



# Cabozantinib-Associated Posterior Reversible Encephalopathy Syndrome

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A 68-year-old male patient visited our clinic in July 2024 with left flank pain. An abdominal computed tomography (CT) scan identified an 8.5 cm malignant mass in the upper pole of the left kidney with invasion into the renal vein. A thoracic CT scan revealed multiple bilateral metastatic lung lesions, the largest measuring 2.5 cm in diameter. A tru-cut biopsy of the renal mass confirmed the diagnosis of renal cell carcinoma (RCC) with sarcomatoid features. Given the diagnosis of metastatic RCC, the patient started cabozantinib at a dose of 60 mg/day in July 2024.

In October 2024, he presented to the emergency department with confusion, hallucinations, and agitation that had persisted for 3 days. On initial neurological evaluation, he was disoriented and uncooperative, but no focal neurological deficits were observed. The primary differential diagnoses included cerebrovascular event (CVE), cranial metastasis, paraneoplastic syndrome, metabolic disorders, infectious diseases, and drug-related neurological adverse effects.

On initial evaluation, the patient exhibited altered mental status and disorientation without fever, seizures, or focal neurological deficits. Physical examination showed a Glasgow Coma Scale (GCS) score of 10 (E3M5V2), with no signs of neck stiffness or meningeal irritation. Cranial nerve evaluation revealed isocoric pupils with intact light reflexes, normal extraocular movements, and bilaterally preserved nasolabial sulcus. Motor examination demonstrated withdrawal responses to painful stimuli in all extremities, normal muscle tone, and normoactive deep tendon reflexes. Sensory and cerebellar assessments could not be adequately performed. Systemic examination showed no evidence of an underlying infectious process.

The patient's blood pressure was 145/85 mmHg, oxygen saturation was 95%, heart rate was 72 bpm, and body temperature was 36 °C. Biochemical and hematological tests were within normal limits,

with no abnormalities suggestive of a metabolic or infectious cause. Cranial CT ruled out intracranial hemorrhage. Contrast-enhanced brain magnetic resonance imaging (MRI) revealed no space-occupying lesions or diffusion restriction, excluding ischemic or hemorrhagic CVE and metastasis. However, T2-FLAIR sequences showed vasogenic edema in the temporal lobes, frontobasal regions, and deep subcortical white matter (Figure 1). Susceptibility weighted imaging sequences identified a millimetric hemorrhagic contrast-enhancing lesion in the posterior right caudate nucleus.

Given the absence of malignancy progression and the presence of distinct neuroimaging abnormalities, paraneoplastic neurological syndrome was considered unlikely, as it is typically associated with normal or non-specific neuroimaging findings. Instead, the T2-FLAIR hyperintensities and vasogenic edema strongly suggested posterior reversible encephalopathy syndrome (PRES). Based on the combined clinical and radiological findings, a diagnosis of drug-induced PRES was made.

The patient was admitted to the oncology service, and cabozantinib was discontinued. Neurological status was closely monitored, and management included intravenous hydration, electrolyte correction, and blood pressure regulation within normotensive ranges. Significant clinical improvement was observed within 48 h, with the GCS score improving to E4M6V5. This rapid recovery was a key distinguishing feature that helped differentiate PRES from other potential diagnoses, particularly paraneoplastic syndromes.

PRES is a clinical-radiological condition characterized by cerebral autoregulatory dysfunction and endothelial injury.<sup>1</sup> It typically presents with headache, confusion, nausea, seizures, and visual disturbances.<sup>2</sup> Common risk factors include immunosuppressive and cytotoxic therapies, hypertension, eclampsia, and metabolic disorders. Brain imaging usually reveals bilateral white matter



