Hypertension-Associated TMA Syndrome

APCN x TSN 2025
Taipei, Taiwan.

Christopher Kun-Hua Tu, M.D.

Kidney Research Center, Department of Nephrology, Chang-Gung Memoral Hospital.
Transplant Immunology Lab, Kidney Transplant Team, Chang-Gung Memorial Hospital
Laboratory of Human Immunology and Infectious Diseases, Chang Gung University.

Disclaimer

- The speaker has nothing to disclose.

Case General Information

- Gender: Female
- Age: 32-year-old
- Marriage: single
- Occupation: just quit from clerk of newspaper office

- Family history: Father had diabetes mellitus
  Grandmother had hypertension and heart failure
- Non-smoker

- Visit our ER on 2021/5/28

Case Presentation

- Chief complaint: progressive dyspnea for 4 days
- Present illness:
  - Progressive orthopnea and exertional dyspnea
  - Associated with chest tightness, nausea and anorexia.
  - No fever, diarrhea, cold symptom, skin lesions, edema, reduced UO.
  - Visit ER on 2021/5/28, vital sign at triage: BP: **251/127**mmHg
  - Initial laboratory data:

    Hgb: **9.3** g/dL; Platelet: **108000**/μL

    BUN: **42.9** mg/dL; Creatinine: **4.30** mg/dL; FeNa: not done.

    24hrs CCr: **9.7** ml/min; 24hrs UTp: **651** mg/day
- Admitted to CCU then cardiology ward for blood pressure control
- Transfer to Nephrology ward for survey of kidney dysfunction

Past History

- No known systemic disease including hypertension
- No known surgical history

Study for secondary hypertension

- Medication or OTC drugs: denied
- Thyroid profile: Free-T4: 1.04 ng/dL; TSH: 2.102 uIu/ml
- 8AM Cortisol: 11.0 µg/dL
- Blood calcium: 8.9 mg/dL
- RAAS system: Renin (direct renin concentration): **88.3** ng/L
  Aldosterone: **15.8** ng/dL
- For pheochromocytoma:
  Urine Norepinephrine: 21.1 µg/day
  Urine Epinephrine: <3.0 µg/day
  Urine Dopamine: 46.6 µg/day

- Kidney sonography: mildly smaller kidneys (L/R: 9.0/8.5 cm), with parenchymal change.

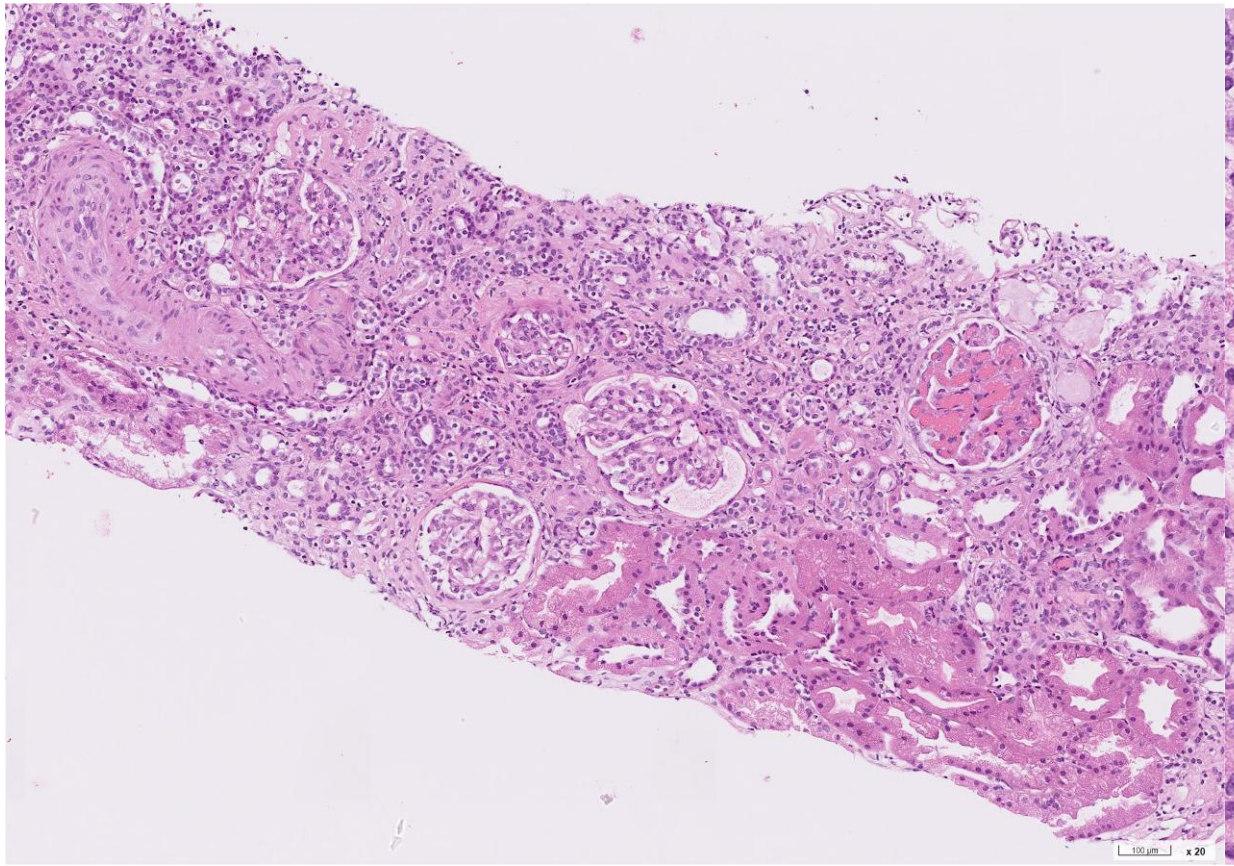
Unknown Kidney Failure: Study before Kidney Biopsy

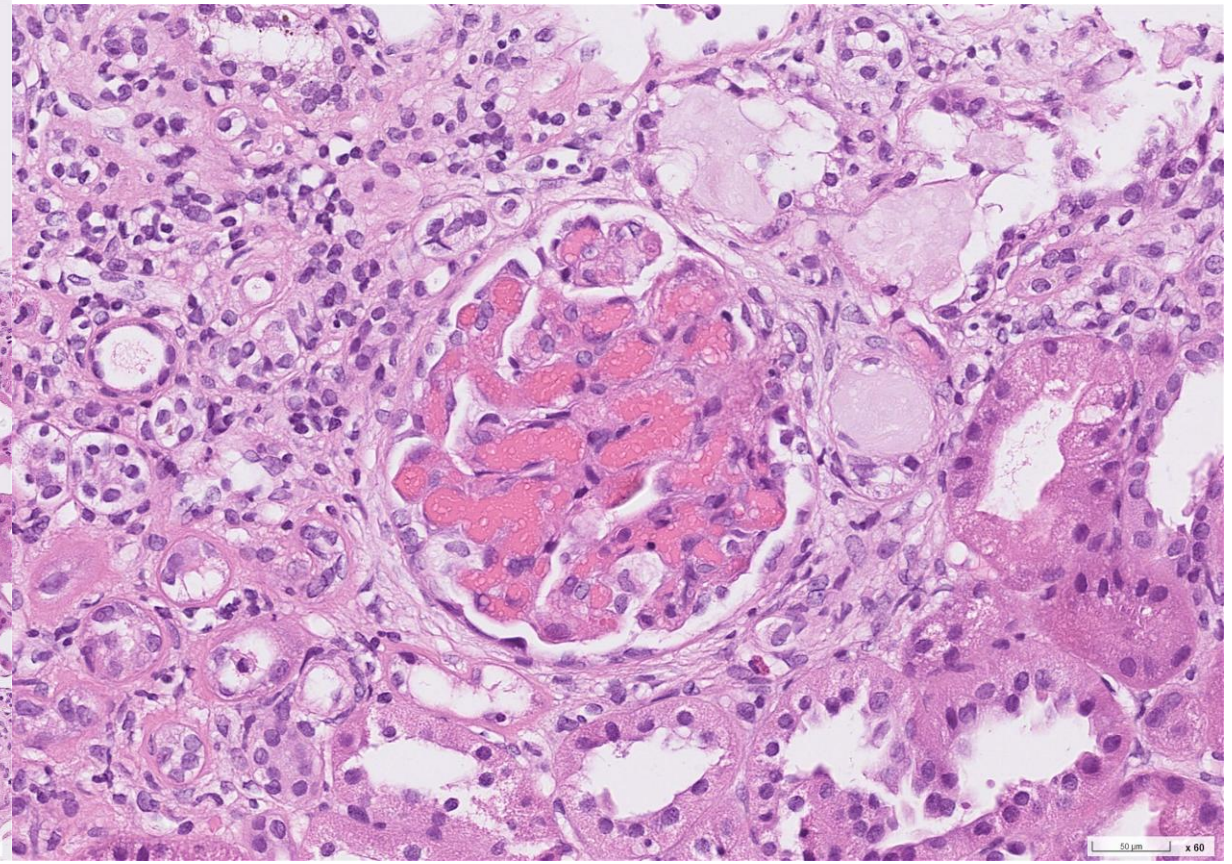
- WBC: 10800/μL
  Hgb: **9.3** g/dL
  Platelet: **108000**/μL
  PT: 11.9 sec
  aPTT: 23.8 sec
- Creatinine: **4.30** mg/dL
  LDH: **300.0** U/L
- Urinalysis
  Protein: **3+**
  Blood: **2+**
  RBC: **21**/μL
  Dysmorphic RBC: 0%
- 24hrs CCr: **9.66** ml/min
  24hrs UTp: **651** mg/day

- Lupus marker:
  ANA: 1:80
  C3: **80.5** mg/dL
  C4: 16.2 mg/dL
  Anti-dsDNA: 7.2 WHOunit/ml
- Immunoglobulin profile
  IgG: 724.00 mg/dL
  IgA: 210.00 mg/dL
  IgM: 59.10 mg/dL
  IgD: <13.38 mg/L
  IgE: <18.80 IU/ml
  FLC Kappa: **60.49** mg/L
  FLC Lambda: **35.18** mg/L
  FLC K/L: 1.72

- MPO-ANCA: <0.2 IU/mL
  PR3-ANCA: <0.2 IU/mL
  Anti-GBM: <1.9 EliAU/mL
- Serum PEP: normal serum pattern
  Serum IFE: no monoclonal protein
  Urine PEP: no monoclonal protein
  Urine IFE: no monoclonal protein
  Cryoglobulin: negative
- Chronic infection profile
  HBsAg: non-reactive
  Anti-HCV: non-reactive
  RPR: non-reactive
  ASLO: <50.90 IU/mL

