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TOPIC REVIEW

Primary gliosarcoma: key clinical and pathologic distinctions from glioblastoma with implications as a unique oncologic entity

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Abstract This report presents the historical experience, clinical presentation, treatment, prognosis, and pathogenesis of gliosarcoma described to date in the English literature. PubMed query of term "gliosarcoma" was performed, followed by a rigorous review of cited literature. Articles selected for analysis included: (1) case reports of gliosarcoma, (2) review articles of gliosarcoma, and (3) studies of the pathogenesis or genetics of gliosarcoma in humans. Our review identified 219 cases of gliosarcoma in 34 reports and eight articles addressing the pathogenesis. Survival in larger series ranged 4-11.5 months. Features unique to gliosarcoma compared to glioblastoma (GBM) include their temporal lobe predilection, potential to appear similar to a meningioma at surgery, repeated reports of extracranial metastases, and infrequency of EGFR mutations. Published experience is limited to small case series, and the pathogenesis remains unclear. Clinical and pathologic characteristics distinct from GBM suggest that they may warrant specific treatment, separate from conventional GBM therapy.

Keywords Gliosarcoma · Primary gliosarcoma · Review

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Introduction

Gliosarcoma was initially described by Stroebe in 1895 as a brain neoplasm consisting of both glial and mesenchymal components [1]. This biphasic tumor subsequently gained general acceptance from detailed histological analyses of Feigen and colleagues [2, 3]. Due to lack of specific and uniform diagnostic criteria however, the term gliosarcoma was also applied to tumors of glial origin that have taken on mesenchymal phenotypes, such as the ability to produce reticulin and collagen [2]. Over time, these tumors were understood as distinct entities, one being a tumor of glial origin taking on mesenchymal characteristics, termed desmoplastic glioma or glioma with desmoplastic metaplasia, the other entity being a tumor with distinct gliomatous and sarcomatous components, termed gliosarcoma [4]. The 2007 World Health Organization classification scheme places primary gliosarcoma (PGS) as a grade IV neoplasm and a variant of glioblastoma multiforme (GBM) [5]. The current accepted definition of PGS is a well-circumscribed lesion with clearly identifiable biphasic glial and metaplastic mesenchymal components [6]. Histologically, the glial component fulfills the cytologic criteria of GBM, and the mesenchymal component may show a wide variety of morphologies with origins from fibroblastic, cartilaginous, osseous, smooth and striated muscle, or adipose cell lineage. The current definition, however, lacks pathologic consensus, particularly regarding the relative predominance of a single element. As clinical and pathologic features of PGS continue to be elucidated, more rigorous diagnostic criteria must be considered. The current classification of PGS as a variant of GBM reflects the fact that they are often treated in the same manner; however anecdotal evidence suggests that PGS are distinct from GBM. In this report we review the published English Fig. 1 Histology of gliosarcoma. a $200 \times$. Immunohistochemical staining for vascular marker CD31, demonstrating focal perinuclear positivity in many of the tumor cells. Positive staining vascular endothelium serves as internal control. b 200×. Focal strong membranous staining of tumor cells with CD34 antibody. Positive staining within vascular endothelium serves as internal control. c 200×. Focal weak cytoplasmic staining with GFAP antibody in tumor cells. This suggests a glial origin. d Hematoxylin and eosin stain, 200×. Vascular endothelial proliferation and myxoid and chondromatous area in a gliosarcoma. The tumor cells show focal myxoid change and epithelioid morphology



language literature to highlight the unique clinical and pathologic features of PGS (Figs. 1, 2, 3).

Methods

Articles were identified through a PubMed query using the keyword "gliosarcoma". The cited references of the sources were also searched. 757 citations reported to date were screened using our inclusion criteria. Articles selected for analysis included: (1) case reports or series of gliosarcoma patients, (2) review articles of gliosarcoma, or (3) experiments studying the pathogenesis or genetics of gliosarcoma in humans. The search yielded 34 case series and reports meeting our criteria and included a total of 219 cases of PGS. Majority of these published series included cases of gliosarcoma.

