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Posterior Reversible Encephalopathy Syndrome Induced by Pazopanib in a Patient with Soft-Tissue Sarcoma: A Case Report

Chien-Ting Wu, Chieh-Tsung Yen, Hsiu-Lan Cheng, Chi-Hui Lee

Department of Pharmacy, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan
Email: xelox78123@gmail.com

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Abstract

Posterior reversible encephalopathy syndrome (PRES), a rare disease is characterized by multiple neurological complications. It has been reported to be associated with the use of angiogenesis inhibitors such as sorafenib, sunitinib, pazopanib, regorafenib, and lenvatinib. We reported a case of 76-year-old woman with history of stage III hepatocellular carcinoma (HCC), who developed adverse drug reactions related to pazopanib induced PRES. Pazopanib, an angiogenesis inhibitor which inhibits the vascular endothelial growth factor (VEGF) pathway may lead to vascular endothelial damage, and these pathophysiological changes may lead to vascular leaks and brain edema. Medical staff must be aware of the possible association between angiogenesis inhibitors and the development of PRES. In patients with retroperitoneal soft-tissue sarcoma undergoing treatment with pazopanib, regular monitoring of their blood pressure and following-up brain magnetic resonance imaging (MRI) should be encouraged.

Keywords

Posterior Reversible Encephalopathy Syndrome, Pazopanib, Hepatocellular Carcinoma, Vascular Endothelial Growth Factor, Magnetic Resonance Imaging

1. Introduction

Posterior reversible encephalopathy syndrome (PRES) is a rare disease, which is characterized by multiple neurological complications [1] such as seizures and hypertensive emergencies [1] [2]. Commonly clinical manifestations of PRES include severe headache, confusion, seizures and visual disturbances, as

well as signs of symmetrical white matter edema [3] under brain magnetic resonance imaging (MRI) study [1]. In the last few years an increased number of case reports involving new targeted drugs, particularly angiogenesis inhibitors such as sorafenib, sunitinib, pazopanib [4], regorafenib [5], lenvatinib [6] and other targeted drugs have been implicated in new cases of PRES [3]. This case represented a patient with hepatocellular carcinoma (HCC) under pazopanib using that developed multiple clinical adverse reactions including signal change under MR image study, which elicits highly suspicious of pazopanib induced PRES.

2. Case Presentation

We present the case of a 76-year-old woman, who has history of stage III hepatocellular carcinoma (HCC), and ureter tumor s/p left nephrectomy and ureterectomy. She also has underlying medical illness such as diabetes and end stage renal disease under regular hemodialysis three times a week in the San Joseph's Hospital. Her HCC and bladder tumor was under regular medical follow-up in the Chia Yi Christian hospital. The HCC was under medication controlled with pazopanib 400 mg BID PO since Oct. 26, 2017, and combined with oral drugs at home since Oct. 7, 2017 (shown in **Table 1**). At 7 o'clock on Oct. 29, the patient was found having four limbs generalized myoclonic movement accompanied with upward gazing with the duration persisted for about 5 minutes at home, and she was then brought to our hospital for medical attention. Her consciousness became drowsy after arrival of the paramedical and similar episode attacked again in the ambulance. She never has any previous history of seizure attack neither fever, chills nor headache. At the ER, her vital signs (T/P/R) were 36.6/98/19 and the NBP was 93/77 mmHg, the neurologic examination demonstrated isocoric pupils with size about 2.5 mm, both reactive to the light, and the muscle power of four limbs were three fractions. Under the impression of myoclonic seizure, 2 mg lorazepam was stat given with intravenous drip, 1000 mg levetiracetam was loading intravenously, and CNS dose ceftriaxone was administrated, and she was admitted into the medical intensive care unit for close monitoring. The MRI obtained on Oct. 30, 2017 revealed multiple high signal change with edematous areas over subcortical region of frontoparietal lobe, periventricular region, occipital lobe, splenium, and hemisphere of cerebellum (**Figure 1**). Owing to the symptoms associated with acute changes in consciousness and seizures, along with exacerbated systemic hypertension (shown in **Table 2**), PRES associated with the use of pazopanib was highly suspected, and pazopanib was discontinued on Oct. 11, 2017. Under the impression of PRES with associated clinical symptoms, she was treated with the anti-convulsant (levetiracetam 500 mg TID PO and clonazepam 0.5 mg HS PO) continuously for more than 1 month, and simultaneously anti-hypertensive drugs were administrated (continuously intravenous infusion of nicardipine for two days, followed by intravenous labetalol, and then switch to amlodipine orally) for keeping systolic blood pressure

