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Gliomatosis cerebri: clinical characteristics, management, and outcomes

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Abstract

Gliomatosis cerebri is a rare diffusely infiltrating primary neoplastic glial process of the brain. Our objective is to review clinical presentation, management, and outcome in a large single institution series of gliomatosis cerebri patients. 54 consecutive gliomatosis cerebri cases presenting to Mayo Clinic Rochester between 1991 and 2008 were retrospectively reviewed. Inclusion criteria included involvement of at least three cerebral lobes, lack of a single discrete mass and pathological confirmation of diffuse glioma. Median overall survival (OS) was 18.5 months. Age, gender, presenting symptoms, and contrast enhancement did not correlate significantly with survival, though there was a trend toward decreased overall survival in patients above the median age of 46 years. Karnofsky performance score <70 was associated with poor OS (median 9.5 vs. 20.5 months, $p = 0.02$). Higher histologic grade was associated with poor progression-free survival

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(PFS; median for WHO grades II, III, and IV: 21.5, 6.5, and 4 months; $p = 0.03$) and OS (median 34, 15.5, and 8.5 months; $p < 0.05$). Radiation therapy was strongly associated with better prognosis (PFS 16.5 vs. 4.5 months, $p < 0.01$; OS 27.5 vs. 6.5, $p < 0.01$), but chemotherapy was not. Gliomatosis cerebri patients have a poor prognosis. Lower KPS upon presentation and higher histologic grade predict decreased survival. Surgery's role is limited beyond biopsy for diagnostic purposes. Radiotherapy appears beneficial, although selection bias could be present in this retrospective study. Chemotherapy's value is not as clear but this must be interpreted with caution given variable treatment regimens in this series.

Keywords

Gliomatosis cerebri; Malignant glioma; Surgery; Radiation; Chemotherapy

Introduction

Gliomatosis cerebri is a rare diffuse neoplastic process of the brain that carries a poor prognosis [1]. The World Health Organization defines it as a diffusely infiltrating glial neoplasm affecting at least three cerebral lobes, usually with bilateral involvement of the cerebral hemispheres and/or deep gray matter [2, 3]. Grossly, gliomatosis cerebri can be categorized as either having no discrete tumor mass (type 1, or the classical form) or having a discrete mass in addition to extensive CNS involvement (type 2). Histopathologically, it is characterized by infiltrating neoplastic astrocytic elements into the surrounding neuropil [4]. Its rarity makes it difficult to define prognostic factors and appropriate management. Most reports have been limited by small sample size or by data pooled from databases and literature without central pathology or imaging review. These studies have presented conflicting data regarding efficacy of certain treatments. Therefore, we present here a series of 54 patients presenting to the Mayo Clinic in Rochester, MN with radiographically and histologically confirmed gliomatosis cerebri. The purpose of our study was to describe the clinical presentation, determine prognostic indicators, and assess the efficacy of differing treatment modalities in gliomatosis patients.

Materials and methods

Patient population

Patients with a diagnosis of gliomatosis cerebri presenting to Mayo Clinic Rochester between 1991 and 2008 were identified through the Mayo Clinic patient database. All aspects of this study were reviewed and approved by the Mayo Clinic Institutional Review Board (Mayo Clinic IRB# 08-007099). Each patient's record was reviewed by a neuroradiologist (JM) and a neuropathologist (CG). Only patients with an MRI illustrating involvement of at least three cerebral lobes and histology consistent with a diffuse glioma were included for further study. All cases were of primary gliomatosis cerebri, in which there was no pre-existing focal glioma prior to initial presentation. Demographics, clinical presentation, MRI findings, histopathological diagnosis, management, progression-free survival, and overall survival were recorded.

