Malignant Hypertension Complicated with Necrotizing Pancreatitis After Starting Treatment: A Case Report

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Final Diagnosis: Malignant hypertension

Symptoms: Epigastric pain

Medication: —

Clinical Procedure: —

Specialty: Nephrology

Objective: Unusual clinical course

Background: Malignant hypertension (MHT), one of the severest forms of hypertension, can have deleterious effects on various organs, such as renal failure, retinopathy, and encephalopathy. These types of organ damage are common complications of MHT, but in several previous cases, damage to other organs, such as the gastrointestinal tract or pancreas, resulting from small vessel lesions, has also been reported, and these cases have had severe clinical outcomes and a poor prognosis.

Case Report: A 32-year-old male patient with untreated hypertension of a 5-year duration presented with breathlessness and edema. His blood pressure was 220/144 mmHg, and he had renal dysfunction, congestive heart failure, and hypertensive retinopathy. He immediately received treatment, including antihypertensive agents and intermittent hemodialysis, but experienced epigastric pain for several days. A cystic lesion appeared in the pancreatic head, and his serum pancreatic enzymes were elevated. Based on these findings, acute pancreatitis with a cystic lesion was diagnosed. He first received fluid management, pain control, and parenteral nutrition but experienced 2 relapses. Finally, he received transpapillary endoscopic drainage for the cystic lesion with suspected walled-off necrosis. Thereafter, his symptoms improved.

Conclusions: The present case of MHT is the first to demonstrate acute necrotizing pancreatitis and it illustrates the difficulty of treatment. Therefore, if a patient with MHT presents with abdominal pain, a thorough workup, including contrast-enhanced computed tomography, should be performed to rule out significant organ involvement.

Keywords: Hypertension, Malignant • Hypertensive Nephropathy • Pancreatitis, Acute Necrotizing

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Background

Malignant hypertension (MHT), a form of hypertensive emergency also known as accelerated-malignant hypertension or hypertensive crisis with retinopathy [1,2], is defined as an extreme elevation (above 120 to 130 mmHg) of the diastolic blood pressure (BP) with grade III or IV hypertensive retinopathy and has the potential to lead to progressive organ damage [3]. The prognosis of MHT is poor without treatment [3,4]; thus, it is important for physicians to diagnose the condition immediately and start treatment to control the BP. Rapidly declining renal function, hypertensive encephalopathy, and acute heart failure are common complications of MHT, but in several previous cases, damage to other organs, such as the gastrointestinal tract or pancreas, resulting from small vessel lesions, has also been reported [5-7]. Herein, we presented a case of a patient with MHT in whom acute pancreatitis with a cystic lesion developed, requiring transpapillary endoscopic drainage during the clinical course of the MHT.

Case Report

A 32-year-old male patient presented to the Emergency Department due to exertional dyspnea and systemic edema. He had Wolff–Parkinson–White syndrome and had received catheter ablation 6 years earlier. He had begun receiving treatment for hypertension at the time but discontinued the medications 5 years earlier. He had no work-up for secondary hypertension and denied any organ dysfunction due to hypertension at that time. His father had hypertension, but there was no family history of kidney disease or pancreatitis. He denied drug abuse and alcohol consumption. He had smoked 20 cigarettes per day for 12 years and stopped a month before his visit.

A physical examination showed no fever. His BP was 220/144 mmHg, his pulse was 102 beats/min, and his respiratory rate was 20 breaths/min. A cardiological examination showed no murmur, and his lungs were almost clear on auscultation, but he had systemic edema. Abdominal and neurological examinations were unremarkable.

Laboratory tests showed the following results: albumin 3.0 g/dL, serum creatinine 10.8 mg/dL, blood urea nitrogen 99.1 mg/dL, creatinine kinase 455 U/L, lactate dehydrogenase 447 mg/dL, amylase 121 U/L, lipase 153 U/L, C-reactive protein 9.73 mg/dL, calcium 8.5 mg/dL, potassium 3.4 mEq/L, triglyceride 111 mg/dL, and HbA1c 5.5% (NGSP). Anemia with thrombocytopenia and schistocytes was ruled out (hemoglobin 13.3 g/dL, platelets 270 000/µL). Urinalysis revealed proteinuria (8.9 g/day) and a few granular and epithelial casts but no hematuria. Tests for antinuclear antibodies, antineutrophil cytoplasmic antibodies, and anti-Sjogren syndrome A antibodies were negative. An electrocardiogram revealed signs of left ventricular hypertrophy, and echocardiography also indicated left ventricular hypertrophy and systolic cardiac dysfunction (the left ventricular ejection fraction was 40%). A chest X-ray revealed cardiomegaly. On unenhanced computed tomography (CT), both kidneys were almost normal in size, and no remarkable lesions were detected in the abdominal organs except for the presence of a small amount of pleural effusion and ascites. A retinal examination revealed a flame-shaped hemorrhage, cotton-wool spots, and papilledema, which were consistent with grade III or IV hypertensive retinopathy. Furthermore, workup for secondary hypertension on the next day revealed hyperreninemia with hyperaldosteronism, with plasma renin activity >20 ng/mL/h and plasma aldosterone concentration 343 pg/mL, respectively. Abdominal Doppler ultrasound was performed, but the interpretation was technologically challenging owing to the presence of subcutaneous fat and edema. Magnetic resonance angiography was performed later during the admission and showed no obvious renal artery stenosis.

