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ORIGINAL ARTICLE

Multiple glioblastomas: Are they different from their solitary counterparts?

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ABSTRACT

Context: Multiple glioblastomas (GBMs) have a reported incidence of 2–20%.

Aims: We intend to study these subsets of GBMs to know whether these are similar to their solitary counterparts.

Setting and Design: A retrospective study.

Materials and Methods: We analyzed 7 cases of biopsy-proven multiple GBMs. Multiple GBMs were described if there were >1 lesion which was at least 1 cm apart. The clinical data, radiological features, histopathological and immunohistochemical analysis and follow-up were recorded.

Results: The mean age was 45 years (range 17–69 years). All cases presented with features of raised intracranial pressure (ICP). Totally, 3 cases presented with hemiparesis and 2 cases with altered sensorium and generalized tonic clonic seizures each. The median Karnofsky performance status (KPS) was 50. Mean duration of symptoms was 40 days. All lesions were contrast enhancing (2 with homogenous enhancement and 5 had ring enhancement). Total excision of the lesion causing mass effect was done in all cases. Histopathologically, small cells were significantly present in 4 cases, and satellitosis was seen in 5 cases. Glial fibrillary acidic protein (GFAP) was absent in all cases in which small cells were significant. In these 4 cases, the proliferation index ranged from 40% to 95%. Totally, 3 patients died within 2 months of surgery, whereas remaining 4 patients underwent chemo-radiotherapy.

Conclusions: We conclude that the cases usually present with features of raised ICP and poor KPS. Histopathologically these lesions show significant small cell population, satellitosis, and GFAP negativity.

Key words: Multiple glioblastomas, secondary structures, prognosis

Introduction

Gliomas remain the most abundant primary brain tumors worldwide, and glioblastoma (GBM) accounts for the majority of them.[1,2] GBMs most commonly occur as solitary lesions with multiple GBMs occurring rarely (with reported incidence of 2–20%)[3-5] Multiple GBMs are further divided into multifocal and multicenteric depending whether dissemination or growth by an established route, spread via commissural or other pathways, (i.e. corpus callosum, fornix, internal capsule, or massa intermedia), or spread via cerebrospinal fluid channels exists or not. Due to rarity, these lesions have not been studied extensively. We present a detailed clinico-radio-pathological findings and also study their outcome. We study seven such cases to determine whether these are similar to the solitary counterparts or not.

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Materials and Methods

This is a retrospective study for which data were collected from a prospective glioma database. The prospective database was collected from January, 2013 to March, 2014. Of the 60 cases of biopsy-proven GBMs, 7 cases of multiple GBMs were identified. Preoperative radiology (contrast enhanced computed tomography [CECT] and/or magnetic resonance imaging [MRI]) were reviewed, and cases with multiple lesions were selected.

Multiple GBMs were defined as two or more lesions which are at least 1 cm apart. Multicentric GBMs were defined as lesions which were in areas of brain which have no apparent neural/vascular connections and multifocal lesions were defined where obvious neural/vascular connections are present. Complete clinical (including Karnofsky performance status scale [KPS]) and radiological profile was noted in immediate postoperative period as well as at 3 months follow-up.

All these patients underwent contrast-enhanced MRI along with MR spectroscopy (MRS) (except one, as the patient presented in flexion response and had to be taken up for emergency surgery). Preoperatively, as multiple intracranial lesions have metastasis, lymphomas and tuberculosis as common differential diagnosis and treatment would differ; various radiological and hematological investigations were done to rule out these differentials. These investigations included X-ray chest (CECT if needed), ultrasound abdomen and pelvis (CECT if needed), Bone scan (Skeletal methylene diphosphonate Tc-99 m scan). Complete blood picture, bone marrow studies and other blood investigations (like prostate specific antigen etc.) were done if needed. There was no evidence of the primary malignancy elsewhere in the body. All patients (except one who was operated outside and referred to our center for further management but he refused any further treatment) underwent surgical excision using standard surgical techniques. Postoperative CECT scans were done in all patients within 24 h of surgery. All patients were advised radiotherapy (RT) and chemotherapy (CT); however, 4 patients did not undergo RT or CT. complete clinical (including KPS) and radiological data were retrieved and noted. Follow-up data were recorded.

