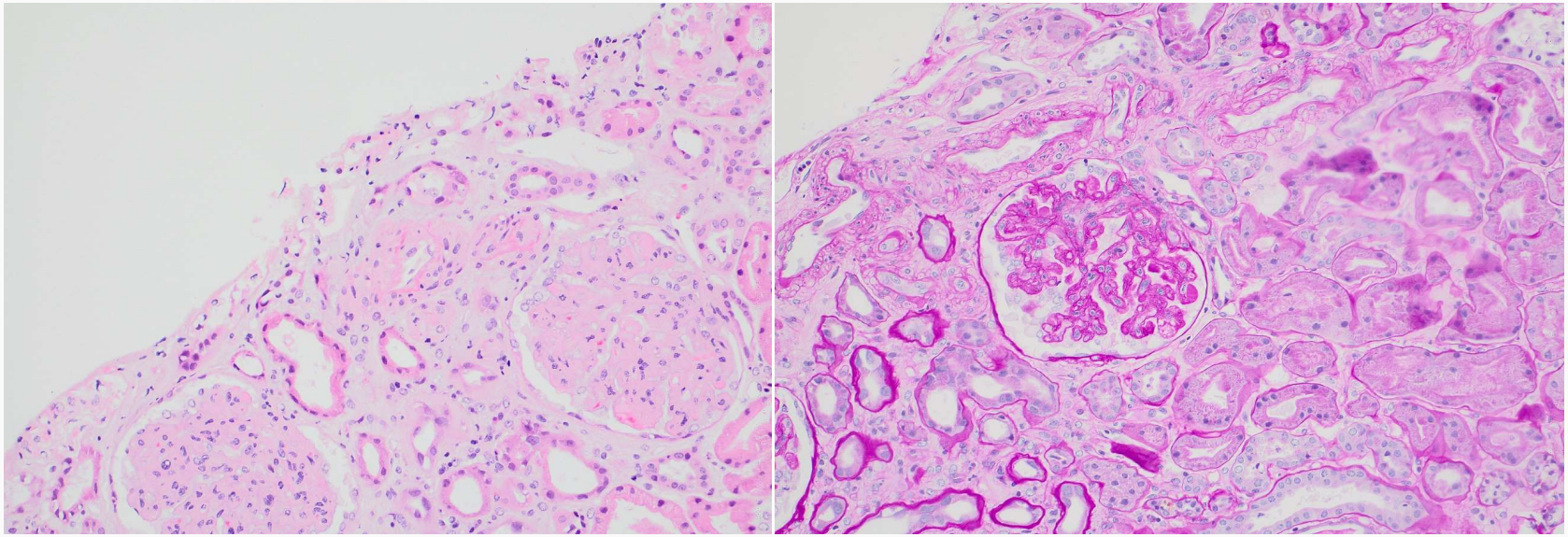
? Recurrent IgA

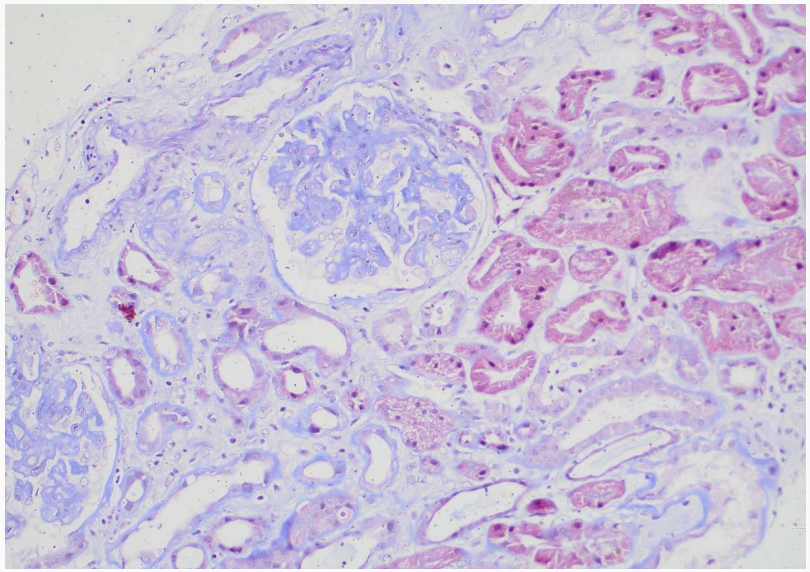
H&E

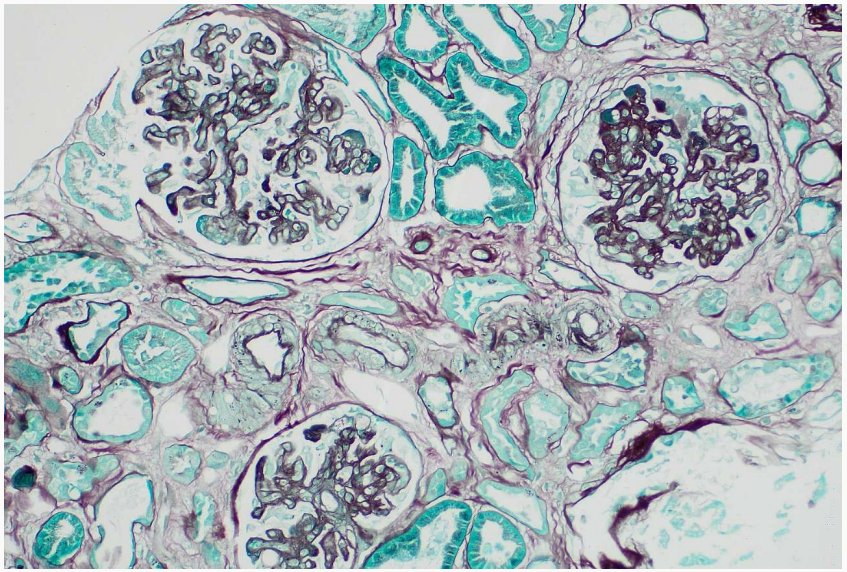




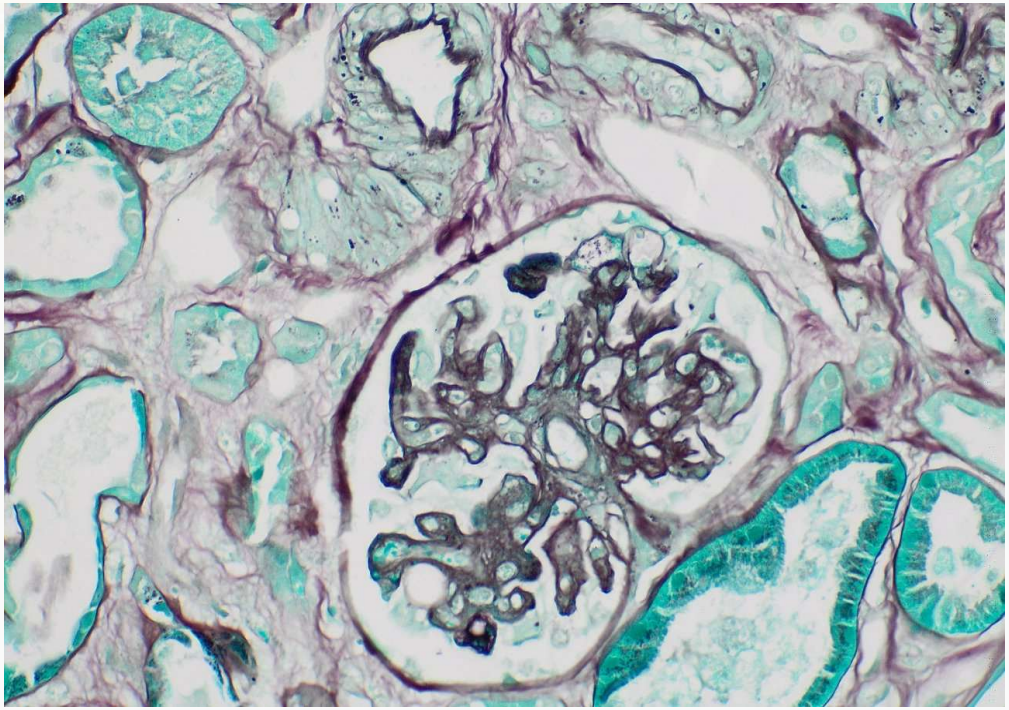
Blood less gloms, hyaline droplets



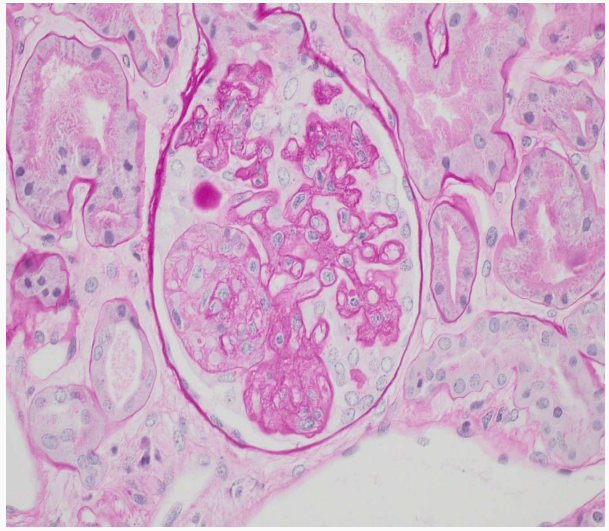