Based on these findings, a hypertensive emergency involving MHT was diagnosed, and treatment with intravenous (i.v.) antihypertensive agents (nicardipine and nitroglycerin) and angiotensin converting enzyme inhibitor (enalapril maleate 5-10 mg) was begun, while avoiding excessive lowering of the BP. For congestive heart failure with renal failure, fluid control using intermittent hemodialysis was also begun owing to the patient’s failure to respond to diuretics on admission. After starting these treatments, his respiratory condition improved and his urine volume gradually increased. As his BP gradually decreased, the dosage of i.v. administered agents was also decreased, and the administration of other oral antihypertensive agents, including calcium channel blocker (cimetidine 5-20 mg, nifedipine 20-80 mg), angiotensin II receptor blocker (olmesartan 10-20 mg), and β-blocker (bisoprolol fumarate 1.25 mg), was begun. However, epigastric pain lasting several days developed after admission. Contrast-enhanced abdominal CT performed on hospitalization day 6 revealed focal enlargement of the pancreas and a cystic lesion with a non-enhanced area within the head of the pancreas, which was not present on admission (Figure 1A, 1B). The serum pancreatic enzyme was also elevated (the maximum amylase value at the onset was 408 U/L), and acute pancreatitis with a cystic lesion was diagnosed. Treatment consisting of i.v. fluid therapy with continuous hemodiafiltration was begun, but the continuous hemodiafiltration was discontinued 3 days later owing to severe pain and the patient’s inability to rest. The patient required pain control with a continuous i.v. injection of fentanyl. Due to treatment, his condition gradually improved; however, the patient had a recurrence of pancreatitis 2 weeks later (Figure 2). Unenhanced CT again showed an increase of fluid collection in the pancreatic head and dilatation of the main pancreatic duct (Figure 1C). Endoscopic ultrasound showed...
Figure 1. (A) Unenhanced computed tomography (CT) image on admission. (B) Contrast-enhanced CT on day 6. Focal enlargement of the pancreas and non-enhanced area within the pancreatic head is observed (arrowhead). (C) Unenhanced CT image on day 35. The main pancreatic duct is dilated (arrowheads). (D) Unenhanced CT image on day 44 shows reduction of the cystic lesion and main pancreatic duct dilatation following nasopancreatic drainage tube placement (arrowhead).

Figure 2. Clinical course during hospitalization. CT – computed tomography; ERP – endoscopic retrograde pancreatography; EUS – endoscopic ultrasound; NPD – nasopancreatic drainage.
the cystic lesion containing heterogeneous solid and fluid contents, and necrotic collection was suspected. However endoscopic retrograde pancreatography showed communication of the main pancreatic duct with the interior of the cystic lesion. The patient therefore underwent nasopancreatic drainage (NPD) tube placement, which drained the fluid and debris from the cyst. Thereafter, the abdominal pain improved markedly, and the amylase concentration decreased. Follow-up CT also showed a reduction of the fluid collection and improvement in the main pancreatic duct (Figure 1D). However, after removal of the NPD tube, the pancreatitis recurred, and the patient underwent NPD tube replacement and pancreatic duct stent placement. He had no further recurrence of pancreatitis following hospital discharge.

At the time of discharge, echocardiography showed improvement in cardiac function. Hypertensive retinopathy, such as papilledema, was also confirmed to have improved with BP control. Intermittent hemodialysis was performed only 6 times in total during the first 2 weeks after admission owing to an increase in urine volume. A renal biopsy performed at 4 weeks after admission revealed 33 glomeruli in total, 1 with focal segmental sclerosis and 10 with global sclerosis on light microscopy. The biopsy also revealed concentric subendothelial edematous thickening of the small arteries (onion skin lesion) with luminal narrowing or obstruction but no fibrinoid necrosis of the arteries (figure not shown). Severe tubulointerstitial fibrosis was clearly observed. An immunofluorescence study and electron microscopy revealed no specific findings. The cumulative findings suggested malignant nephrosclerosis, and the patient’s renal prognosis was considered to be poor.

He received dietary therapy for chronic kidney disease after discharge and has maintained kidney function at about serum creatinine 5 to 6 mg/dL without renal replacement therapy at 1 year after MHT diagnosis.