Histopathological review was done in 6 cases as 1 case was operated outside and tissue was not sufficient for complete analysis (however, diagnosis of GBM was confirmed on slide review). The tissue were received in 10% buffered formalin and were processed for paraffin section and immunohistochemistry following standard techniques using antibodies against glial fibrillary acidic protein (GFAP), synaptophysin and minichromosome maintenance protein 3. The cases which were labeled as GBMs were retrieved from the database. The slides were reviewed by the neuropathologist (lumbar puncture) for further histopathological and immunohistochemical analysis if needed.

Results

Total of 60 cases of GBMs (biopsy proven) presented to our center between January, 2013 and March, 2014. On review of radiology of all these cases, total of 7 cases of multiple lesions were selected for the study. Multiple GBMs consisted of 11.7% of all GBMs. A total of 4 cases were multifocal, and 3 cases were multicentric.

All cases presented with features suggestive of raised intracranial pressure (ICP) with 3 patients presenting with hemiparesis and 2 presenting each with generalized tonic clonic seizures and altered sensorium [Table 1]. The mean duration of symptoms was 40 days and mean age of presentation was 45 years with 1 cases of a child (17 years old) [Figure 1]. The median preoperative KPS was 50 in our study [Table 1]. All cases were contrast enhancing on CT and MRI. Totally, 5 of these cases were ring enhancing and 2 were homogenously enhancing. In 3 cases, corpus callosum was involved. In 2 of these cases, genu of the corpus callosum was involved and in 1 case, splenium was involved and in 1 case where genu of corpus callosum was involved along with sella and supra-sellar region [Figure 1]. Complete excision of the lesion causing raised ICP was done. If another lesion was in close vicinity of the offending lesion, it was also excised/biopsied simultaneously.

Case example-patient 1

A 35-year-old female, presented to the emergency department in altered sensorium and on examination she had only flexion response to pain. On CECT head done 20 days prior to admission, there were two lesions, one in the right posterior frontal, and another in the left anterior frontal with another doubtful lesion in the region of the corpus callosum. Patient was taken up for emergency surgery with complete excision of the right posterior frontal lesion which was causing maximal mass effect. Postoperative CT showed multiple lesions in both hemispheres. We would like to label such cases as "fulminant GBMs" as the difference between the two radiology was less than a month. The patient could not survive and died on the 11th postoperative day [Figure 2].

Table 1: Clinical profile of the patients

Age (in years)/sex	Sex	Presenting symptom	Preoperative KPS	Follow-up and KPS	Recurrence
69	Female	Left hemiparesis, impaired speech and memory×1.5 months, altered sensorium×7 days	50	Died	-
52	Female	Headache×2 months, vomiting×6 days, speech impairment×2 days, right hemiparesis×2 days, altered sensorium×1-day	20	30 at 3 months	Absent
35	Female	Seizure×15 days, headache×5 months, vision loss (bilateral)×1-month	50	Died	-
17	Male	Seizure×2 months, headache and vomiting×15 days	90	90 at 1-year	Present (at 1-year)
56	Female	Headache×12 days, vomiting×1-day, left hemiparesis×10 days	90	80 at 2 months	Absent
27	Male	Bilateral vision loss×2 months, right hemiparesis×1-month	30	Died	-
59	Male	Headache and vomiting×1-month	50	50 at 3 months	Absent

KPS – Karnofsky performance status scale

Case example-patient 2

A 17-year-old male presented with features of raised ICP and seizures, had radiological finding revealed 2 multicentric lesions; one in frontal lobe and another in temporal region, both excised completely. Diagnosed as GBM after histopathological analysis, underwent postoperative RT for 6 months. Remain asymptomatic for 1-year, again on 1-year follow-up he found to have a recurrence with 3 lesion; one at right frontal lobe, second at right temporal lobe and third at right parietal lobe without any neural connection in between. Operated for complete excision for targeted frontal and temporal lesion to reduce the mass effect and postoperative planned for further adjuvant chemo-RT [Figure 3].

