Case Report

Primary Hyperaldosteronism: A Rare Cause of Malignant Hypertension with Thrombotic Microangiopathy in a Kidney Transplant Recipient

Carolina Ormonde, Sara Querido, Nuno Rombo, Rita Roque, Belarmino Clemente, and André Weigert

1Nephrology Department, Hospital do Divino Espírito Santo, Portugal
2Nephrology Department, Centro Hospitalar Lisboa Ocidental-Hospital Santa Cruz, Portugal
3General Surgery Department, Centro Hospitalar Lisboa Ocidental-Hospital Santa Cruz, Portugal

Correspondence should be addressed to Carolina Ormonde; carolina.ormonde@hotmail.com

Received 11 August 2021; Accepted 8 November 2021; Published 15 November 2021

Thrombotic microangiopathy (TMA) is a rare disease that presents with haemolysis and organ damage. The kidney is one of the main affected organs, and TMA is associated with serious complications and increased mortality. In transplanted patients, TMA is even less common and has a variety of possible causes, including thrombotic thrombocytopenic purpura (TTP) and haemolytic-uremic syndrome (HUS), infections, drugs, autoimmune disease, tumours, and malignant hypertension. Transplant-related causes, such as antibody-mediated rejection, calcineurin inhibitors, and viral infections, need to be considered as well. The authors report a rare case of TMA in a kidney transplant recipient, whose investigation revealed malignant hypertension secondary to primary hyperaldosteronism.

1. Introduction

Thrombotic microangiopathy (TMA) is a rare disease that presents with arteriolar and capillary thrombosis [1–3]. TMA is a clinicopathologic diagnosis [4]. It can express with a variety of symptoms that reflect haemolysis and organ damage [5]. The kidney is one of the main affected organs [6, 7]. The presence of haemolytic anaemia, thrombocytopenia, and schistocytes in peripheral blood smear establish the diagnosis that can be confirmed by histology of affected organs [4, 5, 8].

Although rare in kidney transplant recipients, with an incidence of 5.6 cases per 1000 renal transplant recipients per year, TMA is a serious complication in these patients. It associates with poor outcomes, both on kidney allograft and patient [3, 9–11].

Thrombotic thrombocytopenic purpura (TTP) and haemolytic-uremic syndrome (HUS) are the two most frequent causes of TMA. Other less common causes are infections (human immunodeficiency virus, cytomegalovirus), drugs (such as chemotherapy agents and ticlopidine), autoimmune diseases (such as systemic lupus erythematosus and scleroderma), disseminated intravascular coagulation, malignant tumours, HELLP syndrome, malignant hypertension, and bone marrow transplant [2, 4–8, 10, 12, 13]. Any of the listed conditions may cause TMA in kidney allograft, but transplant-related causes also need to be considered: antibody-mediated rejection, calcineurin inhibitors, and viral infections (Cytomegalovirus, Epstein-Barr virus, and Polyoma virus) [13, 14].

TMA secondary to malignant hypertension is a very rare entity [15, 16]. The authors report an uncommon case of
malignant hypertension secondary TMA in a kidney transplant recipient. To our knowledge, this is the first reported case of TMA secondary to malignant hypertension in a kidney transplant recipient. In addition, in this patients, malignant hypertension was caused by hyperaldosteronism, making it even more unique.

2. Case Presentation

A 47-year-old female was evaluated in her routine posttransplant appointment on May 2020. She had a history of end-stage chronic kidney disease due to autosomal dominant polycystic kidney disease. Haemodialysis was initiated in 2005 and she received a deceased donor kidney transplant in 2008. She remained stable for 10 years posttransplant when she developed antibody-mediated acute rejection, for which she was given rituximab and intravenous immunoglobulin, with stabilization but reduced kidney function. Eight months later, she developed a severe CMV colitis with kidney graft biopsy was not performed due to high bleeding risk and stable renal function. The only abnormal finding on physical examination during hospital-stay, besides excessive weight (body mass index of 34.7 kg/m²), was grade 3 hypertension (Figure 2), even under five classes of antihypertensive drugs (previous mentioned plus minoxidil). She also presented persistent hypokalaemia with need for intravenous supplementation. Hypokalaemia workup was suggestive of renal potassium wasting: high urinary potassium excretion (62 meq/L) and a high transtubular potassium gradient (7.0).