Immunohistochemistry

Immunohistochemical staining for mutant isocitrate dehydrogenase-1 (IDH1) was performed in cases in which either unstained sections or paraffin blocks were available using the anti-human IDH1 R132H mouse monoclonal antibody DIA clone H09 (Dianova, Germany) at a dilution of 1:100. Using a Ventana BenchMark XT stainer, pretreatment with Cell Conditioner 1 (EDTA) MILD was followed by a primary antibody incubation time of

32 min at 37 °C and Ventana UltraView detection with Ventana DAB. Hematoxylin Counterstain was performed on the Leica ST 5020.

Statistical analysis

We assessed survival outcomes using Kaplan–Meier analyses. Progression free survival was only examined in patients who demonstrated secondary progression after an initial stabilization of their disease with medical or surgical management. Univariate analysis was performed correlating neurologic presentation, radiographic findings, histology, and therapeutic modalities utilized with survival. Subsequent regression analyses using the log-rank test was performed to establish the level of statistical significance. Statistical analysis was performed using JMP 8.0 software.

Results

Patient population

A total of 80 patients with a preliminary diagnosis of gliomatosis cerebri were identified through the Mayo Clinic database. Of these, 26 patients were excluded based on absence of confirmatory radiographic or histological diagnostic criteria. The remaining 54 patients were the basis of this study. Patient demographics are shown in Table 1. Representative MRI's for two patients are shown in Fig. 1. The median age was 46 years (range 9–87 years). There was a slight male predominance (M:F ratio of 1.4:1). Median Karnofsky performance score at presentation was 80, with the most common presenting symptom being focal sensorimotor deficits (74 %). The vast majority of our patients fit the description of the classic type I gliomatosis cerebri (diffuse cerebral involvement without a discrete mass), with only two patients having a distinct neoplastic mass in addition to the diffuse tumor, causing them to be categorized as type II gliomatosis cerebri. Radiographic findings included enhancement on MRI in approximately three-fifths of our gliomatosis patients. The median number of lobes and/or distinct brain regions involved was six.

Survival data were available in 48 patients, either from their medical chart or from Social Security Death Indexes. The remaining six patients were lost to follow up after their initial presentation and were not U.S. citizens, which precluded us from obtaining survival data. A further 11 patients had incomplete treatment and progression data, resulting in a total of 37 patients for which complete treatment and progression data were available.

Gender, age, performance status, presenting symptoms and survival

Median overall survival in our series was 18.5 months (Fig. 2a). When the patients were divided into patients older than the median age at presentation (>46 years) and those 46 years old or younger, there was a trend toward decreased survival in the older age group (23.5 vs. 12 months, $p = 0.06$). Karnofsky performance score (KPS) at presentation correlated strongly with overall survival (Fig. 2b). Those with a KPS ≥ 70 had a significant survival benefit compared to those with a KPS < 70 (20.5 vs. 9.5 months, $p = 0.02$). The presence of specific presenting symptoms did not show a significant relationship with outcome.

Imaging findings and survival

Signaling patterns on magnetic resonance imaging (MRI) generally showed T1-weighted hypointensity and T2-weighted hyperintensity, with the exception of one patient that exhibited T1 hyperintensity and T2 hypointensity. Presence of enhancement on MRI did not predict prognosis (overall survival 19.5 vs. 11.5 months, $p = 0.18$). Additionally, the number

of areas involved ($p = 0.58$) and the presence of corpus callosum, thalamus, or brainstem involvement did not demonstrate a significant correlation with patient overall survival.

Nineteen patients had computed tomography (CT) scans of the head performed as part of their initial imaging. Interestingly, nine of these patients (47 %) demonstrated hyperdensity on CT, which is an atypical finding in astrocytic neoplasms [5]. This did not correlate with histological grade as the proportion of high grade neoplasms in each cohort did not differ significantly (80 % in the hypodense cohort compared to 89 % in the hyperdense cohort, $p = 0.60$). Of note, there was a trend toward improved overall survival in the hypodense patient population (32.5 vs. 12 months, $p = 0.06$).