Pathogenesis

The pathogenesis of gliosarcoma has been a topic of controversy and currently remains unknown. In addition, there has been no detailed study to date that focuses on genetic and pathologic differences between PGS and secondary gliosarcoma. Early reports suggested that the sarcomatous components originated from neoplastic transformation of hyperplastic blood vessels commonly found in high grade gliomas [2]. This "collision tumor" concept was supported by early descriptions by Feigin of hyperplastic vessels and perivascular arrangement of sarcomatous elements in gliosarcoma [7]. Studies showing histological reactivity of the sarcomatous component to vascular endothelial markers such as factor VIII, von Willebrand factor and CD34 also provided support for this hypothesis [8–10]. However, a number of other studies followed that failed to discover the presence of endothelial markers in the sarcomatous elements [11–13].

An alternative theory that has recently gained favor points to a monoclonal origin of both components of gliosarcoma, with sarcomatous component originating via aberrant mesenchymal differentiation of the malignant glioma. Biernat and colleagues [14] first demonstrated identical p53 mutations in gliomatous and sarcomatous components. Reis and colleagues [15] discovered identical PTEN mutations, p53 nuclear accumulation, p16 deletion, and CDK4 amplifications in both tumor areas. Other authors followed, describing that both components of gliosarcoma shared common genetic alterations and chromosomal imbalances of the type classically described in GBM [16, 17]. These alterations included gains on chromosomes 7, 9q, 20q, and X, and losses on chromosomes 10, 9p, and 13q [16, 17]. Studies found, however, a much lower frequency of EGFR amplification in gliosarcoma than found in primary GBM. While EGFR is amplified in up to half of primary GBMs, the rate of amplification is much lower in gliosarcoma (8% in small series) [15, 16]. Gliosarcomas were also found to have a fewer number of chromosomes involved in imbalances, suggesting



Fig. 2 Morphology of gliosarcoma **a** Smear preparation, hematoxylin and eosin stain, $100 \times$. Portion of the tumor showing sarcomatous, spindle morphology. Other potential differentiation includes osseous, vascular, skeletal muscle, and adipose phenotypes. **b** GFAP, $100 \times$. The sarcomatous component is GFAP negative **c** 400×. The basement membrane is highlighted by Laidlaw Reticulin impregnation in the sarcomatous component of the tumor. Reticulin shows thick uniform atypical appearance

a higher level of genomic stability in gliosarcomas [16]. Although, there is currently a paucity of data supporting these genetic markers to be of prognostic value, detailed



Fig. 3 Neuroimaging of a gliosarcoma before surgery. Gadoliniumenhanced T1-weighted axial images of the patient's left sided temporal lobe gliosarcoma

future clinicopathologic studies will continue to elucidate their role in tumorigenesis, progression, and clinical management of gliosarcomas.

Clinical characteristics

Gliosarcomas are rare and have an incidence 1.8–2.8% that of GBMs [18]. Similar to other glial based tumors, PGS affects adults in the sixth to seventh decade of life, with a significantly higher proportion found in men than in women (M:F ratio 1.4–1.8:1) [12, 18]. The presenting signs and symptoms reported are consistent with those of a rapidly expanding intracranial tumor, including aphasia, headache, hemiparesis, seizures, and cognitive decline, depending on its location. The clinical similarities to GBM have led many authors to conclude that these tumors are clinically indistinguishable [12, 19]. However, there are a number of important and distinct features of PGS that suggest that it is a separate entity.

The striking features of PGS that distinguish it from GBM include its location and its differential radiographic and gross appearance. Gliosarcoma is almost never found infratentorially and the majority of the reports describe its temporal lobe predilection [18, 20, 21] while a few report a higher incidence in the frontal lobe [12, 22]. The published experience describes two distinct appearances of PGS grossly at operation. The early case series by Feigin and Morantz noted the gross appearance of PGS were often firm, well-circumscribed masses commonly found at the periphery in contact with the dura mater, falx cerebri or the skull [3]. However, the series by Perry and colleagues reported that most cases of gliosarcoma [12] were diffusely infiltrating with ill defined margins (exact proportions not given). In contrast the series by Parekh and colleagues found only 2 of 15 cases had such characteristics on gross appearance [12, 21]. These three series illustrate the variety of potential appearances of PGS, despite the use of the same diagnostic criteria described by the WHO.