Having excluded almost all TMA causes, we hypothesized that malignant hypertension could be the cause. Secondary hypertension workup was conducted (Table 2), and an adrenal nodule was found in the abdominal CT scan. MRI was suggestive of a cortical adenoma, and blood analysis was compatible with hyperaldosteronism (Figure 3). Pheochromocytoma was excluded. The patient was then started on 50 mg of spironolactone a day. We observed improved control of hypertension (Figure 2) and suspension of potassium supplementation. However, the patient was still under other 5 antihypertensive drugs.

To confirm a unilateral primary hyperaldosteronism, the patient stopped spironolactone to perform an iodo-methyl norcholesterol scintigraphy. However, she developed hypertensive-induced acute pulmonary oedema, and therefore, the exam could not be performed. After stabilization, she was submitted to successful laparoscopic left adrenalectomy. In the postoperative period, she evolved with controlled hypertension under only three antihypertensive drugs (carvedilol, nifedipine, and clonidine) (Figure 2) and no additional need for potassium supplements. At the 13th day after surgery, she was discharged still with hemoglobin level of 7 g/dL, albeit stable and asymptomatic.

On follow-up appointments, she was asymptomatic and with controlled hypertension. Her blood analysis significantly improved. Four months after discharge, she had normal hemoglobin (12.6 g/dL) and LDH levels (208 U/L), normal serum potassium (4.8 meq/L) without need for supplementation, and stable renal function (creatinine 2.4 mg/dL). Chronic vascular changes (left ventricular hypertrophy and hypertensive retinopathy) remained present. Histopathology examination confirmed adrenocortical adenoma.

3. Discussion

We report a very unusual case of a kidney transplant patient with TMA secondary to malignant hypertension. After extensive investigation, we concluded that it was caused by primary hyperaldosteronism. TMA is one of the most devastating complications in kidney transplant patients [10]. Regardless of its cause, it begins with and event that triggers endothelial injury. Then, proinflammatory and procoagulant mechanisms are activated and generate haemolysis and platelet aggregation. Microcirculation thrombosis occurs, with consequently organ ischemia. It then becomes a vicious cycle of organ damage [5, 16, 17].

The kidney is one of the most frequent affected organs, along with the nervous system, but any system can be afflicted [5]. TMA’s usual clinical findings are haemolytic anaemia, thrombocytopenia, elevated LDH levels, low
Table 1: Thrombotic microangiopathy workup.

| Workup                                | Result (normal range) |
|---------------------------------------|-----------------------|
| INR                                   | 1.0 (0.8-1.1)         |
| aPTT                                  | 33.8 seconds (23-38)  |
| Fibrinogen                            | 5.66 g/L (1.5-4.0)    |
| ADAMTS13 activity                     | 67% (50-160)          |
| Shiga toxin                           | Negative              |
| C3                                    | 136 mg/dL (80-178)    |
| C4                                    | 31.6 mg/dL (12-42)    |
| Functional complement studies         | Normal                |
| Genetic complement studies            | Normal                |
| Antinuclear antibodies                | Negative              |
| Anti-dsDNA antibodies                 | Negative              |
| Antiphospholipid antibodies           | Negative              |
| Extractable nuclear antigen antibodies| Negative              |
| Serum protein electrophoresis         | Normal                |
| Vitamin B12                           | 234 pmol/L (141-489)  |
| Homocysteine                          | 13.3 μg/mol/L (<15)   |
| Serum CMV viral load                  | Negative              |
| Serum and urinary BK and JC viral load| Negative              |
| Serum parvovirus B19 viral load       | Negative              |
| Anti-HIV 1 and 2 antibodies           | Negative              |
| Anti-HCV antibodies                   | Negative              |
| HBs antigen and anti-HBc antibodies   | Negative              |
| Class I HLA antibodies                | Negative              |
| Class II HLA antibodies               | Positive for 5 specificities, non-donor specific, maximum 15,600 MFI |

**Figure 1:** Thrombotic microangiopathy evolution. MTH-EAR: months earlier; Disch: discharge; MTH-FW: months follow-up; Hb: hemoglobin; Ptl: platelets; LDH: lactate desidrogenase; Creat: creatinine. Analytical values presented as hemoglobin in g/dL, platelets in $10^4/uL$, LDH in $10^2$ U/L, and creatinine in mg/dL.
haptoglobin level, and schistocytes in the peripheral blood smear [12, 14].

Apart from the common TMA causes, such as TTP, HUS, drugs, malignant tumours, and auto-immune diseases, in renal transplant patients, other specific causes need to be considered: antibody-mediated acute rejection, calcineurin inhibitors, and viral infections [3, 10, 13, 18].

