CASE REPORT

MALIGNANT HYPERTENSION COMPLICATED BY RENAL THROMBOTIC MICRO ANGIOPATHY: ROLE OF ADAM 13 MUTATIONAL ANALYSES

Ishma Aijazi, Fadhil Al Shama, Lakshmiah Ganapathy Raman, Sara Mukhtiar
Department of Internal Medicine and Histopathology, Dubai Hospital, Dubai-U.A.E

We report a case of a 38-year-old U.A.E national who presented with malignant hypertension and features of thrombotic microangiopathy. He presented with oliguria, renal failure, thrombocytopenia and haemolytic anaemia. He required several sessions of renal replacement therapy. ADAM 13 mutational analysis was sent to differentiate Thrombotic micro angiopathy due to thrombotic thrombocytopenic purpura (TTP) or malignant hypertension. Renal biopsy revealed histopathological features of malignant arteriolar nephrosclerosis (MANS). Haemolytic parameters improved after control of blood pressure and he was subsequently discharged with early nephrology follow up.

Keywords: Malignant hypertension; Thrombotic Microangiopathy; MANS; Malignant arteriolar nephrosclerosis; Haemolytic uremic syndrome; HUS; Thrombotic thrombocytopenic purpura; TTP

J Ayub Med Coll Abbottabad 2017;29(3):502–5

INTRODUCTION

Malignant hypertension is characterized by severe hypertension and target organ damage including progressive heart failure, renal failure and encephalopathy and it is often associated with micro angiopathic haemolytic anaemia. The organ damage in malignant hypertension is due to a constellation of histopathological changes called thrombotic microangiopathy (TMA). However, the combination of malignant hypertension with renal TMA is rare. Roughly 10 cases have been reported in literature.[1] Thrombotic microangiopathy occurs in other syndromes apart from malignant hypertension namely haemolytic uremic syndrome and thrombotic thrombocytopenic purpura (HUS/TTP). Sometimes differentiating the various aetiologies of TMA is difficult. Hence ADAM 13 enzyme mutational analysis (von Wille brand factor (VWF) cleaving protease) can be used as a diagnostic tool for differentiating TTP from other aetiologies of TMA.

CASE

28-year-old gentle man, presented with 2-day history of severe headache, vomiting, visual blurring accompanied with decrease urine output. He had history of hypertension for 2 years but was not compliant with medications. There was no history of palpitations, sweating or fainting attacks. On admission, he was found to have a blood pressure of 222/141. There was no focal neurological deficit. All peripheral pulses were intact and there was no audible bruit. Fundoscopy revealed bilateral multiple flame shaped haemorrhages.

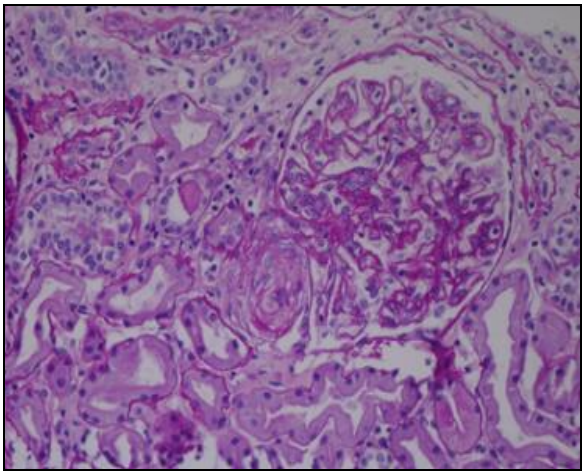

Figure-1: Thickened afferent arteriole of glomeruli with fibrinoid necrosis and onion skin appearance PAS stain x200