The findings on imaging are also variable. On computed tomography (CT), the lesions can appear with large necrotic areas and heterogenous contrast enhancement, similar to that of GBMs, or as hyperdense lesions with well-defined margins and homogenous enhancement, mimicking the appearance of a meningioma [23, 24]. In a small case series of five patients, Maiuri and colleagues [24] reported that PGS resembling meningiomas on CT appeared similar to meningiomas on gross pathology as well. However, this correlation was not found in a subsequent report that included 15 patients with PGS who received surgical resection [21]. Of the 14 patients who were imaged by CT, only 3 showed homogenous enhancement, similar to a meningioma. Of 15 tumors that were excised, 13 showed firm lesions with well demarcated margins, and two were necrotic and infiltrating with ill defined borders. Detailed descriptions of appearance on Magnetic Resonance Imaging (MRI) are lacking, as the majority of large case series were reported during the era when CT was the primary method of imaging. Hence, reports of clinical correlation with findings on MRI are also lacking. Recent case reports show that findings on MRI are similar to those on CT, with masses having heterogeneous enhancement and sharply demarcated or irregular borders [4, 12, 18, 19, 25-30]. A prominent and common feature of gliosarcomas seen on MRI is marked peritumoral edema [18]. The difficulty in establishing the diagnosis of PGS radiologically underscores the importance of establishing methods to make the diagnosis histopathologically. The variability of radiographic and pathologic presentations of gliosarcoma suggests a potential need for an update of the WHO criteria reflecting these potential clinical subtypes.

Despite its variable appearance, initial data have supported uniform aggressive treatment of PGS. Morantz and Feigin as well as Parekh and colleagues [3, 21] warn that an attempt to shell out PGS that resemble meningiomas will likely result in persistence of tumor tissue with subsequent recurrence. Currently, a reasonable approach to these tumors is an attempt at gross total resection when possible. However unlike GBM, there currently are no well controlled studies to support the advantage of a gross total resection of PGS over biopsy or subtotal resection followed by adjuvant therapy.

Metastasis

Extracranial metastases from cerebral gliomas, including GBM, are very rare, while the propensity for gliosarcomas to metastasize is well established. Even in the early days of Feigin, several authors reported cases of metastatic foci that contained admixtures of both gliomatous and sarcomatous elements [2, 31, 32]. The presence of these metastases was a large contribution to the premise that PGS are a clinically separate entity from GBM and truly biphasic in nature. Smith and colleages [33] in the largest metastatic case series to date of seven cases of gliosarcomas, observed that in two cases, the metastatic foci were composed solely of the sarcomatous component. Other case reports followed with similar findings of sarcomatous elements alone in metastases [25, 34-36]. These observations have generated the belief that the metastatic potential of gliosarcoma is due to the sarcoma component and ultimately reflects the strong propensity of sarcomatous neoplasms to disseminate hematogenously.

Most extracranial metastases of gliosarcoma are located in the lung and liver, and there are reports of metastatic foci in cervical lymph nodes, spleen, adrenal glands, kidneys, oral mucosa, skin, bone marrow, skull, ribs, and spine [10, 31–40]. Intramedullary metastasis to the cervical spine has also been observed [41]. There is a rare case of widespread extracranial metastases with intravascular tumor emboli, which is also consistent with the concept that gliosarcoma metastasize via a hematogenous route [25].

Treatment

Treatment modalities described for gliosarcoma include tumor resection, postoperative radiation therapy, and chemotherapy with nitrosureas, misonidazole, dacarbazine, mithramycin, ametophterin, thalidomide, temozolomide, irinotecan, vincristine, cisplatin, or doxorubicin [18, 25, 42]. The majority of information on PGS therapy is derived from published case series. Typically the described therapeutic modality is based on the prevailing treatment for GBM that has demonstrated benefits in randomized trials. In an early series of 24 cases by Morantz and colleagues, all 24 patients underwent surgical resection, 18 patients received radiation therapy, and nine patients received chemotherapy (mithramycin and ametophterin) [3]. The distribution of treatment modalities described in other larger case series are similar with the majority of patients having undergone surgical resection, a smaller portion having received therapeutic radiation, and a few having received a wide range of chemotherapeutic agents (Table 1) [12, 18, 20-22, 43].

