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Case Report

Malignant Hypertension with Thrombotic Microangiopathy and Persistent Acute Kidney Injury

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Malignant hypertension may on occasion be associated with microangiopathic hemolytic anemia. A 45-year-old male presented with stiff neck, nausea, poor appetite, and dyspnea on exertion for 1-2 weeks before admission. He was diagnosed with hypertensive emergency with cardiac and renal dysfunction. The presence of thrombotic microangiopathy (TMA) was determined based on the presence of schistocytes on peripheral smear and laboratory data, including hemoglobin 9 g/dL, total bilirubin 0.5 mg/dL, haptoglobin 72 mg/dL (30-200), platelet count 59 000/μL, and reticular cell count 7.1% (2-0.5%). The cause of TMA was unclear. This patient denied having diarrhea, making hemolytic uremic syndrome unlikely. Normal ADAMTS13 activity also ruled out thrombotic thrombocytopenic purpura. Malignant hypertension-induced TMA was impressed. Plasmapheresis with plasma replacement was arranged. Renal biopsy revealed features of TMA and malignant nephrosclerosis. This patient has been dialysis-dependent for more than 3 months and his hypertension has been treated aggressively with multiple medications.

Keywords: Malignant hypertension, thrombotic microangiopathy, acute kidney injury, dialysis

Introduction

Malignant hypertension (MHTN) is characterized by severe hypertension and acute multi-organ ischemic complications including thrombotic microangiopathy (TMA)[1]. TMA describes a group of disorders that share a common clinical presentation: microangiopathic hemolytic anemia (MAHA), defined as hemoglobin (Hb) <10g/dL, accompanied by evidence of hemolytic anemia; thrombocytopenia (platelet count $<150x10^9$/L); and end-organ dysfunction that in many cases presents as acute kidney injury (AKI; as defined in the Kidney Disease: Improving Global Outcomes guidelines)[2]. Renal TMA with MHTN is associated with thrombosis of small vessels, intravascular hemolysis with red cell fragments (schistocytes), platelet consumption, and elevated lactic dehydrogenase (LDH) levels[3]. There may also be associated oliguric AKI, which rarely requires renal replacement therapy, over varying time periods. Due to the rarity of renal TMA complicating MHTN, its clinicopathologic features and predictors of renal prognosis are largely unknown. Renal TMA complicating MHTN may resemble thrombotic thrombocytopenic purpura (TTP). Distinguishing

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these two entities is important due to therapeutic implications. Plasmapheresis is beneficial in TTP but not in TMA associated with MHTN. We report a case of MHTN with biopsy-proven renal TMA, with-long term dialysis dependency in which a clinicopathologic correlation between MHTN and TMA was determined based on follow-up biopsy findings.

Case report

A 45-year-old male patient was admitted to the hospital with headache, nausea, vomiting, and initial blood pressure (BP) of 220/120 mmHg. Physical examination showed hypertensive retinopathy with flame-shaped hemorrhages and exudates, but no papilledema. Serum creatinine level was initially 4.54 but rose to 11.07 mg/dL over 14 days. Hemoglobin was 10.4 g/L and platelet count was 59000. Over a 4-day period, BP decreased to 140/92 mmHg following administration of olmesartan/amlodipine/hydrochlorothiazide (20/5/12.5 mg/day), Terazosin HCl (2mg daily), and Nebivolol 5 mg/day. However, non-oliguric AKI persisted. Coomb's test was negative. A renal ultrasound showed normal-sized kidneys. Urinalysis demonstrated hematuria, with ~990 mg/day proteinuria. There was evidence of hemolysis with schistocytes on peripheral smear,