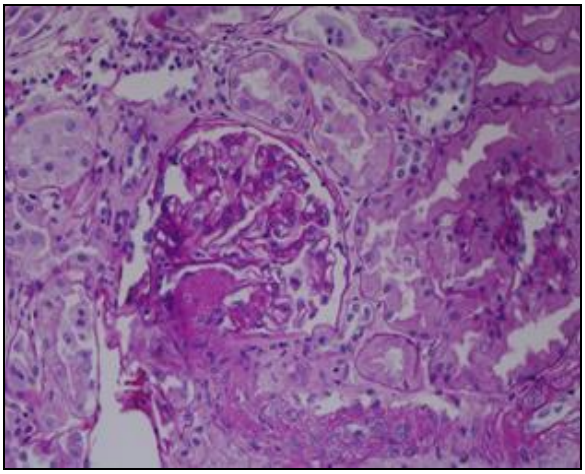

Figure-2: Glomeruli shows sclerosis, PAS stain x200

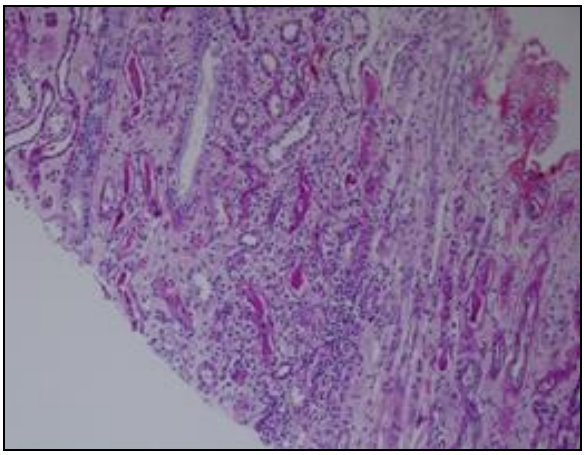

Figure-3: Interstitial fibrosis and lymphocyte inflammatory cell infiltrate PAS stain x100

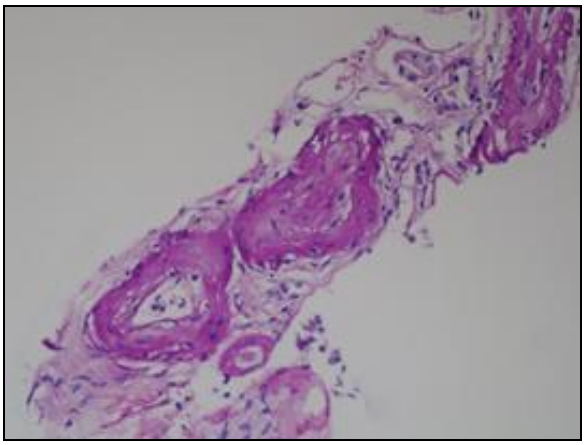

Figure-4: Interlobular arteriolar thickening and medial hypertrophy, PAS stain x100

Table-1: Investigations at admission

Labs	Reference range
Wbc 8700/ul, haemoglobin 10.4 g/dl, platelets 80,000 cubic mm	Wbc (3600–11000), haemoglobin (13–18), platelets (150-400,000)
Reticulocyte count 5.2%	0.5–2.5
LDH 2149 u/l	240–480
Sodium 132 mmol/l, potassium 2.5 mmol/l, urea 54 mg/dl, bi carbonate 24.4 mmol/l	Sodium (136–145), potassium (3.3–4.8), urea (12–40) bicarbonate (20–28)
Creatinine 4.9 mg/dl Uric acid 7.7 mg/dl Parathyroid 115 pg/ml Phosphate 4.7 mg/dl calcium 9 mg/dl	Creatinine (0.7–1.2) Uric acid (3.4–7.7) (6.2–29 pg/ml) (2.7–4.5) Calcium (8.9–10.2)
Direct Coombes test -ve	
LFT: total bilirubin 2.9 mg/dl, indirect bilirubin 1.8mg/dl, albumin 4.8 mg/dl, alkaline phosphate 88U/L, ALAT 22 u/l PT, APTT normal	Total bilirubin (0–1.0), direct bilirubin (0.3) Albumin (3.4–4.8), alkaline phosphatase (40–129) ALAT (0–41)
Urine routine 2+ protein, RBC numerous, glucose trace, wbc 5–10	
Blood film: schistocytes, bitten and polychromasia. Platelets are reduced. Film is consistent with micro angiopathic haemolytic anaemia (MAHA).	
HBAIC 5.3% Septic markers negative. Blood culture no growth	(4.8–6)
Anti-nuclear factor: negative	
Anti-DNA <10	<100 iu/ml (negative)
ENA profile: Negative ENA RIB P-PROT negative ENA RNP /Sm: Negative ENA Sm: Negative ENA SS-A (Ro): Negative ENA AA-B (La): Negative ENA Scl-70: Negative ENA Jo-1: Negative ENA centromeres: negative	
Work up for secondary (endocrine) hypertension Thyroid function test: normal Renin (supine) 5.8ng/ml/hr Aldosterone (supine) 1600 pmol/l Urine (metanephrines)/creatinine 217 ug/g Urine nor metanephrines/creatinine 376 ug/g 24-hour urine vanillylmandelic acid 2.4mg/24h Vanillymandelic acid/creatinine 2.3mg/g	 (0.51–2.64) (28–444) (31–140) (47–310) <6.8 <6
ADAM 13 mutational analysis ADAM 13 (activity) 79.8% ADAM 13 (antigen) 0.71 ug/ml Antibodies to ADAM 13 cannot be detected	 (40–130) (0.60–1.60)
ECG: left ventricular hypertrophy Echo Cardiography: Severe concentric left ventricular hypertrophy. There is normal ejection fraction CT brain (at admission) normal	
MRI brain (3rd day of admission)	Diffuse periventricular and supraventricular white matter hyper intensity? ischemic
Ultrasound kidneys	Both kidneys are normal in shape, size. There is poor cortico medullary differentiation and increase cortical echo texture.
MRI adrenals	Normal adrenals, with no mass visualized