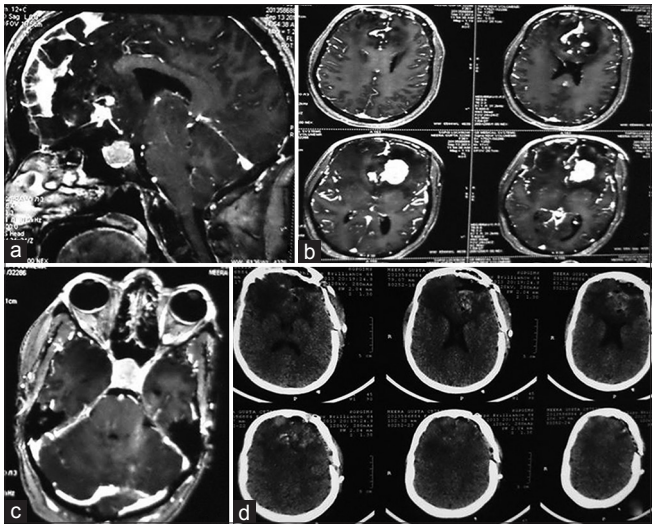

Figure 1: Magnetic resonance imaging contrast showing multiple glioblastoma, involving corpus callosum, frontal as well as sellar region (a-c). Postoperative image (d) showing complete excision of frontal and corpus callosal mass and biopsy taken from sellar mass in same setting

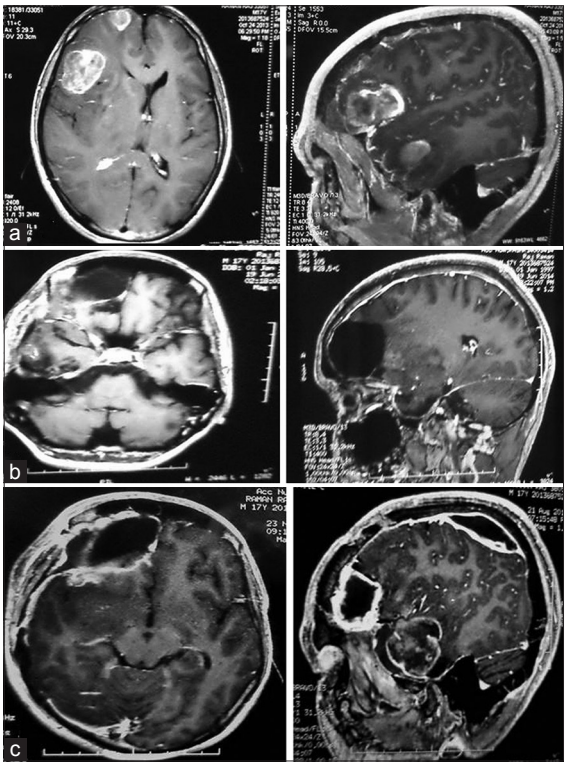

Figure 3: Magnetic resonance imaging contrast showing multocentric glioblastoma (a), postoperative image (b) and recurrence at same site as well as ipsilateral parietal lobe after 1-year of surgery (c)

Histopathological evaluation

On histopathological evaluation of 6 cases, necrosis and microvascular proliferation was seen in all cases and 4 cases had predominant small cell component. One of these 6 cases had predominantly small cell morphology and was labeled as small cell GBM (>80% cells were small cell). The tumor cells showed oval to spindly hyperchromatic nuclei, brisk mitosis and scanty fibrillary stroma [Figure 4]. Vascular endothelial proliferation and necrosis with wreath rosettes were also present. Small cell component was also present

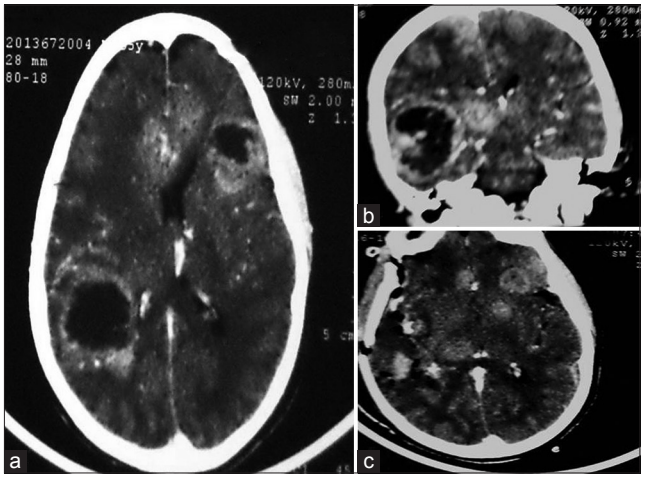

Figure 2: (a and b) Glioblastoma involving multiple supratentorial regions in axial and coronal contrast-enhanced computed tomography, (c) the lesion which was victim for midline shift only targeted for decompression and biopsy

