Malignant Hypertension Presenting as Hemolysis, Thrombocytopenia, and Renal Failure

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This case review describes a patient presenting to the emergency department with malignant hypertension, a medical emergency occurring in up to 1% of the hypertensive population. The features of malignant hypertension resemble those of other diseases. For example, the association between red-cell fragmentation and malignant hypertension is thought to be due to endothelial injury and fibrinoid necrosis, which promote hemolysis, platelet destruction, and varying degrees of renal failure, resulting in a clinical picture similar to that of thrombotic thrombocytopenic purpura. Resolving the hemolysis and improving the renal function can only be achieved through rapid and effective control of the blood pressure. Without treatment, the survival rate for malignant hypertension is 10% to 35%. With appropriate treatment, the 5-year survival rate is 75%.
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A 40-year-old African American male presented to the emergency department (ED) having experienced dizziness, blurry vision, epigastric pain, and vomiting for 2 days. He denied any headache or photophobia. The patient had a grand mal seizure in the ED. He had a medical history of hypertension for which he had not been taking any medications. He denied any significant family history. The patient was a nonsmoker, drank three beers a day, and admitted to occasional use of crack cocaine. The patient's presenting

Table 1
Baseline Laboratory Data

Test (Units)	Value (Normal)	Test (Units)	Value (Normal)
Sodium (mEq/L)	132 (135–145)	WBC (1000/μL)	11.9 (4–11)
Potassium (mEq/L)	3.2 (3.5–5.0)	Hemoglobin (g/dL)	11.9 (14–18)
Chloride (mEq/L)	90 (97–110)	Platelet count (1000/μL)	83 (150–400)
Bicarbonate (mEq/L)	26 (22–32)	MCV (fL)	91 (80–94)
BUN (mg/dL)	134 (8–25)	Reticulocyte count (%)	5.2 (0.5–1.5)
Creatinine (mg/dL)	12.9 (0.5–1.5)	PT (seconds)	11.9 (11.0–13.3)
LDH (IU/L)	1047 (100–250)	aPTT (seconds)	24 (21–32)
D-dimer (ng/mL)	>1000 (0–285)		

BUN, blood urea nitrogen; LDH, lactate dehydrogenase; WBC, white blood cells; MCV, mean corpuscular volume; PT, prothrombin time; aPTT, activated partial thromboplastin time.

blood pressure was 216/149 mm Hg, pulse was 111 beats per minute, respirations were 16 per minute, and temperature was 97.8°F His fundi were not clearly visualized. He was somnolent (secondary to lorazepam and a postictal state), but easily arousable. His chest was clear to auscultation. He had a soft systolic murmur at the left upper sternal border. His abdominal exam was unremarkable and he had no focal neurological deficit. The rectal exam revealed heme-positive stools. Initial laboratory data are summarized in Table 1.

This was the patient's first visit to the hospital, and no prior laboratory data were available for comparison. A chest x-ray was unremarkable and a noncontrasted computed tomography scan of the brain was negative for any acute process. The red cell morphology was significant for the presence of schistiocytes and burr cells, suggesting ongoing hemolysis (Table 2). A urine drug screen was positive for cocaine. Urinalysis was positive for 4+ proteins, a large amount of blood, 5 to 10 white blood cells/high power field (HPF), and 10 to 25 red blood cells/HPF. Renal ultrasound revealed mildly echogenic kidneys, which may represent chronic renal disease.

The admitting physician was very concerned about thrombotic thrombocytopenic purpura (TTP) and considered the need for emergent plasmapheresis. The patient had 4 of the 5 cardinal manifestations of TTP—hemolysis, thrombocytopenia, central nervous system (CNS) manifestations, and renal insufficiency. However, TTP did not explain the severe hypertension. Rapidly progressive glomerulonephritis did not explain the CNS manifestations. Even though the D-dimer was high, the normal prothrombin time and activated partial thromboplastin time argued against the diagnosis of disseminated intravascular coagulation. The patient did not have prosthetic valves or clinical evidence of vasculitis. The presence of severe hypertension, hemolysis, thrombocytopenia, and renal failure was consistent with malignant hypertension and the associated pathophysiology of fibrinoid necrosis.