Pathological findings and survival

The predominant histopathologic tumor type in our series was astrocytoma (with only 2/54 oligoastrocytomas). Thirty-five tumors were grade III (67 %), followed by grade II (21 %) and grade IV (12 %). As expected, tumor grade correlated significantly with both progression-free and overall survival (Fig. 2c, d). Grade II, III, and IV tumors had progression-free survivals of 21.5, 6.5, and 4 months, respectively ($p = 0.03$). This was mirrored in the overall survival data, with survival decreasing from 34 to 15.5 to 8.5 months as grade increased from II to IV ($p = 0.04$). Immunohistochemical staining for mutated isocitrate dehydrogenase-1 (IDH1 R132H) mutation was performed on 26 tissue samples available for examination. Of these, 24 were negative, with one positive case, and one indeterminate case. The one positive patient was deemed to have type I gliomatosis cerebri based on radiographic criteria. Survival data unfortunately were not available for this patient.

Treatment modalities and survival

Of the 37 patients for whom complete treatment and outcome data were available, 30 received radiation therapy. The radiation treatment regimens are outlined in Table 2. There was a striking association between survival and receiving radiation (Fig. 3a, b). Median progression-free survival was longer by 12 months (16.5 vs. 4.5 months, $p < 0.01$) and median overall survival was longer by 21 months (27.5 vs. 6.5 months, $p < 0.01$) in patients treated with radiation. When performing a subgroup analysis of each histologic grade, there remained a statistically significant survival benefit to undergoing radiotherapy. In grade 2 tumors, the median overall survival benefit was 33 months (40 vs. 7 months, $p = 0.0009$). For grades 3 and 4, the difference in overall survival also reached statistical significance (25.5 vs. 8 months, $p = 0.012$; 10.5 vs. 6 months, $p = 0.045$). Recognizing that there may be selection bias inherent to this retrospective review, we examined the demographics of patients that received radiotherapy and those that did not. In general, patients who did not receive radiation were older (median age 63.5 vs. 44 years, $p = 0.13$) and had poorer functional status at presentation (mean KPS 66 vs. 73.7, $p = 0.33$). While these differences did not reach statistical significance, they show a trend toward selecting younger, healthier patients to receive radiation treatment. The range of total dose of radiation utilized was 2,000 to 6,000 Gy, with a median value of 5,490 Gy. Median dose per fraction was 180 Gy. There was no correlation between the total dose received and progression free or overall survival, or between the dose per fraction and PFS or OS.

Nineteen patients (51 %) received some form of chemotherapy. While there was a trend to increased progression-free survival (12.5 vs. 5.5 months, $p = 0.67$) and overall survival (21 vs. 11.5 months, $p = 0.96$) in patients receiving chemotherapy, this did not reach statistical significance (Fig. 3c, d). The lack of survival benefit was noted with both concomitant and adjuvant chemotherapy (data not shown). However, one should note that chemotherapy

received by patients in our series consisted of a wide range of regimens, including procarbazine ($n = 2$), nitrosourea ($n = 4$), and temozolomide ($n = 13$).

Only five patients (13 %) underwent any form of surgical resection. While these patients did have better overall survival (median 35.5 months) compared to the remaining patients who were biopsied only, this was far from statistically significant ($p = 0.88$), with one patient having a worsened neurological status postoperatively.

Discussion

Gliomatosis cerebri is a rare disease, making determining prognostic factors and therapeutic strategies challenging. Previous studies have included conflicting findings, including some that were surprising (e.g., lack of survival benefit with radiation [6]), but these studies lacked central pathological or radiological review. With that in mind, we have presented a large radiographically and histologically confirmed case series of gliomatosis cerebri patients. Our goal in this retrospective case series was to better delineate prognostic factors and optimal treatment strategies.

This study demonstrates that gliomatosis cerebri patients have a shorter survival than other patients with astrocytic tumors of corresponding pathologic grade. The literature cites the median survival of patients with grade 2 astrocytomas as anywhere from 51 to 100 months [7-9], whereas grade 2 gliomatosis patients in our study had a median overall survival of just 34 months. Grade 3 and grade 4 astrocytoma patients have a median survival of approximately 30 [10, 11] and 15 months [12], respectively, while gliomatosis patients of the corresponding grade in our study survived only 15.5 and 8.5 months on average. The poorer prognosis could reflect the inability to obtain a clinically significant surgical resection or possibly a different biologic pathogenesis of gliomatosis tumors.