Kidney Biopsy





Courtesy from Pathologist Dr. Tai-Di Chen

Pathologic Report

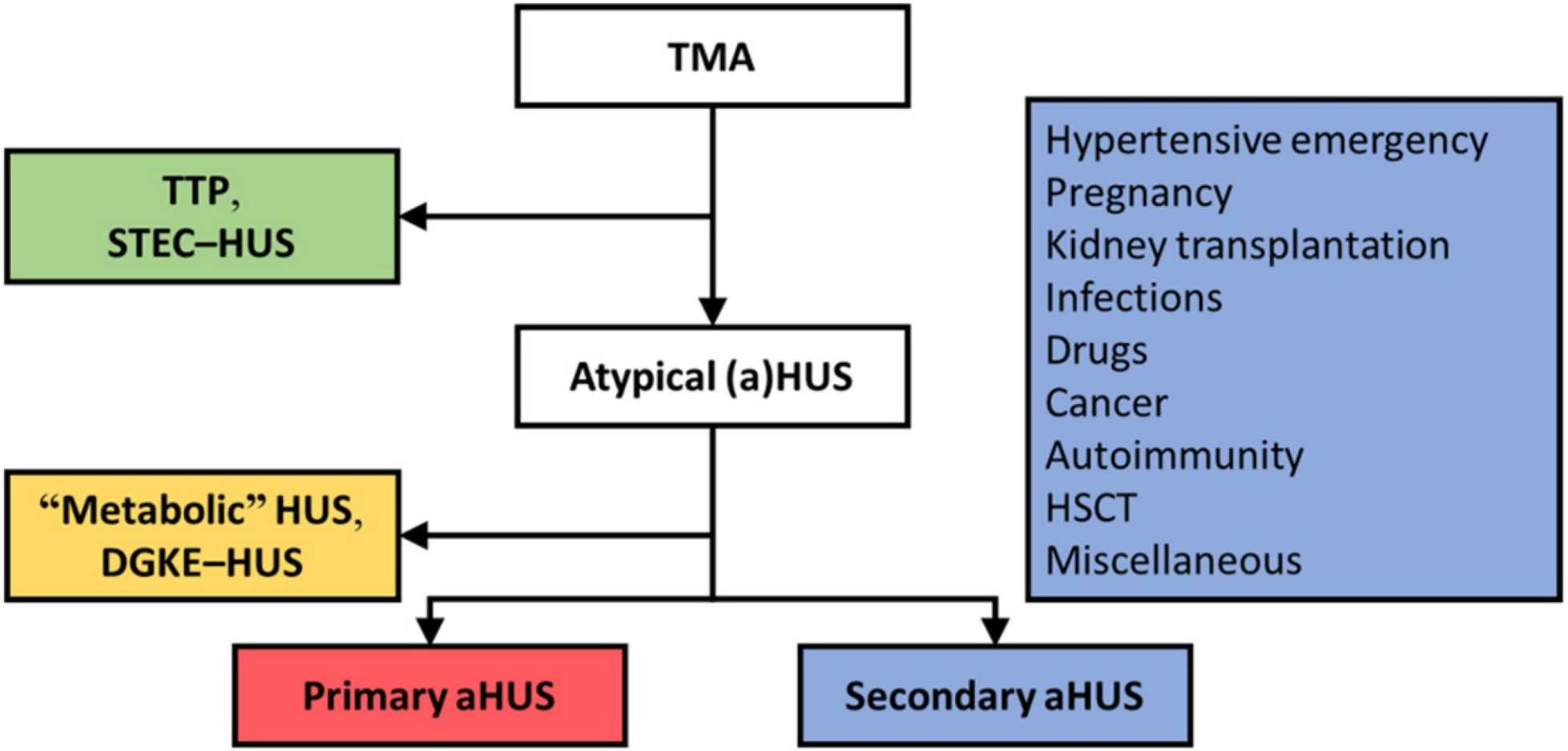
- Kidney, left, biopsy
  ---- **consistent with thrombotic microangiopathy**
  ---- presence of IgA deposits in glomeruli

- Key finding:
  - 1 glomerulus shows congestion which is c/w “paralyzed” glomerulus
  - Other glomeruli show changes associated with endothelial swelling

- Microscopic finding:
  - Glomerulus: total number **19**, **4** globally sclerosed, 0 crescent.
  - Tubulointerstitial fibrosis: **40%**
  - Arterioles: degeneration with hyalinosis and moderate to marked mucoid intimal thickening
- Immunofluorescence study: segmental mesangial staining for IgA (2+) and lambda (1+)
- EM: few mesangial and very occasional subepithelial electron dense deposits

Courtesy from Pathologist Dr. Tai-Di Chen

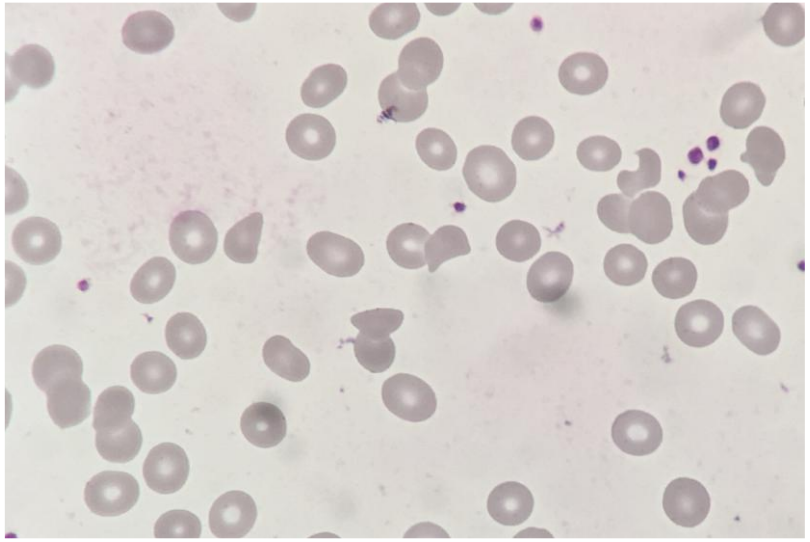
Algorithm of TMA classification



J Clin Med. 2021 Jul 8;10(14):3034.

Study for thrombotic microangiopathy (TMA)

- Hgb: **9.3** g/dL;
  Platelet: **108000**/μL
- Bilirubin (T): 0.4 mg/dL
  LDH: **300.0** U/L
  Haptoglobin: 137 mg/dL
- Direct Coombs' test: negative
- Blood smear: **schistocyte: (+/-)**

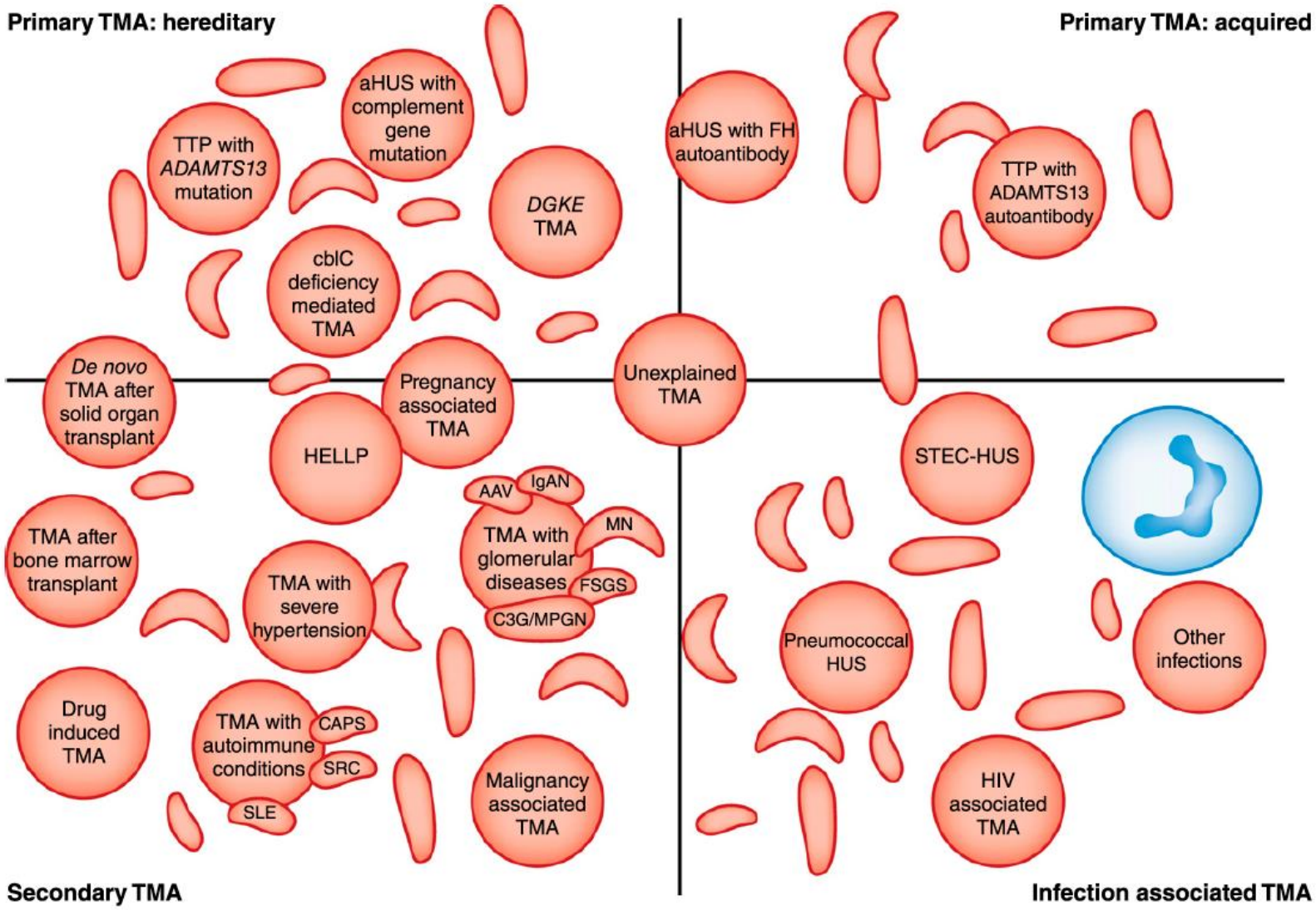


- DIC profile: **elevated d-Dimer/FDP**
  normal fibrinogen
- Vitamin B12: 822 pg/mL
- EBV DNA: no checked
  CMV DNA: no checked
  HCV Ab: negative
  HIV Ag/Ab: no checked
- Anti-Cardiolipin Ab: 1.5 CU
  Anti-Phospholipid IgG/M Ab: <6.25 GPLunits
  Anti-B2-GPI IgM Ab: < 1.1 CU
  Lupus anticoagulant screen: 43.7 sec
- Anti-SCl-70: 22 AU/ml
  Anti-Jo-1: 27 AU/ml
- ADAMTS13 activity: **76.2%**

What happened to this young lady? What will you do?

