Case Series

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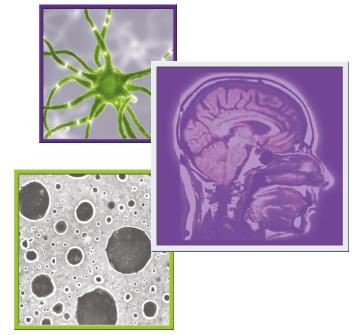

Small cell glioblastoma multiforme: a case series and clinicopathological update

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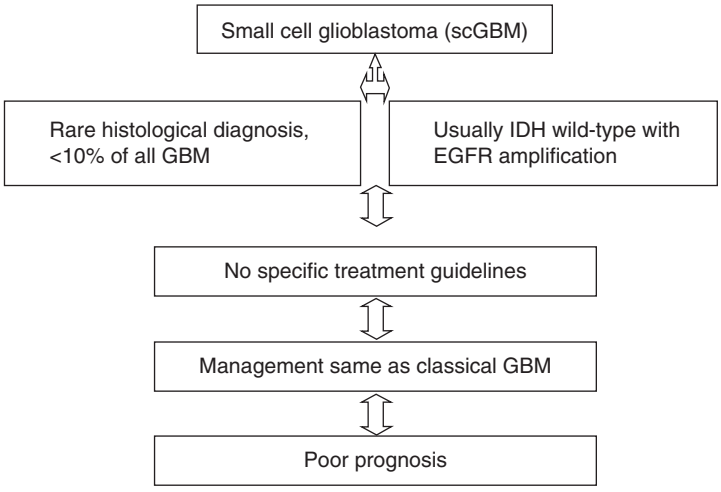
Small cell glioblastoma (scGBM) is a rare histological variant of classical glioblastoma (GBM). Presence of necrosis and microvascular proliferation is not essential for the diagnosis. It is thought to have more aggressive behavior as compared with classical GBM; however, because of its rarity standard treatment guidelines are not available. Adjuvant treatment for these cancers consists of postoperative radiotherapy with concurrent and maintenance temozolomide similar to classical GBM. Here we present a case series of five small cell glioblastoma patients along with the clinical-pathological review.

Graphical abstract:



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Small cell glioblastoma (scGBM) is a rare histological variant of classical glioblastoma (GBM) and constitutes <10% of all GBMs [1]. scGBM is usually *IDH* wild type and shows *EGFR* amplification. Owing to its rarity, clinical behavior and specific treatment guidelines are not available. Previous reports have suggested that it has an aggressive behavior as compared with classical GBM.

Most patients receive treatment on the same protocols as classical GBM. However, it's aggressive nature and different molecular profile suggest a need to explore methods of treatment intensification with either radiotherapy (RT) or targeted therapy. Here we present a case series of five scGBM patients along with clinical-pathological review, differential diagnosis and outcome.

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Case series

Radiotherapy records from the past year were reviewed to identify scGBM patients for analysis. Clinicopathological, demographic, treatment and survival details were entered in a predesigned proforma.

Case 1

A 56-year old male presented with headache and altered sensorium. Contrast enhanced MRI (CEMRI) of the brain showed features of high-grade glioma (HGG) in the right temporal lobe. He underwent craniotomy with subtotal excision of tumor. He received 20 fractions of RT with temozolomide (TMZ) and later defaulted for further radiotherapy. He was on the best available supportive care at nearby government hospital and died 6 months after diagnosis.

Case 2

A 57-year old male patient presented with headache, vomiting and right sided weakness. CEMRI brain showed HGG in the left temporoparietal lobe for which he underwent craniotomy and gross total excision of the tumor. He did not seek any adjuvant chemoradiation due to SARS-CoV-2 related lockdown and was on domiciliary care. Later, his health deteriorated and he died 5 months post diagnosis.

Case 3

A 62-year old male patient presented with headache. CEMRI of the brain revealed multicentric lesions for which he underwent craniotomy and subtotal excision of the tumor. He has completed postoperative RT (PORT) with concurrent TMZ. Currently he is on adjuvant TMZ and has received four cycles of TMZ to date. Patient is asymptomatic at present.

Case 4

A 53-year old male patient presented with headache, nausea and memory disturbance. CEMRI of the brain showed HGG in the left temporoparietal region. He underwent gross total excision of the tumor, but his adjuvant treatment was compromised due to SARS-CoV-2 related travel disruptions. His performance status deteriorated and he died 4 months after his diagnosis.

