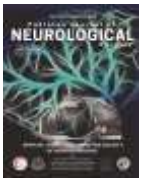

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Original Article

Hemorrhagic Stroke May Be the Sequelae of Brain Tumors

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ABSTRACT

Objective: Hemorrhagic stroke is a common neurosurgical emergency caused by multiple pathological conditions. Brain tumors can also present with acute neurodeficits secondary to hemorrhagic stroke. This study as case series was conducted to report the clinical presentation, radiological findings, causes and management of brain tumors presenting as hemorrhagic stroke.

Materials and Methods: Clinical assessment and radiological investigations were done, including CT brain and MRI brain with contrast. Surgery was done with evacuation of the hematoma and excision of tumor, and the tissue was sent for histopathology. Post operatively patients were shifted to the intensive care unit for monitoring and ventilator support if needed. Adjuvant treatment was guided according to histopathology report.

Results: Total number of patients who were diagnosed to have a bleed in brain tumor were thirteen (n = 13). There were 6 (46%) males and 7 (54%) females. Mean age was 55 years. Among 13 patients, 4 (31%) patients had metastatic brain tumors and 9 (69%) patients had primary brain tumors. Diagnosis was done on CT brain, MRI brain and confirmed on histopathology of tissue obtained during surgery. Out of 13 patients, 5 (38%) patients were asymptomatic prior to hemorrhage and 8 (62%) patients had neurodeficits before and recent episodes of bleeding, which caused deterioration of neurological state.

Conclusion: Malignant primary and metastatic brain tumors can present as acute focal deficits due to brain hemorrhage. Diagnosis is based on clinical presentation, radiological features and histopathology. Timely and aggressive management of tumor related hemorrhagic stroke results in a better prognosis.

Keywords: Brain Tumors, Haemorrhagic stroke, Metastatic brain tumors, Astrocytoma, Oligodendroglioma.

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INTRODUCTION

This study as case-series was conducted to report the clinical presentation, radiological findings, causes and management of brain tumors presenting as hemorrhagic stroke. Non traumatic intracerebral hemorrhage is caused by many pathological conditions. Brain hemorrhage

accounts for around (30%) of strokes.Ischemic stroke accounts for around (70%) strokes.[1] Clinical presentation of hemorrhagic stroke is more devastating than ischemic stroke. These patients must have a comorbid condition like Hypertension, Diabetes mellitus, Coagulopathy.[1,2] Similarly, cerebral AVMs (arteriovenous malformation) and aneurysm can also present with spontaneous intracerebral bleed.[3,4] Primary and secondary brain tumors can also present with spontaneous intracerebral hemorrhage. This is bleed in tumor lying in the parenchyma of the brain. Tumor related brain hemorrhage accounts for around (3.1%) of hemorrhagic strokes.[5] Brain hemorrhage generally occurs late in the course of brain tumors. Most haemorrhages are intraparenchymal, but subarachnoid haemorrhages can also be seen. This might be the initial clinical presentation of brain tumors or it may result in clinical deterioration of patients already diagnosed to have a brain tumor.[3,4] High grade malignancy and highly vascular nature of these tumors are considered as causative factors for hemorrhagic presentation.[5,6] Hemorrhage is more commonly seen in malignant tumors as compared to benign tumors of the brain. Common benign tumors presenting with intracerebral bleed include meningioma and pituitary adenoma.[6,7] Malignant brain tumors presenting with hemorrhage may be primary or metastatic. Brain hemorrhage from metastatic and primary intracranial malignant tumors is seen almost with equal frequency.[8,9] Clinically, the patients with brain hemorrhage presents with either severe sudden onset headache, deterioration of conscious level, right sided or left sided hemiparesis/hemiplegia, facial weakness, dysphasia or diplopia. Brain hemorrhage in patients with brain tumors is often viewed as a catastrophic event with poor prognosis, but better neuroimaging tools, timely intervention and postoperative neurointensive care have certainly improved prognosis of such events. Although, this has been mentioned in literature as case reports or case series, but still differentiation from other causes of spontaneous intracerebral bleed is important as the management of the two conditions is different. Hypertensive bleed is commonly seen in putamen or cerebellum and most the cases are managedconservatively in the intensive care unit with vitals monitoring and to prevent rebleed.[1,2] While patients with brain hemorrhage secondary to brain tumors are treated surgically in most of the cases.[8,9] Initial radiological investigation is CT brain, where hematoma appears as a single or multiple hyperdense lesions with extensive surrounding edema, mass effect and sometime extension to nearby ventricles. It might result in midline shift and hydrocephalus depending upon location of tumors.Appearance of hematoma changes in subsequent CT brain as ring enhancing lesions done after some days.[10] For detailed description of lesions,MRI brain with contrast is done.In case of metastatic brain tumors, it is recommended to do a full metastatic workup including Mammography, CT chest, CT abdomen/pelvis, Bone scan and PET scan.[11] Management of patients include proper neurologicalassessment, looking for comorbid conditions. An emergency craniotomy with evacuation of hematoma and gross total or near total resection of tumor is needed in most of the cases.[12] In case of posterior fossa metastatic brain tumors with hydrocephalus in clinically deteriorated patient, it is advisable to put EVD only.[13] Tumor is sent for histopathology and adjuvant treatment is given according to histopathology report.[12]

