

中文題目：一位非小細胞肺癌合併多處轉移病人在使用血管新生抑制劑 ramucirumab 後發生新出現的缺血性中風

英文題目：New Ischemic Stroke in a Patient with Metastatic Non-Small Cell Lung Cancer After Treatment with the Angiogenesis Inhibitor Ramucirumab

作者：陳國鈺¹，鄭文建^{1,2}

服務單位：¹ 中國醫藥大學附設醫院內科部，² 中國醫藥大學附設醫院胸腔內科

Introduction:

Research interest is growing in various adverse events of anti-vascular endothelial growth factor (anti-VEGF) medication due to its wide use and efficacy in improving the survival of cancer patients.¹⁻³ Myocardial infarction, hypertension, and new-onset proteinuria have been reported as adverse events.⁴ Ischemic stroke is also one of the most concerning clinically relevant adverse events.⁴⁻⁹ However, the relationship between anti-VEGF agents and the incidence of cerebral ischemia is still controversial.⁴⁻⁹ Bevacizumab and ramucirumab are vascular endothelial growth factor (VEGF) signaling pathway inhibitors and are indicated in the treatment of non-small-cell lung cancer (NSCLC) patients.^{10,11} While treatment with bevacizumab has been reported to increase the risk of cerebral ischemia,⁹ stroke cases have rarely been mentioned after the use of ramucirumab. To our knowledge, only one case has been reported of an 82-year-old male with metastatic gastric cancer suffering from multifocal ischemic stroke after treatment with four doses of ramucirumab.¹² We present the first case of an ischemic stroke in an NSCLC patient after treatment with ramucirumab.

Case Presentation:

A 67-year-old female diagnosed with NSCLC harboring the EGFR-L858R mutation, with liver, spine, right rib, bilateral adrenal gland, and brain metastases (Fig.1), visited our chest outpatient department due to frequent dizziness and falls. Her past medical history included type II diabetes mellitus with metformin control and asthma for 30 years. She initially received targeted therapy with a second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) plus ramucirumab for treatment. After receiving ramucirumab for about one and a half months, she began suffering from persistent dizziness and frequent falls.

On examination, she appeared chronically ill but was still alert. She could only say a single word. Her vital signs were stable. A physical examination showed medial side deviation when performing an extraocular muscle function test (the provider moved the object to the left side), poor gag reflex, decreased upper limb muscle power (2 points), mild flattening of the left nasolabial fold, and a positive Babinski sign on the left side. Laboratory tests revealed leukocytosis with neutrophil predominance (WBC: 17,600/uL; neutrophil: 86.8%). Repeated brain magnetic resonance imaging performed due to suspected progression of the disease disclosed partial remission of diffuse intracranial metastatic tumors with residual tumors in the midbrain, cerebellum, bilateral basal ganglia, and bilateral hemispheres of the cerebrum, but

suspected diffuse embolic acute infarctions in the left thalamus, bilateral basal ganglia, bilateral corona radiata, and bilateral temporal, bilateral frontal, bilateral parietal, and bilateral occipital lobes (Fig. 2). The electrocardiogram showed no arrhythmia. Transcranial Doppler sonography results were within normal limits except for very mild atherosclerotic changes in the bilateral bulb. Echocardiography revealed preserved left and right ventricular contractility with normal chamber size and no abnormality in left ventricular regional wall motion. The patient then received rehabilitation and acupuncture for post-stroke care.

Discussion:

