Malignant hypertension as a rare cause of thrombotic microangiopathy associated with end-stage renal disease

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Abstract

Malignant hypertension (MH) can precipitate and worsen renal thrombotic microangiopathy. Also, renal thrombotic microangiopathies (TMA) can cause malignant hypertension. Case reports regarding this clinical presentation are limited. A 36-year-old man presented with low urine output and bilateral leg swelling for five days with two episodes of haemoptysis. He was identified as a patient with hypertensive emergency with hypertension mediated organ damage (HMOD) in cardiac and renal functions with thrombotic microangiopathy. Renal biopsy revealed focal acute tubular injury with moderate tubulointerstitial nephritis and hypertensive vascular changes. Multiple anti-hypertensive medications were used for adequate blood pressure control. Despite that, the patient had worsening renal function, and eventually became dependent on haemodialysis. Malignant hypertension has to be considered as one of the aetiologies of TMA as it can lead to end-stage renal disease (ESRD) and poor outcomes. Diagnosis is difficult when both entities are presenting together.

Keywords: malignant hypertension, thrombotic microangiopathy, tubulointerstitial nephritis, hypertension mediated organ damage

Introduction

Various mechanisms are implicated in the pathogenesis of thrombotic microangiopathies (TMA). (1) Haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are usually associated with TMA. (1) Each of these diseases is unique in pathophysiology. Several pathophysiological pathways are involved in developing TMA, including endothelial injury, intravascular platelet activation, and formation of platelet-fibrin thrombi. (1) Patients with atypical haemolytic uraemic syndrome (aHUS) and MH both present with concomitant hypertension and thrombotic microangiopathy (TMA), making management difficult. (2) The causes of TMA need to be identified and treated as they have therapeutic implications. (3)

Case presentation

A 36-year-old man, a previously known patient with essential hypertension, was transferred to our unit for plasma exchange due to TMA. He had not seen a primary care physician for many years and had defaulted treatment. He had a non-productive cough, mild fever, and a sore throat. He had been diagnosed with mild COVID-19 infection and had been admitted to the intermediate care centre one week prior to the current admission. He was found to have a low haemoglobin level (6 g/dL), low platelets (67,000), and a high creatinine level of 17 mg/dL (0.7-1.3 mg/dL), and was transferred to the base hospital for haemodialysis. He reported low urine output and bilateral leg swelling for the last five days with two episodes of a scanty amount of haemoptysis. He also said that he felt exhausted in the past few days. He
had accelerated hypertension of 280/180 mmHg on examination. He had a blood pressure reading of 230/160 mmHg on his past records and had been advised on medical evaluation which he had defaulted. The patient did not have a family history of hypertension. He denied substance abuse. Examination revealed pallor, icterus, bilateral pitting leg edema, cardiomegaly, gallop rhythm, bilateral pleural effusions, and ascites. Fundoscopy revealed grade 4 hypertensive retinopathy.

Routine investigations were performed to assess end-organ damage. Initial laboratory data revealed a creatinine of 17.0 mg/dL which reduced to 8.0 mg/dL following haemodialysis (HD). His baseline creatinine was 1.3 mg/dL one year back. Haemoglobin was 6 g/dL (with a mean corpuscular volume of 88 femtoliters), indirect bilirubin was 2.0 mg/dL, and platelet count was 69 x 10⁹ /L. Haemolysis was confirmed by a lactate dehydrogenase (LDH) of 1455 IU/dL. A blood smear revealed the presence of schistocytes /fragmented cells and polychromatic cells. The coexistence of haemolytic anaemia, thrombocytopenia, and schistocytes revealed thrombotic microangiopathy. He had left ventricular hypertrophy on the ECG.

His 2D echo showed severe left ventricular hypertrophy with diastolic dysfunction, which was suggestive of hypertensive heart disease. On admission, chest x-ray showed acute pulmonary oedema. HRCT also showed fluid overload with an atypical infection. The urinalysis showed 4+ protein, 3+ haemoglobin, 200 red blood cells/high power field, two red cell casts/low power field, and two granular casts/common power field. Urine protein creatinine ratio confirmed nephrotic range proteinuria (15 g/mmol). The patient was identified to have a hypertensive emergency with end-organ damage to the heart and the kidneys. The left ventricular strain manifesting was suggestive of cardiac dysfunction. The patient also had end stage renal disease (ESRD) at the time of admission. The underlying left ventricular hypertrophy and diastolic dysfunction were indicative of chronic uncontrolled hypertension. The cause of thrombotic microangiopathy is malignant hypertension.

Preliminary investigations were targeted to exclude the common causes of thrombotic microangiopathy. The patient denied diarrhoea over the past few days, making the diagnosis of HUS unlikely. Fever and neurological symptoms were absent, making TTP an unlikely aetiology. He had normal complement levels. USS abdomen revealed bilateral chronic renal parenchymal changes with altered corticomedullary demarcation (left and right renal sizes were 11.3 cm and 10.8 cm respectively). We didn't exclude aHUS, and further testing was not done due to low probability. Rapidly progressive glomerulonephritis (RPGN), vasculitis screens, such as anti-glomerular base membrane antibodies (Anti-GBM antibodies), ANA, Anti-dsDNA, C-ANCA, P-ANCA, HIV, and hepatitis screens, were negative. This patient had bilateral papilloedema with haemorrhages in fundoscopy. It was confirmatory of malignant hypertension, which was the likely cause of the TMA. Unfortunately, his renal disease was advanced requiring HD at the time of admission, and a renal biopsy was done. It revealed two completely sclerosed glomeruli, two partially sclerosed glomeruli, and three viable glomeruli with focal mesangial matrix hypercellularity and expansion. There was no evidence of glomerulonephritis. Focal acute tubular injury, moderate tubulointerstitial nephritis and hypertensive vascular changes were seen. Glomerulosclerosis favours chronic hypertension with hypertensive nephropathy. Secondary causes of hypertension were excluded through investigations.

