Thrombotic Microangiopathy After Spontaneous Pheochromocytoma Rupture: A Rare MEN 2A Case

Spontan Feokromasitoma Rüptüründen Sonra Gelişen Trombotik Mikroanjiyopati: Nadir Bir MEN 2A Olgusu

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Case Report

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Introduction

Tumors that originate from chromaffin cells in the adrenal medulla and secrete catecholamine are called pheochromocytoma (1). Catecholamine producing tumors are rare, and their incidence is 2 to 8 cases/million people yearly (2). This disease commonly affects people in their 40s and 50s, but it occurs earlier in people with disease-associated germline mutations. Although these tumors are typically sporadic, they are also associated with genetic disorders, including multiple endocrine neoplasia syndrome type 2 (MEN 2).

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proximately 80–90% of pheochromocytoma patients, where 50% sustain hypertension, 45% have paroxysmal hypertension, and 5 to 15% are normotensive (4,5). Episodes may occur either spontaneously or due to medications (e.g., anesthetic agents, radiocontrast media, decongestants, beta-adrenergic antagonists, metoclopramide), intra-abdominal pressure increasing maneuvers (e.g., weight lifting, defecation, exercise), posture changes, and anxiety (6). Spontaneous pheochromocytoma rupture may cause malignant hypertension, though its exact mechanism is unknown. A massive catecholamine release is probably associated with the tumor’s vasoconstriction, which is followed by necrosis and bleeding (7). Another rare, devastating, and fatal event is spontaneous hemorrhage within the pheochromocytoma, resulting in the capsule rupture.

Thrombotic microangiopathy (TMA) is a rare disease, where endothelial damage causes thrombosis in capillaries and arterioles. Manifestations, such as thrombocytopenia, anemia, purpura, and renal failure, can be seen in TMA (8). Malignant hypertension causes TMA and may present with symptoms similar to thrombotic thrombocytopenic purpura (TTP) (9).

In this report, we present a patient who developed malignant hypertension and TMA, due to the rupture of pheochromocytoma and recovered through plasmapheresis.

**Case Report**

A 32-year-old male patient was admitted to the emergency department with a sudden onset of left-flank abdominal pain, headache, and palpitation. There was no known chronic illness, drug, alcohol, or illicit substance use, and the family’s medical history revealed that his 37-year-old brother died of pheochromocytoma-induced hypertensive pulmonary edema. During the first evaluation in the emergency department, his blood pressure was 190/135 mmHg, and heart rate was 140 beats/min (sinus tachycardia). There was an increased tenderness in the left upper quadrant. Emergency laboratory tests were normal except for leukocytosis (WBC=15.8x10³/µL) and minimal abnormalities in the liver function test. Abdominal computed tomography (CT) (Figure 1A, B) revealed a 43 mm mass lesion in the left adrenal gland with perirenal hematoma and right adrenal hematoma. The patient was admitted to the intensive care unit with a preliminary diagnosis of pheochromocytoma rupture and hypertensive crisis. Along with the routine examination, a 24-hour urine catecholamine level was planned to explain the etiology. The urology department consulted the patient for an emergency surgical treatment but did not recommend it since his vital signs were unstable, increasing the risk of mortality. Nitroprusside and doxazosin treatment was provided to control blood pressure. On the second day of the follow-up in the intensive care unit, the patient’s blood pressure was 130/80 mmHg, and heart rate was 100 beats/min (sinus tachycardia). The patient was discharged after a 48-hour follow-up with a normal blood pressure and heart rate.

**Figure 1:** A) Adrenal computed tomography (CT) at admission to the emergency department (43 mm left adrenal mass, perirenal hemorrhage). B) Adrenal CT at admission to the emergency department (right adrenal hematoma). C) Adrenal CT taken one year later (7 mm nodular lesion in left adrenal).
care unit, the patient developed fever (38.8°C), blurred consciousness, shortness of breath, and loss of strength in his left arm. Laboratory tests (Table 1) showed deterioration in coagulation markers and renal function tests (azotemia), hemolytic anemia (coombs negative), and thrombocytopenia. Anticoagulant therapy (low molecular weight heparin) and pulse steroid therapy were initiated while investigating the etiology of TMA. Plasmapheresis treatment was provided in 5 sessions. Daily plasma volume of approximately 40 mL/kg was used as a replacement dose for plasma exchange. Fresh frozen plasma was used as the exchange fluid. In the samples, taken during the patient’s admission to the intensive care unit, urinary metanephrine and the normetanephrine levels were 7 and 4 times higher than the upper limit of normal, respectively. However, with the plasmapheresis treatment, the patient’s platelet value and liver function test values returned to the normal level (Figure 2). The ADAMTS13 activity was found to be 35% (40-130), and ADAMTS13 inhibitor was <2 U/mL (<12). TTP was excluded from the diagnosis since the diagnosis of TTP is only supported by the ADAMTS13 activity level of less than 5%. Catastrophic Anti-Phospholipid antibody syndrome (CAPS) was ruled out, and the examinations related to connective tissue diseases were negative as well. The patient was diagnosed with TMA after detecting pheochromocytoma hemorrhagic rupture by the clinical and laboratory values. His urine catecholamine levels were normal before the discharge (Table 2). The patient had low cortisol and elevated adrenocorticotropic hormone levels and was diagnosed with primary adrenal failure and discharged with oral hydrocortisone replacement therapy. High calcium and parathyroid hormone (PTH) levels (calcium 10.73 mg/dl (8.4-10.2), PTH 72 pg/mL (1-65)) were detected in the follow-up and he was diagnosed with