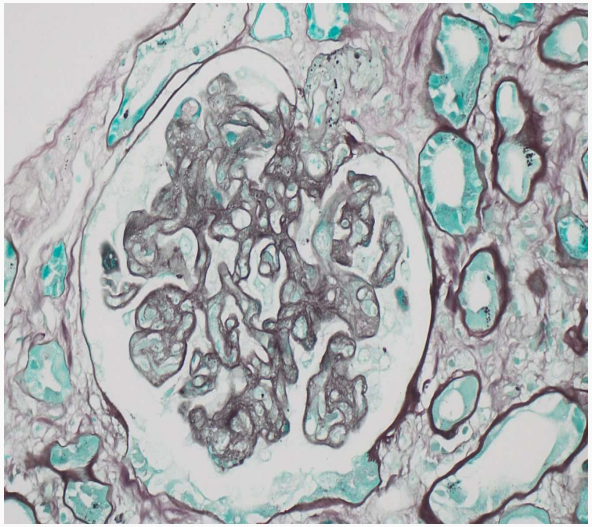


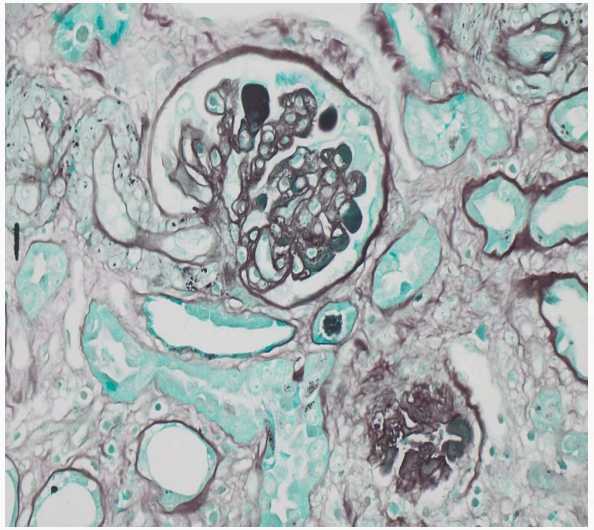
Mesangiolysis and double contours



Double contours







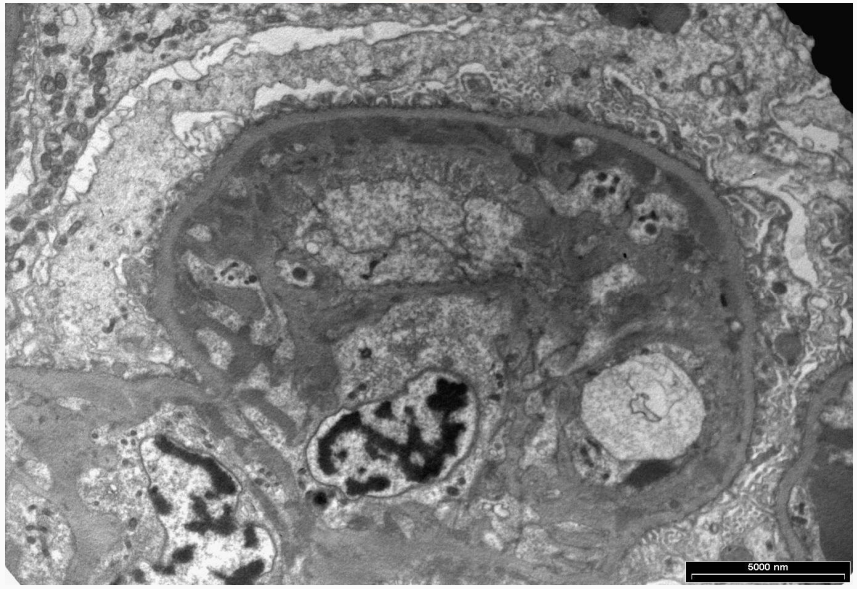
Summary:

- 7 sclerosed gloms /26.
- Viable gloms are bloodless.
- Intracapillary hyaline and foam cells with mesangiolysis.
- GBM shows double contours.
- Ischemic collapse of some glomeruli, visceral podocytes hyperplasia.
- Mild tubular atrophy and interstitial fibrosis.
- No interstitial inflammation.
- Arterioles are normal and one artery show duplication of the internal elastic lamina
- Congo red is negative.