Interestingly, while the predominance of grade 3 tumors in our series compares well to the prevalence of grade 3 histology in the United States, it contrasts with grade 2 constituting the majority of gliomatosis cases in Europe [6]. This may reflect a poorly defined environmental or genetic effect, or it could be an artifact of the small numbers of cases available for review. Alternatively, this difference could be due to differences between neuropathologists' techniques, which adds significance to the fact that all cases in our series were reviewed by a single neuropathologist.

The median overall survival in our series (18.5 months) fell within the range of 14.5 and 38.4 months reported in the literature [6, 13, 14]. Patients older than the median age did show a strong trend to decreased survival compared to the younger subgroup, though this did not reach statistical significance. Clinical presentation was varied in our series, with the majority presenting with focal sensorimotor symptoms. This is compatible with published literature [14-19]. While specific symptomatology did not impact survival, the patients' overall neurologic status as reflected in their KPS correlated strongly with outcome.

We examined in detail whether radiological findings correlated with prognosis. We speculated that our novel observation of hyperdense gliomatosis cerebri lesions in a substantial number of cases might correlate with decreased survival as hyperdense lesions on CT are frequently hypercellular. Unfortunately, we were unable to correlate any suggested hypercellularity with restricted diffusion on MRI as few patients underwent both CT imaging and diffusion-weighted imaging. We did see a trend towards decreased survival in patients with hyperdense lesions (median overall survival: 32.5 vs. 12 months) and the comparison nearly reached statistical significance ($p = 0.06$). However, we did not see a statistically significant association between enhancement on MRI and prognosis. This

suggests that a large portion of non-enhancing gliomatosis cerebri cases may still be high grade (grade III or IV), a finding supported by our data and in keeping with the literature [20-22]. Finally, we were somewhat surprised to find that the number of lobes/cortical areas involved did not correlate with outcome. Therefore, we believe that MRI findings may fail to truly delineate the disease burden in such a diffusely invasive process.

Others have suggested that involvement of specific structures by gliomatosis cerebri impacted survival. For example, Kaloshi et al. [23] reported that the extent of gray matter involvement seems to correlate negatively with patient outcome. Ware et al. [24] actually found improved survival in gliomatosis cerebri patients with corpus callosal involvement. Our study, however, failed to demonstrate a negative (or positive) impact on survival with the presence of thalamus, corpus callosum, or brainstem involvement. This further emphasizes that anatomic MRI findings alone cannot accurately predict patient survival. As an alternative, MR spectroscopy in gliomatosis cerebri has been studied, but no distinguishing features have been identified compared to other gliomas [25-27]. 18F-FDG PET, as it has been used in glioblastoma [28], may be an alternative technique to better characterize the aggressiveness of specific cases of gliomatosis cerebri. More recently, functional diffusion maps have been applied to gliomatosis cerebri for localizing regions of hypercellularity and monitoring overall tumor status [29]. Thus, metabolic imaging may play a larger role in gliomatosis cerebri as imaging technology improves, but its utility currently remains unproven.

The absence of a strong correlation between imaging findings and patient survival highlights the necessity of obtaining tissue to more accurately characterize tumor pathology. In fact, gliomatosis cerebri may exhibit a distinct biology from non-gliomatosis cases. That 70 % of WHO grade II and III astrocytomas and oligodendrogliomas and secondary GBM's express IDH1 mutations [30], while only one sample in our series had mutant IDH1 may suggest that at least type I gliomatosis tumors evolve along a different pathway. However, molecular studies in gliomatosis cerebri to date have not demonstrated unique alterations compared to other gliomas [24, 31-35]. Indeed, Herrlinger et al. [32] showed that molecular genetic alterations in gliomatosis cerebri were similar to those in diffuse astrocytomas.

