ISRTP: Case of the Month-May,23

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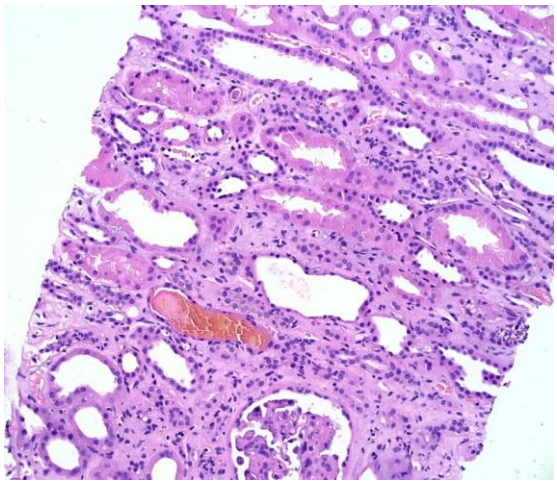

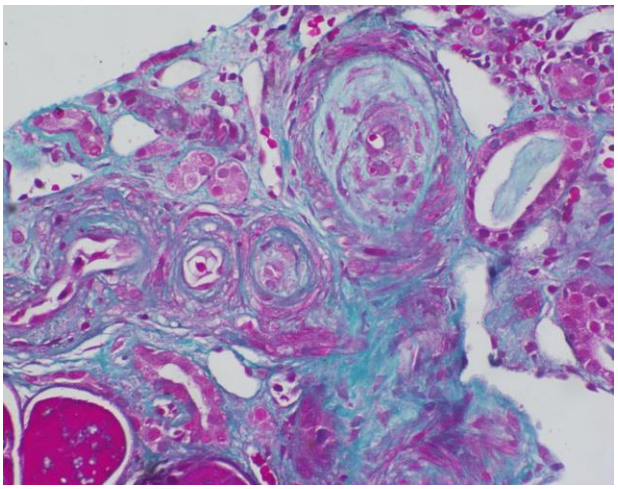

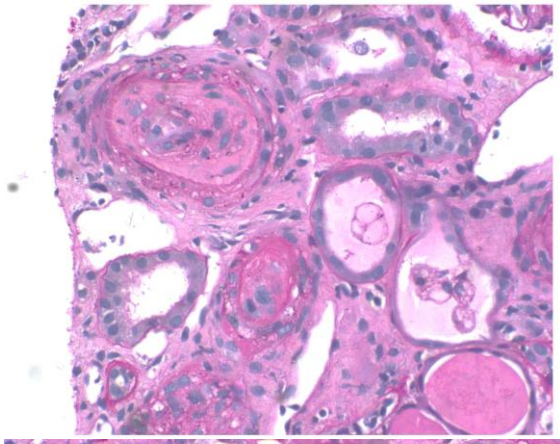

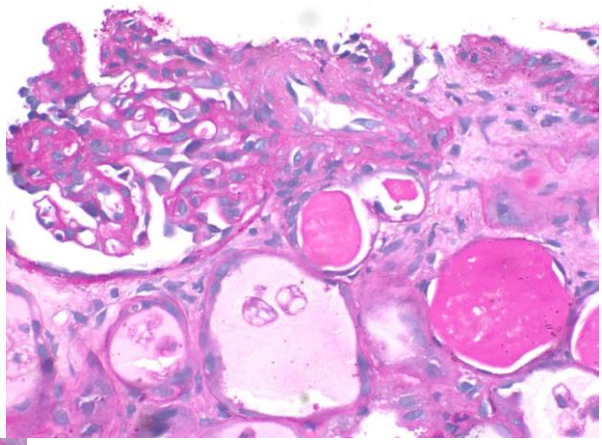

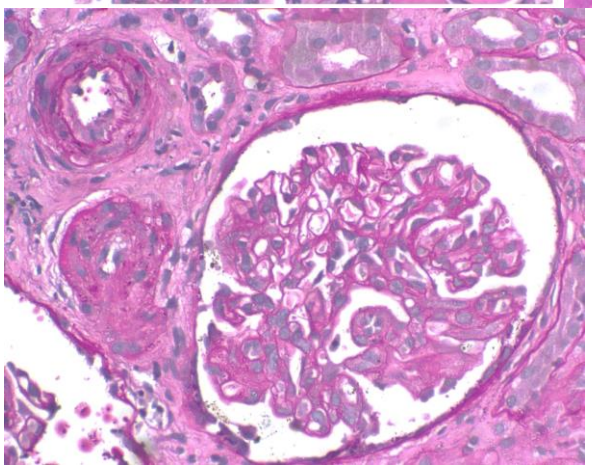

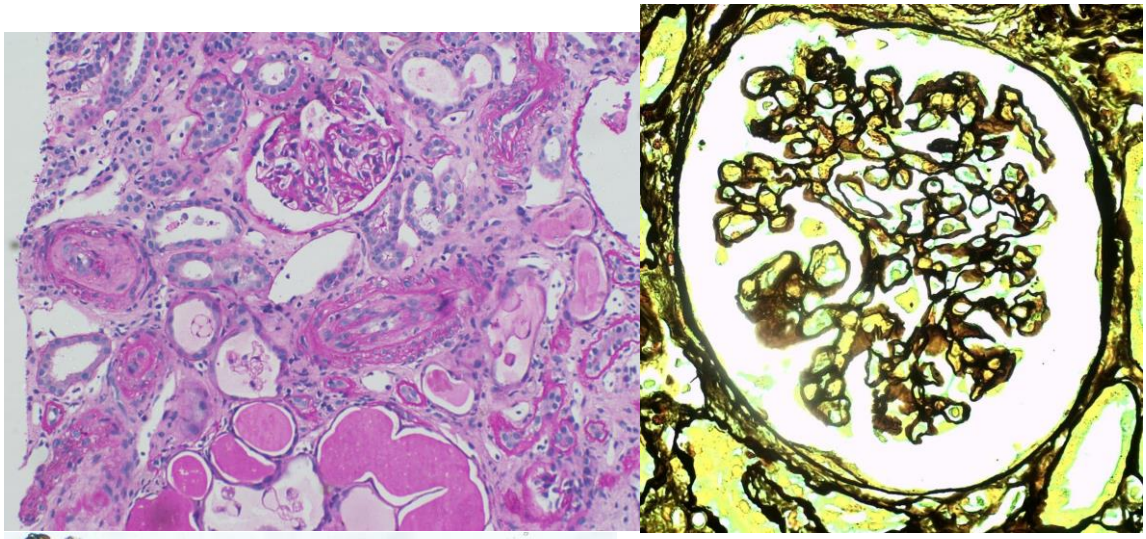

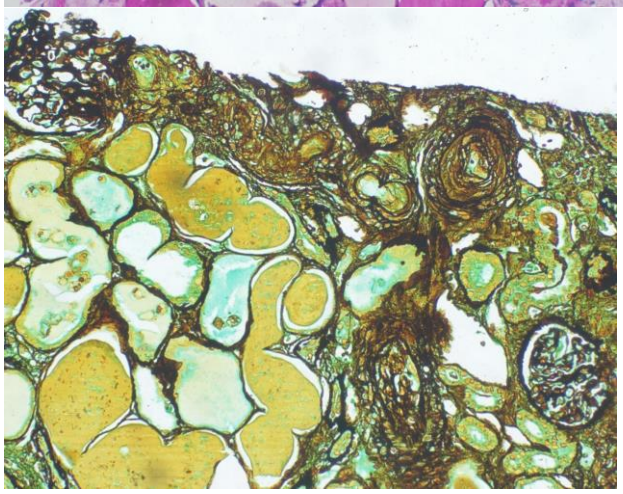

This 33 years male patient recently diagnosed with hypertension (BP 212/160 mmHg) and presented with moderate renal failure with bilateral normal sized kidneys and active urinary sediments. With clinical presentation of renal failure with anemia with transient thrombocytopenia with hypertension, ffurther work up planned for **Thrombotic Microangiopathy (TMA), Rapidly Progressive Renal Failure (RPGN)and Secondary hypertension** (RAS axis) and kidney biopsy planned.