Malignant hypertension is a rare cause of TMA. Its incidence is around 1% of all hypertensive patients [15, 16]. Retinopathy is the most frequent clinical sign, and some patients may have papilledema [19, 20]. Acute kidney injury, acute heart failure, and hypertensive encephalopathy might also be present [17]. Laboratorial changes are similar to other causes of TMA [19]. Support measures and hypertension control are the pillars of treatment, although sometimes plasmapheresis is initiated until laboratory results exclude HUS or TTP. If a secondary cause for hypertension is unveiled, it must be specifically treated as well [5, 15, 20–23]. A study by Cavero et al. suggested that eculizumab could be beneficial in malignant hypertensive TMA, irrespective of complement abnormalities [20].

After ruling out most of TMA common causes, we hypothesized that our patient’s uncontrolled hypertension could explain this clinical condition. In the setting of a 47-

| Workup                                      | Result (normal range) |
|---------------------------------------------|------------------------|
| 24-hour urinary cortisol                    | 25.5 μg/24 h (4.3-45)  |
| Plasma renin activity (PRA)                 | 4.6 ng/mL/h (0.6-4.3)  |
| Serum aldosterone                           | 144.6 ng/dL (4.0-31.0) |
| Aldosterone/PRA                             | 31 (<30)               |
| 24-hour urinary metanephrines               |                        |
| Normetanephrine                             | 284 μg (<632)          |
| Metanephrine                                | 104 μg (<276)          |
| 3-Methoxytyramine                           | 144 μg (<426)          |
| TSH                                         | 4.68 μU/mL (0.5-5.0)   |
| Free T4                                     | 15.8 pmol/L ng/dL (12-30) |
| Renal Doppler                               | Without renal artery stenosis |
| Abdominal CT and MRI                        | Left adrenal nodule 2 × 1.5 cm |
| MIBG scintigraphy                           | Negative for neural crest tumours |
year-old woman with new onset resistant hypertension with end organ damage (recently diagnosed severe hypertensive retinopathy and cardiomyopathy), we studied potential secondary causes. Her unexplained long-term hypokalaemia with high transtubular potassium gradient led us to suspect of hyperaldosteronism, which was then confirmed by the extended study. Pheochromocytoma was excluded by catecholamine analysis and MIBG scintigraphy. She was then diagnosed with a primary hyperaldosteronism due to a functional adrenal adenoma. Although not confirmed by iodo-methyl norcholesterol scintigraphy, impossible to perform due to life-threatening risks of the interruption of spironolactone, all other studies were suggestive, along with the hypertension and hypokalaemia improvement with spironolactone. The fact that she developed acute hypertensive pulmonary oedema after suspending this drug was also very suggestive. The diagnosis was then confirmed by histology of the adrenal mass. Also, gradual improvement of acute laboratory and clinical features in the following weeks and months corroborated our suspicion. Chronic vascular changes remained as it would be expected due to previous long-standing hypertension.

Antibody-mediated acute rejection was the only cause of TMA that was not completely excluded throughout our investigation. To exclude this hypothesis, we would need to perform a graft biopsy, difficult to justify both because of the major risk of bleeding associated with thrombocytopenia, anaemia, and severe hypertension, and because her renal function and proteinuria remained stable during these events, making rejections a less likely explanation. Lastly, even if she had an antibody-mediated rejection, we would be reluctant to give additional immunosuppression due to her previous significant infectious complications.

There are several TMA cases due to malignant hypertension reported in the literature but few in kidney transplant patients or secondary to hyperaldosteronism. Basturk and Pamukcu reported a case of TMA caused by malignant hypertension due to hyperaldosteronism that was successfully treated with spironolactone [23]. In this particular case, an adrenal nodule was not identified. There are recent studies that report that high aldosterone levels could have an important role on malignant hypertension TMA’s pathophysiology [24]. Akimoto et al. showed a positive correlation between aldosterone and LDH levels in hypertensive patients either with or without hyperaldosteronism [19].

In kidney transplanted patients, the differential diagnosis of TMA is wide, and all causes of de novo or recurrent TMA in the graft must be investigated. We report a very rare case of malignant hypertension TMA due to primary hyperaldosteronism in a kidney transplant patient.