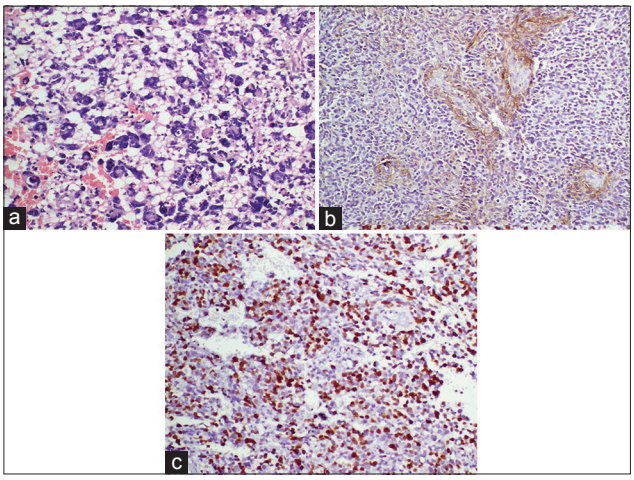

Figure 4: Giant cell glioblastoma (a), small cell glioblastoma showing minimal GFAP positivity around the blood vessels (b), and MCM3 immunoreactivity in >90% tumor cells (c)

in another 3 cases of which one was predominantly of giant cell type. In 5 cases, at places relatively preserved cortical architecture was present with perivascular and perineuronal satellitosis by the tumor cells also known as secondary structures. Subpial infiltration by tumor cells was also present

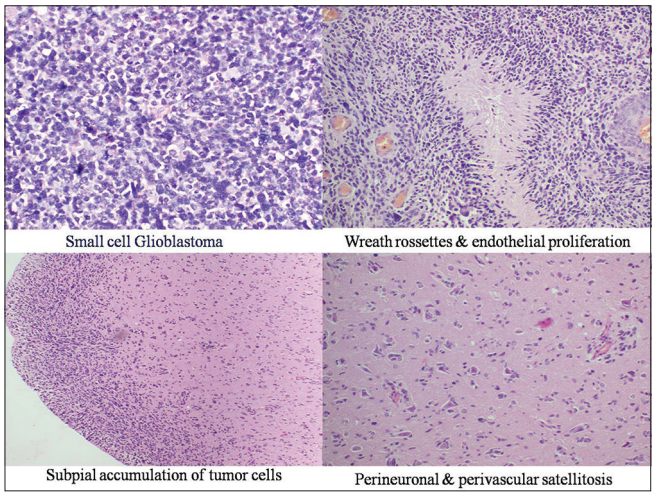

Figure 5: Various pathological characteristics of high-grade glioma

in two cases [Figure 5]. The 5th case showed predominantly necrosis with similar pattern of tumor infiltration. GBM with oligodendroglial component was observed in the 6th case. Immunohistochemically the expression of GFAP was minimal or absent in the small cell areas as well as in the oligodendroglial component. Cell proliferation index was very high in small cell GBM (95%) and varied between 40% and 75% in the tumors with small cell component [Figure 5]. In the last 2 cases, the tumor was predominantly necrotic and the viable area showed the proliferation index of 10% and 15% respectively. There was no immunoreactivity for synaptophysin antibody, which excluded the possibility of primitive neuroectodermal tumors (PNET) or GBM with PNET like areas [Table 2].

Three patients died, 1 at 11th postoperative day, another at 1-month postoperative and another at 2 months postoperative. Remaining four patient underwent chemo-RT under our institute protocols according to KPS score [Table 3]. Patients with poor performance score (KPS score <70), given low dose RT - 35 Gy/7 fraction, whereas inpatient with good performance score (KPS score >70), high-dose RT - 60 Gy/30 fractions were given.