The total dose delivered in radiotherapy ranged from 45 to 81 Gy in these reports. Because the role of radiation in prolonging survival in GBM has been well established, many of the previously mentioned authors implemented postoperative radiotherapy for all patients with PGS, despite lack of evidence for its benefit at the time [12, 18]. The small body of evidence in observational and cohort studies available now supports the benefit of radiotherapy in gliosarcoma. An interesting recent case report describes recurrence of only the sarcomatous component of a PGS after boron neutron capture therapy [26]. This case raises the possibility of differential sensitivities to radiation of the gliomatous and sarcomatous elements, although due to the technique of boron neutron capture therapy, differential accumulation of boron compounds in the glioma component is an alternative explanation.

Although chemotherapy with temozolomide is now standard of care for GBM, the precise role of chemotherapy remains uncertain for PGS. Morantz and colleagues [3] observed a modest increase in survival for PGS patients when chemotherapy with mithramycin and ametophterin (dose not reported) was added to postsurgical radiation alone (36, 33 weeks respectively, no P value given). Other authors did not offer chemotherapy to study participants, citing its ill defined role [18, 43].

Currently, there is very little data regarding the response of gliosarcoma to novel therapies that are being developed and studied for malignant gliomas, such as immunotherapy and cancer vaccine therapies. Most trials with malignant glioma include gliosarcoma as a variant of GBM, and roles of novel therapies in management of gliosarcoma becomes difficult to parse out [44].

Prognosis

PGS has a poor prognosis with median survival in untreated patients of 4 months [3]. For patients who underwent treatment described in case series with 10 patients or more (N = 154), the median survival was between 6.25 and 11.5 months per cohort (Table 1) [3, 12, 18, 20–22, 43]. Although a number of series suggested a slightly better prognosis for PGS than for GBMs, four studies that included a matched GBM control group failed to show a statistically significant difference in survival (all four studies predate the currently accepted radiotherapy with concurrent and adjuvant temozolomide [45], as treatment for GBM, Table 2). Meis and colleagues [22] found that median survival was

14

Study, year, ref. no.	\mathbf{Pts}	Mean age	Surgical resection (no)	Radiation (no)	Total dose (Gy)	Fractionation	Chemotherapy no, (agents)	Survival (median, months)
Morantz, 1976 [3]	24	54	All	18	50-60	MN	9 (mithramycin, ametophterin)	4 (GS all) 7 (GS surgery + RT)
Meis, 1991 [22]	26	50% >60	NM	All	4581	CF, HF, AF	17 (nitrosureas, dacarbazine, misonidazole)	8.3
Perry, 1995 [12]	32	66	31	12	50	CF	6 (nitrosureas)	6.25 (GS all) 11.5 (GS surgery + RT)
Parekh, 1995 [21]	17	52	All	16	NM	NM	3 (NM)	<24 months
Sarkar, 1997 [43]	29	42	All	All	40-60	CF	None	<18 months
Galanis, 1998 [20]	18	56% ≥60	16	All	60-65	CF	18 (nitrosureas)	8.75
Lutterbach, 2001 [18]	12	56	All	All	42–54	AHF, HypoF	None	11.5

Adapted from Lutterbach et al. [18]

Deringer

Study, year, ref. no.	Number, GS/GBM	Median survival GS (months)	Median survival matched GBM (months)	Р
Meis, 1991 [22]	26/1453 (1.8%)	8.3	9.6	Non significant
Galanis, 1998 [20]	18/748 (2.4%)	8.75	8.6	Non significant
Lutterbach, 2001 [18]	12/420 (2.9%)	11.5	8.1	0.36
Miller, 2007 [6]	10/453 (2.2%)	7.6	9.3	0.33

Table 2 Survival of gliosarcoma compared to glioblastoma multiforme

8.3 months for PGS patients compared to 9.6 months for GBM patients (not statistically significant), Galanis and colleagues [20] reported gliosarcoma patients had median survival of 8.75 months and the matched controls with GBM had median survival of 8.6 months (not statistically significant), Lutterbach and colleagues found median actuarial survival to be 11.5 months for the group with gliosarcoma, and 8.1 months for the control group with GBM (P = 0.36) [18]. Miller and Perry [6] observed median survivals of 7.6 months for gliosarcoma group and 9.3 months for the matched GBM controls (P = 0.33).

