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Epithelioid glioblastoma presenting as massive intracerebral hemorrhage: Case report and review of the literature

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Abstract

Background: Glioblastoma multiforme (GBM) is a malignant transformation of glial tissue, which presents as intradural, intraaxial lesions with heterogenous contrast enhancement and mass effect. Intratumoral hemorrhage is a common finding in GBM although it is frequently asymptomatic. Massive, symptomatic, intratumoral hemorrhage is uncommon and poses a diagnostic challenge.

Case Description: Here we discuss a case of GBM, which initially presented as massive, symptomatic intracerebral hemorrhage with underlying mass. Due to size of the hemorrhage and poor neurological status the patient was taken to the operating room for evacuation of this hematoma. On pathology, the mass was found to be epithelioid glioblastoma.

Conclusion: Identification and diagnosis of GBM is generally straightforward. In certain circumstances, the presentation of GBM can vary from the routine. The above case demonstrates how pitfalls in diagnosis can be avoided in order to initiate appropriate therapy.

Key Words: Epithelioid, glioblastoma, intratumoral hemorrhage

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INTRODUCTION

Glioblastoma multiforme (GBM) is the most extreme malignant transformation of glial tissue and also most common, accounting for approximately 60% of gliomas and 40% of all primary brain neoplasms. Classically, GBMs appear as poorly defined intradural, intraaxial lesions with heterogenous contrast enhancement and mass effect. There is a propensity to involve and spread along white matter tracts and deep structures.[23] GBMs can present with intracerebral hemorrhage, intraventricular hemorrhage, or ischemic stroke; they can also mimic arteriovenous malformations and cerebral contusions in their presentation.[5,8,14,17,18] Although GBMs frequently have evidence of intratumoral hemorrhage, this is typically limited and asymptomatic the vast majority of the time. Massive, symptomatic intracerebral hemorrhage (ICH) is an infrequent presentation estimated to occur in only 5% of instances of intratumoral hemorrhage.[16] There can be a significant amount of confusion regarding recognition of underlying tumor in these situations and misdiagnosis may lead to delayed therapy. Here, we present a rare and unique case of GBM masquerading as massive ICH and pertinent review of the literature.

CASE REPORT

History

This 66-year-old African American woman presented with insidious onset of headaches followed by acute onset right-sided weakness and somnolence. She had a history of hypertension and a remote history of breast cancer with prior mastectomy.

Examination

The patient presented to the emergency department of Houston Methodist Hospital and was intubated on arrival for airway protection. Her pupillary exam revealed bilateral reactive pupils with symmetric size of 4 mm. Her motor exam revealed monoplegia of her right arm. She exhibited spontaneous movement of her left side and to a lesser extent her right leg.

Diagnostic imaging

Admission CT scan showed a large (8 × 4.5 cm) parenchymal hematoma in the left temporal lobe extending into the frontal lobe, basal ganglia, and insula. There was evidence of a blood-fluid level within the hemorrhage and midline shift of 8 mm from left to right. Subfalcine and uncal herniation were also present [Figure 1a]. An MRI of the brain with and without contrast was obtained and showed a lobulated enhancing hemorrhagic mass in the left anterior temporal lobe attached by a stalk to the left insula with surrounding vasogenic edema. Acute hemorrhage posterior to the mass was also seen with blood-fluid levels filling a thin-walled cystic space in the left temporal lobe and left inferior frontal lobe [Figure 1b-h]. CT angiograms of the head and neck were performed showing no evidence of a vascular lesion.