Initial investigations revealed a micro angiopathic haemolytic anaemia (MAHA) as evidenced by low haemoglobin, low platelets, elevated LDH and raised reticulocyte count and increase in unconjugated bilirubin. Serological data for complements, immmuno-globulins, anti-nuclear anti bodies, anti – double stranded DNA, anti-nuclear cytoplasmic anti bodies, anti scl-70 were negative. Hepatitis B and hepatitis C and HIV anti bodies were also negative. Coombes test was also negative.

A diagnosis of malignant hypertension with micro angiopathic haemolytic anaemia was made. Patient was admitted in high dependency unit and blood pressure was lowered gradually over a period of 72 hours with intravenous labetalol infusion followed by oral anti-hypertensive medications. 72 hours after admission patient became drowsy and confused. Urgent brain imaging revealed changes in the brain due to thrombotic micro angiopathy.

In view of the mental status changes urgent plasma exchange was done. ADAM13 enzyme for mutation analysis was sent.

Subsequently the patient became anuric and had to be dialyzed. He started having good urine output after 2 to 3 sessions of dialysis and renal parameters showed a down ward trend. During subsequent days (after optimization of the patients' blood pressure) the platelets and haemolytic parameters also normalized. Work up for secondary hypertension was sent which was normal.

He was discharged on 12th day of admission- with early nephrology clinic follow up. At 16 week follow up he had a baseline creatinine of 2 mg/dl.

DISCUSSION

Malignant hypertension is a clinical syndrome characterized by severe hypertension, end organ damage and activation of the renin angiotensin aldosterone (RAAS) system. The end organ damage is due to TMA (thrombotic microangiopathy). It is often associated with microangiopathic haemolytic anaemia (MAHA). MAHA is a non-immune haemolytic anaemia resulting from intra vascular red blood cell fragmentation that produces schistocytes in peripheral smear. The micro vasculature of small arterioles and capillaries are affected. As in our patient, it is characterized by low platelets, raised LDH and reticulocyte count, raised bilirubin and low haptoglobin and negative direct anti-globin test (DAT).

In TMA there is, fibrinoid necrosis, fibrin and platelet clots in the lumina of arterioles, resulting luminal narrowing which leads to erythrocyte fragmentation and platelet consumption.[2] These micro vascular platelet aggregates cause partial or complete obstructive vasculopathy. There is also vessel wall thickening and endothelial injury[3] which activates platelet consumption.

In malignant hypertension, there is activation of the renin angiotensin aldosterone system (RAAS) which causes vaso constriction and increase in the vascular resistance. To compensate for this, the endothelial cells secrete vasodilating substances such as nitric oxide, adrenomedullin, prostacyclin. However, if there is severe hypertension the compensatory mechanism fails and angiotensin 2 promotes expression of inflammatory cytokines. These cytokines activate the coagulation cascade by causing further endothelial damage. This leads to fibrinoid necrosis, oedema of arterioles and platelet aggregation.[4]

In management of malignant hypertension, renal biopsy is not done as a routine. However, in our patient after optimization of blood pressure; renal biopsy was done because it was difficult to determine the temporal relationship between malignant hypertension and renal disease. There were no previous renal function tests available for comparison. Renal biopsy revealed typical features of MANS. Specimen included 39 glomeruli. One was globally sclerosed and one showed segmental sclerosis. Fibrinoid necrotic lesions were identified in small and large caliber arteries, arterioles and capillaries. There was severe intimal and medial hyperplasia, foci of 'onion skinning 'and hence obstruction of vessel lumen. The interstitium showed foci of fibrosis and patchy chronic inflammatory cell infiltration. An immuno florescence study showed no specific staining.

Since renal biopsy did not reveal significant glomerular sclerosis. There was hope of recovery of renal functions after dialysis and optimization of blood pressure. There by our patient started having good urine output after 2 to 3 sessions of dialysis and there was gradual recovery of renal functions.