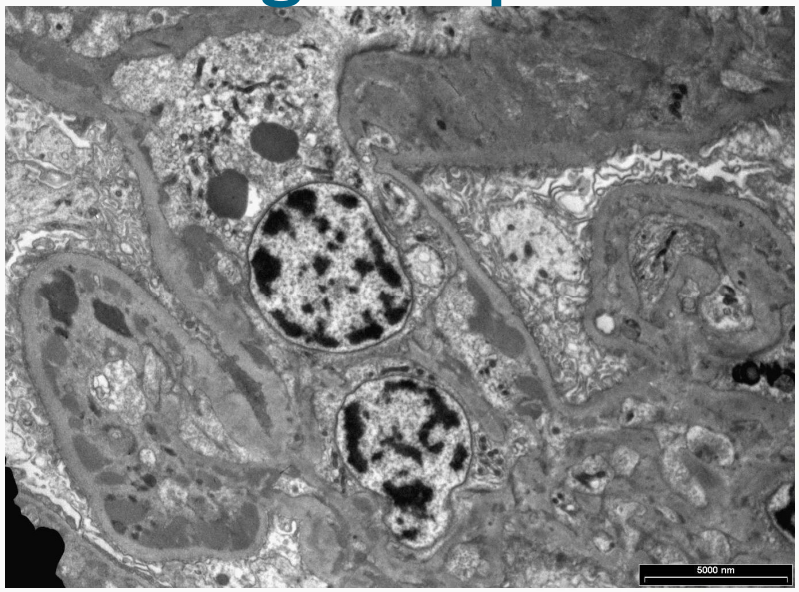
IF

- IF sections contains only one sclerosed glom.
- Negative staining for IgA, IgG, IgM, C3, C1Q, kappa, lambda and fibrinogen.
- Immunohistochemical stains were also negative.

Double contoured GBM



Subendothelial and mesangial deposits



EM summary

- Double contours and widening of the subendothelial space, in keeping with thrombotic microangiopathy.
- Mesangial and subendothelial deposits of uncertain nature.

Thrombotic microangiopathy

Is a morphological pattern, can result from a number of conditions;

- The common association HUS and TTP, others
- Drugs (quinin, mitomycin, cyclosporin, clopidogrel, more recent monoclonal antibodies therapies used in cancer)
- Irradiation
- Malignant hypertension
- Scleroderma
- Antiphospholipid syndrome
- Chronic transplant glomerulopathy
- others

Thrombotic microangiopathy

- Microvascular endothelial injury and thrombosis
- Prothrombotic state
- Complement mediated injury
- The classic example is TTP due to deficiency of ADAMTS13, zinc metalloproteinase that cleaves vWF multimers with resultant prothrombotic state.
- The effect in the kidney can be acute or chronic.

Kidney

- Bloodless glomeruli, thickening of capillary wall, duplication of GBM.
- Focal and segmental glomerulosclerosis.
- Mesangiolysis and microaneurysms.
- Micro thrombi
- Sometimes necrosis within the tufts.
- Features of malignant hypertension can be seen if the main cause in HTN (intimal mucoid edema or sclerosis, onion skinning, endothelial swelling and fibrinoid necrosis).
- Some interstitial fibrosis and tubular atrophy can occur.

Continue

IF:

•Thrombi in glomeruli and blood vessels stain for fibrinogen

•Nonspecific entrapment of C3 and IgM in glomeruli.

