Int J Clin Exp Med 2019;12(1):1147-1151
www.ijcem.com /ISSN:1940-5901/IJCEM0082574

Case Report

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

Ruiqiang Wang*, Pupu Ma*, Bowen Zheng, Biyue Wang, Fengmei Chen, Lin Tang

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

Received July 14, 2018; Accepted September 13, 2018; Epub January 15, 2019; Published January 30, 2019

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 cancer in 2012. Cabozantinib was approved for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior antiangiogenic 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

Table 1. Laboratory data on admission

<Urinary exam>		<Hematology>		<Biochem.>	
RBC	8/uL	WBC	3.2×10^9/L	TP	47.5 g/L
WBC	0/uL			Alb	24 g/L
Protein	3+	RBC	4.02×10^9/L	BUN	1.7 mmol/L
24 hTP	6.19 g			Scr	58 umol/L
T/Cr	5.21 g/g	Hb	114 g/L	UA	128 umol/L
				T-Bil	3.90 umol/L
				Bil	1.90 umol/L
ANCA	(-)	PLT	124×10^9/L	AST	27 U/L
C-ANCA	(-)	MCV	86.40 fL	ALT	17 U/L
MPO-ANCA	15 U/mL	Hct	0.347 L/L	Na	141 mmol/L
PR3-ANCA	12 U/mL			K	3.03 mmol/L
GBM	15 U/mL			Ca	1.95 mmol/L
				P	0.90 mmol/L
		<Coagulation>			
PLA2R	2.3R U/mL	PT	9.50 S	T-CHO	6.99 mmol/L
		PT%	125%		
THSD7A	39.6 ng/mL	INR	0.88		
		APTT	31.70 S		
		Fib	2.67 g/L		
				<Immunology>	
ANA	(-)	TT	17.60 S	CRP	3.5 mg/L
ds-DNA	3 U/mL	Dimer	3.611 mg/L	ESR	40 mm/h
				C3	1.49 g/L
K	4.05			C4	0.17 g/L
λ	2.02				
K/λ	1.84				
IgA	2.70 g/L				
IgG	3.90 g/L				
IgM	1.11 g/L				

lung cancer. After resection, she received postlumpectomy radiotherapy 28 times and adjuvant treatment with intravenous carboplatin docetaxel and trastuzumab for two cycles. On August 2017, results of staging CT scans identified metastasis of the mediastinal lymph node and retroperitoneal lymph node in the left renal region. Then she received two cycles of intravenous carboplatin docetaxel, and trastuzumab. The liver nodules were found on November 2017, and cabozantinib administration was initiated at a dose of 140 mg/day. After cabozantinib initiation for two weeks, the patient was admitted to the hospital for edema in both lower limbs. On admission, the blood pressure was 117/68 mmHg, while the pulse rate was 80 bpm and the respiratory rate was 18/min. The patient's body temperature was 36.9°C. A 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 inravascular coagulation. Transthoracic cardiac ultrsound revealed nothing abnormal. Ultrasonography showed the echogenic kidneys measuring was 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.