Case 5

A 36-year old female presented with headache and vomiting. CEMRI of the brain showed a frontal lesion for which she underwent craniotomy and subtotal excision. She could not make her visits to hospital for adjuvant treatment amidst SARS-CoV-2 related lockdown and died 3 months after her diagnosis.

Histopathological examination

Histopathological examination of all cases showed features of HGG. They were composed of sheets of neoplastic glial cells in a fibrillary background. The cells varied from round to elongated, with high nuclear:cytoplasmic ratio and hyperchromatic nuclei. They showed high mitotic and apoptotic activity. High-grade features, such as necrosis and microvascular proliferation, were present in all. Case 2 showed extensive necrosis with predominantly perivascular preservation of tumor cells. Case 3 and 4 showed focal perinuclear halo and delicate capillary network (Figure 1). Rosette formation could not be appreciated in any case.

On performing immunohistochemistry, all cases showed patchy positivity for GFAP and synaptophysin (Figure 2A & B). CD56 showed membranous staining in one case (Figure 2C). They were negative for cytokeratin, *TTF1*, CD45, CD3, CD20, neurofilament protein and NeuN. All cases were negative for *IDH1R132H* (Dianova, clone H09) (Figure 2D) and showed retained nuclear *ATRX* expression. Ki-67 index was uniformly high in all. All cases were negative for *p53*. FISH was carried out for 1p/19q codeletion using dual color probe (Vysis), all cases found be negative. *EGFR* immunopositivity was detected in two cases (40%, cases 2 and 5); however, *EGFR* amplification by FISH could not be carried out. Thus, these cases were diagnosed as scGBM, grade IV (WHO, 2016).

Table 1 shows clinicopathological and survival details of all five scGBM patients.

Table 2 shows differential diagnosis of scGBM based on immunohistochemistry.

Table 1. Clinicopathological and survival details of small cell glioblastoma patients.

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)/sex		56/male	57/male	62/male	53/male	36/female
Clinical presentation	Features of raised intracranial tension	Headache	Headache and vomiting	Headache	Headache and nausea	Headache and vomiting
	Neurological deficit	–	Right sided weakness	–	–	–
	Sensorium	Altered	–	–	–	–
	Memory	–	–	–	Impaired	–
Duration of symptoms		3 weeks	10 days	1 month	15 days	3 months
Karnofsky performance status (KPS)		70	70	80	60	60
MRI (pre-operation)	Site	Right temporal lobe	Left parieto-occipital lobe	Left frontal parietal, temporal and occipital lobe	Left parietal and occipital lobe	Left temporal lobe
	Focality	Solitary	Solitary	Multifocal	Multifocal	Solitary
	Size (cm)	7.5 × 6 × 5.6	5.6 × 7 × 4	7.3 × 4.7 × 5.9, 2.6 × 2.9 × 2.9 & 2 × 1.6 × 1	5.4 × 2.7 × 4.1 & 4.5 × 3.6 × 2.8	10.3 × 6.7 × 4.6
	Postcontrast enhancement	Absent	Present	Present	Present	Present
	Perilesional edema and mass effect	Absent	Present	Present	Present	Present
Type of surgery		STE	GTE	GTE	GTE	GTE
Histopathology	Percentage of small cell component (%)	40–50	60–70	40–50	50–60	60–70
	Necrosis	Present	Present	Present	Present	Present
	MVP	Present	Present	Present	Present	Present
	Lymphocytic infiltration	Negative	Negative	Negative	Negative	Negative
Immuno-histo-chemistry	*IDH1R132H* mutation	Negative	Negative	Negative	Negative	Negative
	ATRX	Retained	Retained	Retained	Retained	Retained
	p53 mutation	Negative	Negative	Negative	Negative	Negative
	Ki-67	High	High	High	High	High
	1p/19q codeletion	Negative	Negative	Negative	Negative	Negative
	EGFR amplification	Negative	Positive	Negative	Negative	Positive
	Cytokeratin, TTF1 CD45, CD3, CD20, Neurofilament protein and Neu N	Negative	Negative	Negative	Negative	Negative
Improvement/ deterioration after surgery		Improved	Improved	Improved	Improved	Improved
PORT		Defaulted after 20 fractions of radiotherapy	Not received	60 Gy/30 fractions/6 weeks	Not received	Not received
Concurrent TMZ		Yes	–	Yes	–	–
Adjuvant TMZ		–	–	Ongoing (completed 4 cycles)	–	–
MRI (after radiotherapy)		–	–	Partial response	–	–
Survival		Died 6 months post diagnosis	Died 5 months post diagnosis	Alive 8 months post diagnosis	Died 4 months post diagnosis	Died 3 months post diagnosis