To our knowledge, this is the first case report detailing a new-onset ischemic stroke in an NSCLC patient after ramucirumab treatment. A previous case report described a patient with metastatic gastric cancer who suffered from an ischemic stroke after treatment with ramucirumab.¹² However, these cases are rarely reported. Bevacizumab has been well investigated in previous studies that discussed the relationship between angiogenesis inhibitors and the risk of arterial thromboembolism (ATE). In a meta-analysis that evaluated cardiovascular adverse effects in cancer patients after treatment with bevacizumab, Totzek et al.⁹ reported a higher risk of developing cerebral ischemia in the bevacizumab group (relative risk [RR] = 3.11; 95% CI: 1.46–6.65; $p = 0.003$). Another meta-analysis of 77 Phase III trials that primarily included bevacizumab also showed a higher odds ratio for ATE (1.52 [95% CI: 1.17–1.98]).⁵ Nevertheless, only a few studies have targeted ramucirumab for evaluation. A report that examined the incidence of adverse events, possibly due to VEGF signaling pathway inhibition by ramucirumab, revealed 38 (1.4%) and 40 (1.8%) cases of all-grade ATE in the ramucirumab and control arms, respectively (RR: 0.8; 95% CI: 0.5–1.3).⁶ However, patients who had a cerebrovascular accident or transient ischemic attack within 6–12 months prior to randomization were excluded in five of the six trials included in the study, and thus whether or not patients were better selected to reduce the risk of ATE is unknown.⁶ In our case, the patient had long-term diabetes mellitus, but the condition was well controlled by medication. Her cancer status was a partial response of tumor shrinkage noted by imaging. While both are considered risk factors for stroke, the conditions were relatively stable; therefore, their effects might have been slight.

In conclusion, we report a new-onset ischemic stroke in an NSCLC patient after treatment with ramucirumab. The previous study targeting ramucirumab may be limited due to patient inclusion criteria.⁶ Therefore, further extensive studies are necessary to investigate the relationship between ramucirumab and the risk of ischemic stroke.

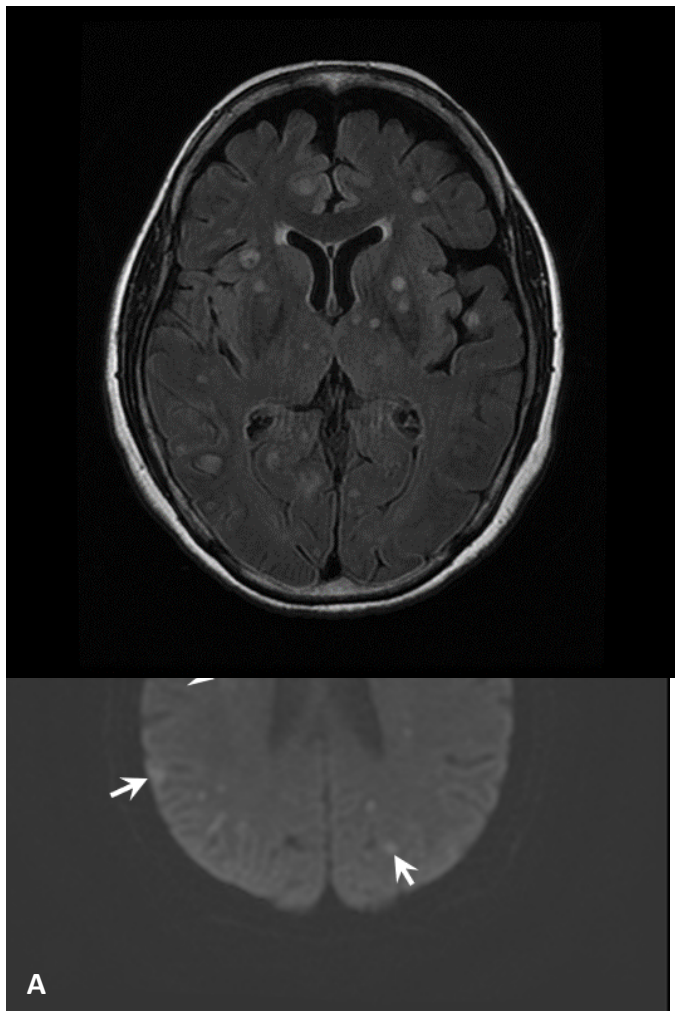
Conclusion:

Vascular endothelial growth factor (VEGF) inhibitors have been widely investigated in the last 10 years, with particular attention paid to their adverse effects due to their efficacy in

improving cancer patient survival. Previous research primarily focused on the monoclonal anti-vascular endothelial growth factor antibody bevacizumab and its adverse outcomes. Reports show a higher risk of ischemic stroke, one of the most concerning clinically relevant events, after treatment with bevacizumab. However, few studies have examined the relationship between anti-vascular endothelial growth factor receptor 2 monoclonal antibody ramucirumab and its adverse events. This article presents the case of a non-small-cell lung cancer patient who experienced a new ischemic stroke after treatment with ramucirumab. The findings suggest that further studies may be necessary to investigate the relationship between ramucirumab and the risk of ischemic stroke.