Detailed work up was done in our patient to rule out secondary hypertension. The high serum and urine metanephrine and nor metanephrine could be explained by the renal failure and also patient has been given high dose of intravenous beta blockers (labetalol) for a few days prior to sample collection.[5] Renin and aldosterone levels were also high, but the renin/aldosterone ratio was not suggestive of conns syndrome.

Theoretically there is no role of plasma pheresis in the management of TMA in malignant hypertension.[6] However, it should be initiated as soon as possible if we are dealing with TMA due to TTP, because in TTP prognosis is quite dismal (>90% mortality) without plasmapheresis.[7] Our patient was offered 2 sessions of plasmapheresis since the features of TTP/HUS and malignant hypertension

overlap significantly and it was difficult to distinguish one from the other. Taking into consideration the fact that our patient had some transient mental status changes after admission, also the result of ADAM 13 mutational analysis takes 2–3 weeks in our centre. Studies suggest that in patient with malignant hypertension and severe TMA (HCT<20%, PLATELETS <10X 109, LDH >600 IU/l, serum creatinine >442 uml/l and or evidence of cerebral dysfunction plasma exchange might be considered.[8]

In the meantime, tests for ADAM 13 enzyme mutational analysis was also sent. ADAM 13 is a zinc containing enzyme (it is a metallo preotease) that cleaves the large von willebrand factor (Vwf) multimere thereby decreasing there thrombogenecity. It is established that in TTP there is congenital or acquired deficiency of ADAM 13 enzyme. However recently there are reports that in malignant hypertension there is an association between severity of TMA and reduced ADAM 13 activity.[9]

However, the very fact that the patient improved clinically and haemolytic parameters improved gradually after optimization of blood pressure and one session of plasma pheresis favours diagnosis of TMA due to MHTN, rather than TTP. Hence no further sessions of plama pheresis were offered. Normal ADAM 13 assay also favoured discontinuation of further sessions of plasma pheresis.

CONCLUSION

Thrombotic micro angiopathy must be considered in patients with malignant hypertension presenting with progressive renal failure, anaemia and thrombocytopenia. Optimizing blood pressure control will lead to resolution of haemolysis and thrombocytopenia. However, kidney injury may persist for a long period of time and require need for prolonged renal replacement therapy.

Adam 13 enzyme mutational analysis will help differentiate whether TMA is due to MHTN or due to TTP/HUS. However, it can be very low in Severe TMA associated with malignant hypertension warranting plasma exchange.

REFERENCES

1. Higashi AY, Nogaki F, Ono T, Fukatsu A. Case of kidney failure with thrombotic microangiopathy lesions in renal biopsy caused by accelerated hypertension in young adult. Nihon Jinzo Gakkai Shi 2009;51(7):878–83.
2. Khanna A, McCullough PA. Malignant hypertension presenting as hemolysis, thrombocytopenia, and renal failure. Rev Cardiovasc Med 2003;4(4):255–9.
3. Bergan JJ, Schmid-Schönbein GW, Smith PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic Venous Disease. N Engl J Med 2006;355(5):488–98.
4. Zhang B, Xing C, Yu X, Sun B, Zhao X, Qian J. Renal Thrombotic Microangiopathies Induced by Severe Hypertension. Hypertens Res 2008;31(3):479–83.
5. Feldman JM. Falsely elevated urinary excretion of catecholamines and metanephrines in patients receiving labetalol therapy. J Clin Pharmacol 1987;27(4):288–92.
6. van den Born BJ, van der Hoeven NV, Groot E, Lenting PJ, Meijers JC, Levi M, *et al*. Association Between Thrombotic Microangiopathy and Reduced ADAMTS13 Activity in Malignant Hypertension. Hypertension 2008;51(4):862–6.
7. George JN. How I treat patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Blood 2000;96(4):1223–9.
8. Shibagaki Y, Fujita T. Thrombotic microangiopathy in malignant hypertension and hemolytic uremic syndrome (HUS)/Thrombotic thrombocytopenic purpura (TTP): Can we differentiate one from the other? Hypertens Res 2005;28(1):89–95.
9. Remuzzi G. Is ADAM 13 defeciency specific to thrombotic thrombocytopenic purpura? No. J Thromb Haemost 2003;1(4):632–4.

Received: 18 January, 2017	Revised: 12 february, 2017	Accepted: 4 April, 2017

Address for Correspondence:
Dr Ishma Aijazi, Department of Internal Medicine, Dubai Hospital, Dubai-U.A.E
Email: engrjaffar@gmail.com