GTE: Gross total excision; MVP: Microvascular proliferation; PORT: Postoperative radiotherapy; STE: Subtotal excision; TMZ: Temozolomide.

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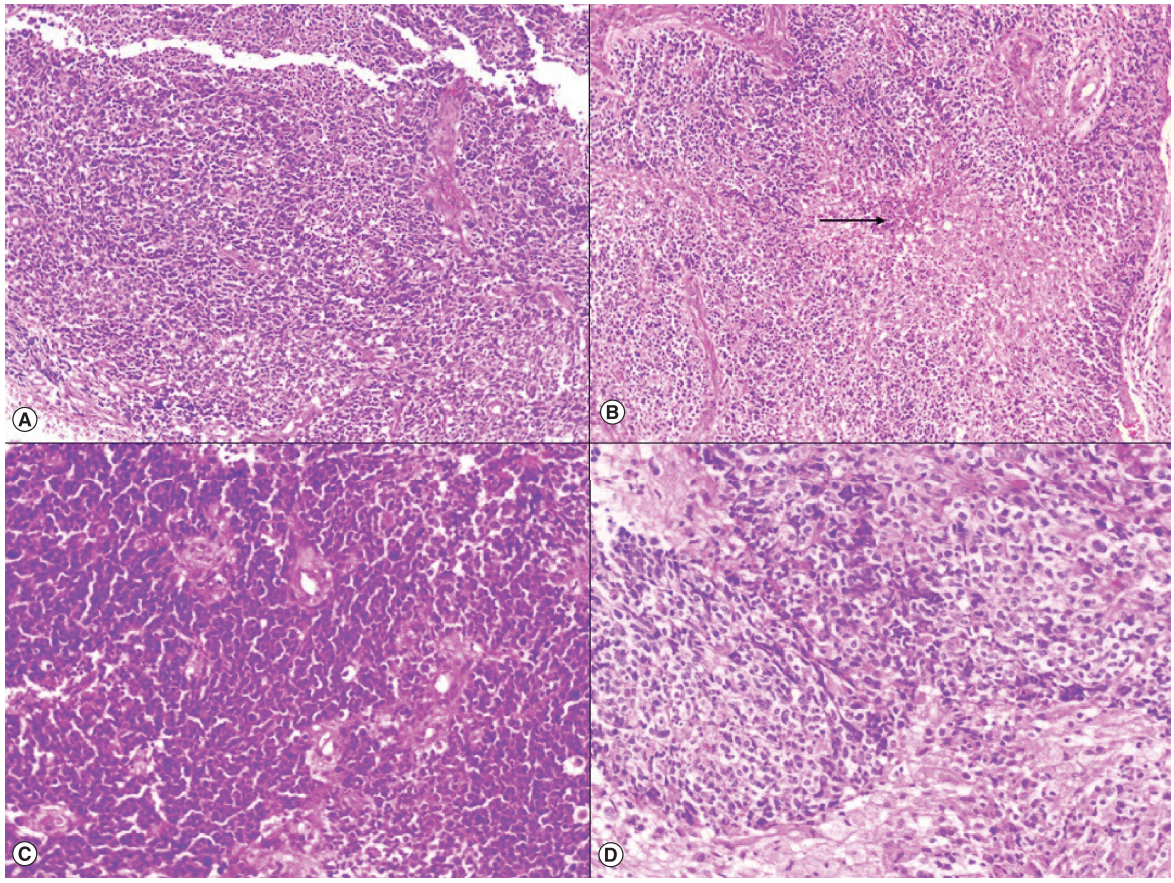

Figure 1. Histological examination. (A) Histological examination of case 1 shows a highly cellular glial tumor arranged in sheets (hematoxylin and eosin, ×100). **(B)** Representative section from case 2 shows areas of palisaded necrosis, shown in black arrow (hematoxylin and eosin, ×100). **(C)** Representative section from case 3 shows sheets of tumor cells with high nuclear:cytoplasmic ratio and hyperchromatic nuclei (hematoxylin and eosin, ×200). **(D)** Representative section from case 4 shows focal perinuclear halo (hematoxylin and eosin, ×200).