References

1. Garon, E.B., et al., Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*, 2014. **384**(9944): p. 665-73.
2. Nakagawa, K., et al., Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*, 2019. **20**(12): p. 1655-1669.
3. Sandler, A., et al., Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*, 2006. **355**(24): p. 2542-50.
4. Faruque, L.I., et al., Systematic review of the risk of adverse outcomes associated with vascular endothelial growth factor inhibitors for the treatment of cancer. *PLoS One*, 2014. **9**(7): p. e101145.
5. Abdel-Qadir, H., et al., Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: A systematic review and meta-analysis. *Cancer Treat Rev*, 2017. **53**: p. 120-127.
6. Arnold, D., et al., Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab. *Ann Oncol*, 2017. **28**(12): p. 2932-2942.
7. Gu, B., et al., Adverse events risk associated with anti-VEGFR agents in the treatment of advanced nonsmall-cell lung cancer: A meta-analysis. *Medicine (Baltimore)*, 2016. **95**(48): p. e3752.
8. Guo, C., et al., The efficacy and toxicity of angiogenesis inhibitors for ovarian cancer: a meta-analysis of randomized controlled trials. *Arch Gynecol Obstet*, 2021. **303**(2): p. 285-311.
9. Totzeck, M., R.I. Mincu, and T. Rassaf, Cardiovascular Adverse Events in Patients With Cancer Treated With Bevacizumab: A Meta-Analysis of More Than 20 000 Patients. *J Am Heart Assoc*, 2017. **6**(8).
10. Bevacizumab [package insert on the internet]. South San Francisco, CA: Genentech, Inc.; 2004 [updated 2021 Jan; cited 2022 Aug 29]. Available from: https://www.gene.com/download/pdf/avastin_prescribing.pdf
11. Cyramza [package insert on the internet]. Indianapolis, IN: Eli Lilly and Company.; 2014 [updated 2020 May, cited 2022 Aug 29]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125477s034lbl.pdf
12. Christiansen, M.E., et al., A Case Report of Ischemic Stroke in a Patient with Metastatic Gastric Cancer Secondary to Treatment with the Vascular Endothelial Growth Factor Receptor-2 Inhibitor Ramucirumab. *Case Rep Oncol*, 2016. **9**(2): p. 317-20.



Recovery (FLAIR) brain MRI for initial cancer
e lesions over bilateral hemispheres, suspect
s.

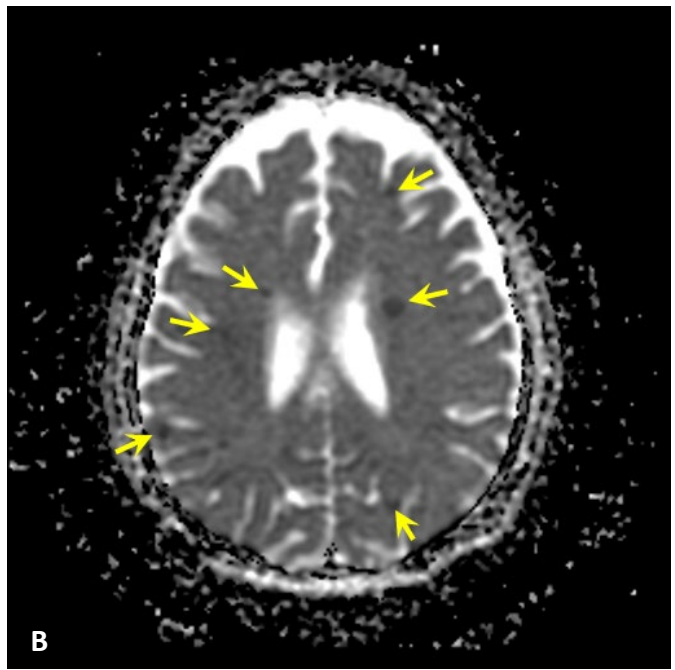


Figure.2 Sequential diffusion-weighted imaging (2A) and apparent diffusion coefficient (2B) of the brain MRI showed multifocal increased signal due to diffusion restriction and corresponding decreased signal intensity, respectively. The result is compatible with ischemic stroke related cytotoxic edema.