- **Hypertensive emergency**
  - No any definite cause of secondary HTN could be found
  - Is it a malignant hypertension?
- **Acute (?!) kidney injury**
  - Acute kidney injury? Rapid progressive glomerulonephritis?
  - Acute on chronic kidney disease?
  - Advanced chronic kidney disease?
- **Anemia**
  - Due to impaired kidney function?
  - Somewhere loss? hemolysis? (no evidence)
- **Thrombocytopenia**
  - Just mild thrombocytopenia, significant?
  - Not c/w DIC, TTP.
  - Hemolysis? (no evidence)

Syndromes of thrombotic microangiopathy

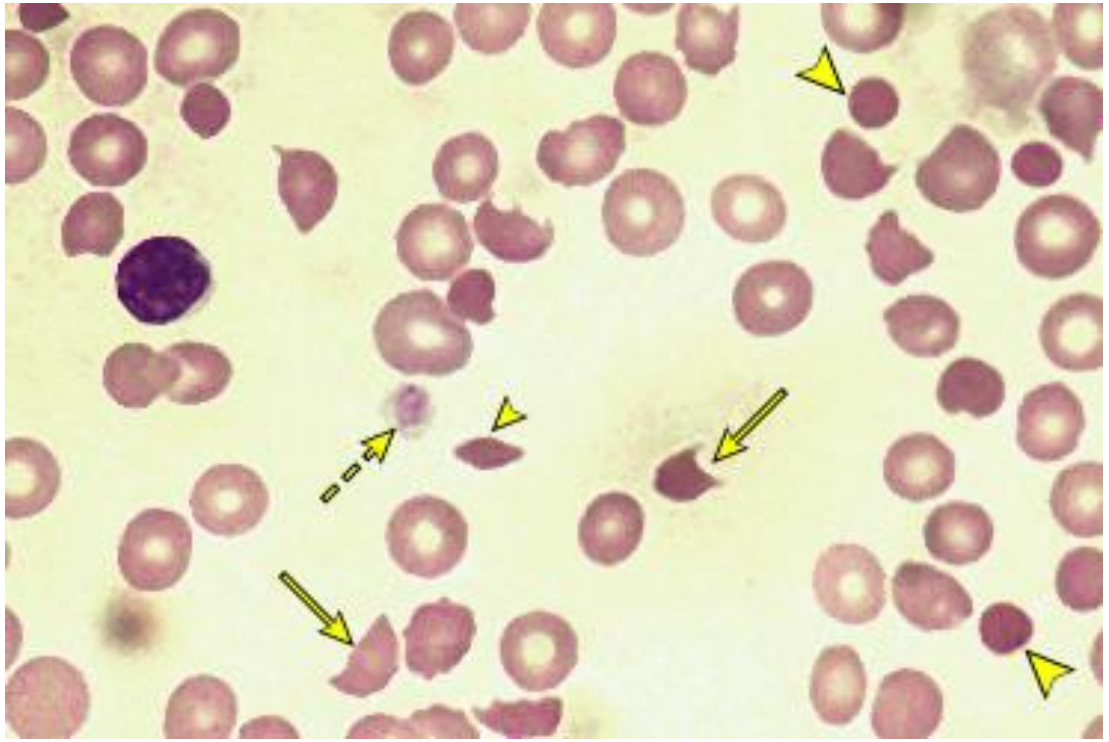


N Engl J Med. 2014;371(7):654-666.
Clin J Am Soc Nephrol. 2018;13(2):300-317.

Microangiopathic hemolytic anemia (MAHA)

- **Hemolytic anemia**: anemia due to hemolysis
- Triad of hemolytic anemia:
  - indirect hyperbilirubinemia
  - elevated LDH
  - decreased haptoglobin
- Mechanism:
  - Intrinsic: enzyme deficiency, hemoglobinopathy, membrane abnormality.
  - Extrinsic: immune-mediated, trauma, direct infection or toxin, entrapment.

- **Microangiopathic hemolytic anemia (MAHA)**: is a descriptive term for non-immune related hemolysis resulting from **intravascular red blood cell fragmentation** that produces schistocytes on the peripheral blood smear.



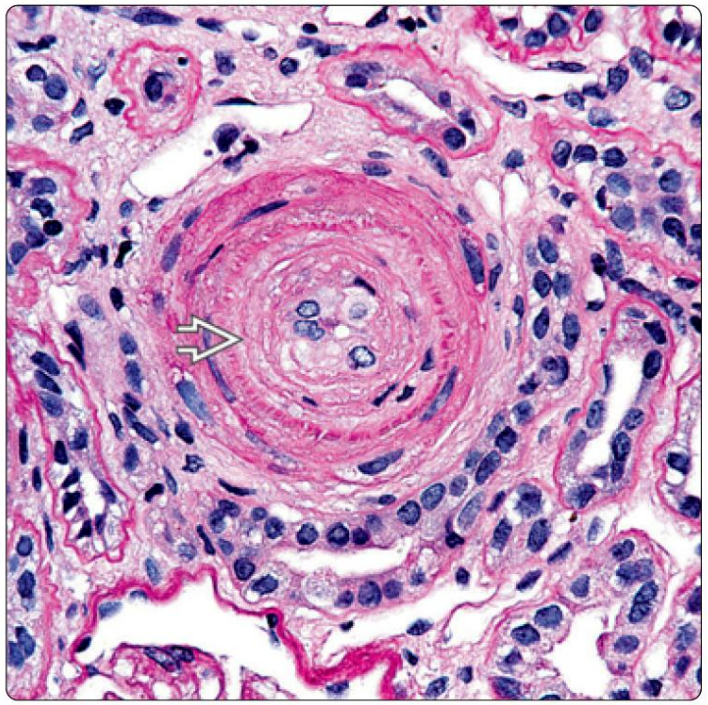
Schistocyte = fragmented red blood cell

Reference: UpToDate

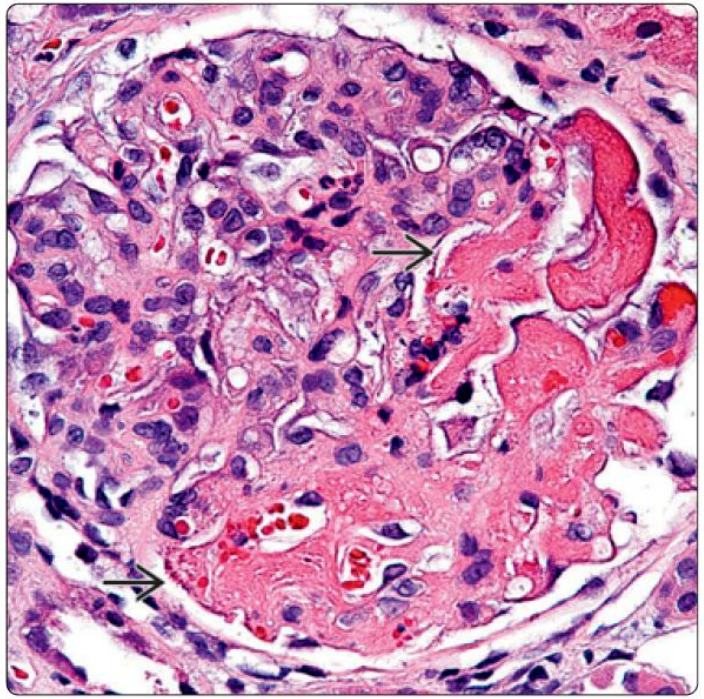
Thrombotic microangiopathy (TMA)

- Mainly as **pathologic** description
- Definition: microvascular **endothelial injury** and **thrombosis**

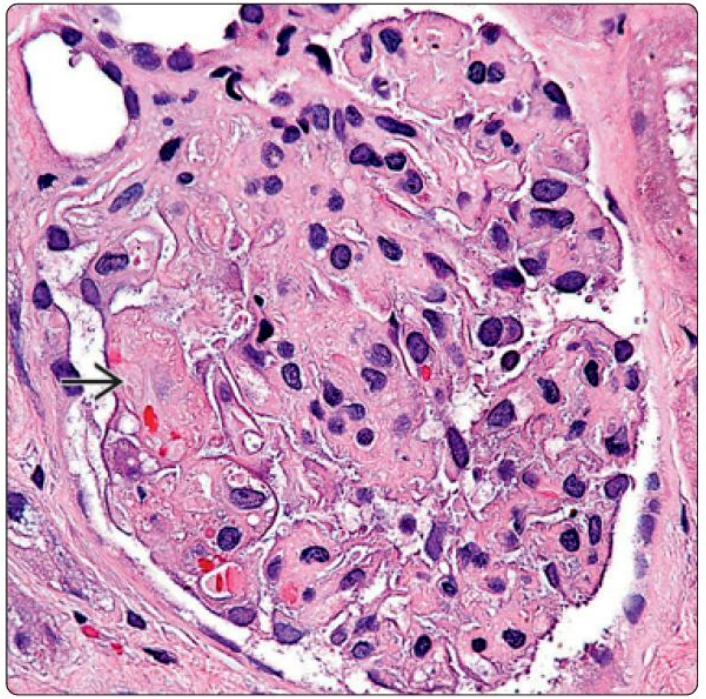
Arteriolar "Onion-Skinning" Changes in TMA