Table 2. Differential diagnosis of small cell glioblastoma on histology.

	Classical GBM	Small cell GBM	Anaplastic oligodendroglioma	Lymphoma	GBM with primitive neuroectodermal component
Cellular morphology	Elongated to polygonal cells	Small cells with high N:C ratio	Small round cells with high N:C ratio and perinuclear halo	Round cells with high N:C ratio, perivascular arrangement	Small cells with high N:C ratio, rosettes may be present
Atypia	Usually marked	Mild	Mild	Mild	Mild
Mitoses	Frequent	Frequent	Frequent	Frequent	Frequent
Necrosis	Present	+/−	+/−	+/−	Usually present
Microvascular proliferation	Present	+/−	+/−	+/−	Usually present
IDH	Negative	Negative	Positive	Negative	Negative
ATRX	Retained	Retained	Retained	Retained	Retained
1p19q codeletion	−	−	+	−	−
CD45	−	−	−	+	−
CD20	−	−	−	+	−
Synaptophysin	−	+/−	−	−	+
CD56	−	+/−	−	−	+

GBM: Glioblastoma; N:C: Nuclear:cytoplasmic ratio.

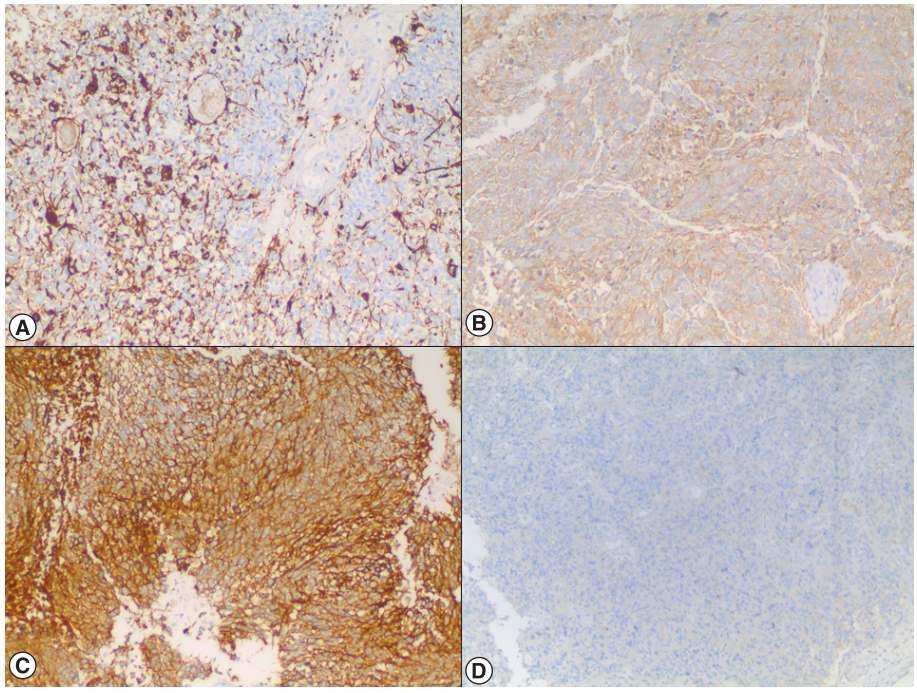

Figure 2. Immunohistochemistry. (A) Patchy strong positivity for GFAP (immunohistochemistry, ×100). **(B)** Patchy and faint positivity for synaptophysin (immunohistochemistry, ×100). **(C)** Diffuse membranous positivity for CD56 (immunohistochemistry, ×100). **(D)** Negative for *IDH1* (immunohistochemistry, ×100).