The patient was placed on a nitroprusside drip. The next morning his blood pressure was 195/94 mm Hg. His hemoglobin had dropped to 7.4 g/dL and platelet count to 75,000/μL. Overnight, the patient had a large melanotic stool. An upper gastrointestinal endoscopy performed on the second hospital day revealed a Mallory Weiss tear, an acute gastric ulcer measuring 25 mm, gastritis, and duodenitis. The ulcer was cauterized, and the patient was transfused with packed red blood cells. Hemodialysis was initiated on the same day secondary to rising creatinine (13 mg/dL) and blood urea nitrogen (142 mg/dL). Due to concerns of toxicity in the presence of renal failure, the intravenous nitroprusside was switched to intravenous nitroglycerine and labetolol drips on the third hospital day. Oral antihypertensives in the form of metoprolol, amlodipine, and hydralazine were also initiated.

On day 5 of hospitalization the patient's hemoglobin was 8.4 g/dL, platelet count was 180,000/μL, creatinine was 7.8 mg/dL, and lactate dehydrogenase was 566 IU/L. The patient was discharged on day 15 with a creatinine of 7.4 mg/dL, hemoglobin of 8.1g/dL, and platelet count of 325,000/μL. At this time, he was set up for permanent dialysis.

Table 2
Differential Diagnosis of Hemolysis, Thrombocytopenia, and Renal Insufficiency

Thrombotic thrombocytopenic purpura
Rapidly progressive glomerulonephritis
Disseminated intravascular coagulation
Effects of prosthetic cardiac valves
Sclerodermal renal crisis
Preeclampsia and abruptio placenta
Vasculitis
Malignant hypertension

Discussion

Malignant hypertension is a clinical syndrome with severe hypertension, encephalopathy, congestive heart failure, acute renal failure, microangiopathic hemolytic anemia, and the presence of papilledema and fundoscopic hemorrhages and exudates. It occurs in up to 1% of hypertensive patients[1,2] and is more common in males and the African American population.[3] The association of red-cell fragmentation and malignant hypertension was first described in 1954.[4] The hemolysis and thrombocytopenia are thought to be secondary to fibrinoid necrosis in the arterioles,[3–5] where the arteriolar wall is invaded by fibrin, and resultant luminal narrowing occurs. An in vitro study demonstrated that erythrocyte fragmentation took place if erythrocytes were forced to pass through a polymerizing fibrin clot.[6] It is postulated that the passage of erythrocytes through these occluded arterioles results in fragmentation. In fact, older erythrocytes or those impaired due to uremia may be more susceptible to the trauma, resulting in more hemolysis.[5] The kidneys show cortical and subcapsular hemorrhages macroscopically, and the glomeruli show the characteristic fibrinoid necrosis (Figure 1).[7]

In the last decade, there have been case reports of similar clinical presentations in patients using cocaine.[8,9] It is thought that cocaine can cause endothelial damage and increase endothelial vasoconstriction,[10,11] resulting in a clinical picture similar to that of the fibrinoid necrosis seen with malignant hypertension. Cocaine use may have played a role in the clinical manifestations of this patient.

Treatment

Immediate and effective control of the blood pressure is the only chance of resolving the hemolysis and improving the renal function. Initial therapy includes the use of intravenous antihypertensive agents. Antihypertensive therapy can reverse the changes of fibrinoid necrosis.[3] Blood should be transfused as needed.

Fenoldopam was approved by the U.S. Food and Drug Administration in 1998 for the treatment of accelerated hypertension. It is a dopamine-1 agonist and is thought to increase renal blood flow. Clinical studies have shown increased natriuresis and creatinine clearance with the intravenous infusion of fenoldopam during hypertensive crisis.[12–14] (Table 3) A prospective, randomized trial compared intravenous nitroprusside with intravenous fenoldopam in 153 patients with severe hypertension.[15] This study demonstrated that both drugs were equally efficacious in lowering blood pressure. In a substudy, urine samples were collected from 28 patients. Patients who received fenoldopam had significant increases in urine output, sodium excretion, and creatinine clearance. In the nitroprusside group, all these parameters decreased, although not significantly.[16]

This study demonstrated that intravenous nitroprusside and intravenous fenoldopam were equally efficacious in lowering blood pressure.