Glomerular Fibrin Thrombi

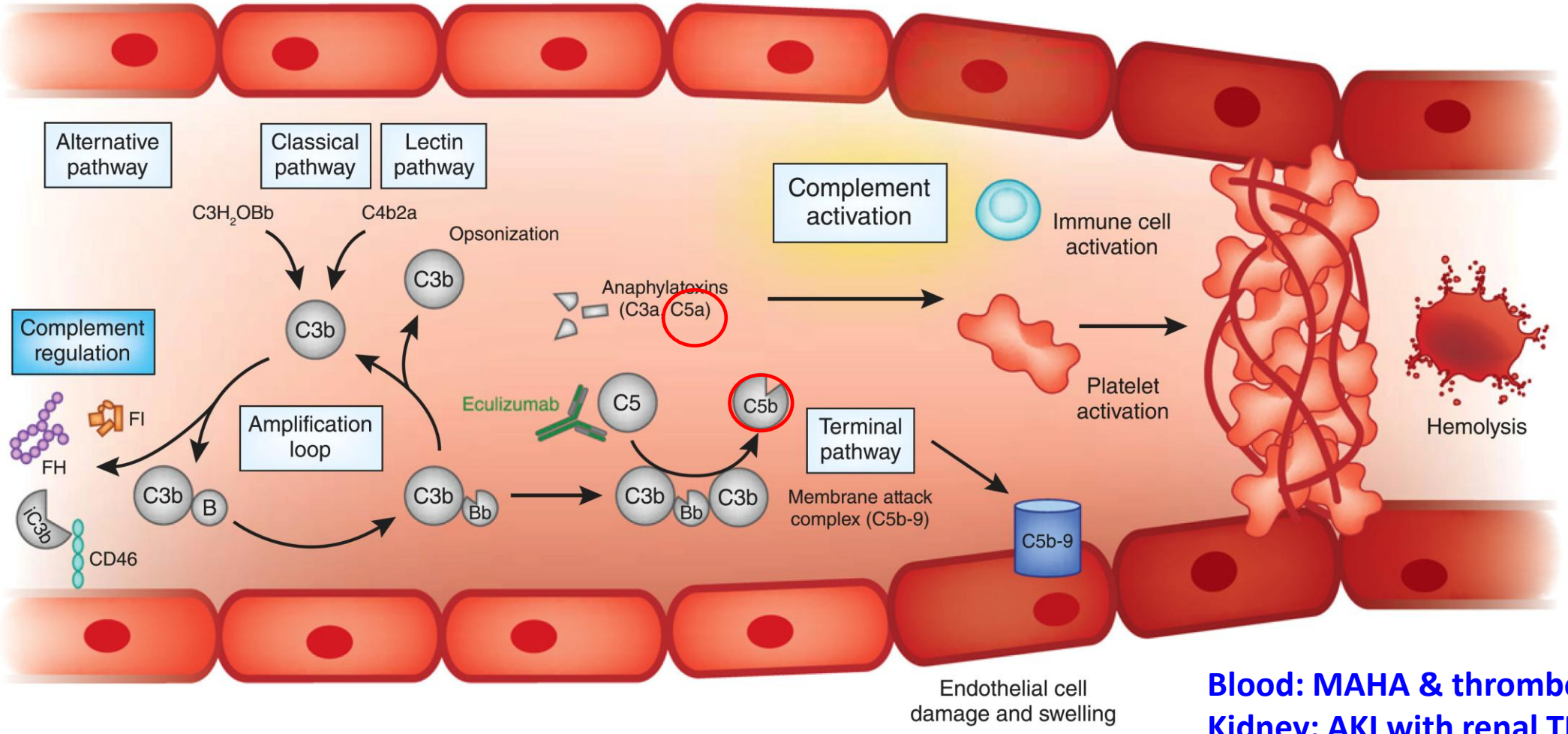


Fragmented RBCs in Acute TMA



Diagnostic Pathology: Kidney disease. 2/e, 2016

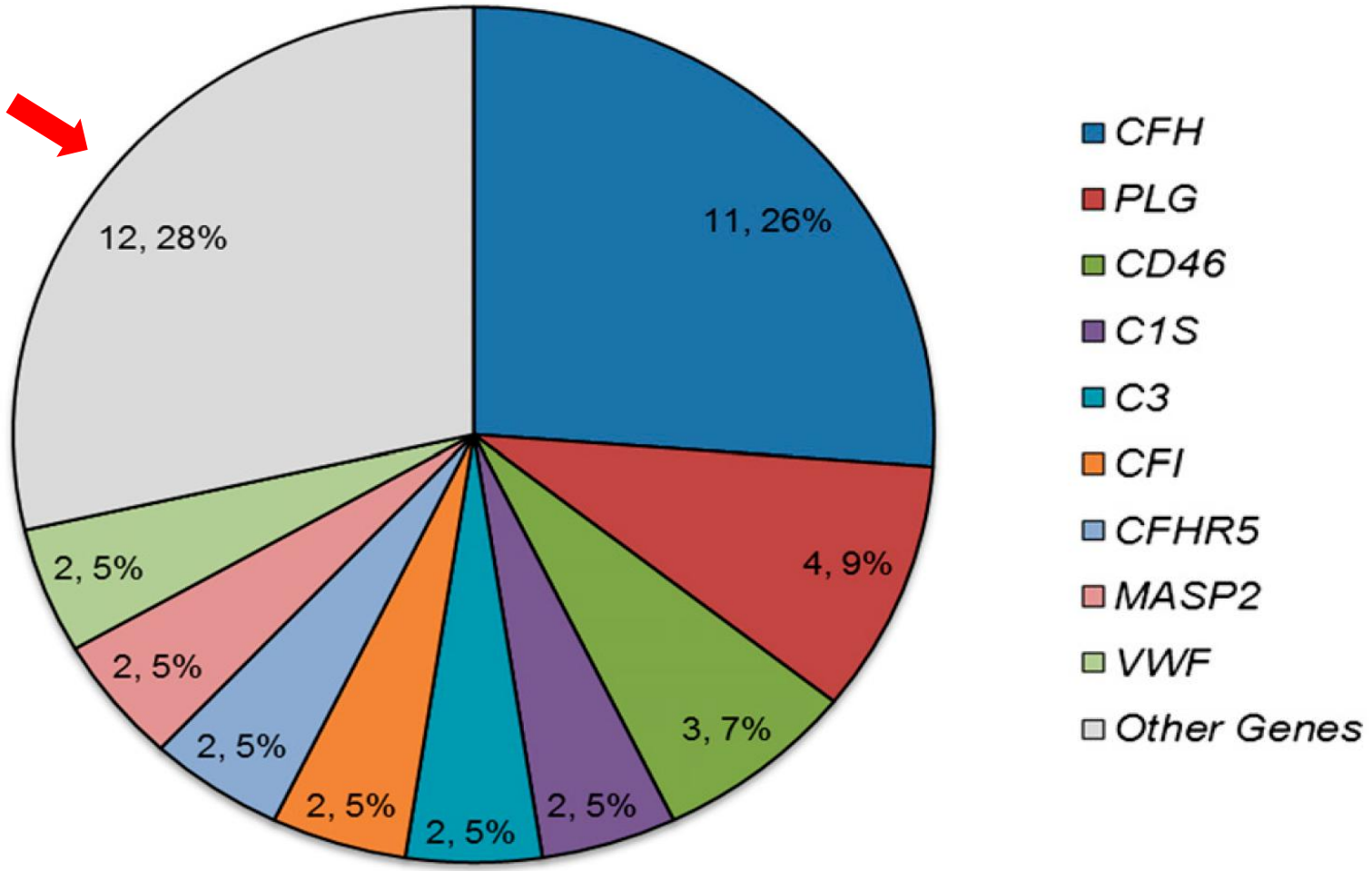
Mechanism of aHUS (CM-HUS/TMA)



Blood: MAHA & thrombocytopenia
Kidney: AKI with renal TMA

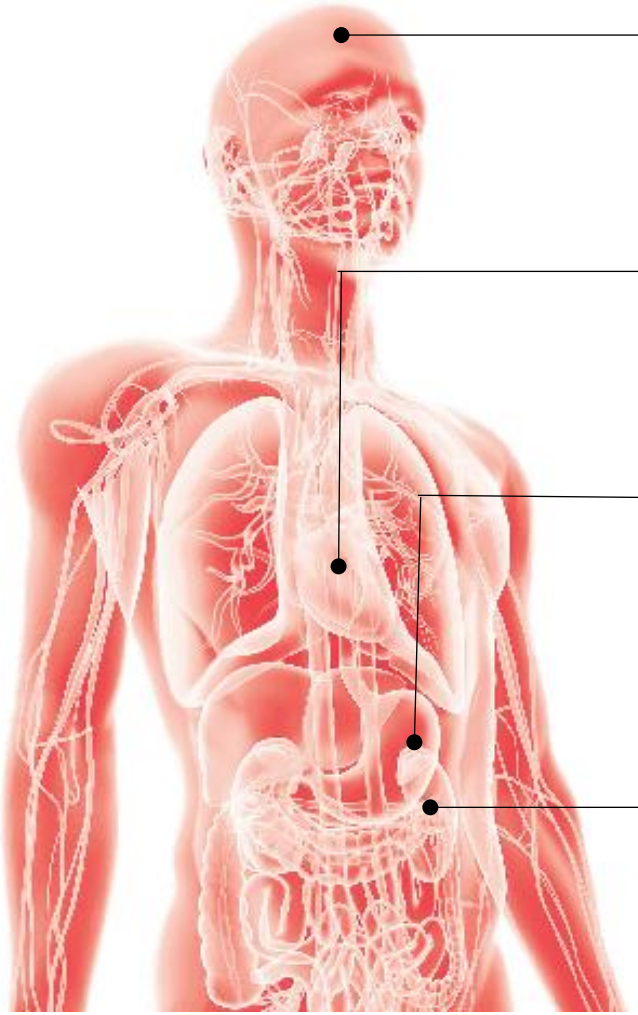
Clin J Am Soc Nephrol. 2018;13(2):300-317.

Gene mutations in patients with atypical HUS



J Am Soc Nephrol. 2014 Jan;25(1):55-64.

