CASE REPORT

Malignant hypertension as a rare cause of thrombotic microangiopathy

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SUMMARY

Malignant hypertension can occasionally be associated with microangiopathic haemolytic anaemia. A 38-year-old male presented with nausea, vomiting, loss of appetite and oliguria for 2 weeks. He was diagnosed with hypertensive emergency with cardiac and renal dysfunction. Interestingly, further workup was diagnostic for the presence of thrombotic microangiopathy (TMA): haemoglobin = 12.7 g/dL, indirect bilirubin = 2.0 mg/dL, haptoglobin $\leq$ 6 mg/dL, platelet count = 121 000/ μ L and schistocytes on peripheral smear. At the outset, the cause of TMA was unclear. Patient denied having diarrhoea, making haemolytic uremic syndrome less likely. A normal ADAMTS13 activity test ruled out thrombotic thrombocytopenic purpura. Malignant hypertension induced TMA was highest on the differential and plasma exchange was deferred. Renal biopsy revealed features of TMA and malignant nephrosclerosis. Patient eventually became dialysis dependent. Aggressive blood pressure control was obtained with multiple medications.

BACKGROUND

Thrombotic microangiopathy (TMA) is a pathological entity caused by diverse mechanisms. Diseases classically associated with TMA include haemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and atypical HUS (aHUS). Each of these diseases are pathophysiologically distinct. However, TMA can also be caused by other pathophysiological pathways including malignant hypertension. Identifying the correct aetiology of the TMA has important implications in its management, as illustrated with our case.

CASE PRESENTATION

A 38-year-old African American male with no medical history presented with multiple complaints. He had not seen a primary care physician for many years. His symptoms included nausea, vomiting and loss of appetite for 2 weeks. He reported low urine output and dark discolouration of urine for the past 1 week. He also reported feeling fatigued for the past few days. On presentation, he was found to be hypertensive and had a blood pressure of 218/40 mm Hg. Although the patient did not have a documented history of hypertension, he was seen at the emergency department 1 year ago and his blood pressure at that time was 184/102 mm Hg. Patient did report a family history of hypertension in his mother. He denied substance abuse. He did not take any over-the-counter or prescription medications.

Complete physical examination was unremarkable, and no abdominal tenderness could be elicited.

Routine investigations were performed to look for evidence of end-organ damage from malignant hypertension. Initial laboratory data revealed a creatinine of 6.0 mg/dL (1.3 mg/dL 1 year ago), haemoglobin of 12.7 g/dL (with a mean corpuscular volume of 80.6 femtoliter), indirect bilirubin of 3.0 mg/dL and platelet count of 121×10^9 /L. The presence of normocytic anaemia and indirect bilirubinemia was suspicious for haemolysis. This was confirmed by a lactate dehydrogenase (LDH) of 494 IU/dL and a haptoglobin of <6 mg/dL. At this point, a peripheral smear was requested, which was remarkable for the presence of schistocytes. The coexistence of haemolytic anaemia, thrombocytopenia and schistocytes was diagnostic of the presence of thrombotic microangiopathy.

Other relevant data included an elevated troponin I of 0.16 ng/mL (upper limit of the assay = 0.04 ng/mL). Patient met the electrocardiographic criteria for left ventricular hypertrophy, but no Shiga toxin (ST) changes were noted on the ECG. Also, the transthoracic echocardiogram showed severe left ventricular hypertrophy with grade II diastolic dysfunction and severe global hypokinesis with an ejection fraction of 30%–35%. Interestingly, the urinalysis showed 2+ protein, 3+ haemoglobin, 200 red blood cells/high power field, 2 red cell casts/low power field and 2 granular casts/low power field.

At this point, patient was identified to have a hypertensive emergency with end-organ damage to the heart and the kidneys. Left ventricular strain manifesting as elevated troponin was indicative of cardiac dysfunction, and patient also had stage III acute kidney injury per Acute Kidney Injury Network classification. His gastrointestinal distress was likely caused by his uremic state. The underlying left ventricular hypertrophy and combined systolic and diastolic dysfunction was suggestive of chronic uncontrolled hypertension. However, the aetiology of TMA and the reason for haematuria, proteinuria and red cell casts was unclear. Further workup was performed to investigate these findings.