MATERIALS AND METHODS

Study Setting and Design

This was an observational, descriptive case series study, conducted at the department of Neurosurgery MTI/Lady Reading Hospital Peshawar for two years during Jan, 2017 to Dec,

2019. A prior ethical approval was taken from ethical review board of hospital.

Data Collection

Diagnosis was made by focusing on a history from patient or attendants.Past history of comorbid conditions like hypertension, diabetes mellitus and history of coagulopathy was noted. Patients' previous records of any systemic extracranial tumors were searched and any treatment given was documented. Examination of patients was done for any new onset focal deficits or deteriorating neurological status. Conscious level of patients were noted in Glasgow coma scale (GCS). After clinical assessment, radiological investigationswere done, including CT brain and MRI brain. Site of hematoma, extension to nearby ventricles and mass effect was noted.

Inclusion Criteria

We included all the patients diagnosed as brain hemorrhage secondary to brain tumors (Primary and metastatic).

Exclusion Criteria

We excluded patients diagnosed with brain hemorrhage secondary to hypertension, coagulopathy, cerebral AVMs and trauma.

Surgery

Patients were initially resuscitated with vitals monitoring. Later on, after an informed high risk consent was taken from family members for a surgical intervention. After evacuation of the hematoma and excision of tumor, the tissue was sent for histopathology. Post operatively patients were shifted to the intensive care unit for monitoring and ventilator support if needed. Adjuvant treatment was guided according to histopathology report.

Data Analysis

Data was analyzed by tables, percentage and fire injury etc.

RESULTS

Age Incidence

Age range of patients was from 42 to 70 years. The mean age of the patients was 55 years.

Table 1: Sex Incidence.

Sex	Number (N)	Percentage	Accumulative Percentage
Male	7	54	54
Female	6	46	46
Total	13	100	100

Table 2: Tumor Origin.

Tumor	Number (N)	Percentage	Accumulative Percentage
METS	4	31	31
Primary	9	69	69
Total	13	100	100

Gender Presentation

There were 6 males and 7 females.

Clinical Presentation and Management

Total number of patients who were diagnosed to have a bleed in brain tumor were thirteen (n = 13). Among 13 patients, 4 patients had metastatic brain tumors and 9 patients had primary brain tumors. Diagnosis was done on CT brain, MRI brain and confirmed on histopathology of tissue obtained. Out of 13 patients, 5 patients were asymptomatic prior to hemorrhage and 8 patients had neurodeficits before and recent episodes of bleeding, which caused deterioration of neurological state. Decrease in conscious level was the most frequent finding following

hemorrhage, with 11 had GCS below 8/15 and 2 patients were alert with hemiparesis (power less than 3/5 in both upper and lower limbs). All patients had CT brain within 12 hours of episodes. The 12 patient's survived and 1 patient died within 4 hours of the episodes. According to the location of the tumor, there was a hyperdense lesion with extensive hypodensity around tumor showing vasogenic edema and mass effect. In 4 patients, there was extension of hematoma to nearby lateral ventricles.