| Table 1. Laboratory findings of the patient. |
|---------------------------------------------|
| **Emergency admission** | **Before plasma exchange** | **After plasma exchange** | **Normal range** |
| Complete blood cell counts | | | |
| WBC | 15.8 | 18.2 | 16.5 | 4-10 (x10³/uL) |
| RBC | 5.6 | 3.3 | 4.3 | 3.6-5.7 (x10⁴/µL) |
| Hemoglobin | 16.9 | 9.8 | 12.7 | 12.1-17.2 g/dL |
| Hematocrit | 46.4 | 26 | 37.3 | 36.1-50.3% |
| Platelets | 248 | 37 | 338 | 150-400 (x10³/µL) |
| MCV | 82.7 | 79.8 | 84.1 | 82.2-99 fl |
| MCH | 30.1 | 30.1 | 29.8 | 27.6-33.3 pg |
| MCHC | 36.4 | 37.7 | 35.4 | 32-36 g/dL |
| Blood chemistry | | | |
| Total protein | 8 | 4.5 | 6 | 6.4-8.3 g/dL |
| Albumin | 4.3 | 2.7 | 3.4 | 3.5-5 g/dL |
| Aspartate aminotransferase | 44 | 629 | 35 | 5-34 u/L |
| Alanine aminotransferase | 74 | 407 | 98 | 0-55 u/L |
| Creatinine | 0.61 | 1.1 | 0.72 | 0.72-1.25 mg/dL |
| Urea | 20.1 | 65 | 32.7 | 15-44 mg/dL |
| Plasma glucose | 119 | 175 | 135 | 70-105 mg/dL |
| Sodium | 139 | 127 | 136 | 136-145 mmol/L |
| Potassium | 4 | 4.8 | 4.6 | mmol/L |
| Calcium | 8.4 | 7.6 | 8.87 | 8.4-10.2 mg/dL |
| Coagulation tests | | | |
| PT | 15.5 | 19.6 | 13.4 | 11-15 sec |
| PT% | 65 | 50 | 98 | 70-120% |
| INR | 1.24 | 1.65 | 1.03 | 1-1.5 INR |
| aPTT | 30.1 | 31.2 | 29 | 26.5-40 sec |

WBC: White blood cell; RBC: Red blood cell; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; PT: Prothrombin time; INR: International normalized ratio; aPTT: Activated partial thromboplastin time.
primary hyperparathyroidism. The thyroid fine-needle aspiration cytology was reported suspicious for malignancy with serum calcitonin level of 2730 pg/mL (0-30). Therefore, total thyroidectomy and parathyroid surgeries were performed. Before the surgery, 24-h urinary catecholamine levels of the patient were normal, and imaging showed that the adrenal mass had almost disappeared. Since primary adrenal insufficiency was developed in the patient, he was operated on stress dose steroids. Final pathology was reported as medullary thyroid carcinoma and parathyroid gland hyperplasia. RET proto-oncogene mutation was found positive and MEN 2A syndrome was diagnosed. After the pheochromocytoma rupture, the patient was followed up for one year, and TMA relapse was not observed. Also, the 24-hour urine catecholamines did not increase, and, in the adrenal CT control (Figure 1C), the mass had reduced significantly.

Discussion

The patient had no typical pheochromocytoma symptoms (e.g., hypertension, headache, palpitations, and sweating episodes). We suspected pheochromocytoma rupture primarily due to the presence of hypertensive crisis on admission to the emergency department. Also, the 43 mm mass in the left adrenal region, perirenal hemorrhage in the abdominal CT, and the history of brother’s death because of hypertensive pulmonary edema due to pheochromocytoma lead to the diagnosis. Paroxysmal hypertension usually occurs in patients with elevated plasma epinephrine levels and is very typical for MEN 2-associated pheochromocytoma (10). Spontaneous, non-traumatic hemorrhage of pheochromocytoma is a complication that can rarely occur in these patients, and is often associated with anticoagulant medications or severe sepsis, with most common symptoms being abdominal pain and hypertensive crisis. In this context, previously, there are only 54 similar cases reported (11). The patient had no known disease history, and he was presented with severe left upper quadrant pain and high blood pressure, which started immediately at rest without any stimulating factor. The patient was admitted for the hypertensive crisis due to excessive catecholamine release after pheochromocytoma rupture, and bilateral adrenal apoplexy due to vasospasm of bilateral adrenal circulation with hypoxia, which may have developed too. Based on this, coagulation tests and platelet levels are expected to be normal. Moreover, since pheochromocytoma originates from the adrenal medulla, the cortex is not expected to be affected by the rupture. However, even after the patient’s clinical condition improved, primary adrenal insufficiency remained permanent with a need to continue steroid replacement therapy while the catecholamine levels decreased to the normal range. This suggested that the bilateral adrenal cortex was permanently affected.