Clinical Presentation of atypical HUS



49% experience neurological symptoms, including[5]:

- Confusion[5]
- Encephalopathy[6,7]
- Stroke[7]
- Seizure[5]

Up to 42% experience CV symptoms, including[8]:

- Arterial thrombosis[7]
- Vascular stenosis[6]
- Hypertension[8]
- Myocardial infarction[6,7]

Up to 51% experience GI symptoms, including[5]:

- Colitis[7]
- Abdominal pain[5]
- Pancreatitis[7]
- Nausea/vomiting[7]
- Gastroenteritis[3]
- Diarrhoea[5]

More than 50% progress to ESRD[4,5]:

- Elevated creatinine[5]
- Decreased eGFR[1]
- Proteinuria[8]

Other macrovascular complications[9]:

- Peripheral arterial disease
- Phalangeal gangrene

Reference: Alexion

HTN-associated TMA with complement abnormalities

Table 1 | Baseline clinical features and laboratory evaluation

Patient No.	Age (yr)	Sex	BP (mm Hg)	SCr (μmol/l)	uProt (g/d)	uRBC	ESRD	Hb (mmol/l)	LDH (U/l)	MAHA[a]	Platelets ($\times 10^9$/l)[b]
1	38.4	F	184/140	1730	NA	NA	Y	5.1	1800	Y	224
2	40.3	M	205/114	1195	2.3	Y	Y	5.7	1104	Y	158
3	37.7	M	200/120	586	3.9	Y	Y	5.3	2125	Y	100
4	32.0	F	180/120	1138	NA	NA	Y	5.9	1486	Y	142
5	65.0	M	195/105	162	1.5	Y	N	7.9	271	N	98
6	41.1	F	180/120	334	0.7	Y	Y	7.5	291	N	285
7	28.5	F	224/122	1065	1.6	Y	Y	5.1	298	N	228
8	27.9	M	240/150	673	1.6	Y	Y	7.9	165	N	133
9	44.0	F	220/120	649	0.4	Y	Y	8.2	339	N	340

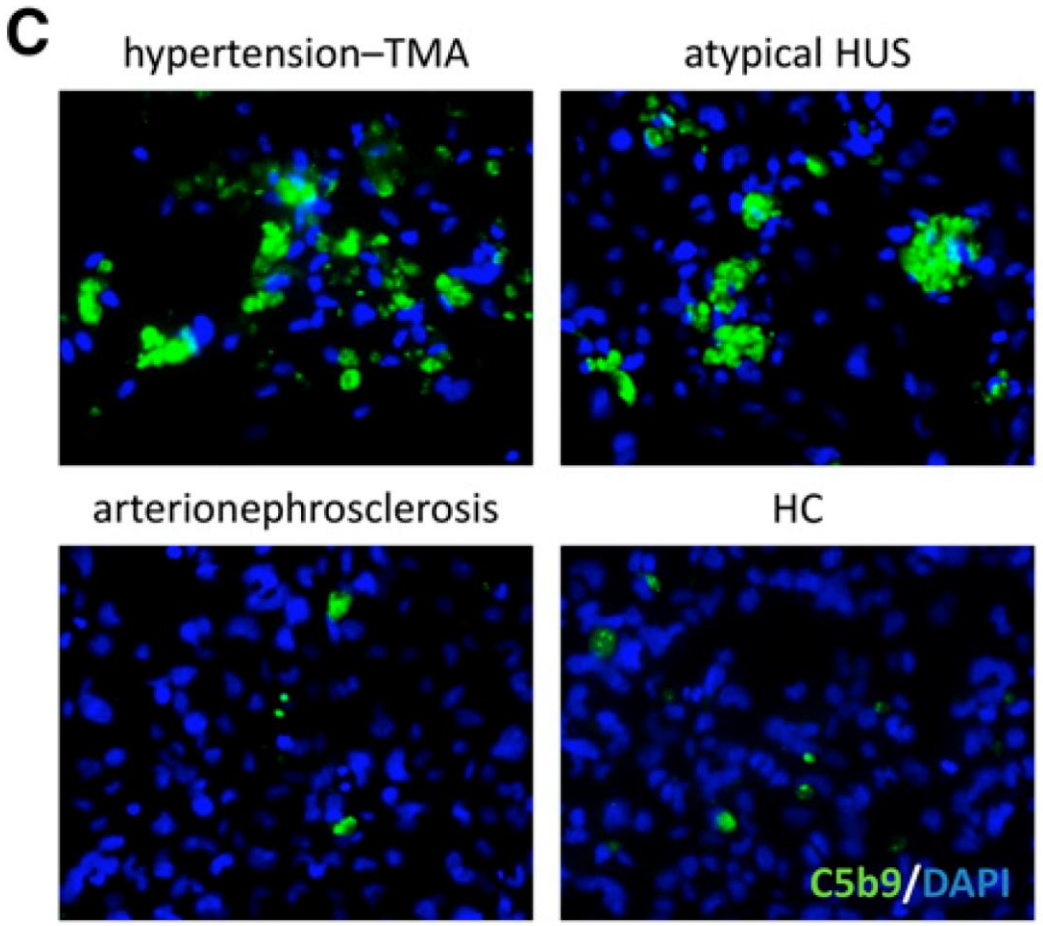
Table 2 | Complement abnormalities

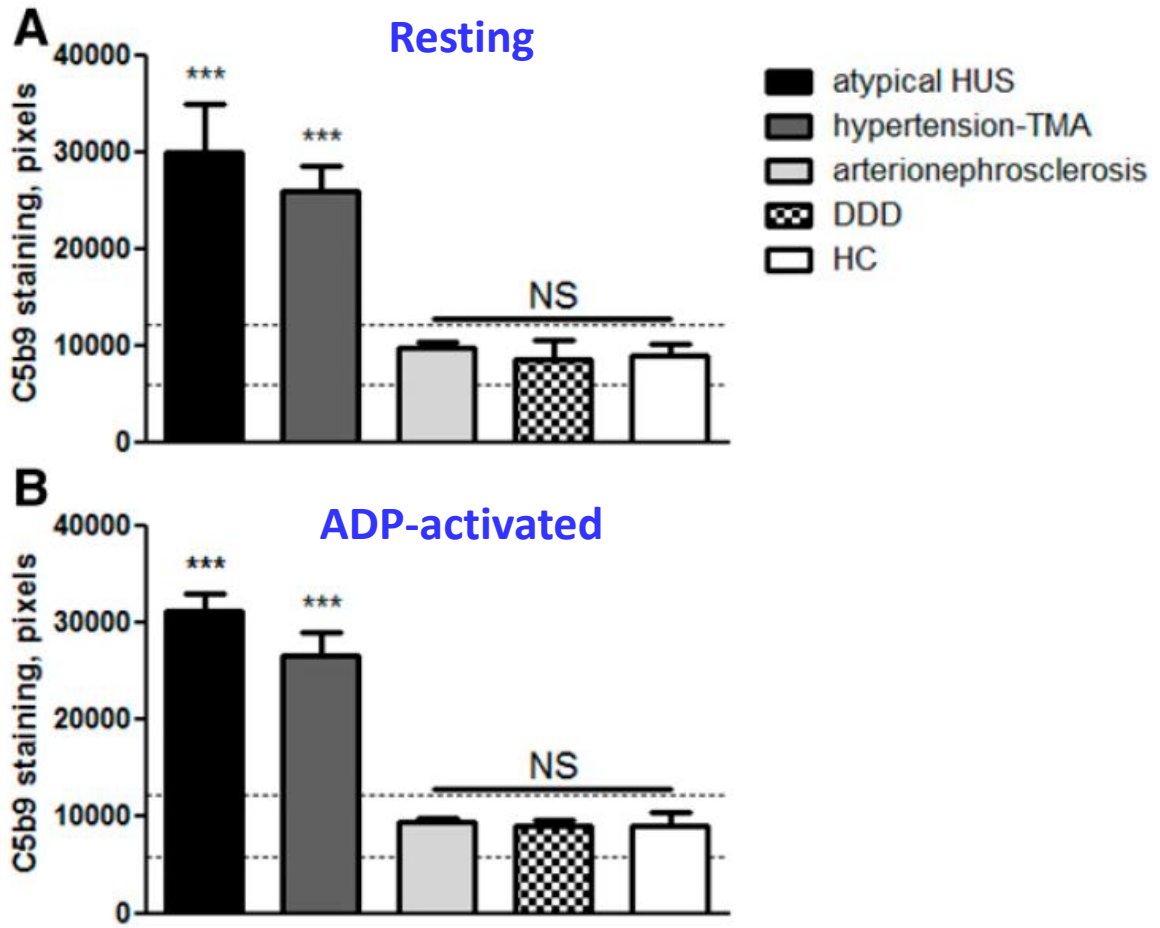
Patient No.	Mutation(s)	*CFH*-H3[11]	FHAA	CP (%)[a]	AP (%)[b]	sC5b-9 (ng/ml)[c]
1	*C3*-R161W[18]	N	Negative	95	64	2800
2	*CD46*-ΔD237/S238,[15] *CFH*-Q950H[11]	Y	Negative	97	107	1000
3	*C3*-R161W[18]	Y	ND	94	97	640
4	*CFH*-C853R[16]	Y	ND	104	71	1840
5	No mutations	N	ND	99	99	1800
6	*CFI*-N151S[14]	N	ND	97	87	4200
7	*C3*-R161W,[18] Δ*CFHR1-CFHR3*[d]	N	Negative	110	62	1840
8	No mutations	Y	Negative	90	74	440
9	No mutations	N	Negative	113	110	3800

Netherlands
Limburg Renal Registry

Kidney Int. 2017;91(6):1420-1425.

Ex vivo serum-based microvascular endothelial cell assay



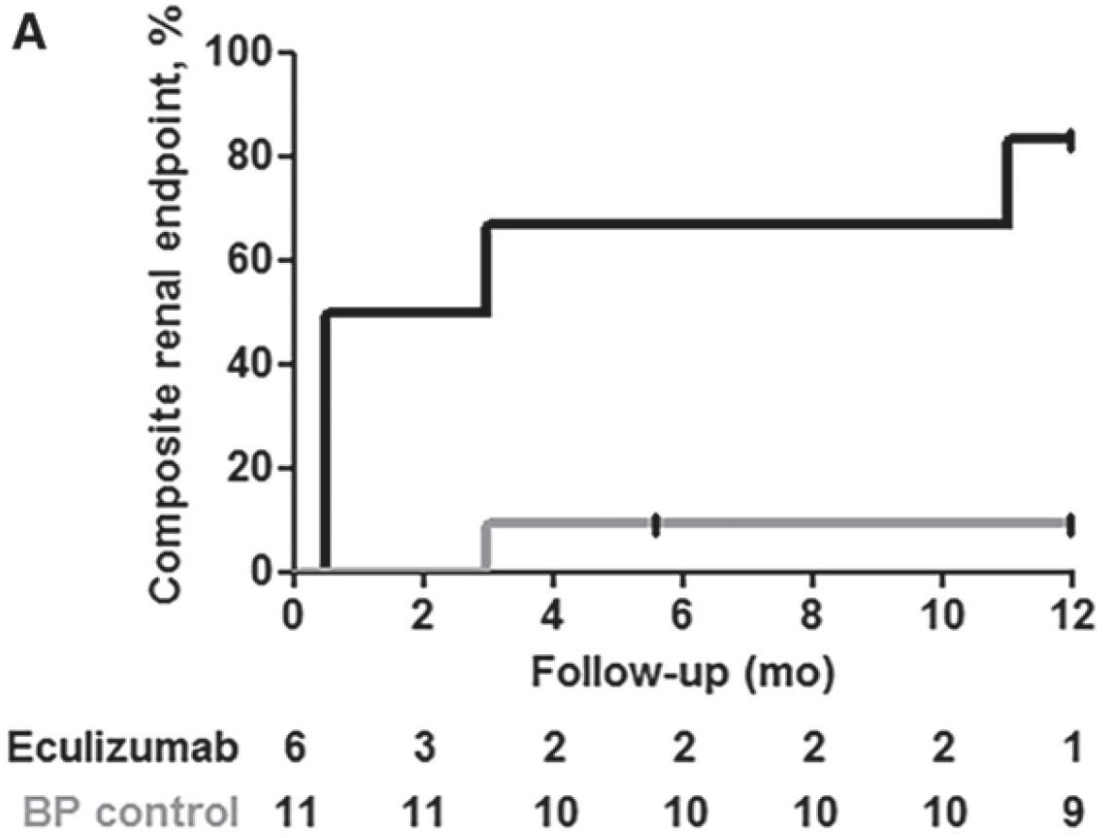


ADP: adenosine 5’-diphosphate

Blood. 2014;124(11):1715-1726.
J Am Soc Nephrol. 2018;29(8):2234-2243.