Table 3: Clinical Presentation Before Haemorrhage.

Clinical Presentation	Number (N)	Percentage	Accumulative Percentage
Asymptomatic	5	38	38
Neurological defects	8	62	62
Total	13	100	100

MRI Brain

We did MRI brain with contrast in two patients only as their sensorium was good to tolerate MRI.In 8 patients, there was a single large supratentorial hematoma so craniotomy with evacuation hematoma and subtotal removal of the tumor was done. In 3 patients, there was a single large hematoma in cerebellum, sub-occipital craniectomy was done with evacuation of the hematoma and near total resection of tumor was done.

Location of tumors and bleed its shown in Table 4. Most of two times were below in the superintendent region with intraventricular extrusion in 3 cases.

Table 4: Location of Tumor/Brain.

Sr. No.	Site	Total (N)	Accumulative Percentage
1.	Supraarterial Intraparacellar	10	77
2.	Introventricular Extension of blood	3	23
3.	Cerebellar	3	23
Total			

Post-Operative Follow-up

Post operatively patients were shifted to the intensive care unit. Ten patients survived with mild to moderate neurodeficits and two patients died after two weeks in ICU. After surgical resection, tissue was sent for histopathology which revealed Glioblastoma as the most frequent primary tumor. One patient had right sided thalamic hematoma in underlying tumor, which has extended to the ventricular system with acute hydrocephalus, so external ventricular drain (EVD) was put in to save the life of the patient. Table 5 describes the detail of the radiological features. Table 6 gives the detail of clinical outcome of the patients.

Table 5: Radiological features.

No.	Site of Hemorrhage	Surrounding Edema	Ventricular Extension	Contrast Enhancement
1.	Left frontoparietal	++	No	+++
2.	Right cerebellar hemisphere	+++	Yes	++
3.	Right parieto temporal	+++	No	+++
4.	Right frontoparietal	+++	Yes	++
5.	Left cerebellar hemisphere	+++	No	++
6.	Left parietotemporal	+++	No	+++
7.	Right occipitoparietal	+++	Yes	+++
8.	Right frontal	++	No	++

9.	Left frontal	+++	No	+++
10.	Left parietotemporal	+++	No	+++
11.	Right thalamus	+++	Yes	+++
12.	Left cerebellar hemisphere	+++	No	++
13.	Right cerebellar hemisphere	0	No	+++

