FATAL INTRACRANIAL HEMORRHAGE WITH HIF-2α INHIBITOR, BELZUTIFAN IN VON HIPPEL-LINDAU DISEASE-ASSOCIATED HEMANGIOBLASTOMA

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INTRODUCTION

Von Hippel-Lindau (vHL) disease is an inherited condition caused by germline mutation in the VHL gene. The principal manifestations are hemangioblastomas in the central nervous system (CNS), retina, renal cell carcinoma (RCC), pheochromocytomas, tumors of the pancreas and endolymphatic sac. CNS hemangioblastomas are commonly located in the cerebellum (45%) and spinal cord (36%) (1). Surgical resection is the mainstay of treatment, but radiation therapy is an option for lesions not amenable for surgery and to reduce morbidity. There has been no systemic therapy available in vHL-associated hemangioblastoma until the approval of a hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor, belzutifan (2,3). The approval is based on the LITESPARK-004 trial (4). The common adverse events were grade 1 and 2 anemia, fatigue, dizziness, and headache. The only intracranial hemorrhage (ICH) reported was a single grade 2 event. No patient had grade 4 or 5 adverse events. We present a case of a patient with vHL-associated recurrent multiple CNS who experienced fatal ICH shortly after initiation of hemangioblastomas belzutifan.

MATERIALS & METHODS

Information was mainly obtained from chart review.

REFERENCES


CASE REPORT

Patient is a 62-years old woman with a genetically confirmed VHL disease. She initially underwent nephrectomy for RCC at age 55. Two years after her initial presentation, she presented with headache, vertigo and was diagnosed with right cerebellar hemangioblastoma, World Health Organization (WHO) grade 1, which was completely resected. Two separate small hemangioblastomas at the dorsal and dorsolateral surface of the medulla were not resected due to the risk of morbidity. Magnetic resonance imaging (MRI) also demonstrated intrathecal 1-2 mm nodules at L1, L2 and L3, presumed to be hemangioblastoma. There was no growth of the lesions for four years. Subsequent MRI after 16 months showed that both lesions increased in size, measuring 1.6 cm lesion in the right dorsolateral surface of the medulla and 0.4 cm lesion in the dorsal surface (Figure 1). There were two smaller new lesions in both cerebellopontine angles. Due to asymptomatic progression of multiple lesions, she was started on belzutifan 120 mg daily. Aside from mildly elevated blood urea nitrogen (23 mg/dl) and creatinine (1.34 mg/dl) levels, basic counts were normal prior to initiating therapy. Five days after treatment initiation, the patient experienced sudden headache, vomiting, and loss of consciousness. She had absent brainstem reflexes at presentation. Vital signs were significant for elevated blood pressure of 202/103 mm Hg. Laboratory studies showed normal platelet count (173,000 k/ul) and no evidence of coagulopathy (International normalized ratio 0.9, prothrombin time 11.2 seconds, and partial thromboplastin time 28 second). Electroencephalogram showed burst suppression pattern. Head computed tomography scan (CT) revealed a large hemorrhage within the right cerebellum, in the region of the enlarging hemangioblastomas. There was subarachnoid and intraventricular extension of hemorrhage with obstructive hydrocephalus (Figure 2). Her family decided against surgical evacuation and pursued comfort care. The patient expired three days after ICH presentation.

DISCUSSION

We believe that our patient is the first documented case of a fatal ICH in a patient with VHL-associated CNS hemangioblastoma treated with belzutifan. Hemangioblastomas have a very low spontaneous bleeding risk. Hence the bleeding in this patient is likely secondary to the intrinsic nature of the tumor. Thus, it is important to recognize that grade 4 or 5 ICH is a significant adverse event associated with belzutifan and needs to be discussed with the patient prior to initiating treatment.

Figure 1: Brain MRI performed four years after complete resection of right cerebellar hemangioblastoma, three months prior to starting belzutifan. A. T1 Pre-contrast, B. Susceptibility Weighted Imaging (SWI), C. FLAIR, D. T1 Post-contrast MR images showed a FLAIR hyperintense enhancing mass measuring 1.6 x 1.3 cm on the right dorsolateral surface of the medulla with no surrounding vasogenic edema. No acute hemorrhage noted on T1-precontrast study. There was a peripheral without intratumoral hemosiderin signal noted on SWI images. T1 post-contrast images showed smaller enhancing masses in the right cerebellopontine (CP) angle measuring 1.0 x 0.81 cm (E), left CP angle 1.0 cm (F), and dorsal surface of the medulla 0.4 cm (G)

Figure 2: Head CT performed 5 days after initiation of belzutifan. Axial (A). Head CT without contrast demonstrated a large right-sided posterior fossa hemorrhage. Severe perifocal mass effect and effacement of the fourth ventricle. There was intraventricular extension of hemorrhage and obstructive moderate hydrocephalus.