Adult Primary Gliosarcoma: Epidemiology

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Abstract

Comprising approximately 2% of all glioblastoma cases, adult primary gliosarcoma is a rare aggressive tumor, composed of a mixture of malignant glial and sarcomatous elements, with dismal outcomes. While the general epidemiology and presentation reflect that of other glioblastomas, gliosarcoma has a much higher rate of metastases, may carry a worse prognosis, and has not been found to carry the hallmark characteristic of EGFR overexpression generally found in glioblastomas. The histogenesis of the disease remains unclear but there is increasing molecular and genetic evidence that the mixed components of the tumor have a monoclonal origin. In part because of a lack of information on the disease, patients with gliosarcoma are generally managed in the same manner as patients with other glioblastomas.

Introduction

Adult primary gliosarcoma is a central nervous system tumor composed of a mixture of malignant glial and sarcomatous elements. Stroebe (1885) described the first reported case in 1895 but it was not a widely accepted diagnosis until 60 years later when Feigin and Gross (1954) described three cases of gliosarcoma in detail. The malignancy is exceedingly rare, and epidemiological studies have been limited to small retrospective studies and case reports. The largest

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study to date has been a SEER database study comparing about 350 gliosarcoma patients to more than 16,000 patients with glioblastoma (Kozak et al. 2009). Currently, the malignancy is considered a variant of glioblastoma but there is growing evidence suggesting that it may be a separate entity. However, the underlying pathogenesis has not been definitively clarified and the disease continues to be managed in the same manner as glioblastoma.

Clinical Presentation and Prognosis

Gliosarcomas account for about 2% (Meis et al. 1990; Galanis et al. 1998; Kozak et al. 2009) of all glioblastoma cases. The annual incidence in North America and Europe is approximately one new case per 1,000,000 (Lantos et al. 1996). Otherwise, the general epidemiology follows that of glioblastoma. The median age at presentation is between 50 and 70 years of age, with the largest study finding a median age of 63 years (Kozak et al. 2009). Like glioblastoma, gliosarcoma patients are slightly more likely to be male (M:F, 1.4–1.8: 1.0) (Morantz et al. 1976; Kozak et al. 2009). Also, similar to other glioblastomas, gliosarcomas are almost always located supratentorially but gliosarcomas specifically have a predilection for the temporal lobe. Kozak et al. (2009) found that approximately 34.0% of gliosarcomas were located in the temporal lobe compared to 23.0% of other glioblastomas.

The clinical presentation of gliosarcoma is similar to that of other rapidly expanding cerebral tumors. Reflecting their location, presenting symptoms of gliosarcomas include headache, weakness, nausea, personality changes and confusion, seizures, and aphasia (Morantz et al. 1976; Perry et al. 1995). Salient signs consist of papilledema, hemiparesis, homonymous hemianopsia, and dysphasia (Morantz et al. 1976). These signs and symptoms correlate strongly to the clinical features of glioblastoma.

Interestingly, in contrast to the majority of glioblastomas, which rarely metastasize outside the cranium, gliosarcomas have a much higher likelihood of hematogenous dissemination to other organs. Han et al. (2009) found that 11% of the reported cases in literature were associated with extracranial metastases. The lungs (72%), liver (41%), and lymph nodes (18%) were most often involved (Beaumont et al. 2007), but gliosarcoma metastases have been reported in a variety of anatomic locations, including adrenal glands, kidneys, skin, oral mucosa, spleen, bone marrow, ribs and spine. Beaumont et al. (2007) reported on one patient who had almost universal spread of disease including to previously unreported organs such as the thyroid, pericardium, myocardium, diaphragm, pancreas and stomach. The past several decades have witnessed an increase in the number of gliosarcoma distant metastasis reports, potentially attributable to both an increased awareness of the diagnosis and the modestly prolonged survival offered by better treatments.

Unfortunately, gliosarcoma is an aggressive disease with dismal outcomes. In fact, overall survival of untreated patients has been reported to be a mere 4 months (Morantz et al. 1976; Kozak et al. 2009). Kozak et al. found that the median survival of all gliosarcoma patients was only 9 months, which is comparable to the median survival found in the smaller retrospective studies. They also found that the prognosis of patients with gliosarcoma was slightly, but significantly, worse than patients with glioblastoma. In addition to receiving treatment, younger age at diagnosis is also associated with a longer median survival. Patients diagnosed before the age of 50 had a median survival of 15 months compared to 7 months for those diagnosed after the age of 50. Furthermore, tumor location has an impact on overall survival; ventricle involvement predicts worse outcomes.