Key: 0 = none, + = Mild, ++ = Moderate, +++ = Marked

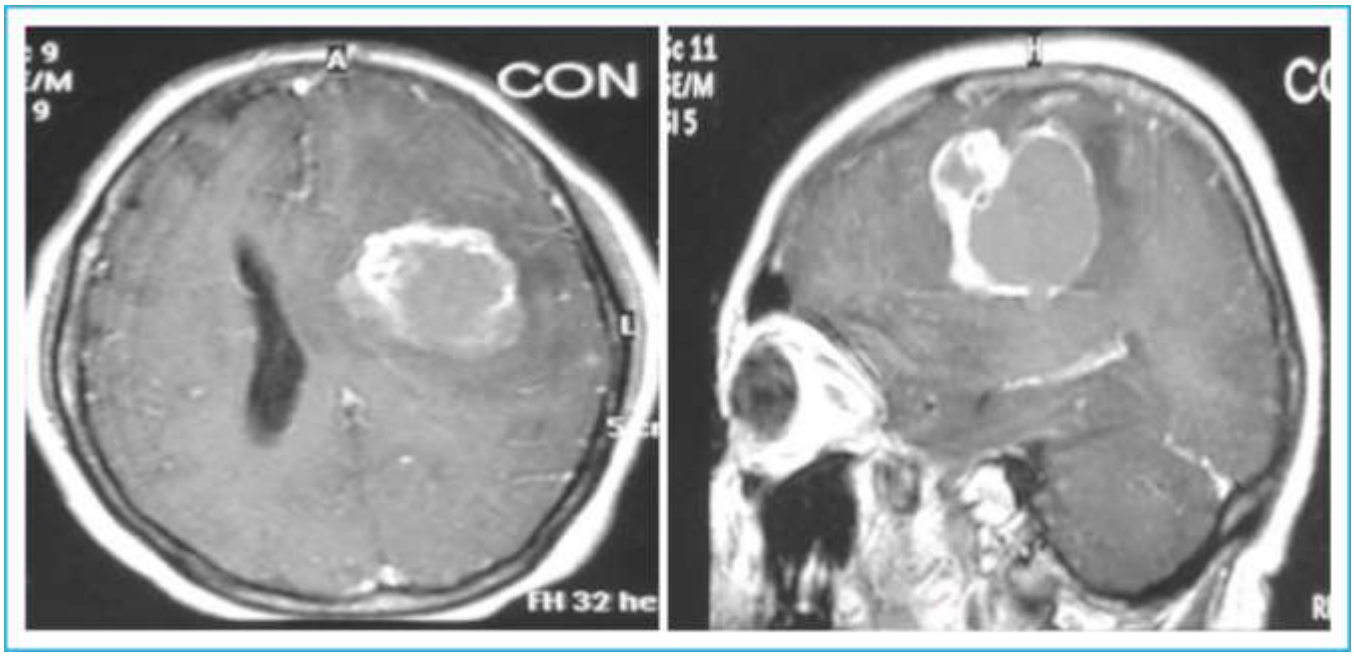

Figure 1: MRI brain with contrast axial and sagittal images showing peripheral enhancing tumor.

Table 6: Clinical details and outcome of patients.

No.	Age/ Gender	Symptoms prior to Haemorrhage	Neurological Conditions Following Haemorrhage	Histopathology of Tumor	Outcome
1.	42 y/F	None	Alert,Right hemiparesis (GCS 15/15)	Oligodendroglioma	Good
2.	48 y/F	Headache,Ataxia, Tremors	Comatose (GCS 7/15)	Adenocarcinoma of breast (Had disseminated metastatic disease)	Died (before surgery)
3.	53 y/M	Headache,Lethargy, Left Hemiparesis	Comatose (GCS 5/15)	Glioblastoma	Died
4.	56 y/M	Personality changes,Seizures	Comatose (GCS 7/15)	GBM	Satisfactory
5.	57/F	Headache,ataxia and diplopia	Comatose (GCS 8/15)	Papillary CA of thyroid	Satisfactory
6.	68 y/M	Headache,Right hemiparesis	Comatose (GCS 6/15)	GBM	Satisfactory
7.	70 y/F	None	Comatose (GCS 5/15)	GBM	Good
8.	42 y/F	Headache,Seizures	Alert,Left hemiparesis	Oligodendroglioma	Good

			(GCS 15/15)		
9.	70 y/M	None	Comatose (GCS 8/15)	Melanoma	Satisfactory
10.	52 y/M	Headache, Right Hemiparesis, Dysarthria	Comatose (GCS 7/15)	GBM	Good
11.	55 y/F	None	Comatose (GCS 5/15)	Right thalamic GBM(On radiological features)	Good
12.	71 y/M	Headache,Slurred speech	Comatose (GCS 5/15)	Bronchogenic CA	Died
13.	42 y/F	None	Comatose (GCS 13/15)	Hemangiopericytoma	Good