**Discussion**

MHT can have deleterious effects on many organs, such as the kidneys, heart, and brain. MHT is a consequence of hypertension affecting the small arteries and arterioles leading to acute arterial lesions. Acute necrosis of the vessel wall with fragmentation of nuclei, a deposition of fibrinoid material, or a cellular thickening of the intima without splitting or reduplication of the elastica intima can be present in the affected organs [8]. In addition, autopsy cases of MHT have reported vascular necrosis in the adrenal gland, pancreas, intestinal tract, and spleen even without overt clinical symptoms [7]. Some survivors of MHT have reported abdominal symptoms due to pancreatitis and gastrointestinal tract lesions [5,9,10]. In a previous case series of 42 patients with MHT [6], 7 patients (17%) had acute pancreatitis, suggesting that the pancreas is one of the most commonly affected organs in MHT. The same study also reported a prolonged clinical course in most cases and a high complication and fatality rate. Most of these patients required renal replacement therapy, and 5 patients died. However, another report of 2 patients with MHT with acute pancreatitis showed that specific therapies in conjunction with effective BP control produced a favorable outcome [5]. In general, the patients tended to have a severe clinical course, poor renal prognosis, and a high mortality rate resulting from delays in diagnosis and treatment. Our patient also had a severe clinical course due to acute pancreatitis with inflammatory fluid collection requiring intervention. Previous reports have shown that some patients with MHT with acute pancreatitis develop pancreatic pseudocysts [6], but no cases of acute pancreatitis complicated with acute necrotic collection or walled-off necrosis have been reported among MHT survivors. Thus, the present case is a rare instance of the successful treatment of this potentially fatal condition.

It was previously thought that pancreatic dysfunction tended to occur as a result of changes due to arteriosclerosis brought about by hypertension [11,12], and pancreatic lesions caused by MHT were described as ischemic infarcts or parenchymal necrosis [6,11]. Previous studies using spontaneously hypertensive rats observed not only atherosclerosis of the pancreas, but also inflammatory cell infiltration, hemorrhage, small necrosis of acinar cells, and fibrosis in the pancreatic tissue [13]. It was also suggested that pancreatic ischemia due to arteriosclerosis caused by facilitation of the sympathetic nervous system was important for the pathogenesis of spontaneous pancreatitis. In addition, recent evidence has shown that persistent hypertension increases oxidative stress on the pancreas [12,14]. Oxidative stress plays an important role in pancreatic inflammation and is ultimately implicated in the development of pancreatitis. However, the exact mechanism of the onset of pancreatitis caused by MHT is not yet fully understood. Further research is needed.

Generally, the 2 main etiological risk factors of acute pancreatitis are alcohol consumption and gallstones [15,16]. Other risk factors include endoscopic retrograde cholangiopancreatography, surgery, drug use, HIV infection, hyperlipidemia, congenital conditions, and smoking. Our patient denied all of the above risk factors except for smoking. However, the possibility that his smoking habit may have been involved in the pancreatitis cannot be denied. Nonetheless, based on the clinical course of the disease, the MHT is likely to have been the main contributor to the onset and severity of the acute pancreatitis. Necrotizing pancreatitis generally develops in 10% to 20% of patients with acute pancreatitis and has a higher mortality rate [17]. While most patients with sterile necrosis do not
require intervention, those who experience ongoing obstruction of the gastric outlet, persistent intestinal or biliary symptoms, or disconnected duct syndrome can require radiological, endoscopic, or surgical intervention [16,18]. In our case, the cystic lesion, newly appearing within the pancreatic parenchyma, caused an obstruction of the main pancreatic duct and persistent symptoms, which raised the suspicion of walled-off necrosis. Intervention was therefore deemed necessary, and endoscopic drainage was performed owing to the finding of the communication of the cystic lesion with the main pancreatic duct.

Pancreatic necrosis is caused by severe hypoperfusion of the pancreatic parenchyma and is known to be associated with organ dysfunction due to the production of cytokines and the activation of pro-inflammatory pathways [19,20]. The present case showed a greater severity of MHT, leading to the progression of ischemia and arterial changes and the development of acute necrotic collection or walled-off necrosis, in contrast to previous cases of MHT survivors. In addition, it is possible that hypoperfusion of the pancreas due to BP control may have exacerbated the pancreatitis because it manifested after the start of treatment. This fact may indicate that organ damage can occur in the acute phase, even with proper treatment. Therefore, clinicians should be aware that MHT may be complicated with acute pancreatitis during its acute phase and should be prepared to provide the appropriate treatment.

We believe that the positive clinical outcome of this case was due to the early diagnosis of pancreatic necrosis. In the differential diagnosis of abdominal pain in patients with MHT, it is necessary to actively exclude pancreatitis, intestinal ischemia/necrosis, splenic infarction, and adrenal infarction, which are likely to lead to serious adverse outcomes. For this purpose, the diagnosis is usually made by combining the characteristics of the abdominal pain with the results of blood tests and imaging studies. Contrast-enhanced CT is the most effective tool to accurately assess the presence of ischemia or infarction and to exclude other possible diagnoses. Although the patient had severe renal dysfunction, contrast-enhanced CT was performed as soon as possible, which led to early diagnosis and therapeutic intervention. The use of contrast-enhanced CT at the appropriate time leads to improved outcomes when serious complications are suspected in MHT patients with renal failure.

**Conclusions**

In conclusion, during the treatment of MHT, clinicians should look for the appearance of new or worsening organ involvement, even after appropriate antihypertensive treatment has been initiated. In patients with MHT who present with abdominal pain, a thorough workup including contrast-enhanced CT should be performed to evaluate for ischemia, necrosis, and infarction.

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**Declaration of Figures’ Authenticity**

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