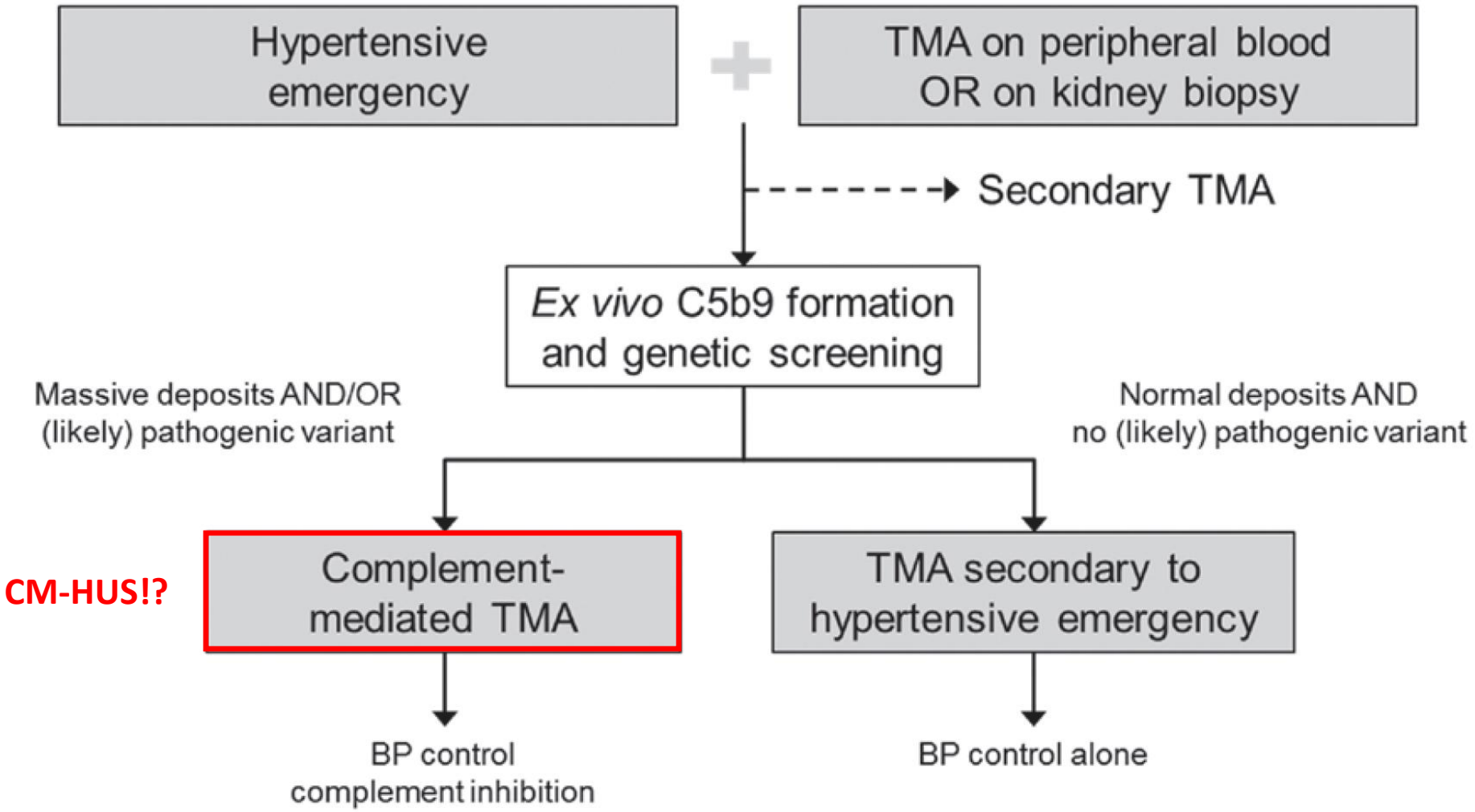
HTN emergency with biopsy-proved renal TMA: use of Eculizumab

Renal recovery or not



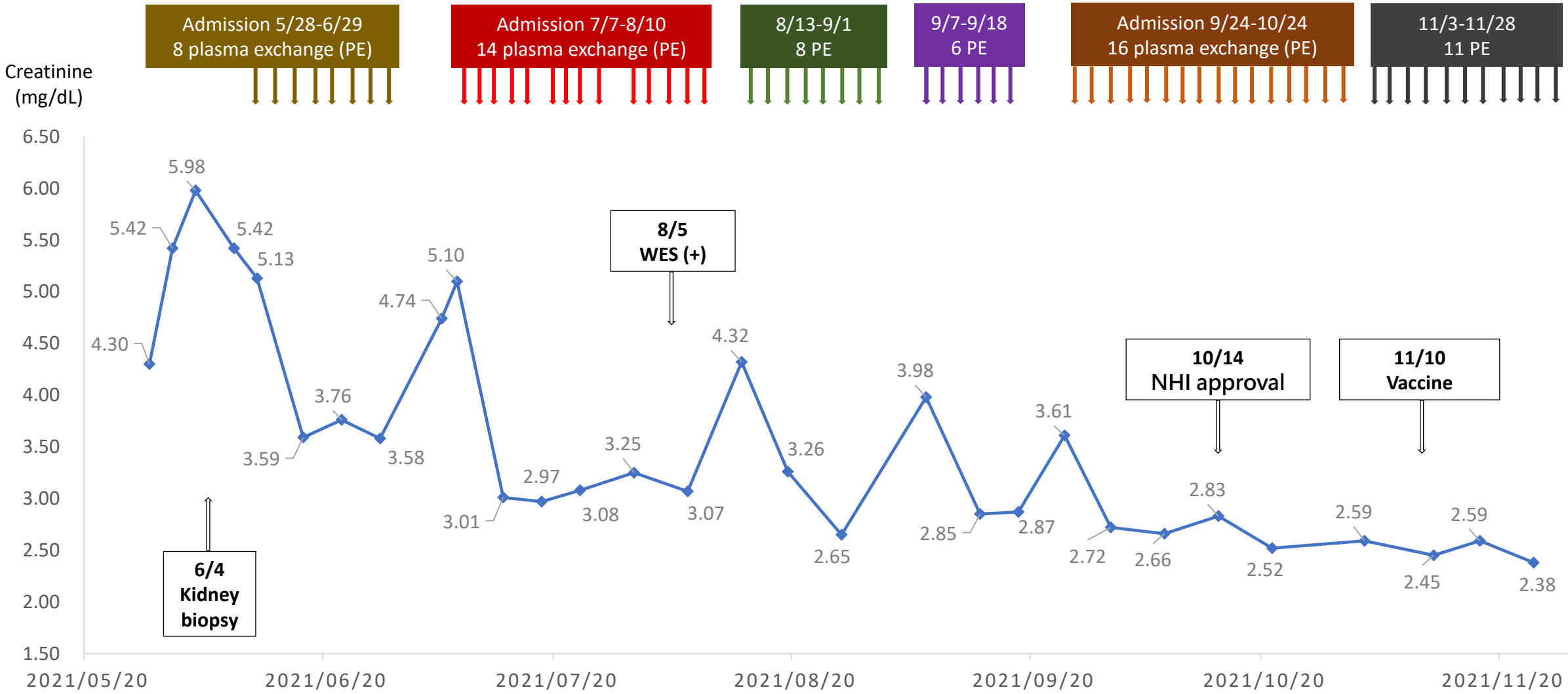
Hypertension. 2020;75(2):422-430.

HTN emergency with biopsy-proved renal TMA: re-classification



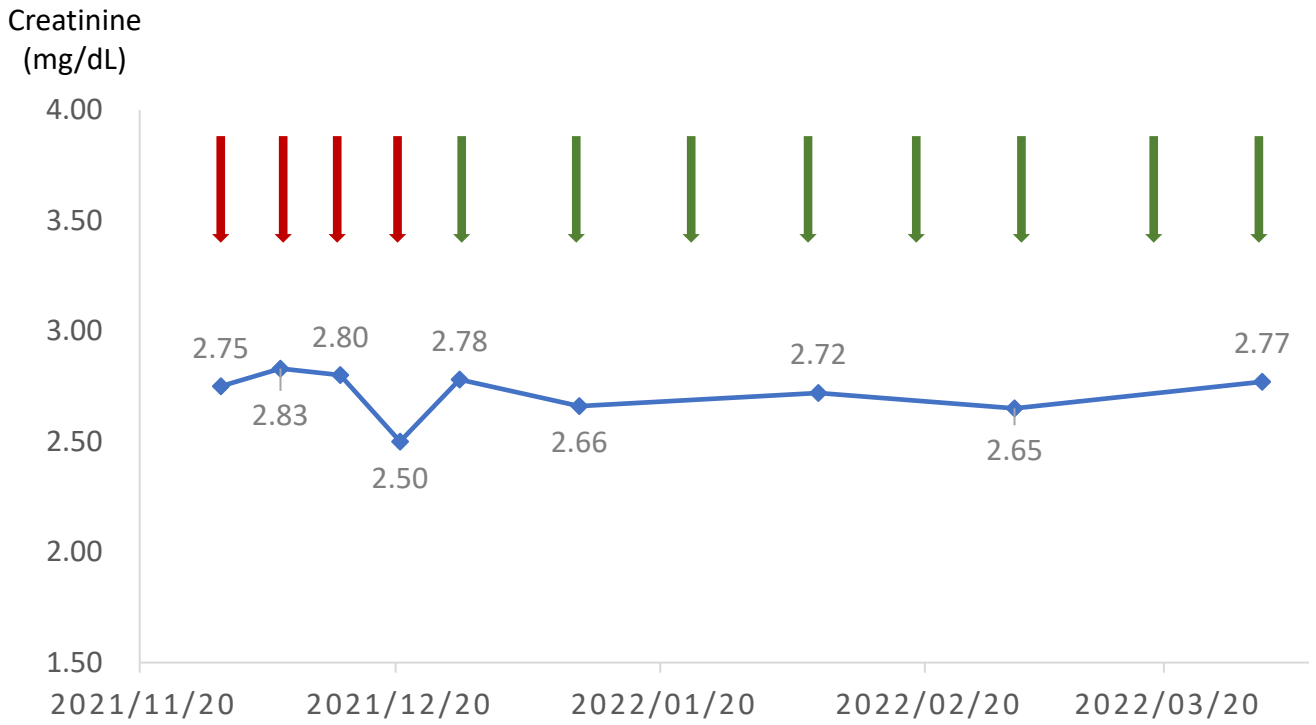
Hypertension. 2020;75(2):422-430.