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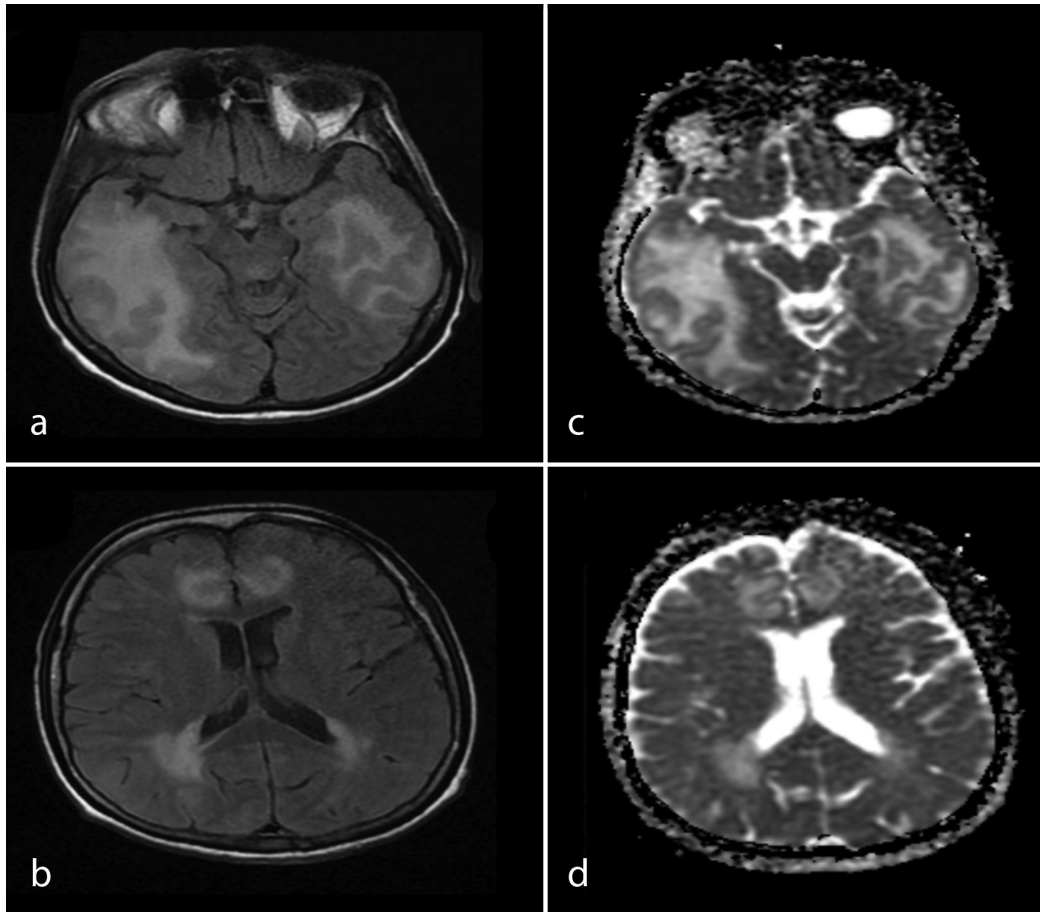
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**FIG. 1.** Axial flair sequence (a, b) images showing hyperintense subcortical and deep white matter signal changes without any diffusion restriction in ADC maps (c, d) representing vasogenic edema in bilateral temporal and frontal lobes.

edema, primarily in the parieto-occipital regions, though atypical patterns can occur.<sup>3</sup> Deep gray matter, brainstem, and cerebellar involvement has also been reported, along with additional findings such as diffusion restriction, leptomeningeal contrast enhancement, and hemorrhage.<sup>4,5</sup>

Cabozantinib is a tyrosine kinase inhibitor (TKI) that targets multiple kinases involved in tumor angiogenesis and metastasis. Its mechanism of action primarily involves vascular endothelial growth factor receptor-2 (VEGFR-2) inhibition, which suppresses endothelial cell proliferation and migration, leading to vascular instability and increased blood-brain barrier permeability. Additionally, inhibition of MET and AXL disrupts endothelial repair, contributing to vascular dysfunction and vasogenic edema. PRES is a serious but treatable adverse effect associated with anti-VEGF agents. Several cases of PRES have been reported with TKIs such as sunitinib and sorafenib, as well as anti-VEGF agents like bevacizumab and aflibercept.<sup>6</sup> A documented case of PRES in a patient receiving pazopanib for RCC presented with confusion and seizures, with brain MRI revealing diffuse, ill-defined cortical and subcortical hyperintensities in the bilateral parieto-occipital lobes, consistent with vasogenic edema.

The patient's condition improved solely with drug discontinuation and blood pressure management.<sup>7</sup> The first reported case of cabozantinib-induced PRES described subcortical T2 and FLAIR hyperintense areas on brain MRI, classified as "atypical PRES".<sup>8</sup> The most recent case in the literature (2022) involved a 69-year-old woman on cabozantinib for metastatic RCC, who developed generalized tonic-clonic seizures 3 months after initiating treatment.<sup>2</sup> Brain MRI revealed posterior FLAIR hyperintensities consistent with PRES, and after discontinuing cabozantinib, both clinical and radiological findings improved.

PRES management focuses on blood pressure stabilization, fluid balance optimization, and addressing underlying causes. Hypertension should be gradually lowered to prevent cerebral hypoperfusion. Seizures, if present, should be treated with antiepileptic therapy as needed. Causative immunosuppressive or cytotoxic agents should be discontinued to prevent disease progression. Electrolyte imbalances and fluid disturbances must also be corrected. In most cases, symptoms resolve rapidly with appropriate intervention, reinforcing the reversible nature of the syndrome.

**Informed Consent:** Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

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