

Posterior Reversible Leukoencephalopathy Syndrome Associated with Pazopanib

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Key Words

Hypertension · Pazopanib · Posterior reversible encephalopathy syndrome · Reversible posterior leukoencephalopathy syndrome · Tyrosine kinase inhibitors

Abstract

A 62-year-old female patient with metastatic renal cell carcinoma under third-line treatment with pazopanib for 8 weeks suddenly developed severe headaches, grand mal seizures and paresis of the left arm in combination with gait instability as well as nausea and vomiting during her vacation abroad. The emergency physician measured systolic blood pressure values over 300 mm Hg and suspected a stroke. The CT imaging without contrast agent in a local hospital did not show any pathologic findings despite bone metastases. The colleagues suspected cerebral metastases or meningeosis carcinomatosa and referred the patient to our department for further diagnostics and treatment planning. An MRI scan ruled out the suspected cerebral metastases or meningeosis carcinomatosa, but showed signs of reversible posterior leukoencephalopathy syndrome (RPLS) in the form of band-like hyperintensities as a sign of cytotoxic edema in the gray and white matter of the left parietal lobe. The patient then reported that similar blood pressure values had been measured shortly after the start of a first-line therapy with sunitinib, so that we discontinued the current treatment with pazopanib. Within 6 days the neurologic symptoms vanished and the patient was discharged. An intermittent hypertension persisted. A follow-up MRI 3 weeks later showed an RPLS-typical cortical infarction in the affected area. RPLS should be considered as the actual reason for neurologic findings in hypertensive patients with known metastatic cancers under tyrosine kinase inhibitor therapy.

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Introduction

Tyrosine kinase inhibitors (TKIs) are a relatively new treatment modality for the treatment of metastatic renal cell carcinoma. Although they have shown promising results, their use is often limited due to adverse reactions. Pazopanib, which is the most recently approved drug for metastatic renal cell carcinoma, is an oral small-molecule TKI that inhibits vascular endothelial growth factor (VEGF) receptors 1, 2, and 3, c-kit, and platelet-derived growth factor receptors alpha and beta. We report on a case of malignant hypertension and occurrence of reversible posterior leukoencephalopathy syndrome (RPLS) in a 62-year-old female patient treated with pazopanib for metastatic renal cell carcinoma.

Case Report

A 62-year-old female patient with known papillary renal cell carcinoma diagnosed in 2004 and under third-line treatment with pazopanib for 8 weeks suddenly developed severe headaches, grand mal seizures and paresis of the left arm in combination with gait instability as well as nausea and vomiting during her vacation abroad. The emergency physician measured systolic blood pressure values over 300 mm Hg and suspected a stroke. Therefore, the patient was hospitalized in a local hospital where she received a CT scan without contrast agent. The CT imaging, however, did not show any pathologic findings despite bone metastases. The patient's husband meanwhile had organized a medical transport back to Germany. Due to the fact that she had been previously treated in our comprehensive cancer center at the University Hospital of Heidelberg and the colleagues abroad had suspected newly formed metastases or meningeosis carcinomatosa clinically mimicking cerebral metastases, she was admitted to our department of radiation oncology for further diagnostics and treatment planning.

At the time of admission, the patient was somnolent and not able to communicate with us because she had received large quantities of intravenous diazepam as an anticonvulsive measure on the plane. We initiated an anticonvulsive therapy with levetiracetam 250 mg twice a day and antiedematous treatment with dexamethasone 8 mg thrice a day. The next day, the patient was fully awake but showed significant anterograde amnesia from the onset of the headaches, psychomotoric deceleration and persistent gait instability. A detailed neurologic examination with EEG by our colleagues showed no signs of epilepsy. The initially suspected brain metastases or meningeosis carcinomatosa were ruled out with an MRI scan which, however, showed signs of RPLS in the form of band-like hyperintensities as a sign of cytotoxic edema in the gray and white matter of the left parietal lobe (fig. 1). The hypertension persisted with values of up to 220/120 mm Hg under triple antihypertensive therapy with metoprolol, amlodipine and candesartan. The patient reported that similar values had been measured shortly after the start of a first-line therapy with sunitinib about 1 year before. With pazopanib being known to cause hypertension we discontinued the current treatment [1]. During her 6-day stay in our department the neurologic findings completely vanished and we were able to discharge her. A follow-up MRI 3 weeks later showed that the patient had developed an RPLS-typical cortical infarction [2] in the affected area (fig. 2). Fortunately she remained without any neurologic symptoms. An intermittent hypertension, however, persisted with values of up to 180/100 mm Hg in this short follow-up. A cardiologic checkup had meanwhile ruled out cardiac genesis.

