CASE REPORT

Pazopanib-associated posterior reversible encephalopathy syndrome with intracerebral haemorrhage

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Accepted 22 March 2017

SUMMARY

Pazopanib is a tyrosine kinase receptor antagonist used for renal cell carcinoma and soft tissue sarcoma that inhibits tumour growth and angiogenesis. A common side effect of pazopanib is hypertension. We report a case of a 69-year-old woman with clear cell renal cell carcinoma who developed a large right occipital intracerebral haemorrhage 3 weeks after initiating pazopanib. Although this was initially suspected to be a haemorrhagic metastasis, MRI revealed bi-occipital oedema, supporting a diagnosis of posterior reversible encephalopathy syndrome (PRES). A craniectomy was required. Immunohistochemical stains for renal cell carcinoma antigen, CA IX and PAX8 were negative. This case suggests that PRES and intracerebral haemorrhage may result from pazopanib use and are important complications to consider prior to initiating this agent.

BACKGROUND

Our case illustrates the potential catastrophic complication of pazopanib-induced posterior reversible encephalopathy syndrome (PRES) with this first reported association with intracerebral haemorrhage. Although symptoms from PRES are generally reversible, intracerebral haemorrhage often leads to death or permanent disability. This is a critical side effect to consider prior to initiation of therapy, warranting careful blood pressure monitoring and frequent follow-up for individuals started on this agent.

CASE PRESENTATION

A 69-year-old woman with a history of clear cell renal cell carcinoma (stage IV) and hypertension was started on pazopanib in March 2016 in the setting of progressive metastatic disease. The patient was originally diagnosed with renal cell carcinoma in 2012, when a positron emission tomography-computed tomography revealed mild fluorodeoxyglucose (FDG) avidity in the upper portion of her left kidney and left humerus. She subsequently underwent left kidney microwave ablation and left humeral chemoembolisation and resection, with a biopsy of the left humeral lesion revealing clear cell renal cell carcinoma. She then underwent left nephrectomy with negative margins in 2013 due to growth despite local therapy. Surveillance imaging in 2015 revealed a new subcarinal soft tissue mass, thyroid mass and bilateral pulmonary nodules.

Biopsies were consistent with recurrent disease, and the patient was, therefore, initiated on pazopanib.

Three weeks after starting pazopanib, the patient developed a holoccephalic headache and left-sided weakness, leading to a fall. A non-contrast CT brain revealed a 5.8 cmx3.5 cmx3.8 cm right occipital intracerebral haemorrhage with surrounding oedema and 9 mm of midline shift (figure 1). Imaging also revealed a right holohemispheric subdural hematoma measuring 5 mm in maximal thickness, likely due to her fall. From February 2016 until admission, the patient's systolic blood pressure ranged from 140 to 150 mm Hg, and she was compliant with her home losartan-hydrochlorothiazide 100–12.5 mg daily and doxazosin 4 mg every night. However, blood pressure at presentation was 204/92 mm Hg, and continued to range from 180 to 200 systolic while she was in the emergency department. Persistently elevated blood pressure required initiation of a nicardipine continuous infusion. Laboratories were notable for normal renal function, a platelet count of 114 000/ μ L, and normal coagulation studies. The patient was on aspirin 325 mg daily but not on any anticoagulants. According to institutional neurosurgical practice, one unit of platelets was transfused to mitigate aspirin-induced platelet dysfunction. She was also started on 3% hypertonic saline. She also received dexamethasone 20 mg intravenous at presentation given initial concern for haemorrhagic metastasis. She received a computed tomography (CT) angiogram of her brain with and without contrast, which did not show a vascular malformation. A traumatic aetiology for her intracerebral haemorrhage was felt to be unlikely given the absence of bone fracture or contrecoup haemorrhage. A hypertensive aetiology was also felt to be unlikely because haemorrhages due to hypertension typically occur in the basal ganglia, thalamus, pons or cerebellum and are not usually lobar.