Furthermore, gliomatosis cerebri is not a homogeneous entity. Two radiographic subtypes have been identified: the classic subtype without a solid component (type I) and a second subtype with a solid component (type II). In addition to this imaging classification, the underlying molecular pattern may be different in the two categories. IDH1 mutations (common in lower grade astrocytomas and secondary glioblastomas [36]) have been reported as more prevalent in type II gliomatosis cerebri [33]. In keeping with this, only one sample out of 26 was positive for the IDH1 R132H mutation in our study, likely representative of the fact that our series consisted primarily of patients with type I gliomatosis cerebri (only two patients had type II gliomatosis cerebri, neither of which had tissue available for immunohistochemical assays). While IDH1 mutation may be a favorable prognostic factor in type II gliomatosis [37], it appears to bear no significance in patients with type I gliomatosis cerebri.

We demonstrated a statistically and clinically significant association between survival and radiotherapy. Given that this is a retrospective study, the conclusions regarding the utility of radiotherapy and/or chemotherapy remain speculative. Still, while acknowledging the selection biases inherent within a retrospective review, we feel that our data argue in favor of radiation therapy in appropriately selected gliomatosis cerebri patients. This is corroborated by most [24, 38-41] but not all [6] prior reports. However, we did not see a statistically significant association between chemotherapy and survival in our series. This may simply reflect the limited number of patients who received chemotherapy.

Alternatively, it might reflect the dramatically changing chemotherapy protocols for gliomas over the study period. In the future, more data about patients who received concurrent radiation/temozolomide followed by adjuvant temozolomide (as is now standard for glioblastoma multiforme [12]) may become available. Others have reported benefit for chemotherapy in gliomatosis, including temozolomide [42-46] and nitrosoureas (especially for tumors with an oligodendroglial component) [47]. Thus, our series does not definitively rule out a role for chemotherapy in gliomatosis cerebri. Furthermore, chemoresponsiveness for any given tumor may depend on its particular molecular signature, such as MGMT methylation in GBM or 1p19q co-deletion in oligodendroglial tumors [48, 49]. Kaloshi et al. [50] have reported that 1p19q co-deletion in gliomatosis patients is associated with MGMT promoter methylation and improved response to temozolomide. Therefore, the future of gliomatosis cerebri therapy may lie in tailoring a chemoradiation protocol to a tumor's genomic background.

Our data do not support the general employment of surgery in the management of gliomatosis patients beyond biopsy to obtain a histologic diagnosis. However, two patients undergoing surgical resection had symptoms of increased intracranial pressure (headaches), and a third had signs of subfalcine herniation on MRI. It is possible that these patients with signs and symptoms of raised intracranial pressure might have had worse outcomes without a debulking procedure. Thus, surgical judgment is still important and some form of resection may be appropriate in a small number of highly selected patients.

Summary

Gliomatosis cerebri has an extremely poor prognosis. The overall survival is worse than for other gliomas of the corresponding histologic grade, possibly reflecting the inability to perform meaningful surgical resection or inherent features of gliomatosis biology. While age and performance status correlate with survival, the strongest determinant of patient outcome is histological grade. Although the role for surgical resection is limited, radiotherapy is associated with improved survival. While our study did not particularly support the use of chemotherapy, it also did not find compelling evidence to challenge its use. Hopefully, the detection of more specific molecular markers will allow for improved patient-specific therapy in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Representative axial fluid-attenuated inversion recovery (FLAIR) MRI sequences of two patients with gliomatosis cerebri. **a** Nineteen year old man with a Karnofsky performance score (KPS) of 70 and grade II astrocytoma on biopsy who went on to receive radiation; overall survival 27 months. **b** Fifty year old man with a KPS of 50 and grade III astrocytoma who did not receive radiation; overall survival 8 months

Fig. 2.