Discussion

VEGF inhibitors and TKIs which block the VEGF receptor itself are known to be associated with hypertension and other cardiovascular symptoms [3, 4]. For sunitinib 30% of patients were reported to develop hypertension under therapy [5] and the phase III trial on the data of which pazopanib was approved for treatment of metastatic renal cell carcinoma by the US Food and Drug Administration in October 2009 reported that 40% of patients treated with pazopanib developed hypertension [6]. Currently the exact mechanism of anti-VEGF therapies causing high blood pressure remains unknown, but increased peripheral resistance and vascular tone may play a role [4]. Hypertension has been described as the cause of RPLS [7], and various case reports have been published about patients developing RPLS under sunitinib, sorafenib and bevacizumab therapy [8–15]. Only recently two cases of RPLS under treatment with pazopanib have been reported [16, 17]. The history of our patient shows that if hypertension occurs under treatment with one TKI there is a strong possibility that it will occur under another TKI as well. Although symptoms of RPLS usually disappear within a few days to 1 month [11], blood pressure values should be closely monitored under TKI therapy to prevent malignant hypertension and its consequences. Furthermore, with our case being already the third published report on RPLS under pazopanib treatment and one of multiple case reports on RPLS under TKI therapy in general, RPLS clinically mimicking cerebral metastases should always be considered as the actual reason for neurologic findings in patients with known metastatic cancers under TKI therapy.

To enable a better risk stratification for the patients, further investigations on the mechanisms of how TKIs cause hypertension are necessary. However, anti-VEGF therapy-induced hypertension may be an indicator for an improved outcome. Both progression-free survival and overall survival were significantly increased in patients developing hypertension under treatment with anti-VEGF-directed substances [18, 19]. Hence, development of hypertension is no contraindication to TKI treatment. If required, patients should receive anti-hypertensive therapy.

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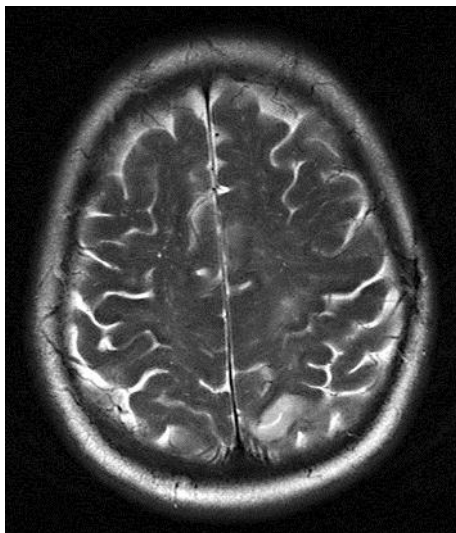


Fig. 1. T2-weighted image showing band-like hyperintensities in the gray and white matter of the parietal lobe.

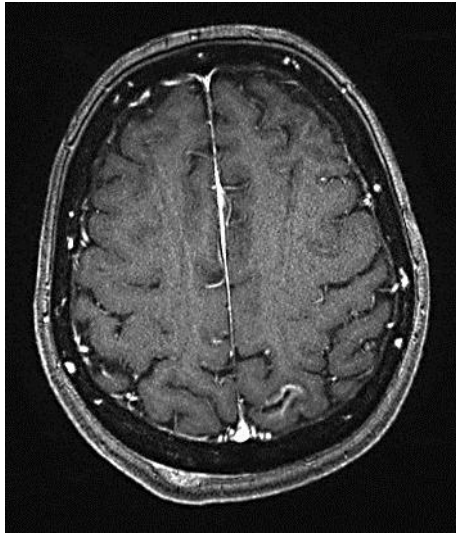


Fig. 2. T1-weighted image with gadolinium showing a cortical infarction.