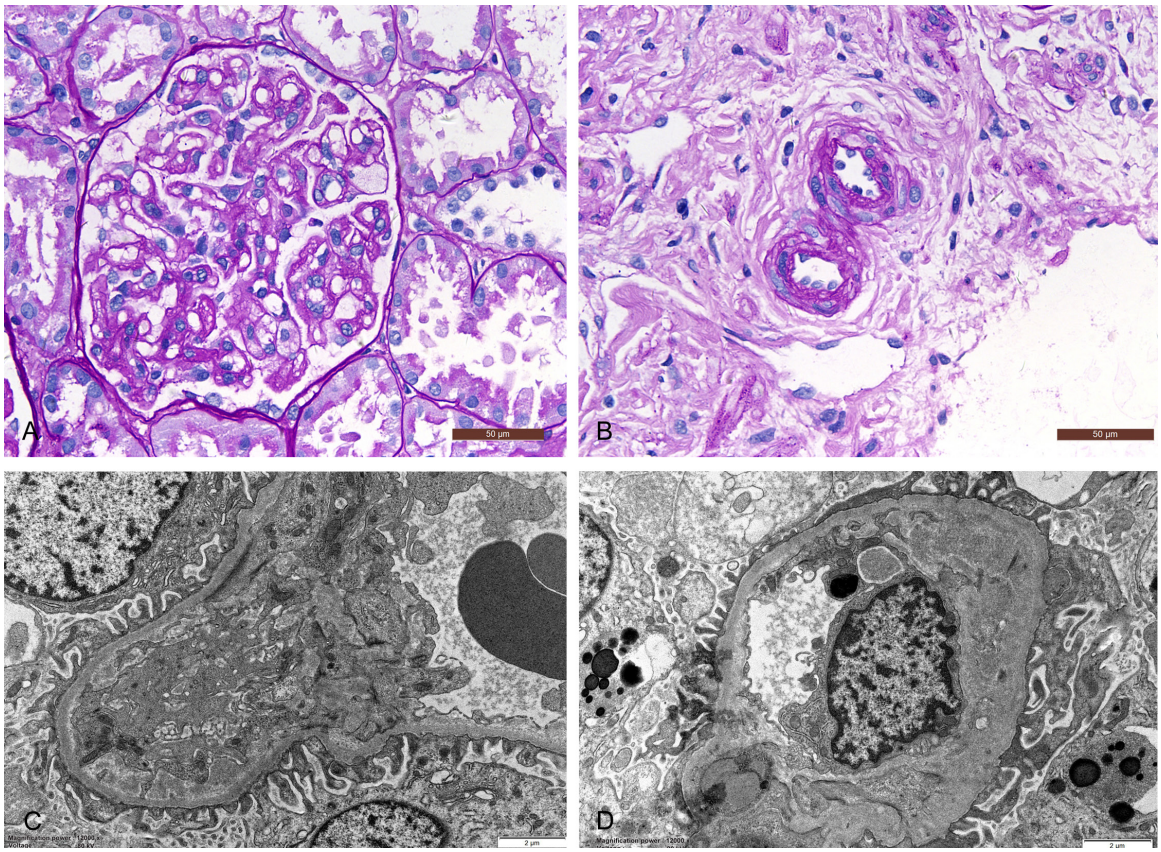

Figure 1. A. Periodic acid-Schiff reaction. ×400 the glomeruli showmesangiolysis, endothelial swelling and reduplication of the basement membranes. B. Masson's trichrome. ×400 the glomeruli show mesangiolysis, endothelial swelling and reduplication of the basement membranes. C. Periodic acid-Schiff reaction. ×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

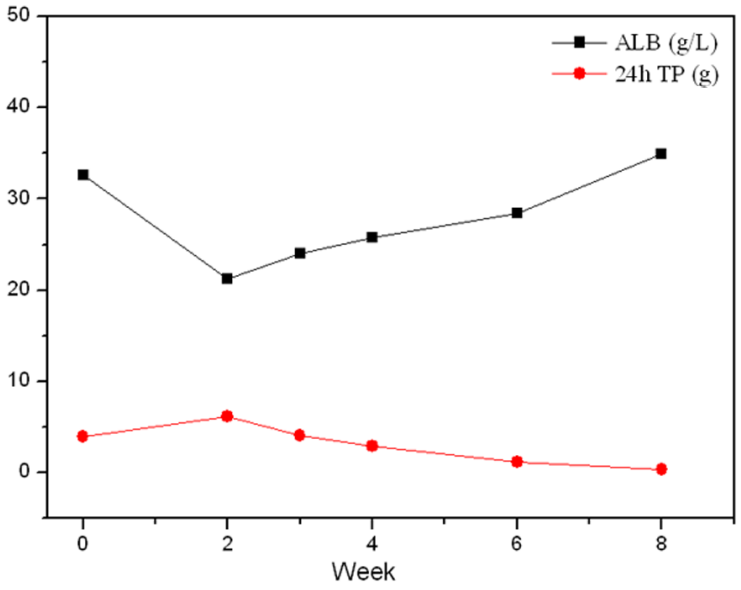

Figure 2. Laboratory tests demonstrate changes in parameters associated with the plasma albumin (ALB) and twenty-four hour total urine protein excretion (24 hTP) of the patient after withdrawal from Cabozantinib.

inhibitor, resulting in defective fibrinolysis and microthrombi deposition [14]. Typical clinical features of an immune-mediated reaction were acute onset of symptoms following the recent initiation (defined criteria as within 21 days) of a drug administered daily or within hours of exposure to a drug taken intermittently (defined criteria as within 24 hours) [15]. Clinical features of dose-related toxicity were either the acute onset of symptoms following exposure to a toxic substance or toxic dose of a drug, or gradual development of toxicity, often manifested as kidney failure. When typical features of an immune-mediated reaction were not present, the drug was assigned to the toxicity category [3].

In this case, the patient had already been treated with intravenous carboplatin docetaxel and trastuzumab for nearly one year with good tolerance and had never presented TMA. However, after receiving treatment of cabozantinib for 2 weeks, the symptoms of TMA were observed. The treatment of cabozantinib may promote the occurrence of 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 carbentinib. 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.

