Case Report

Use of cabozantinib in a lung adenocarcinoma patient presenting with thrombotic microangiopathy: a case report and literature review


Department of Nephrology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China. *Equal contributors.

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Abstract: Thrombotic microangiopathy (TMA) syndromes are defined clinically by microangiopathic hemolytic anemia, thrombocytopenia, organ injury, and arteriolar and capillary thrombosis. It is an unusual and recognized complication of chemotherapy. We describe herein the case of a patient with lung adenocarcinoma who developed thrombotic microangiopathy after 2 weeks treatment of cabozantinib. The results show that an overdose of cabozantinib may sometimes lead to TMA. We suggest that renal biopsy and discontinuation of cabozantinib is necessary. Angiotensin-converting enzyme inhibitor drugs are recommended for treatment. It is important for clinicians to be aware that TMA may occur in patients who are treated with cabozantinib.

Keywords: Case report, cabozantinib, thrombotic microangiopathy, angiotensin-converting enzyme inhibitor

Introduction

Thrombotic microangiopathy (TMA) was first introduced by Symmers in 1952 as the shortened version for thrombotic microangiopathic haemolytic anaemia [1, 2]. It is a group of disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ injury due to thrombi in the microcirculation. TMA includes thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndromes (HUS) [3].

TMA can be triggered by many factors such as various drugs, bone marrow transplantation, infections, and malignant diseases [4]. An adverse reaction of drugs is one of the most common causes of TMA [5]. It is reported that about one-fifth of TMA cases are associated with pharmaceuticals [6].

Cabozantinib is a new type of molecular targeted drug and is approved for the treatment of progressive metastatic medullary thyroid carcinoma in 2012. Cabozantinib was approved for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy in 2016 [7]. Cabozantinib has been studied in many types of tumor and is generally well tolerated with promising clinical activity. In recent years, cabozantinib has been clinically assessed in non-small cell lung cancer [8, 9].

Here, we report a case of a female patient with lung adenocarcinoma. She presented with proteinuria after treatment of cabozantinib for 2 weeks. Results of the renal biopsy indicated TMA.

Case report

A 43-year-old woman with a two-week treatment of cabozantinib presented with proteinuria. Her past medical history comprised the treatment of lung adenocarcinoma for one year. She was diagnosed in 2016 at the age of 42 years with lung adenocarcinoma. A lower lobectomy for lung adenocarcinoma was performed on the right lung. Pathology revealed a 3.5 cm adenocarcinoma, 10 of 18 axillary lymph nodes was positive for malignancy. Genotyping showed that KIF5B-RET is 0.82% of RET gene. The patient was classified as having stage pT4N2
Overdose of cabozantinib leads to TMA

Physical examination revealed severe edema in both lower limbs. Breathing sounds were not vesicular and no murmurs were audible. No abnormalities were observed during the abdominal and neurologic examinations.

The results of pathological examinations are shown in Table 1. The urinary examination revealed proteinuria. The results of blood test indicated hypoproteinemia. The results of blood coagulation tests were within normal limits and did not indicate disseminated intravascular coagulation. Transthoracic cardiac ultrasound revealed nothing abnormal. Ultrasonography showed the echogenic kidneys measuring 10.6 cm (right) and 11.5 cm (left).

Renal biopsy was performed 2 weeks following admission. Five glomeruli were sampled for immunofluorescence. There was 1 + global mesangial staining for IgM. There were all negative with IgA, IgG, C3, C4, C1q, kappa, and lambda. Forty-one glomeruli were reviewed on light microscope. Some had segmental mesangiolysis, capillary endothelial cell swelling, glomerular basement membrane thickening, and double-contour formation. Three had segmental glomerulosclerosis. Mild tubular atrophy and interstitial fibrosis was observed for approximately 5% of the cortex samples. Arteries endothelial cells were swelling. Electron microscopy showed a thickened glomerular basement membrane and expansion of the lamina rara interna. The foot process was segmental fusion. There were no electron dense deposits. Renal biopsy demonstrated TMA as shown in Figure 1.