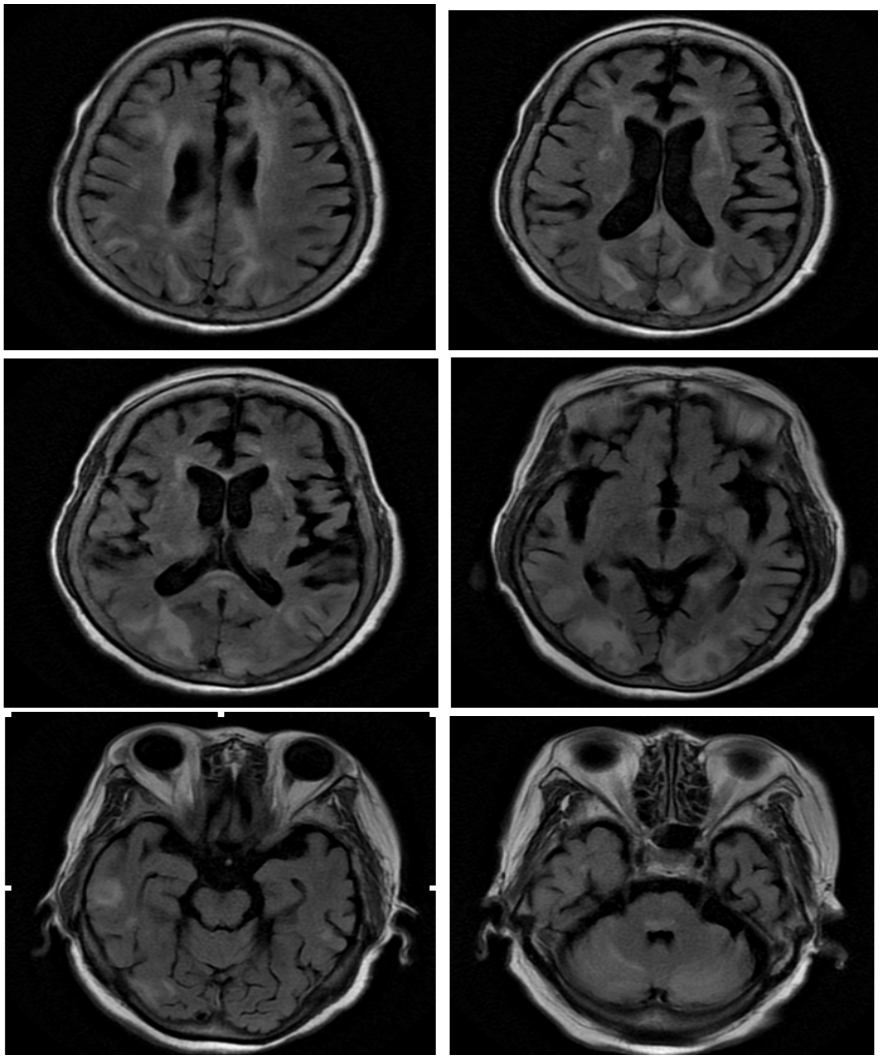

Figure 1. Brain MR images revealed hyper-intense signals over subcortical region of bil. frontoparietal lobe and periventricular area (top 2 figure), splenium (mid. left), and bil. occipital lobes (mid. right), right lateral-temporal lobe (bottom left), and dorsal pons, as well as bil. hemisphere of cerebellum (bottom right) in the patient with PRES.

Table 1. Daily oral drugs before PRES presentation with the patient.

Name of Drugs	Dosage	Frequent	Oral Route
Pazopanib	400 mg	BID	PO
Thiamine & Riboflavin	50 & 5 mg	QD	PO
Folic Acid	5 mg	QD	PO
Famotidine	20 mg	BID	PO
Calcitriol	0.75 mcg	QW135	PO
Cortisone	25 mg	QD	PO
Clonazepam	0.25 mg	TID	PO
Clonazepam	0.5 mg	HS	PO

Table 2. Daily vital sign in the patient with PRES within the seventh hospital day.

Date	Time	Temperature (˚C)	Pulse Rate (min)	Respiratory Rate (min)	Blood Pressure (mmHg)
10/29	1100	36.5	98	21	175/89
	1600	36.5	100	22	191/100
	2100	37.2	92	20	189/96
10/30	900	36.5	80	20	166/85
	1300	36.6	66	16	168/85
	2100	35.7	79	18	109/61
10/31	900	36.5	90	16	150/67
	1300	36.3	96	16	131/68
	2100	36.6	76	16	135/69
11/1	900	37	88	15	160/71
	1300	37	78	15	120/58
	2100	36	80	18	147/69
11/2	900	36.7	81	20	116/67
	1300	36.4	79	18	121/65
	2100	36.8	83	19	145/76
11/3	900	36.5	72	18	109/60
	1300	36.2	65	18	104/50
	2100	36.7	76	21	131/57
11/4	900	37.1	77	18	109/64
	1300	37.2	73	22	113/56
	2100	36.6	78	20	138/66

around 100 to 130 mmHg. Her symptoms were gradually improved on the fifth hospital day. Due to advanced blood pressure control, she completely regained consciousness with gradually symptom improved on the fifth hospital day, and there was no subsequently new onset neurologic deficits nor clinical seizure attack on the following days, and she was discharged on Oct. 27, 2017. The anti-epileptic drugs such as levetiracetam and clonazepam were continued for symptoms control after discharge.