Plasmapheresis was not considered as the aetiology for TMA was malignant hypertension. Multiple oral medications were used for aggressive blood pressure control. Despite the medications, his renal function did not improve, and he became dependent on dialysis. He was discharged after stabilisation. Family counselling was arranged regarding renal transplantation. He is currently followed up regularly in the clinic.

**Discussion**

Various mechanisms cause TMA, but the final event is platelet activation.(4) A tendency for platelet activation or endothelial damage is caused by various distinct aetiologies.(4) The formation of microthrombi in the microvasculature results from the activation of platelets.(1) Renal vessels are involved in this process, and impaired renal function is seen in TMA syndromes.(5) TTP, HUS, and aHUS usually cause TMA.(5) TTP is due to hereditary or acquired deficiency of ADAMTS13, an enzyme needed for von Willebrand factor (VWF) lysis.(6) Increased VWF at the site of endothelial injury increases platelet adhesion. (6) High shear stress-induced endothelial injury in TMA is postulated to be due to malignant hypertension.(6)

The presence of thrombocytopenia due to microangiopathic haemolytic anaemia is needed to diagnose TMA.(1) Microangiopathic haemolysis is
Table 1 - Summary of investigations for the aetiology of end-stage renal disease (ESRD)

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B surface antigen</td>
<td>Negative</td>
</tr>
<tr>
<td>HIV antigen &amp; antibodies</td>
<td>Negative</td>
</tr>
<tr>
<td>Hepatitis C surface antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-nuclear antibody (ANA)</td>
<td>Negative</td>
</tr>
<tr>
<td>perinuclear (P-ANCA) or cytoplasmic (C-ANCA) anti-neutrophil cytoplasmic antibodies</td>
<td>Negative</td>
</tr>
<tr>
<td>Complement levels</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum protein electrophoresis</td>
<td>Normal study</td>
</tr>
<tr>
<td>Serum calcium level</td>
<td>9.2 mg/dl (8.5-10.5mg/dl)</td>
</tr>
<tr>
<td>Anti glomerular basement membrane antibodies (Anti GBM Ab)</td>
<td>Negative</td>
</tr>
<tr>
<td>Renal artery doppler</td>
<td>Normal study, no stenosis of renal artery</td>
</tr>
</tbody>
</table>

associated with the standard features of haemolysis such as normocytic anaemia, indirect bilirubinaemia, high LDH level, low haptoglobin level, and presence of schistocytes on blood picture additionally. All TMA syndromes will have these findings regardless of the aetiology. The aetiology must be treated promptly if TMA is identified. If HUS is suspected, Shiga-like toxin PCR will help to confirm the diagnosis. Neurological symptoms and fever are pathognomonic for TTP. ADAMTS13 enzyme activity is also assessed. Complement factors 3 and 4 levels may be low in patients with atypical HUS.

However, aHUS is not ruled out by normal complement factor levels. aHUS can be confirmed by genetic testing. However, the availability of genetic testing is limited. The presence of papilloedema is needed to diagnose malignant hypertension as per the previous definition. However, recent definitions propose that damage to a minimum of three target organs is considered malignant hypertension. The typical target organs involved are the brain, heart, kidney, and microvasculature. TMA is also viewed as a manifestation of acute HMOD. Extremely high pressure is noted in MH-induced TMA compared to hypertension secondary to TMA. Alternative aetiologies for TMA need to be excluded through combined history, examination, and investigations. If malignant hypertension is identified as an aetiology of TMA, there is no place for plasmapheresis or eculizumab therapy which are established therapies for other causes of TMA. Blood pressure control is the only intervention that needs to be done in patients with malignant hypertension-induced TMA.

Our patient had an unusual laboratory finding of a urinary red cell cast. These are usually associated with glomerulonephritis and renal vasculitis. These sediments are distinctive in malignant hypertension-induced TMA. However, severe malignant hypertension can have this sediment due to focal ischaemic necrosis associated with microangiopathic haemolytic anaemia. Despite the global glomerular ischaemic injury, glomerular necrosis was not identified in our patient's renal biopsy. This may be due to the limited number of glomeruli extracted during the renal biopsy.

Conclusion

TMA is a unique clinicopathologic entity where the constellation of findings is identified through investigations. Aetiology for TMA has to be actively sought as it has therapeutic implications. If MH is found to be a cause of TMA, tight blood pressure control is the only available treatment. The incidence of renal failure is very high in patients with MH-induced TMA, and it signifies a poor prognosis.
Declarations

Author contributions
JCC and SY have contributed equally to the manuscript’s conception and preparation. JCC and SY have been involved in the management of the patient. All authors read and approved the final manuscript.

Conflicts of interest
The authors declare that they have no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

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