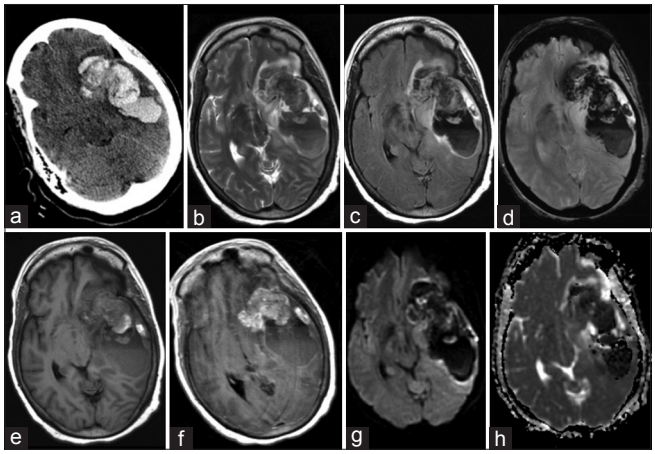

Figure 1: Epithelioid glioblastoma. (a) Noncontrast head CT shows a large parenchymal hemorrhage centered in the left temporal lobe and significant mass effect on surrounding brain, including left uncal herniation. Brain MRI with (b) T2 FSE, (c) T2 FLAIR, (d) GRE, (e) pre- and (f) post-contrast T1 FSE images demonstrates a lobulated enhancing hemorrhagic mass in the left anterior temporal lobe attached by a stalk to the left insula, moderate surrounding edema, and central vascular flow voids from the left middle cerebral artery. Acute hemorrhage with blood-fluid levels fills mostly a thin-walled cystic space posterior to the mass in the left temporal lobe as well as a smaller region in the left inferior frontal lobe. (g) DWI and (h) ADC map show a region of reduced diffusion medial to the mass within the left insula, probably infiltrative hypercellular tumor or acute ischemia from the mass

Operation

The patient underwent a left frontotemporal craniotomy for evacuation of the hematoma and associated mass. The dura was opened in a c-shaped fashion and a corticectomy was performed through the inferior temporal gyrus as we were on the dominant hemisphere. A large clot was immediately encountered and evacuated to decompress the surrounding brain and relieve mass effect. This continued until all evident clot had been removed; there was no gross evidence of tumor at the time of surgery due to the significant amount of hemorrhage.

Pathologic findings

Microscopically, there were perivascular sheets of markedly atypical epithelioid cells with pleomorphic nuclei and frequent multinucleation. Brisk mitotic activity and abundant apoptotic bodies were seen. Prominent microvascular proliferation and many blood vessels with organizing thrombi were also noted. Recent hemorrhage was seen in the background [Figure 2].

Immunohistochemically, the tumor cells were positive for glial fibrillary acidic protein (GFAP) [Figure 3] and S-100 protein. Pancytokeratin, HMB-45, and Melan-A were negative. These histological features as well as immunohistochemical profile were consistent with a diagnosis of epithelioid glioblastoma.

DISCUSSION

Hemorrhage associated with glioblastoma

Clinically overt hemorrhage from brain tumors is an infrequent but clinically significant phenomenon. Wakai

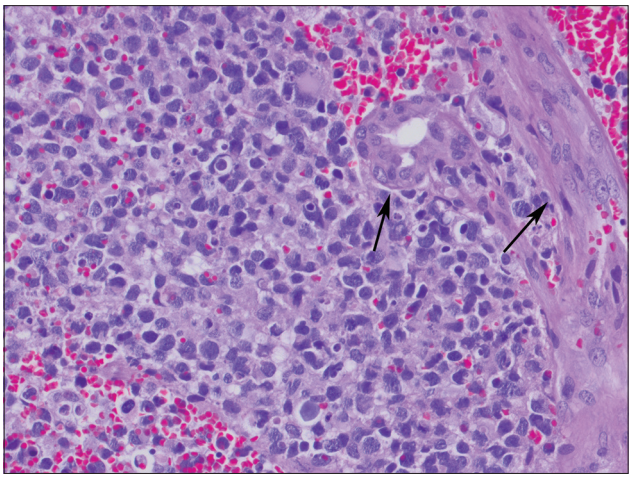

Figure 2: Diffuse sheets of markedly atypical epithelioid cells with pleomorphic nuclei are noted in a hemorrhagic background. Prominent microvascular proliferation is seen (arrows)

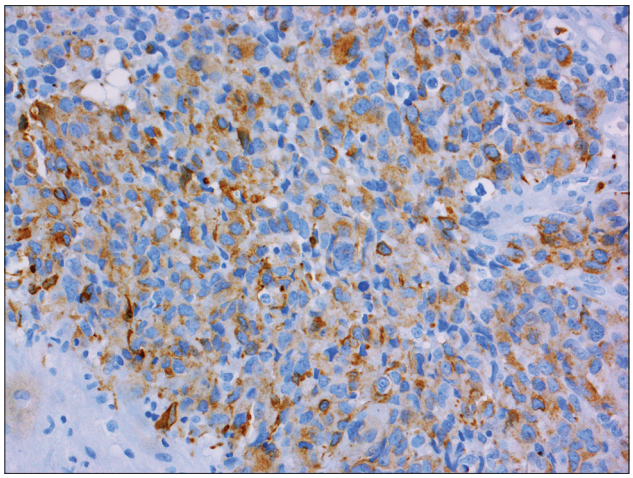

Figure 3: Glial fibrillary acidic protein immunohistochemical stain reveals cytoplasmic positivity in tumor cells