3. Discussion

After reviewing medication profile and further analyzing with reference of relevant literatures, we suspected PRES associated with the use of pazopanib. PRES, which can be fatal, was reported in patients who received pazopanib. Pazopanib should be permanently discontinued if patients associated with the development of PRES [7]. Pazopanib is an oral tyrosine kinase inhibitor (TKIs) that blocking vascular endothelial growth factor (VEGF), platelet-derived growth factor receptor and c-Kit signaling to inhibit the proliferation of tumor cells, and is ap-

proved for use in advanced renal cell carcinoma and soft-tissue sarcoma, currently [2] [8]. Pazopanib significantly improved the progression-free survival (PFS) of patients with soft tissue sarcoma, but 41% of patients will cause hypertension, acute and severe hypertension may cause vasodilation and imbalance of brain auto regulation (disruption of cerebral autoregulation), which causes a breakdown of the blood-brain barrier [1]. In Neurologic effects, 10% of patients cause headaches, confusion, seizures, and visual impairment. Inhibition of the VEGF pathway may lead to vascular endothelial damage, and these pathophysiological changes may lead to vascular leaks and brain edema, which seriously causes PRES [1]. The hallmark of PRES in the majority of the cases of clinical symptoms and brain imaging findings, usually occurs within days to weeks. The major adverse events include: malignant hypertension, preeclampsia, eclampsia and some post-transplant drug treatments (tacrolimus and cyclosporine) or autoimmune disease [3]. In a typical case, angiogenic edema in the apical and posterior frontal lobes is usually seen on the neuroimaging [1] [3]. On vascular images, there are often diffuse vasoconstriction, irregular or partial vasoconstriction of blood vessels, and vasodilation [2] [9]. In a randomized, double-blinded, controlled study of soft tissue sarcoma treatment, the results found that approximately 42% of patients with soft tissue sarcoma who received pazopanib associated with the development of hypertension (systolic blood pressure > 150 or diastolic blood pressure ≥ 100 mmHg) and hypertensive crisis. Hypertension occurs early in the course of treatment (40% of cases occurred before the 9th day, 90%) [10]. The case occurred within the first 18 weeks), so blood pressure should be monitored early after starting treatment (not more than one week), 4% to 7% of patients receiving pazopanib which have grade 3 hypertension; approximately 1% of patients who received pazopanib permanently discontinued treatment due to hypertension [10]. In the literature, an initial goal of blood pressure reduction not more than 25% within several hours of the onset of PRES using continuous intravenous administration of anti-hypertensive agents was recommended [11]. PRES should be considered as the actual reason for neurologic findings in hypertensive patients with metastatic cancers under TKI therapy. As with other conditions, fluctuations of blood pressure should be avoided and the continuous administration of antihypertensive drugs should be considered under hemodynamic monitoring [12]. In our case, we have been closely monitoring her blood pressure during hospitalization for this patient with end stage renal disease under regular hemodialysis.

4. Conclusion

According to the Naranjo algorithm, the PRES was probably related to pazopanib usage, we concluded that pazopanib has probably caused the adverse reactions (Naranjo Algorithm Score of 5) in this patient (shown in **Table 3**). Medical staff must be aware of the possible association between angiogenic inhibitors therapy and the development of PRES. In patients undergoing treatment with

Table 3. Naranjo algorithm.

Naranjo Algorithm: Pazopanib				
Question	Yes	No	Do Not Know	Score
1) Are there previous conclusive reports on this reaction?	+1	0	0	
2) Did the adverse event appear after the suspected drug was administered?	+2	−1	0	
3) Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4) Did the adverse event reappear when the drug was re-administered?	+2	−1	0	
5) Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	
6) Did the reaction reappear when a placebo was given?	−1	+1	0	
7) Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8) Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9) Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10) Was the adverse event confirmed by any objective evidence?	+1	0	0	
			TOTAL	5

pazopanib, regular monitoring of their blood pressure and follow-up with brain MRI should be encouraged.

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Conflicts of Interest

None to declare. Each author certifies that he or she has no financial organization (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article. There are no other conflicts of interest. The case described in the article was performed with funding from Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chia-Yi, Taiwan.

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