Pointers towards TMA:

- Anemia (+)
- Thrombocytopenia (transient +)
- LDH=1426 (+)
- Indirect bilirubin=2.0mg/dl (+)
- 4-5% schistocytes on PBS (+)

Pointers towards Glomerular: RPGN/Acute on CGN:

- Urinary active sediments (+)
- Proteinuria (+)
- E/o chronic HTN: grade IV HR on fundus examination(+)

Pointers towards Secondary hypertension:

- Hypokalaemia (+)

- Alkalosis (+)
- **Fundus examination** revealed multiple **hemorrhages** and **grade IV HTR**.
- ECG showed changes s/o **LVH with strain** pattern.

Renal Artery Doppler: **WNL**

Kidney biopsy performed:

- Renal biopsy evaluated with 3 micron serial sections stained with H&E, PAS, PSM and Masson Trichrome (MT) stain.
- Biopsy showed had sixteen glomeruli with 2/16 had global glomerulosclerosis, 1/16 had fibrocellular crescent.
- Rest all glomeruli showed fibrillary appearance, thickened capillary wall and blending of mesangial area with the capillaries and ischemic wrinkling and focal duplication of GBM
- Blood vessels were thickened with mucous interstitial change, near luminal occlusion by thrombi and fragmented RBC in wall
- Mild Acute Tubular Injury (ATI) with moderate Interstial Fibrosis and Tubular Atrophy (IFTA) was present.
- Direct Immunofluorescence: negative for IgG, IgM, IgA, C3 and C1q.

BIOPSY DIAGNOSIS: LIKELY ACCELERETED HYPERTENSION RELATED ACUTE AND CHRONIC TMA

- **Features S/O Acclereated hypertension related TMA:**
    - Higher BP at presentation
    - Signs of HTN-heart disease
    - HTN retinopathy
    - Relatively higher platelet count
    - Significant renal failure

Patient managed with stopping amlodipine, metoprolol, arkamine and switched to dilzem, prazopress and BP monitoring. At the time of discharge patient's blood pressure was adequately controlled and was symptomatically better and dialysis independent.

Further workup suggested

- Workup for RAAS activation
- Workup for primary TMA
    - Anti CFH Ab
- Workup for Thrombotic Thrombocytopenic Purpura
    - ADAMTS13

Discussion:

TMA describes a specific pathologic lesion in which abnormalities in the vessel wall of arterioles and capillaries lead to microvascular thrombosis. TMA is a pathologic

diagnosis made by tissue biopsy, typically a kidney biopsy. However, it is commonly inferred from the observation of Microangiopathic hemolytic anemia (MAHA) and thrombocytopenia in the appropriate clinical setting.[1] TMA presents both clinically and histologically in two main forms; acute and chronic TMA.

There are two classic TMAs, hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura, as well as an atypical HUS. Atypical HUS includes a broad spectrum of disorders with diverse aetiologies and shares clinical manifestations with classic TMA; however, it frequently lacks typical clinical and laboratory findings. These traits can confuse clinicians and pathologists in terms of renal pathologic diagnosis, especially in cases where TMA is associated with other glomerulopathies or hypertensive renal disease.[2]

Table 1 Etiological Classification of TMA[3]