A 32yo lady with HTN emergency with AKI….



Clinical Course

After totally **63** plasma exchange and vaccination for meningococcus, start complement inhibition therapy (Eculizumab) since 2021/11/29.



Loading: Eculizumab (Soliris) 3vial in N/S 90ml run 45 mins QW

Maintaining: Eculizumab (Soliris) 4vial in N/S 120ml run 60 mins QOW

BP: 144/88mmHg; Pulse:64BPM
Edema: nil

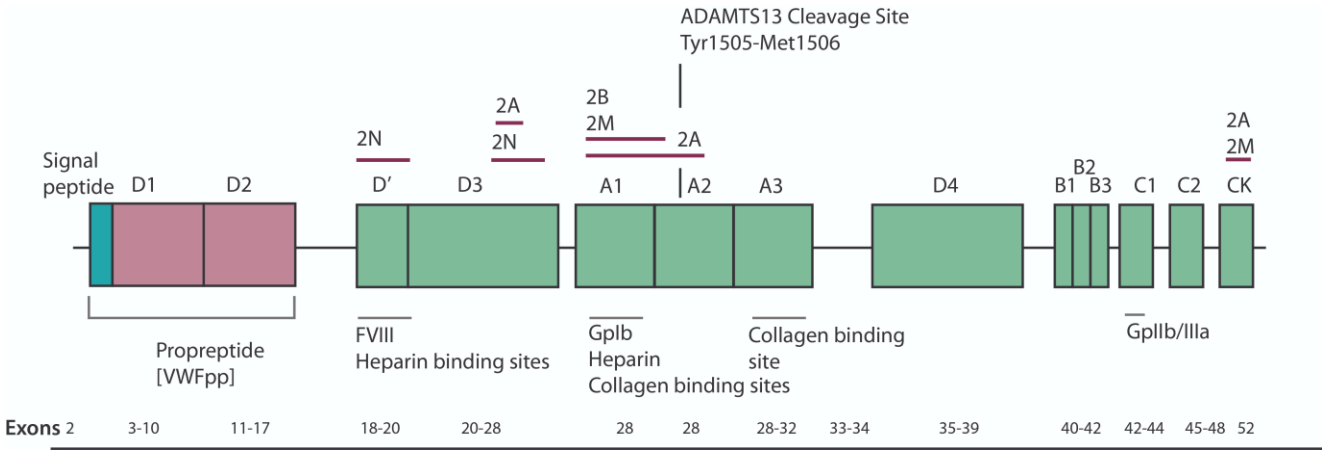
Laboratory data
Hemoglobin: 11.8 g/dL
Platelet 199000/μL
Creatinine: 2.77 mg/dL
LDH: 157 U/L
UPCR: 2.67 g/g

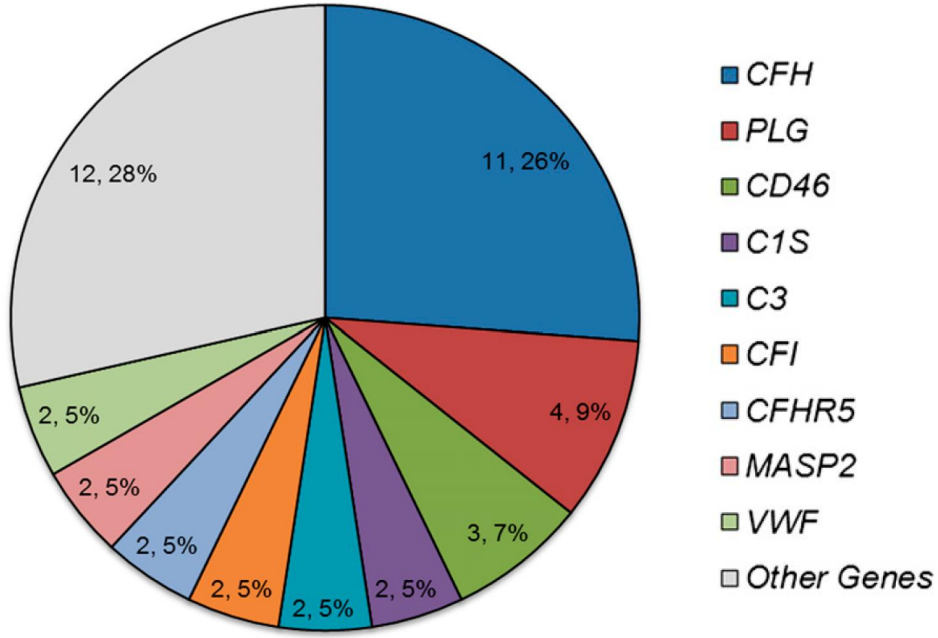
Current Medication

Amlodipine 5mg/tab	1pc	BID
Carvedilol 25mg/tab	0.5pc	BID
Losartan 50mg/tab	0.5pc	HS

Whole exome sequence (WGS)

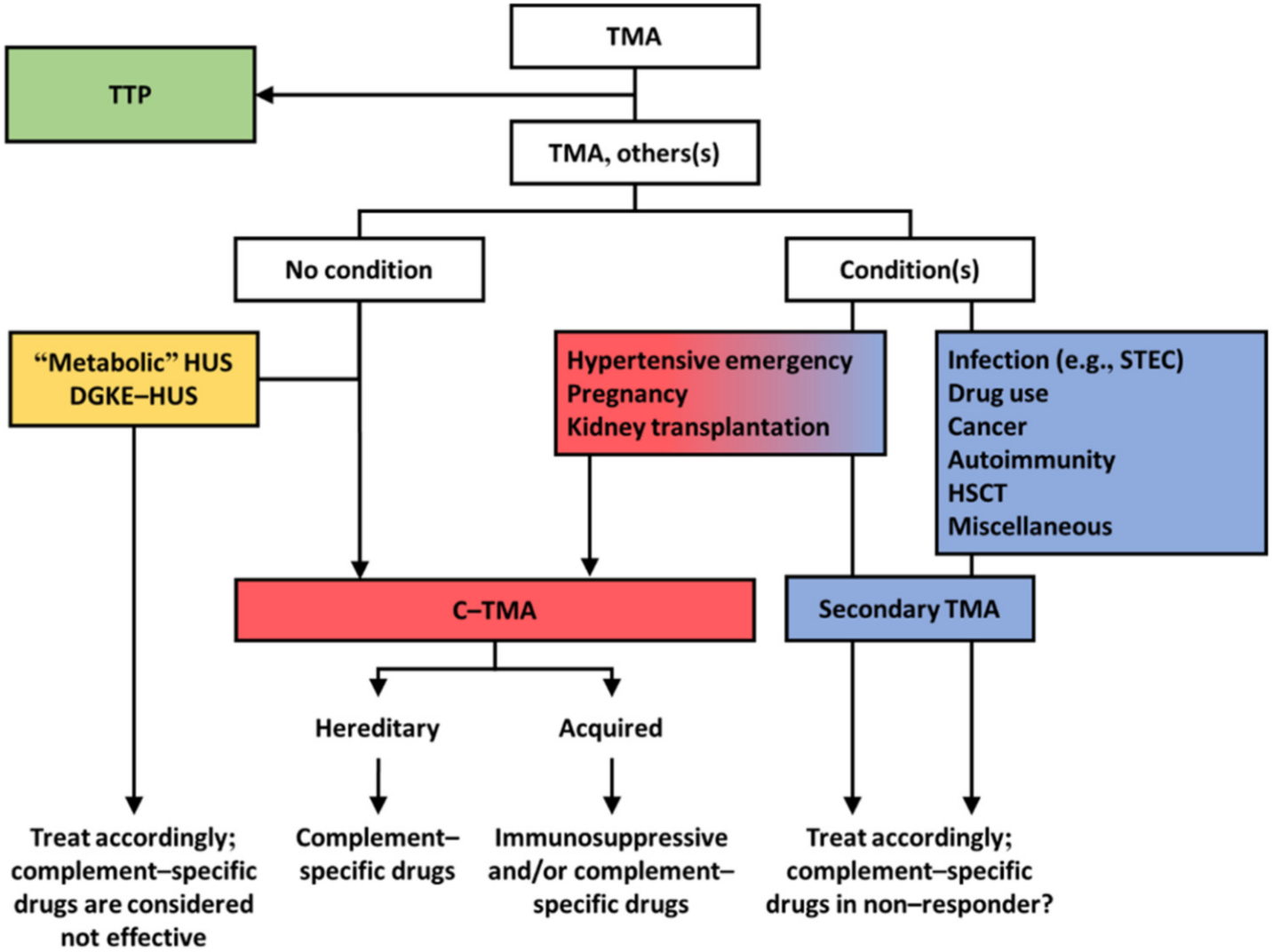
VWF: NM_000552:exon37:c.G6860A:p.R2287G (heterozygous)





J Am Soc Nephrol. 2014 Jan;25(1):55-64.

Latest Revised Algorithm of TMA syndrome



J Clin Med. 2021 Jul 8;10(14):3034.