The patient was transferred to the neurointensive care unit (NICU) for further management. An MRI brain with and without contrast did not reveal a contrast-enhancing lesion suggestive of metastasis. However, T2/FLAIR cortical and subcortical hyperintensities in the contralateral (left) occipital region represented oedema without associated haemorrhage (figure 1). Bilateral oedema in the posterior regions of her brain strongly supported a diagnosis of PRES as opposed to haemorrhagic metastasis or

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To cite: Miller-Patterson C, Fehnel CR. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2016-218221

Figure 1 (A) Axial CT brain without contrast showing right occipital haemorrhage. (B) Axial FLAIR MRI brain without contrast showing left occipital oedema without associated haemorrhage (arrow).

other possible causes of intraparenchymal haemorrhage, such as amyloid angiopathy or trauma. This was corroborated by persistently elevated blood pressure above her baseline. Dexamethasone and pazopanib were discontinued, and her oncologist planned to initiate an alternative immunotherapeutic agent on follow-up. She was transferred to the neurology floor once she was weaned off hypertonic saline.

On the neurology floor, the patient continued to have persistent hypertension, requiring continuous nicardipine infusion. A renal ultrasound did not show evidence of renal artery stenosis. Her blood pressure was eventually well controlled with maximisation of several antihypertensive agents. However, she subsequently became lethargic, prompting a repeat CT brain without contrast. This revealed that the subdural hematoma had developed into an enlarged hygroma, with 15 mm of right-to-left midline shift and subfalcine herniation. She was transferred back to the NICU. Neurosurgery evacuated the hematoma, which was sent to pathology for immunohistochemical staining. Stains for renal cell carcinoma antigen, CA IX and PAXB, were all negative, further supporting our suspicion that the patient's haemorrhage was not due to metastatic renal cell carcinoma. The patient's mental status subsequently improved, and she did not have any significant focal neurologic deficits when discharged.

INVESTIGATIONS

- ▶ CT and CT angiography of the head
- ▶ MRI with and without gadolinium of the head
- ▶ Electroencephalogram
- ▶ Immunohistochemistry for renal cell carcinoma antigen

DIFFERENTIAL DIAGNOSIS

- ▶ Haemorrhagic cerebral metastasis
- ▶ Amyloid angiopathy
- ▶ Trauma-associated haemorrhage

TREATMENT

- ▶ Cessation of apparent offending agent (pazopanib)
- ▶ Blood pressure control
- ▶ Hypertonic saline administration for cerebral edema
- ▶ Decompressive hemicraniectomy

OUTCOME AND FOLLOW-UP

The patient followed up with her oncologist, who started her on a new immunotherapeutic agent, nivolumab, at a dose of 240 mg

Figure 2 Axial sections of patient's follow-up MRI brain, which show ring-enhancing lesions with surrounding vasogenic oedema suspicious of metastatic disease (arrows).

intravenous every 2 weeks. Nivolumab is an IgG4 antibody to programmed cell death-1 (PD-1) expressed on the surface of T cells. PD-1 binds programmed cell death-ligand 1 (PD-L1), which inactivates T cells. PD-L1 is expressed by renal cell carcinoma to prevent T cells from attacking the tumour, so nivolumab was chosen because it is a second-line agent for renal cell carcinoma when an antiangiogenic agent has failed. She also saw a neurologist and neurosurgeon as an outpatient. She received a repeat MRI brain with and without gadolinium approximately 3 months after her prior MRI, which showed encephalomalacia in the region where she had the haemorrhage. However, it also showed new rim-enhancing lesions with surrounding vasogenic oedema in the right frontal lobe and left parietal lobe, locations separate from where she had the haemorrhage. On the basis of these radiographic findings, the patient was diagnosed with metastatic disease to her brain (figure 2). She was referred to a radiation oncologist, who plans on initiating gamma knife radiosurgery. She was also referred to a neurooncologist, who plans to obtain an MRI of the spine to ensure that there is no evidence of spinal metastasis and a repeat MRI brain at an interval of 6–8 weeks from radiation. Further systemic treatments are being considered. Her Karnofsky Performance Status is 80%, ECOG grade is 1 and extracranial disease is currently stable.