Interestingly, two distinct morphological types of gliosarcomas have been described on gross appearance, suggesting that there may be two variants of gliosarcomas. On surgical resection, some gliosarcomas are firm, well-circumscribed, easily resectable tumors, often attached to the dura, resembling meningiomas. Other tumors are necrotic and diffusely infiltrating and thus difficult to resect, resembling glioblastomas (Salvati et al. 2005). On histological

analysis of 11 patients, Salvati et al. (2005) found that the meningioma-like tumors had a more prevalent sarcomatous component, while the glioblastoma-like tumors had a more prevalent gliomatous component. Han et al. (2010a) found that patients with meningioma-like tumors had a median survival of 16 months compared to 9.5 months for patients with glioblastoma-like tumors. Furthermore, the time to progression after treatment (resection and radiotherapy with concurrent tomozolamide) was also longer in the former group, supporting the findings of previous studies (Salvati et al. 2005; Maiuri et al. 1990). The more favorable prognosis of the meningioma-like tumors may simply reflect the greater ease of achieving macroscopic total resection rather than an inherent difference in disease natural history.

Histology

The 2007 World Health Organization classification defines gliosarcoma as "a malignant grade IV neoplasm with both glial and phenotypically mesenchymal components" (Louis et al. 2007). The gliomatous component follows the histologic criteria for glioblastoma while the mesenchymal component displays a variety of morphologies, including fibroblastic, cartilaginous, osseous, smooth muscle and adipocytic differentiation. In order to differentiate from other sarcomas and gliomas, the 2007 WHO criteria recommends that the glial areas stain positive for glial fibrillary acidic protein (GFAP) while the sarcomatous areas stain negative for GFAP but positive for reticulin.

There has been much controversy concerning the pathogenesis of gliosarcomas. Feigin and Gross (1954) supported the "collision" theory, which purports that the hyperplastic blood vessels of high grade gliomas undergo a neoplastic transformation. The theory suggested that excessive stimulation of endothelial cells by neoplastic glial cells induced a malignant transformation. This early theory has been supported by the finding that the sarcomatous areas of some tumors are reactive to vascular endothelial markers such as factor VIII, von Willebrand factor, and *Ulex europaeus* agglutinin-1, a lectin that binds to surface glycoproteins on endothelium (Perry et al. 1995). However, these markers are not a ubiquitous finding, shedding doubt on the veracity of this explanation.

More recently, the idea of a monoclonal origin of both the sarcomatous and glial components has become popular. The monoclonal hypothesis suggests that the neoplastic glial cells undergo a metaplastic transformation, acquiring sarcomatous phenotypes (Meis et al. 1990). Numerous genetic studies support this hypothesis. Biernat et al. (1995) and Reis et al. (2000) found that in many gliosarcoma tumors both the glial and sarcomatous cells have identical *TP53* mutations. Reis et al. (2000) also found identical PTEN mutations, p16 deletion, and CDK4 amplification. In fact, 57% of all chromosomal imbalances detected in a gliosarcoma tumor are shared by both components of the tumor (Actor et al. 2002). Kleihues et al. (2000) also reported *TP53* and PTEN mutations in approximately 25 and 35%, respectively, of glioblastomas while Reifenberger et al. (1999) reported CDK4 amplification in glioblastomas. Further studies have demonstrated many other glioblastoma-like genetic alterations common to both areas.

While gliosarcomas generally arise *de novo*, there have been 11 reported cases following whole brain irradiation for either another primary brain tumor or acute lymphoblastic leukemia. In their retrospective study of 32 cases of gliosarcoma, Perry et al. (1995) reported that seven of the cases consisted of tumor recurrence in patients who received 50-Gy whole-brain irradiation for a primary glioblastoma. Thus, in these patients, the radiation apparently induced gliosarcomatous transformation of the initial glioblastoma. The median time to tumor recurrence, which correlates with the time from irradiation of the primary malignancy, was 36 weeks. In a review of radiation induced primary gliomas and brain sarcomas, Kaschten et al. (1995) found that in contrast to gliomas, radiation-induced sarcomas did not occur at doses below 20 Gy. The four cases of radiation-induced primary gliosarcomas occurred following a mean dose of

37 Gy. The time from irradiation of the primary disease to presentation of the secondary malignancy varied significantly, from 1 to 12 years.

More recently, there has been some debate about the possibility of gliosarcomas being a separate entity from glioblastoma. As previously mentioned, gliosarcomas are strikingly different in their tendency to metastasize and possibly have a worse prognosis than other glioblastomas. Though gliosarcomas do share some of the genetic alterations found in other glioblastomas, significant differences have also been found. Actor et al. (2002) discovered that although the number of imbalances per tumor did not vary significantly between gliosarcomas and glioblastomas, the number of chromosomes affected by an imbalance was lower for gliosarcomas. That is, they found that gliosarcomas have a greater degree of chromosomal stability than glioblastomas. Their finding was corroborated by cell culture studies showing that a gliosarcoma-derived cell line had a far lower number of chromosomal imbalances compared to nine glioblastoma-derived cell lines.

Importantly, no case of gliosarcoma has demonstrated EGFR overexpression/amplification, which is considered one of the molecular hallmarks of primary glioblastomas (Reifenberger et al. 1999; Actor et al. 2002). The rarity of gliosarcoma and the modest utility of EGFR inhibitors in glioblastoma management suggest the therapeutic implications of this observation remain undefined. In light of the paucity of data, patients with gliosarcomas will continue to be managed with the same trimodal approach as patients with other primary glioblastomas.

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