Table 1. Laboratory data of a patient with MHTN and TMA

Laboratory test	Result		Laboratory test	Result	
WBC	11670		ANA	Negative	<1:80
Seg	75.8	%	dsDNA	12.51	<200 IU/ml
Hgb	9	g/dl	ANCA	Negative	<1:40
PLT	59	K/ul	C3	83	152-79 mg/dl
BUN	140	mg/dl	C4	21.3	38-16 Mg/dl
Creatinine	11.07	mg/dl	IgG	869	1560-751 Mg/dl
Glucose	116	mg/dl	IgA	253	453-82 Mg/dl
Albumin	3.9	g/dl	IgM	44.4↓	304-46 Mg/dl
Cholesterol	200	mg/dl	HBsAg	non-reactive	
LDL	115	mg/dl	anti-HCV	non-reactive	
Triglyceride	122	mg/dl	anti-HBs	non-reactive	
Uric Acid	11.4	mg/dl	anti-HIV	non-reactive	
Calcium	8.8	mg/dl	RPR/VDRL	non-reactive	
K	3.4	mmol/l	TPPA/TPHA	1:80 negative	
Phosphate	9.4	mg/dl	Rheumatoid factor	<20	
LDH	435	g/dl	Immunoelectrophoresis (serum)	Polyclonal gammopathy	
Total bilirubin	0.5	mg/dl	Immunoelectrophoresis (urine)	Polyclonal gammopathy	
Haptoglobin	72	mg/dl	reticular cell count	7.10%	2-0.5 %
			Coombs' test (direct/indirect)	negative	

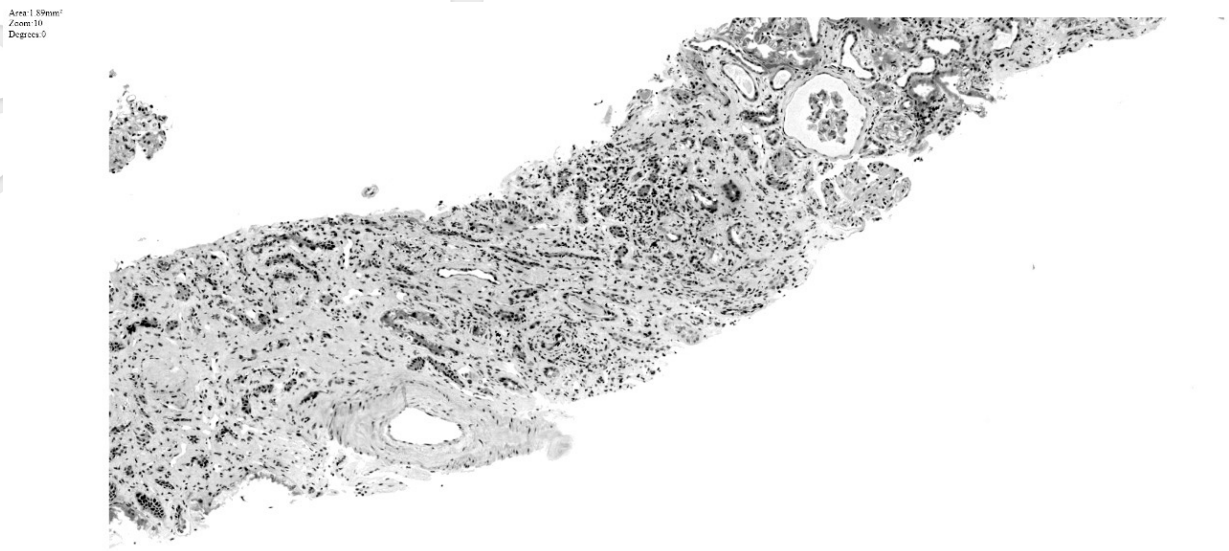

Fig. 1 Renal pathology showed Thrombotic microangiopathy (TMA) with hyperplastic arteriolosclerosis, focal segmental glomerulosclerosis, active interstitial nephritis, and moderate cortical scar with fibrinoid necrosis of arterioles and arteriolar thrombosis

high LDH, and high reticular cell count. Serologic tests such as anti-nuclear antibody, hepatitis B and C, C3, C4, human immunodeficiency virus (HIV), and ADAMTS-13 Activity: 77.1% (reference range: 40 – 130 %) were all negative. Clinical data is shown in Table 1. Hemodialysis was initiated due to uremic symptoms and persistent AKI. Renal pathology showed TMA with hyperplastic arteriolosclerosis, focal segmental glomerulosclerosis, active interstitial nephritis, and moderate cortical scar with fibrinoid necrosis of arterioles and arteriolar thrombosis (Figure 1). Plasmapheresis with plasma replacement was performed. This patient remains dialysis-dependent.