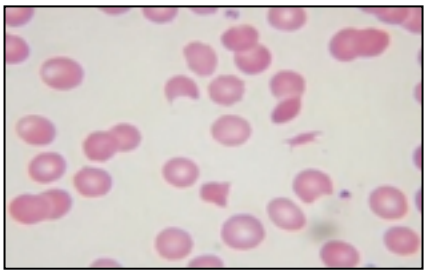

Figure 1. *Peripheral blood smear from the patient showing fragmented red cells and schistiocytes.*

Prognosis

Without treatment, the mortality rate for malignant hypertension is 65% to 90%. Scarpelli and colleagues followed 53 patients with essential malignant hypertension and reported 24 survivors at a mean follow-up of 142 months.[17] Twenty (83%) of these surviving patients had baseline creatinine less than 2 mg/dL and all of these patients

Table 3
Baseline Laboratory Data

Type of Emergency	Drug(s) of Choice
Hypertensive encephalopathy	Nitroprusside
Intracranial hemorrhage	Nitroprusside or labetolol
Subarachnoid hemorrhage	Nimodipine
Cardiac ischemia and heart failure	Nitroglycerine
Aortic dissection	Nitroprusside + ß-blockers, labetolol
Hematuria or acute renal failure	Fenoldopam
Pheochromocytoma	Phentolamine
Eclampsia	Hydralazine, methyldopa, magnesium

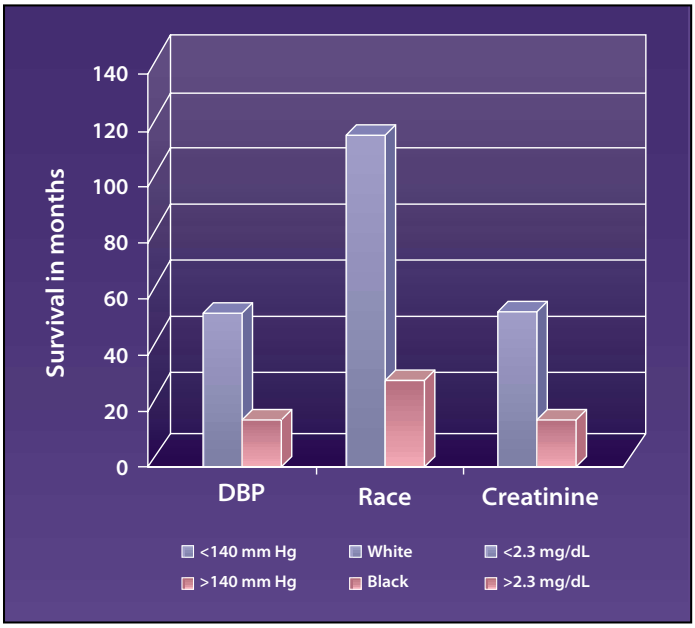

Figure 2. *Effect of baseline characteristics on survival in patients presenting with malignant hypertension. DBP, diastolic blood pressure. Data from Lip et al.*[19]

maintained renal function. Another investigation studied 24 patients who had survived the malignant phase of hypertension between 1969 and 1979.[18] Over a 5-year observation period, 6 of the 7 (85%) patients with baseline creatinine of 448 ± 105 μmol/L (5 ± 1.2 mg/dL) had died, whereas only 1 of the 17 (6%) with baseline creatinine of 169 ± 19 μmol/L (1.9 ± 0.2 mg/dl) had died. In a study of 315 patients with malignant hypertension, Lip and colleagues[19] demonstrated that black race, creatinine higher than 200 μmol/L (2.3 mg/dL), presence of hematuria or proteinuria, or diastolic blood pressure greater than 140 mm Hg predicted decreased survival. Unfortunately, our patient had all of these unfavorable predictors on presentation. These studies suggest that a baseline creatinine of less than 2.0 mg/dL is critical in maintaining long-term renal function and survival (Figure 2). Effective antihypertensives and dialysis have markedly improved prognosis. In the current era, with appropriate treatment, the 5-year survival rate is 75%.[1,4] ■

These studies suggest that a baseline creatinine of less than 2.0 mg/dL is critical in maintaining long-term renal function and survival.

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Main Points

- Malignant hypertension, which occurs in up to 1% of hypertensive patients, is a clinical syndrome with severe hypertension, encephalopathy, congestive heart failure, acute renal failure, microangiopathic hemolytic anemia, and the presence of papilledema and fundoscopic hemorrhages and exudates.
- Malignant hypertension is associated with red cell fragmentation, which is believed to result from endothelial injury and fibrinoid necrosis, which promote hemolysis, platelet destruction, and varying degrees of renal failure.
- The clinical presentation of malignant hypertension resembles that arising from other causes, such as thrombotic thrombocytopenic purpura, effects of prosthetic cardiac valves, rapidly progressive glomerulonephritis, and disseminated intravascular coagulation.
- Rapid and effective control of blood pressure, involving the use of intravenous antihypertensive agents, is essential and greatly increases chances of survival.

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