Figure 3: CT scan. Axial and coronal planes of CT scan showing left adrenal mass (indicated by red arrow).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] V. Mundra and R. Mannon, “Thrombotic microangiopathy in a transplant recipient,” *Clinical Journal of the American Society of Nephrology*, vol. 13, no. 8, pp. 1251–1253, 2018.
[2] L. Palma, M. Sridharan, and S. Sethi, “Complement in secondary thrombotic microangiopathy,” *Kidney International Reports*, vol. 6, no. 1, pp. 11–23, 2021.
[3] C. Teixeira, H. Tedesco Silva Junior, L. de Moura et al., “Clinical and pathological features of thrombotic microangiopathy influencing longterm kidney transplant outcomes,” *PLoS One*, vol. 15, no. 1, article e0227445, 2020.
[4] D. Arnold, C. Patriquin, and I. Nazy, “Thrombotic microangiopathies: a general approach to diagnosis and management,” *Canadian Medical Association Journal*, vol. 189, no. 4, pp. E153–E159, 2017.
[5] V. Brocklebank, K. Wood, and D. Kavanagh, “Thrombotic microangiopathy and the kidney,” *CJASN*, vol. 13, no. 2, pp. 300–317, 2018.
C. Aigner, A. Schmidt, M. Gaggl, and G. Sunder-Plassmann, “An updated classification of thrombotic microangiopathies and treatment of complement gene variant-mediated thrombotic microangiopathy,” Clinical Kidney Journal, vol. 12, no. 3, pp. 333–337, 2019.

X. J. Yu, F. Yu, D. Song et al., “Clinical and renal biopsy findings predicting outcome in renal thrombotic microangiopathy: a large cohort study from a single institute in China,” Scientific World Journal, vol. 2014, pp. 1–9, 2014.

C. Masias, S. Vasu, and S. Cataland, “None of the above: thrombotic microangiopathy beyond TTP and HUS,” Blood, vol. 129, no. 21, pp. 2857–2863, 2017.

D. Roberts, I. Siegman, N. Andeen et al., “De novo thrombotic microangiopathy in two kidney transplant recipients from the same deceased donor: a case series,” Clinical Transplantation, vol. 34, no. 7, pp. 1–6, 2020.

F. Abbas, M. E. Kossi, J. J. Kim, A. Sharma, and A. Halawa, “Thrombotic microangiopathy after renal transplantation: current insights in de novo and recurrent disease,” World Journal of Transplantation, vol. 8, no. 5, pp. 122–141, 2018.

T. Kawanishi, J. Hasegawa, M. Kono et al., “Thrombotic microangiopathy after kidney transplantation successfully treated with eculizumab: a case report,” Transplant Reports, vol. 3, no. 2, pp. 5–8, 2018.

X. Zheng and J. Sadler, “Pathogenesis of thrombotic microangiopathies,” Annual Review of Pathology, vol. 3, no. 1, pp. 249–277, 2008.

T. Nadasdy, “Thrombotic microangiopathy in renal allografts: the diagnostic challenge,” Current Opinion in Organ Transplantation, vol. 19, no. 3, pp. 283–292, 2014.

M. Noris and G. Remuzzi, “Thrombotic microangiopathy after kidney transplantation,” American Journal of Transplantation, vol. 10, no. 7, pp. 1517–1523, 2010.

Z. Bawany, Z. Tariq, T. Sodeman, and A. Mutgi, “Malignant hypertension masquerading as thrombotic thrombocytopenic purpura,” British Journal of Medical Practitioners, vol. 4, no. 2, pp. 28–29, 2011.

N. Khanal, S. Dahal, S. Upadhyay, V. Bhatt, and P. Bierman, “Differentiating malignant hypertension-induced thrombotic microangiopathy from thrombotic thrombocytopenic purpura,” Therapeutic Advances in Hematology, vol. 6, no. 3, pp. 97–102, 2015.

Y. Shibagaki and T. Fujita, “Thrombotic microangiopathy in malignant hypertension and hemolytic uremic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP): can we differentiate one from the other?,” Hypertension Research, vol. 28, no. 1, pp. 89–95, 2005.

M. Bukhari, A. al-Thumali, E. Yousif, M. Bukhari, N. Almalki, and R. Magrabi, “Concomitant thrombotic microangiopathy and rejection in a recent kidney transplant: a case study,” Transplant Case Reports, vol. 1, no. 1, pp. 1–4, 2020.

A. Akimoto, S. Muto, C. Ito et al., “Clinical features of malignant hypertension with thrombotic microangiopathy,” Clinical and Experimental Hypertension, vol. 33, no. 2, pp. 77–83, 2011.

T. Cavero, E. Arjona, K. Soto et al., “Severe and malignant hypertension are common in primary atypical hemolytic uremic syndrome,” Kidney International, vol. 96, no. 4, pp. 995–1004, 2019.

S. Van Laecke and W. Van Biesen, “Severe hypertension with renal thrombotic microangiopathy: what happened to the usual suspect?,” Kidney International, vol. 91, no. 6, pp. 1271–1274, 2017.