Discussion

TMA is a pathologic description of the clinical presentation of thrombocytopenia, MAHA, and organ injury[2,4,5]. It can manifest in a range of conditions with variable presentation. AKI is a common and prominent feature due to the apparent propensity of the glomerular circulation to endothelial damage and occlusion[6]. TMA is associated with significant mortality and morbidity, including end stage renal disease, although prompt initiation of supportive and specific management can change the outcome. In this case, the clinical and laboratory features reflected non-autoimmune hemolysis and AKI in uremic stage. Renal pathology showed TMA. Hemodialysis and plasmapheresis with plasma replacement were performed.

Historically, classification of TMA has been based on clinical findings: TTP for predominant neurologic involvement and hemolytic uremic syndrome (HUS) for predominant renal involvement. TTP is defined by severe ADAMTS13 deficiency and STEC-HUS by the presence of shiga toxin–producing Escherichia coli[5].

This patient denied having diarrhea, making the diagnosis of hemolytic uremic syndrome (HUS) unlikely. Renal biopsy was performed and showed features of TMA and malignant nephrosclerosis. MHTN-induced TMA was diagnosed pathologically.

The kidney is commonly affected in TMA, which includes MHTN and TTP, although rarely a severe feature of TTP[7]. According to a previous report, the prevalence of TMA and MHTN in combination is 27-44%[8]. In some cases, the presentations of these two entities overlap. However, their pathogenesis and treatment differ. This case presented with MHTN and renal TMA and received plasmapheresis with plasma replacement 5 times

over the course of 7 days with an increase in platelet count to 210×10^9/L by the 7th day. ADAMTS-13 Activity: 77.1% (reference range: 40–130 %) was tested 2 weeks later. This patient continued receiving antihypertensive medications with normalized platelet count and LDH within 8 days. However, he became dialysis dependent.

MHTN and TTP are sometimes difficult to distinguish both clinically and histologically[9,10]. However, their differentiation is vital for early plasmapheresis in HUS/TTP. It has been suggested that severe thrombocytopenia is one of the most useful points of differentiation for HUS/TTP and MHTN. Early performance of plasmapheresis is justified in both TMA and thrombocytopenia. Due to the presence of uremic syndrome and thrombocytopenia, this patient received hemodialysis and plasmapheresis with fresh frozen plasma infusion. The uremic symptoms and thrombocytopenia improved. However, he developed end stage renal disease.

Thrombocytopenia in MHTN might be due to causes other than HUS/TTP. In such cases, plasmapheresis is useless and can even be harmful. Recently, the plasma level of ADAMTS13 (disintegrin and metalloprotease domain with thrombospondin type 1 motif 13), a von Willebrand Factor cleaving protease, has been shown to be very low in familial or sporadic cases of TTP. A low level of ADAMTS13 is very specific to TTP. Some reports have demonstrated that patients with a very low plasma level of ADAMTS13 respond well to plasmapheresis. In this case, there was severe hypertension, TMA, and uremic syndrome but normal ADAMTS13. Therapeutic strategies included hemodialysis, plasmapheresis with fresh frozen plasma infusion, and anti-hypertensive medications. Symptomatic treatment was effective, resulting in normal blood pressure and improved thrombocytopenia. However, he became dialysis-dependent.

The choice of plasmapheresis should be based on the degree of thrombocytopenia[10]. Patients with a low ADAMTS13 activity might respond well to plasmapheresis or plasma infusion. In patients with severe hypertension and TMA, ADAMTS13 activity may prove to be a promising adjunctive tool for differentiating TTP from TMA due to other etiologies. In this patient, a normal ADAMTS13 activity test ruled out TTP. Measuring ADAMTS13 and its inhibitors may prove useful in arriving at the proper diagnosis. Although plasmapheresis is a safe procedure, the risk of exposing the patient to plasma and possible infection secondary to the placement of apheresis catheter should be considered. In this study, clinical presentation and normal ADAMTS13 were significant factors in the decision to stop the apheresis procedure.

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