CGMH Experience: severe HTN with kidney TMA

No.	Age	Sex	HTN Hx	BP	Cr	Initial H/D	Hgb	PLT	LDH	Haptoglobin	Schistocyte	ADAMTS13	Retinopathy	Acute HF	Neuro Sx
1	39.0	F	N	254/144	3.1	N	11.4	302	200	ND	negative	ND	Y	N	N
2	34.8	M	N	213/157	5.7	Y	10.4	230	314	ND	negative	ND	ND	Y	N
3	42.1	M	N	265/164	2.1	N	13.7	239	170	ND	+/-	ND	ND	Y	N
4	29.2	M	Y	229/140	13.7	Y	8.2	202	ND	ND	ND	ND	ND	ND	N
5	41.2	F	N	230/140	10.5	Y	6.0	309	331	ND	+/-	ND	ND	Y	N
6	32.0	F	N	251/157	5.4	N	9.3	108	300	137	+/-	76.2	ND	N	N
7	25.3	M	N	218/143	19.1	Y	6.9	66	657	<7.81	+/-	77.1	Grade 4	N	n
8	27.6	M	N	232/152	6.1	N	11.8	75	376	53.10	+/-	88.3	ND	N	N
9	50.0	M	Y	175/117	3.4	N	11.1	224	167	247	negative	ND	ND	N	N
10	44.0	F	N	224/151	1.5	N	14.2	235	424	ND	ND	93.6	ND	N	N
11	25.6	M	N	252/155	15.6	Y	7.3	178	798	34.40	+/-	76.3	Y	Y	N
12	27.7	M	N	216/163	3.7	N	11.1	400	309	375.00	negative	104.7	Y	N	Y
13	38.7	M	N	149/113	10.2	Y	8.8	222	249	170.00	1+	84.6	Y	Y	N
14	70.7	F	N	187/80	5.1	Y	6.5	88	608	<7.75	2+	48.1	ND	N	N
15	23.6	M	N	188/103	4.2	N	7.3	205	280	<7.31	2+	109.2	N	N	N
16	38.4	M	N	232/127	16.7	Y	5.7	109	2269	<7.31	2+	54.2	ND	N	N
17	44.5	F	N	220/145	6.8	Y	10.3	58	491	27.20	1+	44.5	Y	N	N
18	45.2	M	Y	191/117	4.0	N	11.2	55	342	164	1+	98.6	N	Y	Y

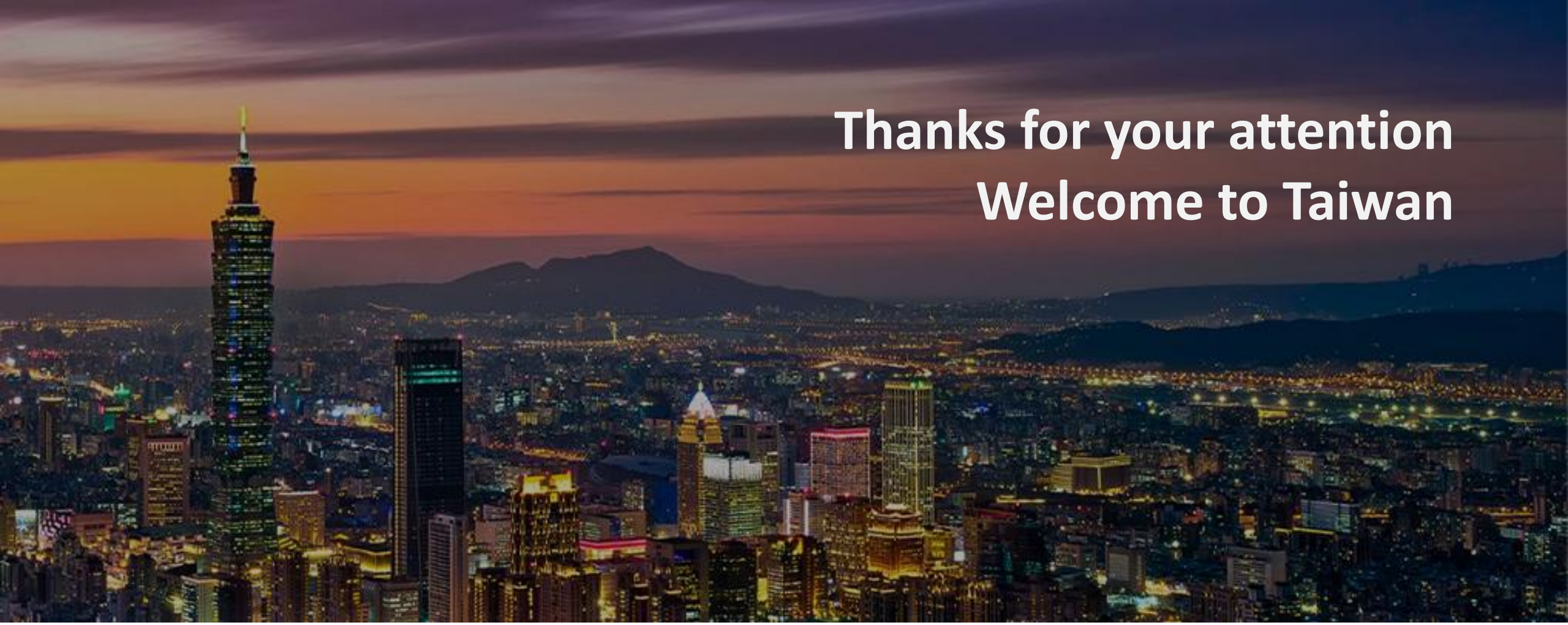
Unpublished data

CGMH Experience: severe HTN with kidney TMA

No.	C3	C4	CH50	Kidney biopsy	C3c deposits	Mutation(s)	PLEX	PLEX response	Anti-C5	ESRD
1	92.5	18.9	ND	Arterioles TMA, double-contour(+).	negative	ND			N	N
2	137.0	28.3	ND	Arterioles TMA, 1 crescent	negative	no mutation			N	Y
3	156.0	33.3	ND	Glomerular and arteriole TMA; fibrinoid necrosis+	negative	ND			N	Loss f/u
4	93.8	24.2	ND	Glomerular TMA	inadequate	ND			N	Y
5	121.0	20.4	ND	Arteriole TMA, fibrinoid necrosis+	negative	VWF:c.4927G>A	10	**Improved, stable CKD.**	N	N
6	80.5	16.0	208	Glomerular and arteriole TMA	negative	VWF:c.6860G>A	63	**Dependent**	Y	N
7	99.9	33.6	186	Arteriole TMA, fibrinoid necrosis+	negative	no mutation	10	**No response**	N	Y
8	109.0	29.0	70	Arteriole TMA	negative	CR1:c.7310T>C CFH:c.1920T>A			N	Y
9	101.8	41.8	201	Arteriole TMA	negative	no mutation			N	Y
10	109.6	30.8	ND	Arteriole TMA	negative	C4BPA:c.1667T>C THBD:c.1619G>A			N	N
11	83.0	31.5	46	Arteriole TMA; TIN+	negative	no mutation	10	Mildly improved	Y	N
12	142.6	37.6	78.5	Arteriole TMA; mild endocapillary hypercellularity	negative	no mutation	5	**No response**	N	Y
13	90.7	21.8	79.8	Arteriole TMA	negative	no mutation	10	Mildly improved	N	N
14	65.8	17.3	51.2	Glomerular TMA, focal MPGN injury	negative	no mutation	5	**No response**	N	Y
15	94.1	32.1	77.9	Glomerular chronic TMA, DMN+	negative	CFH:c.3172T>C CFH:c.3178G>C	15	**No response**	Y	Y
16	70.6	21.4	69.6	Arteriole and glomerular TMA, 1 cellular crescent	negative	no mutation	4	Hema resolution Kidney no response	Y	N
17	107.3	21.8	83.0	Arteriole TMA	negative	no mutation	18	**Improved, stable CKD.**	N	N
18	95.0	16.0	79.8	Arteriole TMA	negative	no mutation	5	Hema resolution Kidney mildly improved	N	N

Take Home Message

- TMA syndrome contains lots of disease with varied clinical presentations, presenting with thrombocytopenia, MAHA, renal injury, and lots of extra-renal symptoms.
- Diagnosis of atypical HUS need comprehensive work-ups, to exclude TTP and other diseases associated with TMA syndromes.
- Malignant HTN-TMA presented with hypertension emergency and AKI. It have similar outcome with primary atypical HUS. Malignant HTN-TMA might be a specific form of primary atypical HUS.
- Next time we encounter a hypertensive emergency with acute kidney injury, we should consider primary atypical HUS as a possible cause.



Christopher Kun-Hua Tu, M.D.

EMAIL：christopher.tu@gmail.com

Kidney Research Center, Department of Nephrology, Chang-Gung Memorial Hospital.

Transplant Immunology Lab, Kidney Transplant Team, Chang-Gung Memorial Hospital

Laboratory of Human Immunology and Infectious Diseases, Chang-Gung University.

長庚紀念醫院
Chang Gung Memorial Hospital

HYD
Lab of Human Immunology and Infectious Diseases

Comparison of all form of TMAs

	Primary TMA		Secondary TMA								
	TTP	aHUS	STEC	Pregnancy	Auto-immune	Malignant HTN	Cancer	Infection	Transplant	DITMA	Others
N	18	15	35	197	48	20	105	184	96	144	31
Anemia	100%	95%	100%	90%	100%	100%	100%	100%	100%	100%	100%
PLT count	10	71	37	74	72	71	41	48	69	66	108
Low PLT	100%	95%	97%	93%	92%	86%	95%	93%	90%	91%	84%
MAHA	100%	87%	100%	63%	81%	88%	86%	83%	76%	79%	88%
High LDH	100%	100%	100%	94%	85%	100%	88%	90%	78%	83%	79%
LDH (xUNL)	7	4	8	3	2	3	3	3	2	2	2
Low Hapto	94%	95%	97%	91%	84%	90%	91%	86%	89%	90%	97%
High D-Bil	89%	50%	46%	39%	27%	28%	57%	61%	36%	40%	77%
SCr	1.3	4.6	4.8	0.8	2.2	5.5	1.3	1.7	1.9	1.8	1.1
AKI	78%	86%	88%	36%	77%	100%	56%	70%	65%	63%	63%
Dialysis	3%	67%	66%	4%	25%	60%	12	26	27	24	10
ESRD risk	Low	High	Variable	Variable	Variable	High	Low	Variable	Variable	Low	N/A

Clin J Am Soc Nephrol. 2019 Apr 5;14(4):557-566.