EM:

•Increased matrix in mesangium and subendothelium

•Duplication of GBMs

•Mesangial cell interposition

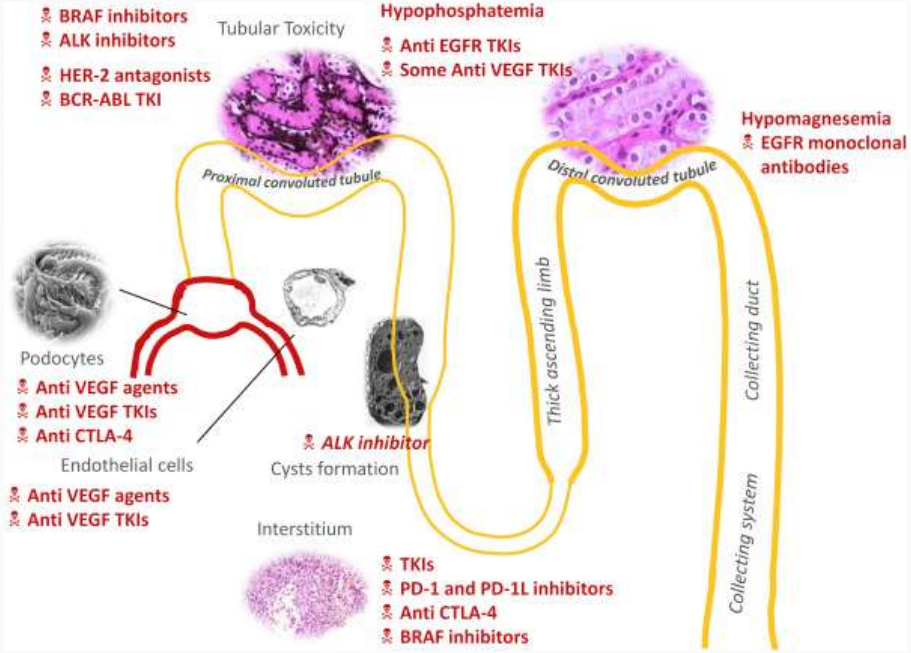
•Podocyte foot processes often effaced

Targeted therapies effect

- Targeted therapies provide better outcome for cancer patients, with this there is still some adverse effect including renal toxicities:
- Electrolytes disturbances(mostly hypokalemia then hypomagnesaemia and hyponatremia)
- Renal impairment
- Hypertension

Effect of some targeted therapies on the kidney

Jhaveri KD, Wanchoo R, Sakhiya V, Ross DW, Fishbane S. Adverse Renal Effects of Novel Molecular Oncologic Targeted Therapies: A Narrative Review. Kidney Int Rep. 2016 Sep 21;2(1):108-123.



Anti VEGF & Anti VEGFR

Anti angiogenic therapy is used to reduce the vascular supply of tumours. Bevacizumab and aflibercept can produce asymptomatic albuminuria, nephrotic syndrome and TMA.

- The VEGF ligand inhibitors (bevacizumab and aflibercept) bind to the VEGF molecule, preventing it from binding to the receptor → inhibition of endothelial proliferation and neovascularization.
- Can also affect podocytes→ renal limited TMA

Anti VEGF & Anti VEGFR

- The effect and the severity is affected by the patient's pre-existing conditions, particularly renal disease.
- Proteinuria is common to all agents targeting VEGF pathway, however factors associated with occurrence and severity are unknown.
- Thought to be due to disruption of glomerular filtration barrier.

Anti VEGF & Anti VEGFR

The hypertension is multifactorial:

- Reduced levels of nitric oxide → endothelial dysfunction, capillary rarefaction, pressure natriuresis and decreased lymphangiogenesis→ fluid overload → HTN.
- Those patients might need to change their HTN medications into a new class.

Blood pressure control

- First class: (ACEI) or angiotensin receptor blocker (ARB) inhibition
- Second class: Calcium channel blockers.
- If this fails centrally acting antihypertensive or diuretic agent is added and close monitoring is required.

Between the rock and the kidney

The decision to discontinue or change therapy is based on balancing the response and the effect and on an MDT setting after reviewing the renal biopsy, but in general

- If the patient develops hypertensive crisis or encephalopathy, cancer the treatment need to be discontinued.
- Nephrotic-range proteinuria and TMA are generally considered reasons to discontinue the offending agent.

After biopsy, in this case

- A decision wad made to stop bevacizumab treatment.
- Antihypertensive medications modified with dose reduction.
- Blood pressure starts to improve, 135/80 two months after stopping bevacizumab.

Last oncology visit during May 2024

- The patient's blood pressure is still controlled.
- Urea: H 11.1 mmol/L, creatinine: H 138 µmol/L, microalbumin/Create: H 175.1 mg/mmol cr.
- Estimated GFR :L 34 mL/min/1.73m²

References

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Dr. Jing Jing Li

Thank you.