The patient was treated with Losartan Potassium 50 mg/d. The index data of serum albumin and 24 hour urine protein after treatment with Losartan Potassium are shown in Figure 2. After cessation of the drug, albumin gradually improved and proteinuria gradually reduced. The treatment alleviated the symptoms of nephritic syndrome.
Overdose of cabozantinib leads to TMA

Figure 1. A. Periodic acid-Schiff reaction. ×400 the glomeruli show mesangiolysis, endothelial swelling and reduplication of the basement membranes. B. Masson’s trichrome. ×400 the glomeruli show mesangiolysis, endothelial swelling and reduplication of the basement membranes. C. Periodic acid-Schiff reaction. ×400 the small interlobular arteries exhibit endothelial swelling. D. Electron microscopy shows a thickened glomerular basement membrane and expansion of the lamina rara interna. The foot process was segmental fusion.

Discussion

Thrombotic microangiopathy is currently used to describe cases of non-idiopathic hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and clinically indistinguishable cases of HUS/TTP [10]. The most common clinical features observed in patients with HUS involve microangiopathy hemolytic anemia, acute renal failure, and thrombocytopenia. TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurologic deficits, renal failure, and fever [11].

Many different drugs have been reported to cause TMA, including immunosuppressants, anti-aggregating agents, and cytotoxic chemotherapies [12]. Cabozantinib is active in patients with advanced RET-rearranged lung cancers [9]. Cabozantinib is a multikinase inhibitor with low nanomolar (IC50 5.2 nM) activity against rearranged during transfection (RET), in addition to its activity against human hepatocyte growth factor receptor (MET), vascular endothelial growth factor receptor 2 (VEGFR2), human tyrosine kinase with immunoglobulin like and EGF-like domains 2 (TIE2), and stem cell factor receptor (KIT) [13]. By targeting multiple pathways, cabozantinib blocks proliferation and metastatic escape pathways. It can produce rapid and durable responses in patients with RET-rearranged lung cancers [9].

There are two speculated pathophysiologic pathways underlying chemotherapy-induced TMA. One is that TMA develops after immune complex formation and deposition within the renal vasculature. The second pathophysiologic model of TMA involves direct chemotherapy-induced endothelial toxicity. In this model, TMA was caused by decreased tissue plasminogen activator and increased plasminogen activator...
Overdose of cabozantinib leads to TMA

The doses of cabozantinib studied in trials differed depending on the indication [7]. The US Food and Drug Administration approval in April, 2016, of cabozantinib 60 mg per day for renal cell carcinoma suggests that it has an acceptable overall safety profile as monotherapy [8]. Linh Nguyen’s experiment showed that single oral doses of 60 mg cabozantinib capsules appeared to be generally well tolerated with no difference in the incidence and severity of adverse events in subjects with impaired renal or hepatic function and in healthy control subjects [16]. In this case, the patient took cabozantinib 140 mg/d, which is far more than the normal dose of 60 mg/d. The high dose of cabozantinib may be the inducement of TMA in this case.

Conclusion

Thus, it is important for clinicians to be aware that TMA may occur in patients who are treated with cabozantinib. The early diagnosis may be vital. Care should be taken to avoid using carbentinib at an overdose. It is necessary to monitoring the renal function and urine protein during the use of carbenitinib. Drugs suspected to have induced TMA must be discontinued immediately. Furthermore, it is suggested that renal biopsy be performed to make clear whether there are other factors causing proteinuria. ACEI/ARB drugs can be used to reduce urinary protein.

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Disclosure of conflict of interest

None.

Address correspondence to: Drs. Ruiqiang Wang and Lin Tang, Department of Nephrology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450001, Henan, China. Tel: 86+13938421047; E-mail: wangruqiang@zzu.edu.cn (RQW); Tel: 86+13-783623040; E-mail: tanglin@zzu.edu.cn (LT)
Overdose of cabozantinib leads to TMA

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