Table 2: Histopathology of multiple glioblastomas

Histo-pathology	Small cell component	Necrosis/mitosis	Micro-vascular proliferation	GFAP	MCM3 labeling index (%)
Small cell GBM	Predominant	+	+	Negative	>95
GBM	+	+	+	Negative	75
Giant cell GBM	+	+	+	Negative	45
GBM	+	+	+	Positive in nonsmall cell areas	40
GBM, predominantly necrotic	-	+	+	Positive	10
GBM with oligodendroglial element	-	+	+	Focally positive	15

GFAP – Glial fibrillary acidic protein; MCM3 – Minichromosome maintenance protein 3; GBM – Glioblastoma multiformae

Table 3: Summary of given chemo-radiotherapy to all patients according to our institute protocol

Serial number patients	Age (years)/sex	Radiotherapy	Chemo therapy TMZ	KPS* at follow-up (KPS scale)
1	69/female	No (patient expired)	No	-
2	52/female	No (consent not given)	No	30
3	35/female	No (patient expired)	No	-
4	17/male	60 Gy/30 fractions/6 weeks+concurrent - TMZ 75 mg/m² per dose -One month gap- Adjuvant - TMZ 150 mg/m² day 1-5/month if tolerated, then further TMZ 200 mg/m² day 1-5 every 28 days×5 cycles Total 6 cycles given	Yes	90
5	56/female	60 Gy/30 fractions/6 weeks+concurrent - TMZ 75 mg/m² per dose -One month gap- Adjuvant - TMZ 150 mg/m² day 1-5/months if tolerated, then further TMZ 200 mg/m² day 1-5 every 28 days×5 cycles Total 6 cycles given	Yes	80
6	27/male	35 Gy/7 fractions/2.5 months alternate day - 40 Gy/15 fractions/3 weeks daily concurrent - TMZ 75 mg/m² per dose dialy adjuvant - TMZ 6 cycles	Yes	-
7	59/male	35 Gy/7 fractions/2.5 months alternate day - 40 Gy/15 fractions/3 weeks daily concurrent - TMZ 75 mg/m² per dose dialy adjuvant - TMZ 6 cycles	Yes	50

*KPS score: patients with poor performance score (KPS score <70), given low dose radiotherapy-35 Gy/7 fraction, whereas inpatient with good performance score (KPS score >70), high dose radiotherapy-60 Gy/30 fractions were given. KPS – Karnofsky peformance status scale; TMZ – Temozolomide

Discussion

Gliomas remain the most abundant primary brain tumors worldwide, and GBM accounts for the majority of them. In spite of a number of scientific advances made in the field of diagnosis and treatment of GBMs over the last few decades, it remains a fatal disease with median survival of no >15 months even with the best current therapy.[1,2]

Glioblastomas most often present as single parenchymal lesion and multiple GBMs are very rare. Multiple GBMs can be either multifocal or multicentric in nature, and all lesions may be present simultaneously (synchronous) or may appear subsequently (metachronous).[2] Because of rarity, literature on multiple GBM is sparse. In this article, we discuss the clinical presentations, radiological characteristics, pathological features (including proliferation index) and treatment of multiple GBMs in 7 patients and present an extensive review of literature. We also coin the term "fulminant GBM" in this report.

The true incidence of multiple gliomas is not known. However, various studies have quoted their incidence to be in between 2% and 20%.[3,5] The incidence of multifocal GBM is likely to be even lesser. Widespread application of MRI and increased use of surgical excision even in multiple tumors have contributed to increase reporting of these lesions in the modern era. In our study, the incidence of multiple GBMs was 11.7% of all GBMs.

Multiple gliomas were initially classified by Budka into four categories: Diffuse, multiple, multicentric, and multi-organ. In 1963, Batzdorf and Malamud distinguished two types of multiple gliomas namely multifocal and multicentric gliomas. Multifocal gliomas are those which result from dissemination or growth of tumor cells by a preformed route like commissural fibers, cerebrospinal fluid pathway or by local metastasis. On the other hand, multicentric gliomas are located wide apart in different lobes or hemispheres, and their concurrence cannot be explained by previously mentioned mechanisms. The clinical significance of labeling multiple GBMs as either multifocal or multicentric is fading out. Various studies show that there is no apparent clinical utility in distinction between the two groups.[2,6] We did not find any difference in the pathology of multifocal and multicentric GBMs. For this reason, we have not distinguished GBMs into these groups and have clubbed them together into multiple GBMs.

