PRES—a potential side effect of gemcitabine

Niyati Modi, MD,[1] and Dulabh Monga, MD[2,3]

[1]Department of Internal Medicine; [2]Temple University of School of Medicine; [3]Division of Hematology Oncology, Allegheny General Hospital, Pittsburgh, Pennsylvania

A 50-year-old woman presented to her primary care physician with abdominal pain and jaundice. Computed tomographic (CT) scan of the abdomen revealed a pancreatic head mass. Exploratory laparotomy showed a tumor obstructing the duodenum and encasing the portal vein and superior mesenteric artery, deeming it unresectable. Biopsies confirmed it to be an adenocarcinoma with mucinous differentiation.

The patient received concurrent chemo- and radiation therapy with oral capecitabine. The follow-up CT scan revealed a decrease in the size of the pancreatic head mass. Subsequently, she received palliative chemotherapy with gemcitabine 1000 mg/m^2 on days 1, 8, and 15, every 28 days with erlotinib 100 mg orally daily. Following day 1 of cycle 5 gemcitabine (5.5 months after discontinuation of concurrent capecitabine and radiation), she developed tonic-clonic seizures and was admitted to the hospital. The results of the CT scan of the head mass that was performed during this admission were unremarkable, and she was discharged on an antiepileptic. However, she continued to manifest headaches with photophobia. She presented to the emergency department 1 week later with recurrent tonic-clonic seizures, and was obtunded and hypertensive. A repeat CT scan of the head was negative for metastatic lesions. Brain magnetic resonance imaging (MRI) with and without gadolinium revealed interval development of extensive signal abnormality in the subcortical white matter of the bilateral occipital, posterior parietal, and superior frontal lobes involving watershed territories characteristic of posterior reversible encephalopathy syndrome (PRES; Figure 1).

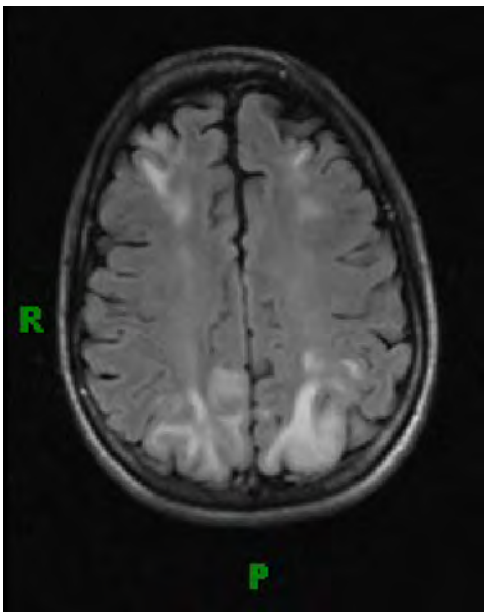

FIGURE 1 Brain magnetic resonance imaging with and without gadolinium revealed interval development of extensive signal abnormality that was characteristic of PRES.

Cerebrospinal fluid examination was negative for meningitis and leptomeningeal involvement. Herpes simplex virus polymerase chain reaction was negative.

Paraneoplastic syndrome was considered in the differential diagnosis, but was ruled out after rapid reversibility of symptoms and classic MRI findings.

The patient's mental status improved on the second day of her hospital admission without any new seizures. She remained stable, and gemcitabine and erlotinib were discontinued. A repeat MRI 4 weeks later showed almost complete resolution of lesions (Figure 2).

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Correspondence to: Niyati Modi, MD, Hospital Medicine, Allegheny General Hospital, 320 East North Avenue, Pittsburgh, PA 15212; e-mails: modi_niyati@yahoo.com, dmonga@wpahs.org.
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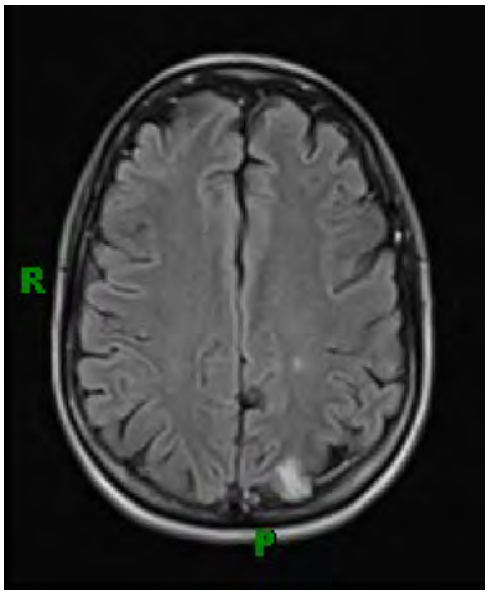

FIGURE 2 Magnetic resonance image 4 weeks after the discontinuation of gemcitabine and erlotinib shows greatly reduced evidence of lesions.

Gemcitabine and PRES

PRES is a rare but reversible clinicoradiologic syndrome that is characterized by headache, visual disturbances, hypertension, drowsiness, stupor, and seizures.[1,2] The most common attributing factors are hypertensive encephalopathy, preeclampsia/eclampsia, chemotherapeutic/immunosuppressive drugs, and renal failure.[1-3]

The pathogenesis of PRES is controversial. The most accepted hypothesis is the hyperperfusion or vasodilatation theory, in which severe hypertension results in disruption of cerebral autoregulation, which leads to extravasation of fluid and cerebral edema.[2-4] Although severe hypertension has been noted with the development of PRES, this syndrome has been observed in normotensive patients.[4] This may be due to the hypoperfusion or vasoconstriction theory that results in cerebral ischemia. The mechanism by which chemotherapeutic agents can cause PRES is less clear. Possibly, a direct cytotoxic or immunogenic effect on brain capillary endothelial cells leads to disruption of the blood-brain barrier.[4]

The first case of PRES resulting from gemcitabine was identified in 2001.[5] PRES is fully reversible within a period of days to weeks of discontinuing gemcitabine. However, fatalities and permanent neurological disabilities, especially in association with cerebral infarction or hemorrhage, have been reported in cases of PRES.[2]

Conclusion

Gemcitabine is a widely used chemotherapeutic agent in an array of malignancies. Thus, it is relevant for oncologists to consider PRES in the differential diagnosis in the setting of acute onset of neurological symptoms. A high index of suspicion would ensure complete reversibility of neurological deficits upon discontinuation of the drug.

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