Discussion

scGBM is rare pathological variant of classical GBM. Radiologically it does not differ from conventional GBM; however, multifocality is more common in scGBM. Morphologically, scGBM is composed of small sized astrocytes with high cellular density. The cells are round to elongated and show high nuclear cytoplasmic ratio and mitotic activity. Areas showing conventional GBM-like appearance are interspersed with predominantly small cell-like areas. There may be varying degrees of necrosis and microvascular proliferation, but these features are not essential for the diagnosis of scGBM, in contrast to conventional GBM [1]. scGBM is a diagnosis that can be certainly made only on histopathology; however, immunohistochemistry may be required to exclude differential diagnoses, including anaplastic oligodendroglioma, lymphoma, primitive neuroectodermal tumor and metastatic small cell carcinoma. FISH for 1p/19q codeletion is necessary to rule out anaplastic oligodendroglioma, which is the closest differential diagnosis. All our cases were negative for *IDH1* and showed retained *ATRX* expression.

Owing to its rarity, standard treatment guidelines are not available for scGBM and patients are treated with the same protocols as used for classical GBM. Huang *et al.* analyzed 281 GBM patients, of which 18 (6%) patients had scGBM [2]. All patients received adjuvant chemoradiation including TMZ but a higher RT dose was used for scGBM, resulting in similar median survival for both groups (15.3 months for GBM and 16 months for scGBM). This led the authors to assume similar clinical outcomes [2]. Takeuchi *et al.* reported the clinicopathological features of 14 scGBM patients diagnosed over a period of 10 years (2005–2015) [3]. Ten of their patients received PORT with TMZ, one patient received PORT and carboplatin–etoposide chemotherapy while three patients received only TMZ. Overall survival ranged from 5 to 23 months. No patient survived over 2 years from diagnosis, depicting aggressive behavior. In another case report, the patient received standard PORT and TMZ; however, his disease progressed after three cycles of adjuvant TMZ and he needed two more lines of chemotherapy (Irinotecan and lomustine as second line, bevacizumab and carboplatin as third line) to which he had partial response before progression [4].

Salvage options for recurrent GBM are limited. Bevacizumab has been approved for treatment of recurrent HGG and improves the steroid-free interval and progression-free survival, albeit without an impact on overall survival [5]. EGFR amplification is associated with poor response to bevacizumab in recurrent GBM [6]. As most scGBMs show EGFR amplification, the role of bevacizumab is unclear. The role of EGFR inhibitors is limited despite the patients'

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EGFR amplification as most antibodies cannot penetrate blood–brain barrier. A dull immune response in scGBM suggests the role of immunotherapy [3].

Our study has the limitation that three patients could not receive adjuvant chemoradiation due to unforeseen circumstances (SARS Cov-2 lockdown) and one patient defaulted after receiving few fractions of radiotherapy. All these four patients died within 3–6 months after diagnosis, which indicates the aggressiveness of scGBM. Only one patient who received adjuvant treatment is alive, thus highlighting the importance of chemoradiotherapy.

Conclusion

Small cell Gliobalstoma is an aggressive malignancy. It is a rare histological variant of classical Glioblastoma. Specific treatment guidelines are not available despite the different molecular profile as these tumors are generally not analyzed separately in clinical trials due to the rare occurrence. Inclusion of these rare histologies in clinical trials with follow-up details may help in consolidating knowledge and understanding of their clinical behavior and treatment strategies.

Future perspective

Future of GBM lies in molecular research and establishing molecular classification of predictive and prognostic markers so that patients benefit most as per there classification sub type. It would also help in evolving targeted therapy according to their molecular subtype.

Executive summary

- Small cell glioblastoma (scGBM) is a rare histological variant of glioblastoma (GBM), accounting for <10% of all GBM cases.
- scGBM is associated with aggressive behavior and a poor outcome.
- *EGFR* amplification is more common for scGBM than classical GBM.
- Most of the scGBM patients are *p53* negative.
- Anaplastic oligodendroglioma, lymphoma, primitive neuroectodermal tumors and metastatic small cell carcinoma of the lung are common differential diagnoses.
- Standard treatment guidelines for scGBM are unavailable.
- Most scGBMs are treated like classical GBM, with postoperative radiotherapy (60 Gy/30 fractions over 5 weeks) alongside concurrent and adjuvant temozolomide.
- Salvage options for recurrent scGBM are limited.

Author contributions

AK Yadav: writing the manuscript, literature review; R Madan: concept, editing the manuscript, patient radiotherapy planning; D Chatterjee: provided pathology inputs; S Dhiman: did telephonic communication with the patients, spelling and grammar check; S Goyal: editing the manuscript, literature search; N Kumar: editing the manuscript; SK Sahoo: surgical inputs.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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