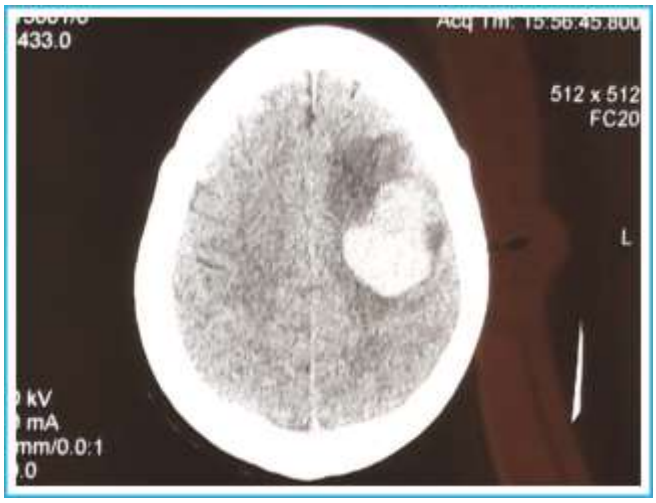

Figure 2: CT BRAIN showing hyperdense hematoma with surrounding edema.

DISCUSSION

Brain tumors are one of the well-established cause of spontaneous intracerebral bleeds. However, it occurs infrequently, and has been documented in literature rarely.[1,7,8,9] It is considered as catastrophic and terminal event, but limited data on outcome exists. Most existing literature is available as autopsy based. Russell et al reported 2% brain tumors in 461 autopsied cases of spontaneous intracerebral bleed.[14] Mutlu et al reported less than 1% brain tumors in 225 cases of brain haemorrhage.[10] Current clinical studies show increasing number of patients with brain tumors that present with brain haemorrhage.[13] This might be due to widespread availability of better imaging investigations and differentiating haemorrhage in a brain tumor from other causes of spontaneous intracerebral bleed. Highgrades, extensive and abnormal vascularity of tumors seems as probable cause of bleeding in these tumors.[8,12,21] Both primary malignant and secondary/metastatic brain tumors are seen to present as hemorrhagic stroke with almost equal frequency.[13] Non malignant tumors like meningioma and pituitary adenoma may also present with an apoplectic episode of hemorrhage,[4,6,9] but we didn't see such patients in our series and most of brain tumors in our series were malignanttumors. Hypertension is another common cause of brain hemorrhage and it has a particular tendency towards specific sites of the brain like putamen and cerebellum.[14] In our study, CT brain showed hemorrhage mostly in lobar locations, extensive surrounding vasogenic edema and peripheral contrast enhancement. Hypertension was found in some of our patients, but this could be secondary to the Cushing phenomenon (Hypertension, Bradycardia, Irregular respiration) as they had no previous history of hypertension. Coagulopathyis also considered as a cause of brain haemorrhage,[16] but in our study there was no patient with clinical and laboratory evidence of bleeding disorders andnone of the patient has received anticoagulants.

In our series, Glioblastoma was the most common primary brain tumor to present with a

brain hemorrhage, this could be secondary to the proliferation of endothelium, cluster of thin walled vessels and necrotic areas seen in tissues obtained for histopathology during surgery. Hemorrhage is uncommonly seen in low grade gliomas[19] and this could be because of the absence of abnormal blood vessels and absence of necrosis in these tumors. Among low grade glial tumors, Oligodendroglioma appear to present with brain hemorrhage more frequently than astrocytoma[16] possibly because of the presence of numerous dilated, thinwalled blood vessels and endothelial proliferation as predisposing factors. Similarly, there was one patient with cerebellar hemangioblastoma having a contrast enhancing mural nodule with a cyst, which is mentioned in literature as highly vascular dysplastic tumor[21] and this pathological vascular architecture is responsible for hemorrhage.In our series metastatic brain tumors presenting with hemorrhage were melanoma, carcinoma of lung, breast and thyroid. These tumors and choriocarcinoma are most frequently mentioned to result brain hemorrhage in metastatic lesions.[2,13,17,8,19]