INVESTIGATIONS

Initial testing aimed at ruling out the common causes of TMA. Patient unequivocally denied having loose stools over the past few days, making the diagnosis of HUS less likely. PCR test for ST

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Table 1 A list of important causes of thrombotic microangiopathy in adults

Disorder	Cause of TMA	Characteristics
HUS	ST-mediated endothelial damage (also known as ST-HUS)	Mainly seen in the paediatric age group but can be seen in adults. Patients invariably have a history of diarrhoea, primarily supportive treatment. Plasma exchange and eculizumab have been used in patients with neurological involvement.
TTP	Hereditary or acquired deficiency of ADAMTS13 reduces vWF destruction and increases platelet adhesion.	Fever and neurological symptoms are common. Plasma exchange is the mainstay of treatment.
aHUS	Hereditary mutations of various complement factors or acquired inhibition of factor H causes excessive complement activation, further leading to platelet activation.	aHUS is rare. It is important to exclude HUS and TTP. Both plasma exchange and eculizumab can be used.
Drug-mediated TMA	Best reported with quinine; mechanism involves immune-mediated endothelial damage	Management involves removal of drug and supportive care.
Malignant hypertension-induced TMA	Endothelial activation from high shear stress.	Management involves adequate blood pressure control. Plasma exchange and eculizumab are not indicated.

aHUS, atypical haemolytic uremic syndrome; HUS, haemolytic uremic syndrome; ST, Shiga toxin; TMA, thrombotic microangiopathy; vWF, von Willebrand factor.

came back negative. Patient did not have the classic clinical features of TTP as he did not have any fever or neurological symptoms. ADAMTS13 activity was normal, thereby ruling out TTP. Patient's complement levels were normal. Although this did not completely rule out aHUS, further testing was not performed due to low pretest probability. Due to the unclear aetiology of TMA and abnormal urinary findings, a renal biopsy was performed and tissue was sent out to a referral centre for analysis. The biopsy showed obliterative glomerulopathy with evidence of glomerular and arteriolar thrombi suggestive of TMA. Severe segmental or global ischaemic changes were seen in several glomeruli, but no glomerular necrosis was present. Prominent onion skinning was seen in small arteries and arterioles, which is typical of malignant nephrosclerosis. There was no evidence of glomerulonephritis.

Workup for secondary causes of hypertension was performed. Patient was hypokalemic on admission (serum potassium level 3.2 Meq/L) and hyperaldosteronism was a concern. Plasma renin activity (PRA) and serum aldosterone levels were checked on admission and were found to be elevated. However, this was later thought to be due to acute activation of the renin–angiotensin–aldosterone system (RAAS) in the setting of malignant hypertension. Interestingly, repeat PRA and aldosterone levels on day 6 of admission were found to be normal. Morning cortisol, serum metanephrine and serum normetanephrine levels were checked and were all found to be normal.

DIFFERENTIAL DIAGNOSIS

At this point, malignant hypertension was identified as the direct cause of thrombotic microangiopathy after considering all other potential causes (see [table 1](#)). Extensive testing effectively ruled out other causes of TMA. Furthermore, malignant nephrosclerosis was identified as the most likely cause of haematuria and red cell casts; renal biopsy showed no evidence of glomerulonephritis.

TREATMENT

Plasma exchange was initially contemplated but was deferred when malignant hypertension was suspected to be the cause for the thrombotic microangiopathy. Thereafter, aggressive blood pressure control was obtained with multiple oral medications. However, patient's renal function did not improve and he became dialysis dependent.

OUTCOME AND FOLLOW-UP

The patient was discharged with planned outpatient follow-up. Patient was followed up 3 months after the discharge, and he remained dialysis dependent at that point.

DISCUSSION

Thrombotic microangiopathy can be caused by diverse mechanisms but the common final event is platelet activation in the microvasculature. This can be caused by microvascular endothelial damage or by a predilection for platelet activation. Platelet activation leads to the formation of platelet microthrombi in the microvasculature.¹ This cascade often involves the renal vasculature, and renal dysfunction is commonly seen in TMA syndromes. TTP, HUS and aHUS are classically associated with TMA. TTP results from hereditary or acquired deficiency of the enzyme ADAMTS13, a metalloprotease responsible for cleaving von Willebrand factor (vWF) multimers. Higher concentration of vWF increases platelet adhesion at the site of endothelial injury. HUS is caused by ST-mediated endothelial damage, whereas aHUS results from excessive activation of the complement pathway and platelet activation. Finally, endothelial injury due to high shear stress in malignant hypertension has been postulated to cause TMA. A list of the important causes of TMA is depicted in [table 1](#).