Typical Hemolytic Syndrome (HUS)	**Atypical HUS (& Forms of TMA; Clinical Overlap With TTP)**	**Thrombotic Thrombocytopenic Purpura (TTP)**
Enteropathogenic infections (Escherichia coli, Shigella dysenteriae)	Nonenteric infections (e.g., Streptococcus pneumoniae, HIV, Mycoplasma pneumoniae, Coxsackie A & B)	Familial (Mutations in gene encoding ADAMTS13, a vWF cleaving protease; large vWF multimers cause increased platelet aggregation)
	Genetic defects in complement activation & regulation (mutations in genes CFH, MCP (CD46), CFI, CFB, C3	Autoimmune (Autoantibodies against ADAMTS13)
	Genetic defects in cobalamin metabolism & coagulation pathway	Drugs (Ticlopidine, Clopidogrel)
	Drugs (cyclosporine, tacrolimus, sirolimus, anti-VEGF therapy, mitomycin-C, cisplatin, quinine, vaccines)	Hereditary (Homozygous or compound heterozygous ADAMTS13 gene mutations)
	Bone marrow transplantation	
	Radiation	
	Pregnancy & post-partum	
	Systemic sclerosis	
	Autoimmune (antiphospholipid antibody syndrome, SLE, anti-factor H autoantibodies)	
	Malignant hypertension	

	Antibody-mediated rejection in transplantation	
	Neoplasms such as adenocarcinomas (especially mucin producing) &, rarely, myeloproliferative neoplasms, leukemia & lymphoma	
	Idiopathic	

Renal biopsies are not routinely performed for classical cases of diarrhea positive (D+) HUS and TTP-associated TMA. Atypical presentations and secondary causes of TMA require renal biopsy for confirmation. However, at times, TMA on a renal biopsy is identified without clinical suspicion.[4]

Differentiating malignant hypertension induced thrombotic microangiopathy (TMA) from thrombotic thrombocytopenic purpura (TTP) is important in the management and prognosis of TMA. Several important similarities and differences between malignant hypertension induced TMA and TTP. Both TTP and malignant hypertension-induced TMA mostly present with neurological and gastrointestinal symptoms. In malignant hypertension-induced TMA, however, patients do not have fever. Prior history of hypertension and higher mean arterial pressure at presentation are possible clues to a diagnosis of malignant hypertension. The greater degree of renal impairment at diagnosis, relatively modest thrombocytopenia and lack of severe ADAMTS-13 deficiency (activity <10%) can further differentiate malignant hypertension from TTP. unlike TTP, patients with malignant hypertension respond well to antihypertensive agents and do not require plasma exchange.

Severe hypertension (eg, systolic blood pressure >220 mm Hg; diastolic blood pressure >100 mm Hg) can cause MAHA and thrombocytopenia. Kidney injury may be present, but sometimes kidney dysfunction is modest or absent. In patients with severe hypertension, control of the blood pressure is the most critical initial management and may be the only management required If possible, it is important to clarify the temporal relationship between the hematologic abnormalities and the hypertension. However, patients with severe kidney dysfunction rarely have TTP, so the urgency of plasma exchange in this setting is less critical. [5]

References:

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2. Kim YJ. A new pathological perspective on thrombotic microangiopathy. Kidney Res Clin Pract 2022;41:524-32
3. Kant S. Kidney Biopsy of the Month: Thrombotic Microangiopathy [Internet]. Renal Fellow Network. 2020 [cited 2023 Mar 20]. Available from:

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4. Manickam N, Agrawal V, Prasad P, Jain M, Prasad N. Clinico-Histological Features of Thrombotic Microangiopathy in Renal Biopsies: A Retrospective Study. Turk Patoloji Derg. 2022;38:1-8
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Answers to Questions:

- **Diagnosis?**: : TMA
- **Probable aetiology ?:** Accelaerated Hypertension induced TMA
- **Further diagnostic workup?:** As mentioned in above . Aim of further work-up would be rule out other possible causes – atypical HUS & TTP as there are management implications.
- **Management ?** : In this case control of HT is important and as emphasized may be the only management required with no requirement for plasma exchange {PLEX]. In contrast in other TMA situations, PLEX is performed as it removes thrombogenic substances that have triggered the TMA & provides the anti-coagulants & fibrinolytics to achieve hemostatic balance.