| Table 2. Endocrinological tests of the patient. |
|-----------------------------------------------|
| **A/D** | At the time of discharge | A year after discharge | Normal range |
|--------|----------------------------|------------------------|--------------|
| Urinary metanephrine | 2244 | 94 | 33 | 52-341 µ/24 h |
| Urinary normetanephrine | 1629 | 213 | 277 | 88-444 µ/24 h |
| Urinary epinephrine | 249 | 1,7 | 2-22 µ/24 h |
| Urinary norepinephrine | 769 | 26 | 20-81 µ/24 h |
| Urinary dopamine | 274 | 69 | 40-400 µ/24 h |
Focal neurological deficits may develop in TTP/hemolytic-uremic syndrome (HUS)/TMA. These are usually transient and can last up to 24 h, such as transient ischemic attacks. These neurological deficits can be in the form of monoparesis or hemiparesis in one half of the body or bilaterally. The patient had a loss of strength in his left arm. No pathology could explain the clinical picture of the cranial imaging, and his neurological symptoms improved in a short time.

Surgery is the final treatment option for pheochromocytoma, and pharmacological treatment is still vital in preoperative and intraoperative blood pressure control. The patient was evaluated by the urology department for the surgical treatment, but it was postponed because of his unstable vital signs.

TMA, which causes thrombosis in capillaries and arterioles, may be hereditary or acquired. Hereditary TTP, also called Upshaw-Schulman syndrome, is caused by hereditary TMA (12) whereas the acquired TMA is caused by the following: Shiga toxin-dependent TMA (also known as a HUS), classical ADAMTS13 deficiency acquired TTP, complement-mediated TMA (also called atypical HUS), and drug-mediated TMA. Apart from the aforementioned disorders, autoimmune diseases such as systemic sclerosis and systemic lupus erythematosus, severe preeclampsia, disseminated cancer, systemic infections, malignant hypertension, hematopoietic stem cell transplantation, and organ transplantation can also cause TMA. Additionally, there is another disease similar to TTP that develops after surgery, known as postoperative TTP (13). The type of TMA determines the success of treatment and prognosis. Plasma infusion or exchange allows the replacement of proteins necessary for the complement cascade and helps in treating the patients with atypical HUS and TTP (14).

In literature, some cases have been presented with TMA and diagnosed with pheochromocytoma. However, unlike these cases, our case was presented with a TMA that developed as a result of pheochromocytoma rupture (15-17).

In our case, pulse steroid and plasma exchange treatments were started once the sample was taken for ADAMTS13 activity because the clinical and laboratory findings were compatible with TTP. Plasma exchange is recommended for the patients diagnosed with primary TMA, or suspected TTP (18). Considering the secondary causes of TMA in the patient, necessary examinations were performed, such as tests for antiphospholipid antibody syndrome and other collagen tissue diseases, especially for systemic lupus erythematosus. The results excluded the patient from the diagnoses, and ADAMTS13 activity was also found normal.

After excluding the primary TMA and the possible secondary causes, the patient was evaluated for secondary TMA due to malignant hypertension after the rupturing of pheochromocytoma. Although plasma exchange is recommended for primary TMA, some studies show that plasma exchange therapy is beneficial in secondary TMA as well (19-22). Since the platelet count of the patient increased above 200 \((x10^3/\mu\text{L})\), along with a sufficient increase in hemoglobin level, plasma exchange therapy was discontinued.

Our case study is the first reported case of TMA associated with malignant hypertension, secondary to pheochromocytoma, where the patient was benefitted from plasmapheresis. Plasmapheresis should be performed empirically in patients with TMA, which is caused by malignant hypertension until ADAMTS13 activity is assessed. Possible benefits of plasmapheresis should be considered in patients advancing to multiple organ failure, even if ADAMTS13 activity is normal.

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**Conflict of Interest**

No conflicts of interest between the authors and / or family members of the scientific and
medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: İlker Çordan; Design: Melia Karakoş; Control/Supervision: Mustafa Kulaksızoğlu, Feridun Karakurt; Data Collection and/or Processing: Hatice Çalışkan Burgucu; Analysis and/or Interpretation: İlker Çordan; Literature Review: Seda Yılmaz; Writing the Article: Muhammet Kocabaş, İlker Çordan; Critical Review: Muhammet Kocabaş, Mustafa Can; References and Fundings: Mustafa Can; Materials: İlker Çordan.

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