Clinically, the presence of TMA is recognised by thrombocytopenia due to platelet consumption and by microangiopathic haemolytic anaemia (MAHA). Microangiopathic haemolysis is characterised by normocytic anaemia, indirect bilirubinemia, high LDH level, low haptoglobin level and the presence of schistocytes of peripheral smear. All TMA syndromes, irrespective of aetiology, are expected to have this constellation of findings. Once TMA is recognised, further workup should be directed towards identifying the precise aetiology. HUS is suspected if there is a history of diarrhoea; ST PCR can help confirm the diagnosis. TTP is classically associated with neurological symptoms and fever; ADAMTS13 activity can be tested. Patients with atypical HUS may have low levels of complement factors 3 and 4. However, normal complement factor levels do not rule out aHUS. Genetic testing can help confirm aHUS but its availability is limited.

Classic definitions of malignant hypertension required the presence of papilloedema as one of its manifestations. However, more modern definitions proposed recently consider the involvement of at least three different target organs as malignant

hypertension.² The target organs typically involved are kidney, heart, brain and microvessels. Notably, TMA in hypertension is now considered a form of target organ damage. Although hypertension can be seen in other TMA syndromes, blood pressure in malignant hypertension-induced TMA is often extremely high. Other aetiologies of TMA in these patients should be carefully ruled out by history and other investigations. Recognising hypertension as the direct cause of TMA is important as it precludes the use of plasma exchange or eculizumab, which are established therapies used in some of the other TMA syndromes.¹ The only intervention needed for malignant hypertension-induced TMA is strict blood pressure control.

The presence of malignant hypertension, especially in younger patients, may warrant workup for secondary causes of hypertension. However, the testing for RAAS should be deferred until the acute phase of the hypertensive emergency has passed. This is because activation of RAAS is central to the pathogenesis of hypertensive emergency.³ Briefly, chronic uncontrolled hypertension leads of remodelling and narrowing of the renal vasculature, which causes activation of RAAS. This leads to worsening of hypertension, and this vicious cycle culminates in acute severe elevation of blood pressure. This concept was illustrated well in our case. PRA and serum aldosterone levels were initially elevated, but they normalised on day 6 of admission.

In a retrospective analysis of 97 patients admitted with malignant hypertension, 26 patients had evidence of microangiopathic haemolysis.⁴ Patients with MAHA were more often black (73%; $p<0.01$) and had significantly higher creatinine levels (mean creatinine level 7.8 mg/dL vs 1.36 mg/dL; $p<0.01$). These patients also had higher systolic blood pressure (SBP) readings on presentation (mean SBP 242 vs 225; $p<0.01$) and had a higher incidence of eventual dialysis dependence (15 patients (58%) vs 2 patients (3%)). Out of the 15 patients with MAHA who became dialysis dependent, dialysis could be stopped in 6 of them within the next 2 years. Hence, some degree of recovery of renal function can be expected in these patients.

Another peculiar laboratory finding in our case was the presence of red blood cell casts in the urine. Nephritic urinary sediment is typically seen in glomerulonephritis and renal vasculitides. However, it should be noted that the nephritic sediment can rarely be present in other conditions, including malignant hypertension. The mechanism of nephritic sediment in malignant hypertension patients is likely focal ischaemic glomerular necrosis due to severe renal microvascular disease, which can be exacerbated by the presence of concomitant TMA.⁵ Although severe glomerular ischaemic changes were present, glomerular necrosis was not seen in renal biopsy of our patient. This may have been due to the limited number of glomeruli evaluated.

Sporadic cases of patients with malignant hypertension with nephritic urinary sediments have been reported in the literature.^{5,6}

Learning points

- ▶ Thrombotic microangiopathy (TMA) should be recognised as a distinct clinicopathological entity that can be identified from a classic constellation of laboratory findings.
- ▶ Identification of TMA should invite further workup to identify the underlying aetiology. It is important to recognise malignant hypertension as a potential cause of TMA as this has therapeutic implications. When malignant hypertension is associated with TMA, it often portends a worse prognosis and a higher incidence of renal failure.
- ▶ The renin–angiotensin–aldosterone system (RAAS) pathway is often stimulated during the acute phase of malignant hypertension. Testing of RAAS should be deferred until the acute phase has passed.
- ▶ Nephritic urinary sediment can rarely be seen in patients with malignant hypertension.

Contributors Both authors contributed to the manuscript as follows. GT was part of the primary team who admitted the patient and KK was on the nephrology team, which was consulted for the patient at that time. Hence, both authors were directly involved with patient care. GT did the literature review and manuscript write-up. KK revised the manuscript critically for important intellectual content. Both authors gave their final approval of the version to be published.

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