In a series of five gliosarcoma patients, Maiuri and colleagues [24] noted an association of longer survival with radiologic appearance similar to that of a meningioma and prevalence of the sarcomatous element on histology. Cervoni and Celli [26] also found in six patients that there was increased survival in patients with PGS that resembled meningiomas, and had dominance of the sarcomatous component in comparison with those that did not (14 vs. 7 months, no *P* value given).

The benefit of radiation therapy on survival of patients was described by Perry and colleagues [12], as radiation treated patients had median survival of 10.6 months, compared to 6.25 months in patients not treated with radiation (P < 0.025). The effect of chemotherapy has only been commented on by Morantz and colleagues showing a modest improvement in survival. Strong evidence supporting the benefit of chemotherapy for PGS patients is lacking.

One peculiar case of a patient with prolonged survival has been described by Winkler and colleagues [30]. A 61-yearold patient with PGS experienced a recurrence 20 years after initial diagnosis and treatment with repeated histological confirmation. During the 2 years following recurrence, she underwent multiple resections, radiotherapy, radiosurgery, and intracavitary radioimmunotherapy, and ultimately passed away 22 years after initial diagnosis [3, 12, 43].

Future direction of pathogenesis and clinical management

Current hypotheses on the pathogenesis of PGS include (1) GBM promoting differentiation of local or circulating mesenchymal stem cells into sarcoma, (2) sarcoma cells converting local or circulating stem cells into differentiating into GBM, (3) one stem cell lineage ultimately giving rise to both GBM and sarcoma, and (4) differentiated glial cells of GBM undergo dedifferentiation and give rise to the sarcoma. The concept of sarcoma induction by GBM is consistent with the early hypothesis of Feigin based on hyperplasia of vasculature seen in GBMs [2]. Alternatively, primary CNS sarcomas have been reported, and the sarcoma may induce malignant transformation in glial cells, resulting in gliosarcoma. This hypothesis could be explored by experiments co-culturing sarcomas and glial cells and observing for possible malignant changes in glia. The last two hypotheses, suggesting a monoclonal origin of both parts of gliosarcoma, have been tested in experiments identifying common genetic alterations in each cell type [14–17]. However, in the case of PGS, there is the possibility that transformations to glioma and sarcoma may involve different genetic mutations. Considering the current evidence to date, the monoclonal origin hypothesis seems the most likely, or at least the most frequent method of pathogenesis; however, further investigation is necessary elucidate the exact mechanism of pathogenesis in gliosarcoma.

Future clinical trials of malignant glioma would likely benefit from considering gliosarcoma as a unique entity, in order to limit confounding by the potential differential characteristics between gliosarcoma and other gliomas in prognostic markers as well as response to novel therapies. However, comprehensive large prospective studies of gliosarcoma remain challenging due to the rarity of these tumors.

Conclusions

PGS represents a clinically challenging group of tumors, due to its rarity, poor prognosis, and the limited experience in published literature. Many of its clinical and pathogenetic characteristics remain to be revealed, and there is much room for future studies focusing on these biphasic tumors. The current reported literature does provide a number of distinguishing clinical and pathogenetic features of PGS to suggest they are indeed separate entities from GBMs. These differences include gliosarcomas' temporal lobe predilection, their potential to appear similar to a meningioma grossly at operation, their increased metastatic potential, and the infrequency of EGFR mutation. Evidence for survival and efficacy of treatments is also limited due to the difficulty of conducting prospective trials. However, properly designed studies are necessary to optimize their management by considering their differential clinical behavior and pathogenesis from GBM. Although the precise etiology of PGS remains unknown, the interplay of glioma and sarcoma genesis requires further investigation to reveal potential targets for clinical applications.

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