The exact pathogenetic mechanisms of multifocal/centric gliomas are not known. However, recent studies have greatly contributed to our existing knowledge regarding genesis of these lesions. The hypothesis forwarded by Willis suggested a two-step tumorigenesis giving rise to multiple gliomas. In the first stage, a large area or perhaps the whole brain underwent some transformation which was labeled as initiation. This step was considered as something that made the brain very susceptible for frank malignant changes. In the second step, due to various kinds of stimulation, like mechanical, viral or biochemical, there occurred excessive cellular proliferation at multiple sites giving rise to gliomas at different places.[7] This process, known as "promotion" also explained metachronous development of these tumors. On the other hand, zulch argued that multicentricity was actually a kind of metastasis along a yet unknown pathway.[7]

From pathological point of view, GBMs appear to be the most common type of multiple GBM. However, other gliomas like low-grade astrocytomas and ependymomas have also been reported to present in a multicentric fashion. Most often, the lesions are supratentorial in location but at times, a combined supra and infratentorial lesion may also be encountered. We analyzed pathological appearance of these lesions. Of the 6 cases, 5 had features suggestive of secondary structures (which are a marker of tendency to spread). These secondary structures may be noted in other highly infiltrative tumors like gliomatosis cerebri.[8] These secondary structures include sub-pial infiltration, perineural and perivascular satellitosis. These structures are a marker that the tumor has a tendency to spread which explains the multiplicity of these lesions. Interestingly, these were present irrespective of whether the lesions were multifocal or multicentric. These lesions are also seen in gliomatosis cerebri which is also an infiltrative tumor and although histopathologically it is grade II but their biological behavior is of grade III. Similarly, these multiple glioblatomas may behave in a much worse manner than solitary GBMs.

Another interesting feature was predominant small cell components in our study which were present in 4 of the 6 cases. In a study on small cell GBMs by Perry *et al*. they found the incidence of small cell GBMs to be nearly 10%.[9] In contrast to this, two-third of our cases had significant small cell component. All these cases were GFAP negative indicating loss of the glial nature. Of the 6 cases, 4 had very high proliferation index (>40%). All these features indicate that multiple GBMs are more aggressive pathologically as compared to solitary GBMs. There did not appear to be any difference between multifocal and multicentric GBMs, and these might be similar lesions with different mechanisms of spread.

Kyritsis *et al*. reported germline p53 gene mutations in 6 of 19 patients with multifocal glioma.[2,6] Kong *et al*. showed that a greater proportion of c-Met overexpressing GBMs had multifocal features. They also showed a significant association between c-Met expression and matrix metalloproteinases 2 and 9, which could explain the increase of invasive and multifocal features.[2,10] Lim *et al*. found that GBMs showing contact with the subventricular zone (which harbors neural stem cells) with cortical infiltration were significantly associated with multifocal disease on presentation and

recurrence.[2,11] Patil *et al*. analyzed expression of phosphorylated mitogen-activated protein kinase, phosphatase and tensin homolog, O6-methylguanine-DNA methyltransferase, laminin b1 and b2, as well as epidermal growth factor receptor amplification, and found no significant differences between the multifocal and unifocal GBM groups.[2]

Multiple lesions are detected mainly on MRI/CT scans. Symptoms are usually due to one of these lesions either because of the size or dysfunction pertaining to the area of the brain involved. While we have to concede that MRI has been useful in the detection of these multiple lesions, one has to understand that it is not an easy job to make a definitive diagnosis based only on the imaging. The common radiological differentials include cerebral abscess, metastasis, lymphomas and demyelinating disease like multiple sclerosis. MRS may help in differentiating between the various possibilities.