DISCUSSION

PRES was first defined by Hinchey et al.¹ It is a syndrome that is diagnosed radiographically in the appropriate clinical context, with presenting symptoms, including seizures, headache and visual loss. On imaging, it is characterised by symmetric white matter oedema, typically in the parieto-occipital regions, which is reversible after stopping the inciting factor. Disruption of cerebral autoregulation and endothelial dysfunction both likely play a role in pathogenesis. Cerebral autoregulation involves arteriolar vasoconstriction in response to high blood pressure so as to maintain an appropriate cerebral blood flow. When blood pressure is above the limit of cerebral autoregulation, vasodilation occurs, leading to extravasation of blood products into white matter parenchyma. Direct toxic effects on endothelial cells likely lead to blood–brain barrier breakdown and subsequent vasogenic oedema.¹ Haemorrhage is believed to occur either due to arterial rupture secondary to significantly elevated blood pressure or postischemic reperfusion injury.² While commonly associated with hypertension and eclampsia,

a number of chemotherapeutic and immunosuppressive agents have also been linked to PRES.³ Renal impairment has also been associated with the syndrome.⁴ Treatment of PRES involves addressing the inciting aetiology; for example, lowering blood pressure when hypertension is present or stopping the inciting chemotherapeutic or immunosuppressive agent.⁵

Tyrosine kinase inhibitors that have been associated with PRES are thought to induce the syndrome through disruption of cerebral autoregulation. This is likely via hypertension and/or direct endothelial injury. Notably, these reported tyrosine kinase inhibitors partially exert their antitumour effect through inhibition of vascular endothelial growth factor receptor (VEGFR) and, in turn, angiogenesis.⁶ Although the exact mechanism is unclear, vascular endothelial growth factor receptor (VEGFR) inhibition has been theorised to play a prominent role in the development of PRES in these agents because VEGFR inhibition leads to endothelial dysfunction, which, in turn, leads to capillary leakage and cerebral oedema.⁷ The role of VEGFR inhibition is supported by one report of a patient who developed PRES without a significant change in blood pressure while on bevacizumab, which is a monoclonal antibody that also inhibits VEGFR.⁸

Pazopanib is an oral tyrosine kinase inhibitor targeting VEGFR, platelet-derived growth factor receptor and c-Kit. It is typically given at a dose of 800 mg daily for both renal cell carcinoma and soft tissue sarcoma. Several case reports have already associated pazopanib with the development of PRES, although none of them were associated with intracerebral haemorrhage. In the first reported case, the patient presented with a seizure after 3 weeks of pazopanib therapy for renal cell carcinoma.

She had elevated blood pressure (up to 165 systolic) and had an MRI of her brain which showed bilateral parieto-occipital oedema.⁹ In the second case, the patient presented 1 month after starting the drug with headache and nausea. He had a peak systolic blood pressure of 219 mm Hg and MRI brain showed bilateral parieto-occipital oedema.⁷ In the most recent case, the patient presented with seizures and left arm paresis 8 weeks after starting pazopanib. He had a peak systolic blood pressure over 300 mm Hg and his MRI brain showed left parietal oedema.¹⁰ Similar to these cases, symptoms in our patient developed several weeks after starting the drug, and blood pressure on arrival was significantly elevated above baseline (peak systolic 204 from a baseline systolic 140–150). However, none of these cases were associated with haemorrhage. The patient had normal renal function, and a renal ultrasound eliminated renal artery stenosis as a potential contributor to her persistent hypertension. Therefore, our case supports the idea that significant hypertension and, subsequently, dysfunction of cerebral autoregulation is a major contributor to the development of PRES in patients who are initiated on oral pazopanib. As discussed previously, this significant hypertension likely led to haemorrhage via either arterial rupture or post-ischaemic reperfusion injury.

Contributors CMP wrote the manuscript and prepared the figure. CRF provided edits to and suggestions for the manuscript, which were incorporated.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Patient's perspective

Sometimes I feel very confused because I'm seeing one doctor after another and I don't remember who is doing what.

Learning points

- ▶ More frequent and intensive blood pressure control may help prevent pazopanib-associated posterior reversible encephalopathy syndrome (PRES) and intracerebral haemorrhage.
- ▶ Pathogenesis in pazopanib-induced PRES likely involves significant elevations in blood pressure above the limit of cerebral autoregulation, leading to extravasation of blood products into white matter parenchyma.
- ▶ While the neurologic deficits in PRES are generally reversible, pazopanib-induced PRES can be associated with intracerebral haemorrhage, which may lead to permanent neurologic deficits or even death.

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