In metastatic brain tumors, hemorrhage result from vascular invasion and rapid growth of tumors into adjacent brain parenchyma.[13] This bleed is located in cortex of the brain mostly with extension to nearby white matter or ventricle[15] depending upon location. On a histopathological examination of these tumors, numerous such walled blood vesselswere found which seem to be the probable cause of bleeding. Bleeding in a tumor is almost always symptomatic like any space occupying lesion with signs and symptoms of raised intracranial pressure like headache, nausea, vomiting and decreasing level of consciousness and this might be the initial clinical presentation of a patient.[3,5,6,13,16,22] In our series, four patients were asymptomatic before hemorrhage with sudden onset of deterioration and the apoplectic presentation has been documented in other studies too.[3,5,7,18] Hemorrhage due to brain tumorhas a similar clinical presentation like hypertensive hemorrhage or ruptured cerebral AVM or saccular aneurysm. These patients need timely intervention, so craniotomy/craniectomy was done with evacuation of the hematoma and safe surgical resection of tumor.Hematoma was found near to the surface in most of the cases, therefore the access was easy with minimal gray matter and white matter dissection. Due to the catastrophic presentation of the patients, the surgery is always a challenge in such cases. So, preoperatively and preoperatively bolus doses of IV dexamethasone and Mannitol were given to reduce tumor related edema. A wide craniotomy was done to cope up with post-operative brain swelling and decompressive craniotomy, if needed. The hematoma was evacuated at first instance for safe surgical resection of underlying tumor. The enbloc resection was carried out in most cases. Postoperatively, the patients were kept in Neuro ICU for monitoring and timely management of complications. Outcome of patients depends of presenting status, tumor histology, degree of resection and postoperative care. Postoperative neurointensive care has significantly changed the outcome of these patients. Adjuvant treatment with radiotherapy and chemotherapy was given to patients with histology report of Glioblastoma, Oligodendroglioma and metastatic tumors.

CONCLUSION

Malignant primary and metastatic brain tumors can present as acute focal deficits due to brain hemorrhage. Diagnosis is based on clinical presentation, radiological features and histopathology. Outcome is good with timely and aggressive management of tumor related hemorrhagic stroke.

