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18.1 Introduction

Gliomatosis cerebri (GC) is a rare form of diffuse glioma with growth pattern which involves at least three lobes of the cerebrum and frequently presents as bilateral growth and may have an infratentorial extension [1]. Gliomas of different grade and cell origin which includes astrocytes and oligodendrocytes, can grow in the pattern and this leads to difficulty in defining the molecular profile of the disease. The lesion has significant discordance in the pattern of presentation as it usually remains silent but the radiological imaging reveals extensive disease. Considered as a disease entity, the status has been removed from the 2016 WHO update on the classification of CNS Tumors [1]. The prognosis associated with GC is poor with around 25–50% of the patient population surviving less than a year from symptom onset [2, 3]. The peak incidence is seen between 20 and 50 years age with median age of 48 years (Range 46–53 years) [4] and equal gender involvement with slight male preponderance (1.5:1) [5]. The newer classification entitles the tumor to be classified under the subtype of glioma the disease resembles and they have been found to have poor prognosis compared to corresponding diffuse glioma of the similar molecular grade. The low incidence of the disease has led to poor understanding of the tumor biology and thereby lead to effective treatment options.

Classification GC can be classified into two types [6, 7]:

1. Primary GC—arises de novo; further classified as:
 - (a) Type I—Classic type, when no obvious mass is present
 - (b) Type II—Diffuse infiltrative pattern with associated tumor mass

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2. Secondary GC—Infiltrative spread of tumor cells from previously diagnosed glioma and may be associated with prior radiation or antiangiogenic therapy.

Further, the tumors can be classified according to the histologic grade and molecular findings.

- GC—Diffuse Astrocytoma; IDH mutant or wild type
- GC—Anaplastic Astrocytoma; IDH mutant or wild type
- GC—Glioblastoma; IDH mutant or wild type
- GC—Oligodendroglioma; IDH mutant and 1p/19q co-deleted
- GC—Anaplastic Oligodendroglioma; IDH mutant and 1p/19q co-deleted

18.2 Symptoms and Signs

- Median age at diagnosis ranges from 46 to 53 years; Slight male preponderance.
- Clinical presentation is insidious and variable.
- Depend on the tumor location and patient's age.
- Include: Seizures, fatigue, mood changes, focal weakness, sensory loss, changes in thinking and memory with dementia-like features, and headaches.
- Signs: Corticospinal tract, spinocerebellar, sensory-motor and visual field deficits, cranial neuropathies, papilledema, myelopathy, hemiparesis, ataxia, and cranial neuropathies.

18.3 Diagnosis

- A. *CT scan*:
- (a) Can be normal and lesion can present as isodense to normal brain parenchyma
 - (b) Ill-defined asymmetry or subtle hypoattenuation of involved brain parenchyma
- B. *MRI*: It forms the investigation of choice for establishing diagnosis [8, 9].
- (a) Loss of grey-white matter differentiation and diffuse gyral thickening.
 - (b) Mass effect and enhancement are often minimal.
 - (c) T1: iso- to hypointense to grey matter.
 - (d) T2: hyperintense to grey matter.
 - (e) T1 contrast: typically, no or minimal enhancement.
 - (f) DWI: Usually no restriction.
- C. *MR Spectroscopy*:
- (a) Elevated Choline: Creatine and Choline: NAA ratio
 - (b) Marked elevation of myoinositol
 - (c) Perfusion study: Low/normal rCBV—no vascular hyperplasia

- D. *Positron emission Tomography (PET)*: [10, 11]
- (a) It is of not much use in establishing diagnosis; Usually shows hypometabolism
 - (b) Can be useful for tumor extent or treatment response assessment
- E. *Biopsy*: Histopathologically, the lesion needs to be confirmed with a biopsy. At least two different samples need to be taken from the same needle tract at different depths. This helps increase the sample amount without developing significant complications [12].

18.4 Histopathology and Molecular Classification: [13]

1. Gross: Firm, edematous areas with flattened gyri and loss of grey-white interphase.
2. Diffuse, irregular parenchymal infiltration of glial cells.
3. On microscopy, small, astrocytic cells with elongated fusiform nuclei which stain for glial fibrillary acidic protein (GFAP) are seen; however, neovascularization, high mitotic activity, and necrosis are uncommon.
4. Histological grading: GC is encompassed from Grade II-IV
 - (a) *Grade II* gliomatosis cerebri are mid-grade tumors and they have a higher chance of recurrence.
 - (b) *Grade III and IV*—They are fast-growing tumors and often become resistant to treatment.
5. Molecular Profiling: [14, 15]
 - (a) There are no characteristic features or subgroups noted for GC.
 - (b) Astrocytic variants are the most common with non-co-deleted 1p/19q variants.
 - (c) Difference in the molecular profile of pediatric and adult GC is noted where IDH mutation and oligodendroglioma type is uncommon in the pediatric population.