and colleagues estimated that the rate of hemorrhage from brain tumors is approximately 5.1 percent based on a series of 1861 cases. Pituitary adenomas were found to hemorrhage most often. Of the 129 cases of GBM in this series, there were 10 cases where hemorrhage was present. The extent of hemorrhage was not detailed but cases of microscopic and macroscopic hemorrhage were included.[21] Kondziolka and colleagues completed a similar study finding that the hemorrhage rate of all tumors excluding pituitary adenoma was 14.6 percent in a series of 905 patients. There were 264 cases of GBM in this series; 17 of these cases had macroscopic hemorrhage and 34 of these cases had microscopic hemorrhage. Hypertension and the use of anticoagulants were not found to be associated with a higher risk of hemorrhage from tumor in this study.[13] Little and colleagues presented a series of 15 patients with ICH due to brain tumor. GBM was found to occur in 7 of the 15 cases.[15] Schrader and colleagues reported 50 cases of ICH due to neoplasm in a series 2041 patients with confirmed tumor and 692 patients with ICH. Of these 50 cases, 18 were metastatic lesions and 15 were WHO grade IV GBM. Interestingly, the authors suggested that neoplasm may be responsible for as high as 10% of all cases of ICH when considering only cases of ICH where the patient undergoes surgery.[19] It is often not possible to determine the etiology of an intraparenchymal hemorrhage by history and imaging alone. Given this data, it would be prudent to send a pathologic specimen in cases of idiopathic ICH that require surgical evacuation.

Location of hemorrhage, irregular shape, and surrounding edema can be utilized to distinguish between tumor associated hemorrhage and hemorrhage from other causes. Hematomas due to GBM are located more peripherally in the cerebral hemispheres. Other atypical locations for hemorrhage due to any neoplasm include the dural membranes and close proximity to major cerebral veins and sinuses.[15,19] Surrounding edema is a common characteristic of hemorrhage secondary to neoplasm. Edema is generally absent in the acute phase of spontaneous ICH but frequent in growing lesions such as tumors.[19] On CT imaging, hemorrhage due to tumor can have varying density in the central region with multiple punctate hemorrhages in periphery.[24] Hemorrhage of varying ages may also be encountered in the setting of neoplasm.[7] MRI is of great assistance when differentiating spontaneous ICH and tumor hemorrhage but not always immediately available.[19]

Hemorrhage due to GBM can be partially explained by the proliferation of malformed vasculature. GBM initially spreads along pre-existing vasculature. The expression of angiopoietin-2 and matrix metalloproteinases causes disruption of the basement membrane of normal vasculature, inducing hypoxia and necrosis.[9] This leads to proliferation of endothelium with the initial migration of local endothelial cells.[4] The secretion of vascular endothelium growth factor (VEGF) causes the migration of endothelial precursor cells from the bone marrow,[2] inducible by hypoxia. In contrast to the normal vasculature of the brain, the vasculature of GBM is disorganized and tortuous. There is loss of the blood brain barrier (BBB), which subsequently leads to vasogenic edema.[20] In terms of the capillaries, GBM tends to have retiform capillaries, which are convoluted and take tortuous paths, with lack of external support. Hemorrhage from GBM tends to be larger and more conspicuous when compared to oligodendroglioma and lower grade astrocytoma.[16] It has been demonstrated in the literature that GBM can present with large ICH and it poses a diagnostic dilemma.[1,3,6,10,11,22]

Epithelioid glioblastoma

Histological differential diagnosis of this case includes metastatic carcinoma and metastatic melanoma (amelanotic melanoma). In general, the histological differential diagnosis among metastatic carcinoma, metastatic amelanotic melanoma and epithelioid glioblastoma is extremely difficult, and all of these tumors can present with massive intracranial hemorrhage. Immunohistochemistry is of great help with this differential diagnosis.

Metastatic carcinoma is pancytokeratin positive, GFAP negative, and S-100 protein usually is negative. Metastatic melanoma is S-100 protein, HMB-45, and Melan-A positive. Glioblastoma is GFAP positive, S-100 protein positive, and negative for HMB-45 and Melan-A.

Radiologic features of epithelioid glioblastoma include frequent areas of cystic necrosis with nodular enhancement. In contrast to lower grade tumors that share this trait (ganglioglioma, pleomorphic xanthoastrocytoma, and pilocytic astrocytoma), epithelioid glioblastoma will have significant adjacent vasogenic edema, mass effect,

and midline shift. These tumors have also been shown to occasionally have superficial attachments to the dura, appear well circumscribed, and have significant hemorrhage on MRI.[12]

CONCLUSION

Identification and diagnosis of GBM is generally straightforward. In certain circumstances, the presentation of GBM can vary from the routine. One such example is GBM presenting as massive ICH. The above case demonstrates how pitfalls in diagnosis can be avoided in order to initiate appropriate therapy.

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