Kaplan–Meier survival curves of the 48 patients in our cohort for whom survival data was available. Median overall survival was 18.5 months (**a**). **b** Survival curves comparing patients who presented with a high Karnofsky performance score (KPS ≥ 70) and a low KPS (KPS < 70) were significantly different (20.5 vs. 9.5 months, $p = 0.02$). **c** Progression free survival curves and **d** overall survival curves comparing patients with different histologic grades. Median PFS and OS decreased significantly with increasing grade (PFS: 21.5, 6.5, and 4 months for grades II, III, and IV, respectively; $p = 0.03$. OS: 34, 15.5, and 8.5 months for grades II, III, and IV, respectively; $p = 0.04$)

Fig. 3. Survival curves with and without treatment. Progression free survival (**a**) and overall survival (**b**) were both higher in patients undergoing radiotherapy (PFS: 16.5 vs. 4.5 months, $p < 0.01$; OS: 27.5 vs. 6.5 months, $p < 0.01$). Though there was a trend towards improved progression-free (**c**) and overall survival (**d**) in the cohort receiving chemotherapy, this difference did not reach statistical significance (PFS: 12.5 vs. 5.5 months, $p = 0.67$; OS: 21 vs. 11.5 months, $p = 0.96$)

Table 1**Patient demographics**

Median age	46 years (range 9–87)
Gender	
Male	32 (59 %)
Female	22 (41 %)
Median KPS	80 (range 10–90)
Presenting neurologic symptom	
Focal sensorimotor deficit	74 %
Seizure	52 %
Increased ICP (Headache, nausea/vomiting)	39 %
Cognitive deficits	21 %
Constitutional symptoms	9%
Median number of lobes/cortical areas involved	6 (range 3–10)
Bilateral involvement	72 %
Only left hemispheric involvement	15 %
Only right hemispheric involvement	13 %
Corpus callosal involvement	49 %
Brainstem involvement	32 %
Thalamic involvement	28 %
Percent hyperdense on CT	47 %
Percent enhancing on MRI	58 %
Histologic grade	
Grade 2	21 %
Grade 3	67 %
Grade 4	12 %
Histopathology	
Fibrillary astrocytoma	66.7 %
Small cell astrocytoma	5.5 %
Oligoastrocytoma	3.7 %
Astrocytoma not otherwise specified	24.1 %

Table 2

Radiotherapy regimens

Age	Gender	Grade	Type of radiation	Total dose (cGy)	# of fractions	Dose per fraction
72	F	2	Whole brain	4,100	15	273
57	M	2	Whole brain	5,580	31	180
35	M	2	Whole brain	5,400	30	180
34	M	3	Whole brain	5,940	33	180
87	F	3	N/A ^a	N/A	N/A	N/A
72	M	2	Whole brain	N/A	N/A	N/A
73	F	2	Whole brain	5,580	31	180
57	M	3	Whole brain	5,940	33	180
57	M	2	Whole brain	N/A	N/A	N/A
19	M	4	Whole brain	4,660	28	160
59	M	3	Whole brain	2,000	5	400
35	M	3	Whole brain and focused	5,580	30	186
43	M	2	Whole brain	4,500	25	180
41	M	4	Whole brain	4,800	15	300
45	M	2	Whole brain	5,400	30	180
43	M	3	Whole brain	5,940	33	180
53	M	3	N/A	N/A	N/A	N/A
39	F	2	N/A	N/A	N/A	N/A
47	F	2	Whole brain	2,000	5	400
22	M	3	Whole brain	5,940	33	180
31	F	3	N/A	N/A	N/A	N/A
31	F	3	Whole brain	5,940	33	180
74	M	3	Focused	N/A	N/A	N/A
67	M	3	Focused	6,000	30	200
36	M	3	Focused	5,940	33	180
39	M	4	Whole brain	N/A	N/A	N/A
46	M	4	Focused	5,890	31	190
31	M	2	Focused	5,940	33	180
71	M	3	Whole brain	N/A	N/A	N/A
43	F	3	Focused	5,600	33	200

^aRecords indicate that the patient received radiation treatment at an outside facility but the details of the treatment were not available for review