18.5 Differential Diagnosis: [7, 16]

1. Progressive multifocal leukoencephalopathy
2. Multifocal/multicentric glioblastoma
3. Primary CNS lymphoma
4. Viral encephalitis
5. Behcet's disease
6. Vasculitis
7. Subacute sclerosing panencephalitis
8. Idiopathic intracranial hypertension
9. Tubercular encephalitis
10. Leukodystrophy
11. Primary progressive multiple sclerosis

Treatment There is no standard treatment defined for GC due to lack of clinical trials in view of the rare incidence. The disease has a poor prognosis with 25–50% patient population surviving for less than 1 year indicating towards the rapidly progressive nature of the disease.

A. *Surgery:*

- (a) Role of surgery lies in providing tissue diagnosis, as resection is not feasible considering the diffuse involvement of the cerebral regions by the tumor.
- (b) Partial resection can be considered when the patient presents with symptoms due to mass effect and T2-weighted or T1 contrast images can help in tumor debulking.
- (c) There is no significant benefit on the survival outcomes on the extent of resection (21 months with resection vs 18 months post biopsy; $p = 0.96$) [17].

B. *Radiation Therapy:* The role of radiation therapy presents a dilemma as the fields involved are extensive and the tumor appears radioresistant. The disease entity is treated similar to a high-grade glioma. Adult cases can be treated either with radiation alone or chemo-radiation; however, the role of chemotherapy is under evaluation in the children. The various trials conducted do not show any correlation between the radiation dose and treatment volumes with the survival outcomes and the dose delivered is controversial [18–21].

- (a) The radiation field involved and the doses delivered are:

Whole Brain Radiation—20–60 Gy with 1.8–2Gy per fraction delivered. The total dose depends on the performance status of the patient and the toxicity assessment while on treatment [4, 5].

Focal Radiation—54–66 Gy with 1.8 Gy per fraction delivered [17]. The volume included the visible disease on T2-weighted or T1 contrast images which constituted the gross tumor volume (GTV). A margin of 1–1.5 cm to this volume constituted the clinical target volume (CTV). An additional PTV was given with 0.5 cm to the CTV.

- (b) The survival outcomes differ in the literature with one study showing no difference in the overall survival (OS) with addition of radiation therapy and another contrasting study showed a significant OS benefit with addition of radiation therapy (27.5 vs 6.5 months; $p < 0.01$) [5, 7].

C. *Chemotherapy:*

- Chemotherapy has been delivered either alone or with radiation therapy, but none of the studies in the literature available have shown a benefit in this disease entity.
- In a prospective phase II single arm study, NOA-05, the role of procarbazine and lomustine was evaluated as upfront chemotherapy option in this disease [22]. It showed a progression-free survival benefit of 14 months and an overall survival of 30 months and they concluded, upfront addition of chemotherapy could have potential benefits in the management of GC.
- Other chemotherapy options used include temozolomide (TMZ) and procarbazine, lomustine and vincristine (PCV) combination. On retrospective analysis of these chemotherapy options, the PFS benefit was of around

16 months and OS of 26 months for both TMZ and PCV. However, toxicities were found to be higher with PCV [6, 23].

- TMZ needs to specifically be considered for the cohort with oligodendroglial pathology with 1p/19q co-deletion as they have improved PFS and OS [24].
- D. *Role of Immunotherapy*: Immunotherapy is an option being explored for high-grade gliomas; however, it has not been studied for GC. In view of IDH-mutations being common in GC, there are trials underway looking into the role of IDH inhibitors (NCT02746081).

18.6 Future Trials

- HIT-HGG-2013 trials is looking into the role of valproic acid and chloroquine along with radiation and TMZ in children (>3 years age) with high-grade glioma including GC.
- NCT02758366: A Phase II trial which is looking into the role of doxorubicin in combination with radiation and TMZ in high-grade glioma including GC.
- Another Phase I/II study is looking into the role of gefitinib with radiation therapy in pediatric patients with GC (NCT00042991).

18.7 Conclusion

Gliomatosis cerebri is a rare disease entity which has a poor prognosis and has not been completely understood. The treatment options continue to be a dilemma for the oncologists due to lack of clinical trials. Radiation with or without chemotherapy seems to be the current standard of care. Radiation therapy has shown significant improvement in the overall survival; however, the doses and treatment fields are still a controversy. The increasing role of molecular profiling will help better classify the disease and there is a need for prospective trials to comprehensively define the treatment options for this disease.

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