CASE REPORT

Axitinib-induced reversible posterior leukoencephalopathy syndrome in a patient with metastatic renal cell carcinoma

Kogenta Nakamura¹ · Hiroshi Saiki¹ · Hiroyuki Muramatsu¹ · Shingo Morinaga¹ · Ikuo Kobayashi¹ · Keishi Kajikawa¹ · Genya Nishikawa¹ · Yoshiharu Kato¹ · Masahito Watanabe¹ · Kent Kanao¹ · Makoto Sumitomo¹

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Abstract A 61-year-old woman with metastatic renal carcinoma was treated with axitinib as a second-line tyrosine kinase inhibitor. Thirteen days after the treatment, the patient developed reversible posterior leukoencephalopathy syndrome (RPLS). Her symptoms and imaging findings resolved after withdrawal of axitinib, blood pressure control, and administration of glycerin and levetiracetam. RPLS should be kept in mind as a possible rare adverse event after axitinib administration.

Keywords Renal cell carcinoma · Axitinib · Reversible posterior leukoencephalopathy syndrome

Introduction

Reversible posterior leukoencephalopathy syndrome (RPLS) is a disease caused by vascular hyperpermeability due to vascular epithelial damage. The manifestations of RPLS are similar to that of eclampsia and hypertensive encephalopathy [1]. Here, we report on a case in which treatment with axitinib, a vascular endothelial growth factor (VEGF) receptor antagonist, resulted in RPLS.

Case report

The patient is a 61-year-old woman. Her past medical history includes surgery for uterine myoma in addition to a history of hypophyseal adenoma. In 2014, the patient underwent an open radical nephrectomy for a left renal carcinoma with multiple lung metastases (staging was cT2aN0M1). Pathological results revealed clear cell renal cell carcinoma, pT2a, G3 > 2/Fuhrman Grade 3–4, INF α , v0, ly0, e.g., fc0, im0, rc-inf0, rp-inf0, s-inf0. After surgery, the patient started receiving 37.5 mg/day sunitinib (2 days on, 1 day off). Her blood pressure was the normal range after administering sunitinib as a first-line therapy (Fig. 1).

Three months later, the metastatic foci in the lungs were observed to be reduced. However, sunitinib was halted because of observed thyroid gland malfunction. Owing to recrudescence of the lung tumor foci, the patient was then started on 10 mg/day axitinib. We recommended her to measure blood pressure by herself and explained to come to our hospital immediately when her blood pressure was in the high range. But she did not measure blood pressure by herself. On day 13 of axitinib administration, the patient developed a headache and nausea and was emergently transported to our hospital. During transport, the patient experienced a clonic convulsion lasting 1 min.

At admission, the patient's Glasgow coma scale was E3V4M4; blood pressure, 160/77 mmHg; and heart rate, 101 beats per minute. Head computed tomography did not reveal any obvious hemorrhage or infarct. However, head magnetic resonance imaging (MRI) revealed bilateral scattered lesions in the cortex and white matter of the occipital lobe. The lesions appeared faintly hyperintense on diffusion-weighted imaging and hyperintense using the apparent diffusion coefficient map, suggesting vasculogenic

✉ Kogenta Nakamura
kogenaka@aichi-med-u.ac.jp

¹ Department of Urology, Aichi Medical University School of Medicine, 1-1 Karimata, Yazako, Nagakute, Aichi 480-1195, Japan

Fig. 1 Demonstration of treatment response. **a** Head magnetic resonance imaging (FLAIR) shows reversible posterior leukoencephalopathy syndrome (RPLS). **b** After 7 days, the RPLS has resolved

edema rather than cerebral ischemia. The findings were not typical of a brain metastasis.

Based upon the imaging studies and the patient history, we suspected RPLS and began treatment by withdrawing axitinib, controlling blood pressure, starting intravenous glycerin, and administering antiepileptic agent. Head MRI 1-week later revealed that the bilateral lesions in the cortex and white matter of the occipital lobe had fully disappeared. The metastatic foci in the lungs have been stable disease after axitinib therapy. The patient did not continue receiving VEGF receptor antagonist, so she has been treated anti-PD-1 antibody therapy.

Discussion

RPLS arises from etiologies including hypertension, drug reactions (due to immunosuppressants, chemotherapeutic agents, and molecular-targeted drugs), and renal dysfunction.

The pathogenesis of RPLS involves the development of blood vessel hyperpermeability due to vascular endothelial damage, resulting in failure of the blood–brain barrier and of cerebral blood flow autoregulation. These changes lead to vasculogenic edema, manifesting in symptoms such as seizures and headaches [1].

In 90% of cases, MRI FLAIR imaging reveals a hyperintense region in the occipital lobe [2, 4]. Key elements of treatment include removal of precipitating factors, treatment of brain edema, and blood pressure control [3]. The symptoms and imaging findings are reversible, with 70% of cases normalizing within 20 days [4].

Molecular-targeted drugs used for renal carcinomas include sunitinib, sorafenib, pazopanib, and axitinib. All of these VEGF receptor antagonists can potentially cause RPLS. While cases of RPLS due to renal carcinoma targeted therapies are rare, reports involving sunitinib have been most frequent [5–13]. We report herein the second

case, to our knowledge with RPLS induced by axitinib [13]. Adverse events have been observed most often in women, with symptoms appearing within 2 weeks after the start of treatment in half of all cases. In the present case, symptoms began 13 days after treatment, and axitinib-mediated vascular endothelial damage led to a sharp rise in blood pressure, resulting in RPLS. Appropriate treatment led to the resolution of symptoms and imaging findings within 7 days.

There were not any cases in which a restart VEGF receptor antagonists. Hadj et al. reported second-line treatment with oral everolimus was used after sunitinib therapy [7]. RPLS has not been reported in association with everolimus or other mTOR inhibitors. As mTOR inhibitors are believed to exert antitumor effects by direct inhibition of tumor cell growth and proliferation, as well as the inhibition of angiogenesis.

We believe that administration of an antihypertensive agent along with axitinib may have avoided the onset of RPLS. Strict monitoring of blood pressure is thus necessary during treatment with VEGF receptor antagonists, and RPLS should be kept in mind as a possible adverse event during axitinib administration.

Compliance with ethical standards

Funding None declared.

Conflicts of interest All authors declare that they have no competing interest.

Informed consent Informed consent was obtained from the patient including this report.

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