The ideal management of these lesions remains debatable. This stems from conflicting reports which on one end recommend no treatment at all while the other extreme advocates an aggressive (maximal surgical excision followed by chemo-RT).[12] Surgical biopsy is however, desirable to establish diagnosis and to decide further adjuvant therapy. Stereotactic biopsy is recommended for deep-seated lesions while open surgical decompression is used in sizeable lesion with features of raised ICP.[13]

Whether the prognosis of these multiple GBMs is any worse than their solitary counterparts is not very clear. In a study by Parsa *et al*., did not find any survival difference between the two.[14] However, in another study, the authors found that the survival of the multiple group was worse than the solitary group.[15] After controlling for age, KPS score, treatment, and extent of resection with matching, study by Patil *et al*. showed that patients with newly diagnosed multifocal GBM experience significantly worse survival than patients with solitary GBM (6 months vs. 11 months, respectively). Patients with multifocal disease in the modern temozolomide era had 1-year and 2-year survival rates of only 28.5% and 4.3%, respectively.[2]

Conclusions

Multiple GBMs account for nearly 11.7% of all GBMs. Raised ICP is the most common manifestation. All these lesions are contrast enhancing. histopathologically, majority of the lesions showed secondary structures like perineural and perivascular satellitosis, subpial accumulation of tumor cells, GFAP negativity and a high proliferation index. All these findings point that these lesions might be more aggressive than solitary counterparts.

References

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
2. Patil CG, Yi A, Elramsisy A, Hu J, Mukherjee D, Irvin DK, *et al*. Prognosis of patients with multifocal glioblastoma: A case-control study. J Neurosurg 2012;117:705-11.
3. Batzdorf U, Malamud N. The problem of multicentric gliomas. J Neurosurg 1963;20:122-36.
4. Borovich B, Mayer M, Gellei B, Peyser E, Yahel M. Multifocal glioma of the brain. Case report. J Neurosurg 1976;45:229-32.
5. Chadduck WM, Roycroft D, Brown MW. Multicentric glioma as a cause of multiple cerebral lesions. Neurosurgery 1983;13:170-5.
6. Kyritsis AP, Bondy ML, Xiao M, Berman EL, Cunningham JE, Lee PS, *et al.* Germline p53 gene mutations in subsets of glioma patients. J Natl Cancer Inst 1994;86:344-9.
7. Izci Y, Akay KM, Gurkanlar D, Deveci MS. Radiation-induced glioblastoma multiforme following surgery for medulloblastoma in a child with neurofibromatosis-1: Case report. Turk Neurosurg 2005;15:71-5.
8. Louis DN, Ohgaki H, wiestler OD, Cavenee WK, editors. WHO Classification of Tumours of the Central Nervous System. Lyon: IARC; 2007. p. 36-7.
9. Perry A, Aldape KD, George DH, Burger PC. Small cell astrocytoma: An aggressive variant that is clinicopathologically and genetically distinct from anaplastic oligodendroglioma. Cancer 2004;101:2318-26.
10. Kong DS, Song SY, Kim DH, Joo KM, Yoo JS, Koh JS, *et al.* Prognostic significance of c-Met expression in glioblastomas. Cancer 2009;115:140-8.
11. Lim DA, Cha S, Mayo MC, Chen MH, Keles E, VandenBerg S, *et al.* Relationship of glioblastoma multiforme to neural stem cell regions predicts invasive and multifocal tumor phenotype. Neuro Oncol 2007;9:424-9.
12. Agrawal A, Makannavar JH, Shetty JP, Shetty L, Varkey B. Multifocal Glioblastoma multiforme. Eur J Gen Med 2012;9:289-91.
13. Balériaux D, Parizel PM, Matos C, David P, Bank WO. Stereotactic indications for neuroradiological differential diagnosis. Acta Neurochir (Wien) 1993;124:31-3.
14. Parsa AT, Wachhorst S, Lamborn KR, Prados MD, McDermott MW, Berger MS, *et al.* Prognostic significance of intracranial dissemination of glioblastoma multiforme in adults. J Neurosurg 2005;102:622-8.
15. Hassaneen W, Levine NB, Suki D, Salaskar AL, de Moura Lima A, McCutcheon IE, *et al.* Multiple craniotomies in the management of multifocal and multicentric glioblastoma. Clinical article. J Neurosurg 2011;114:576-84.

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