Acknowledgements

This work was supported by 2016 Key Science and Technology Plan Project of Henan Province (162102310198), Henan Province Health Department General Project (201403046) and Youth Innovation Fund of the First Affiliated Hospital of Zhengzhou University.

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: wangruiqiang@zzu.edu.cn (RQW); Tel: 86+13-783623040; E-mail: tanglin@zzu.edu.cn (LT)

References

[1] Symmers W. Thrombotic microangiopathic haemolytic anaemia (thrombotic microangiopathy). Br Med J 1952; 2: 897-903.

[2] Siau K, Varughese M. Thrombotic microangiopathy following docetaxel and trastuzumab chemotherapy: a case report. Med Oncol 2010; 27: 1057-9.

[3] Al-Nouri ZL, Reese JA, Terrell DR, Vesely SK, George JN. Drug-induced thrombotic microangiopathy: a systematic review of published reports. Blood 2015; 125: 616-8.

[4] Regierer AC, Kuehnhardt D, Schulz CO, Flath B, Jehn CF, Scholz CW, Possinger K, Eucker J. Breast cancereassociated thrombotic microangiopathy. Breast Care (Basel) 2011; 6: 441-5.

[5] Tada K, Ito K, Hamauchi A, Takahashi K, Watanabe R, Uchida A, Abe Y, Yasuno T, Miyake K, Sasatomi Y, Nakashima H. Clopidogrel-induced thrombotic microangiopathy in a patient with hypocomplementemia. Intern Med 2016; 55: 969-3.

[6] Andersohn F, Bronder E, Klimpel A, Garbe E. Proportion of drug-related serious rare blood dyscrasias: estimates from the Berlin case-control surveillance study. Am J Hematol 2004; 77: 316-8.

[7] Schmidinger M, Danesi R. Management of adverse events associated with cabozantinib therapy in renal cell carcinoma. Oncologist 2017; 22: 1-10.

[8] Neal JW, Dahlberg SE, Wakelee HA, Aisner SC, Bowden M, Huang Y, Carbone DP, Gerstner GJ, Lerner RE, Rubin JL, Owonikoko TK, Stella PJ, Steen PD, Khalid AA, Ramalingam SS; ECOG-ACRIN 1512 nvestigators. Erlotinib, cabozantinib, or erlotinib plus cabozantinib as second-line or third-line treatment of patients with EGFR wild-type advanced non-small-cell lung cancer (ECOG-ACRIN 1512): a randomised, controlled, open-label, multicentre, phase 2 trial. Lancet Oncol 2016; 17: 1661-1671.

[9] Drilon A, Rekhtman N, Arcila M, Wang L, Ni A, Albano M, Van Voorthuysen M, Somwar R, Smith RS, Montecalvo J, Plodkowski A, Ginsberg MS, Riely GJ, Rudin CM, Ladanyi M, Kris MG. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. Lancet Oncol 2016; 17: 1653-1660.

[10] Murgo AJ. Cancer- and chemotherapy-associated thrombotic microangiopathy. In: Kaplan BS, Trompeter RS, Moake JL, editors. Hemolytic-uremic syndrome and thrombotic thrombocy-topenic purpura, (Kidney Disease S v. 10), vol. 22. New York: Marcel Dekker Ltd.; 1992. pp. 271-295.

[11] Raiss H, Péron J, Tartas S, Trillet-Lenoir V, Freyer G, Errihani H. Palbociclib-induced thrombotic microangiopathy in metastatic breast cancer patient surviving for 18 years: case report and review of the literature. Clin Breast Cancer 2017; 18: e263-e266.

[12] Niu J, Mims MP. Oxaliplatin-induced thrombotic thrombocytopenic purpura:case report and literature review. J Clin Oncol 2012; 30: e312-4.

[13] Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, Qian F, Chu F, Bentzien F, Cancilla B, Orf J, You A, Laird AD, Engst S, Lee L, Lesch J, Chou YC, Joly AH. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther 2011; 10: 2298-308.

[14] Iams W, Beckermann KE. Thrombotic microangiopathy during docetaxel, trastuzumab, and carboplatin chemotherapy for early-stage HER2$^+$ breast cancer: a case report. Med Oncol 2013; 30: 568.

[15] Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. New Eng J Med 2007; 357: 580-7.

[16] Nguyen L, Holland J, Ramies D. Effect of renal and hepatic impairment on the pharmacokinetics of cabozantinib. J Clin Pharmacol 2016; 56: 1130-40.