REFERENCES

1. Graus F, Rogers LR, Posner JB. Cerebrovascular

complications in patients with cancer. Medicine, 2016; 64: 16–35.
2. Jellinger K. Pathology of intracerebral hemorrhage. Zentral J Neurosurgery, 2015; 38: 29–42.
3. Yamauchi K, Umeda Y. Symptomatic intracranial haemorrhage in melaonma: analysis of CT and autopsy findings. JNS. 2018; 244: 94–100.
4. Padt JP, De Reuck J, Eecken HV. Intracerebral hemorrhage as initial symptom of a brain tumor. JNS. 2017; 73: 241–251.
5. Gildersleeve N, Koo AH, McDonald CJ. Metastatic tumor presenting as intracerebral hemorrhage. J Radiology, 2019; 124: 109–112.
6. DiMaio SM, DiMaio VJ, Kirkpatrick JB. Sudden, unexpected deaths due to primary intracranial neoplasms. J Forensic Med Pathol. 2015; 1: 29–45.
7. Schrader B, Barth H, Lang EW, et al. Spontaneous intracranial haematomas caused by neoplasms. Acta Neurochir, 2016; 142: 979–985.
8. Benveniste RJ, Manzano G, Petito CK. Multifocal glioblastoma multiforme with synchronous spontaneous hemorrhage: case report. J Neurooncol. 2014; 89: 55–58.
9. Kim IY, Jung S, Jung TY, Kang SS, Choi C. Primary central nervous system lymphoma presenting as an acute massive intracerebral hemorrhage: case report with immune histo chemical study. Surg Neurol. 2013; 70: 308–311.
10. McIver JI, Scheithauer BW, Rydberg CH, Atkinson JL. Metastatic breast carcinoma presenting as Brain hemorrhage: case report. JNS. 2015; 49: 447–449.
11. Wakai S, Yamakawa K, Manaka S, Takakura K. Spontaneous intracranial hemorrhage caused by brain tumor: its incidence and clinical significance. JNS. 2017; 77: 54-60. 10: 437–444.
12. Kondziolka D, Bernstein M, Resch L, et al. Significance of hemorrhage into brain tumors: clinicopathological study. J Neurosurg. 2016; 67: 852–857.
13. Yuguang L, Meng L, Shugan Z, et al. Intracranial tumoural haemorrhage: a report of 58 cases. J Clin Neurosci. 2002; 9: 637–639.
14. Bitoh S, Hasegawa H, Ohtsuki H, Obashi J, Fujiwara M, Sakurai M. Cerebral neoplasms initially presenting with massive intracerebral hemorrhage. Surg Neurol. 2016; 22: 57–62.
15. Kase CS. Intracerebral hemorrhage: non-hypertensive causes. Surg Neurol Stroke, 2011; 17: 590–595.
16. Russel DS. Spontaneous intracranial haemorrhage. Surg Neurol. 2018; 47: 689–693.
17. Mutlu N, Berry RG, Alpers BJ. Massive cerebral hemorrhage: clinical and pathologic correlations. Arch Neurol. 2009; 8: 644–661.
18. Locksley HB, Sahs AL, Sandler R. Report on the cooperative study of intracranial aneurysms and subarachnoid hemorrhage, 3: Subarachnoid hemorrhage unrelated to intracranial aneurysm and A-V malformation—a study of associated diseases and prognosis. J Neurosurg, 2018; 24: 1034–1056.
19. Kothbauer P, Jellinger K, Flament H. Primary brain tumour presenting as spontaneous intracerebral haemorrhage. Acta Neurochir. 1979; 49: 35–45.
20. Cahill DW, Ducker TB. Spontaneous intracerebral hemorrhage. Clin Neurosurg, 1982; 29: 722–779.
21. Licata C, Turazzi S. Bleeding cerebral neoplasms with symptomatic hematoma. J Neurosurg Sci. 2013; 47: 201–210.
22. McCormick WF, Rosenfield DB. Massive brain hemorrhage: a review of 144 cases and an examination of their causes. Stroke, 2016; 4: 946–954.
23. Lieu AS, Hwang SL, Howng SL, Chai CY. Brain tumors with hemorrhage. J Formos Med Assoc. 1999; 98: 365–367.
24. Kyrnetskiy EE, Kun LE, Boop FA, Sanford RA, Khan RB. Types, causes, and outcome of intracranial hemorrhage in children with cancer. J Neurosurg. 2015; 102: 31–35.
25. Oldberg E. Hemorrhage into gliomas: a review of eight hundred and thirty-two consecutive verified cases of glioma. Arch Neurol Psychiatry, 2017; 30: 1061–1073.
26. Drake CG, McGee D. Apoplexy associated with brain tumours. Can Med Assoc J. 2018; 84: 303–305.
27. Scott M. Spontaneous intracerebral hematoma caused by cerebral neoplasms: report of eight verified cases. J Neurosurg. 2019; 42: 338–342.
28. Mandybur TI. Intracranial hemorrhage caused by metastatic tumors. Surg Neurology, 1977; 27 (7): 650–655.
29. Liwnicz BH, Wu SZ, Tew JM. The relationship between the capillary structure and hemorrhage in gliomas. J Neurosurg. 2018; 66: 536–541.

Additional Information

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Human Subjects: Consent was obtained by all patients/participants in this study.
Conflicts of Interest:
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Financial Relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.
Other Relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

AUTHORS CONTRIBUTIONS

Sr.#	Author's Full Name	Intellectual Contribution to Paper in Terms of:
1.	Adnan Khaliq	1. Study design and methodology.
2.	Farooq Azam	2. Paper writing, referencing, data calculations and
3.	Mumtaz Ali	3. Data collection and calculations.
4.	Akramullah	4. Analysis of data and interpretation of results etc.
5.	Hamayun Tahir	5. Literature review and manuscript writing.
6.	Nayab Gul	6. Analysis of data and quality insurer.