Five Patients with Gliosarcoma

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ABSTRACT

Gliosarcoma is a rare primary malignancy of the central nervous system, classified by the World Health Organization as a high-grade glioma and a variant of glioblastoma multiforme. This report is of 5 patients with gliosarcoma, with emphasis on the pathology and radiology.

Key Words: Glioblastoma; Gliosarcoma; Radiotherapy

INTRODUCTION

Gliosarcoma is a rare primary malignancy of the central nervous system, classified by the World Health Organization (WHO) as a high-grade glioma and a variant of glioblastoma multiforme. Gliosarcoma accounts for <2% of all gliomas and 5% of all astrocytomas. The tumour has a clinical presentation, natural history, and radiological profile similar to glioblastoma multiforme. This report is of 5 patients with gliosarcoma, with emphasis on the pathology and radiology.

CASE REPORTS

Patient 1

A 67-year-old man presented in 2000 with sudden onset of left arm weakness and left facial droop. Neurologically, the patient’s condition deteriorated quickly, and he developed slurring of speech within a few hours of presentation. The provisional diagnosis was cerebral ischaemia as the patient had had 2 transient ischaemic attacks 4 years previously.

Computed tomography (CT) scan demonstrated a peripherally enhancing lesion with surrounding vasogenic oedema in the right temporal area (Figure 1). The appearance was felt to be consistent with a neoplastic phenomenon rather than a stroke.

The patient underwent right temporal stereotactic craniotomy with subtotal resection and duraplasty with insertion of a catheter for intracranial pressure (ICP) monitoring. Histology testing of the frozen section showed results consistent with high-grade glioma. The pathological diagnosis was gliosarcoma. The tumour had glial cells mixed with cells with a spindle morphology, in a typical biphasic pattern (Figure 2). Marked vascular proliferation and patches of necrosis were present. The tumour tissue stained strongly positive for glial fibrillary acidic protein (GFAP) and weakly positive for keratin. Stains for melanoma and metastatic sarcoma were negative. CT scan
done 24 hours postoperatively revealed a 3-cm periphery-enhancing lesion at the medial right temporal lobe that was highly suspicious for residual tumour. The patient started dexamethasone 4 mg 4 times daily, and recovered completely with no residual neurological deficit after surgery. He was offered postoperative adjuvant external beam radiation, and concurrent and adjuvant oral temozolamide-based chemotherapy as per the glioblastoma multiforme protocol. The patient declined adjuvant therapy. CT scan done 3 months after surgery demonstrated recurrent disease. The patient continues steroid therapy alone but has had a deterioration in clinical status.

**Patient 2**

A 25-year-old woman presented in 1990 with twitching in the right facial muscle and saliva leaking from the corner of her mouth for 6 months. CT scan revealed a well-circumscribed round hyperdense mass in the left temporal parietal area, with significant oedema.

The patient underwent total excision of the sharply demarcated firm tumour. Pathology showed gliosarcoma with a predominant sarcomatous pattern. No documentation regarding immunochemistry was available. The patient received postoperative adjuvant radiation therapy to a total dose of 58 Gy in 29 fractions followed by 6 cycles of procarbazine, carmustine, and vincristine chemotherapy. The patient has been well, both radio- logically and clinically for 16 years.

In 2006, the patient presented with a red lesion, approximately 1 cm in size, on the craniotomy scar for the previous 6 months. Needle aspiration performed on 2 occasions showed no malignant cells. CT scan did not show any intracranial extension at the time of examination. The lesion was observed for 5 months, during which time it progressively increased in size. Repeat CT scan showed recurrence in the anterior part of the skull. There was soft tissue density with an intracranial and subcutaneous component measuring approximately 3 cm in size. There was frank bony destruction and a lobulated extracranial mass situated on top of the craniotomy flap (Figure 3). The extracranial mass was indenting the left parietal lobe and causing a localised mass effect with adjacent white matter oedema.

The patient underwent craniotomy and excision of bone, with wide local excision of skin, cranioplasty, instillation of an intracranial pressure monitoring system, and duraplasty. Due to leakage of cerebrospinal fluid, the patient underwent a further operation. The bone flap was repaired with flap rotation and a new titanium plate was inserted.

The pathology showed grade IV gliosarcoma with a predominant sarcomatoid pattern. The astrocytic element had papillary architecture and stained positive for S-100 and GFAP (Figure 4). The sarcoma component stained positive for actin and caldesmon, but negative for desmin, suggesting myoid differentiation. The patient recovered well postoperatively, and started temozolamide-based oral chemotherapy. She remains recurrence free after 6 months.
Patient 3
A 65-year-old woman presented in 2003 with progressive difficulty naming objects and remembering names. Neurologically, she had dysphasia and hyper-reflexia on the right side. CT scan of the head revealed a ring-enhancing lesion in the anterior portion of the temporal lobe, with surrounding oedema, consistent with glioma.

The patient underwent craniotomy and total resection of the tumour, with instillation of an ICP monitoring system and duraplasty. The pathology showed extensive necrosis with neovascularisation. Cytology showed glial and sarcomatous components. The staining pattern was characterised by areas of astrocytic cells, which were weakly positive for α-1-antitrypsin and strongly positive for GFAP. The sarcomatous cells had reticulin fibres that were weakly positive for α-1-antitrypsin and negative for GFAP. These results were consistent with gliosarcoma (Figure 5).

CT scan showed no residual disease after surgery, and the patient recovered fully. She received external beam radiation to a total dose of 61 Gy in 33 fractions to the tumour bed. The patient remained well for 1 year. In 2004, she presented with a history of partial seizures for 1 week. She was scheduled for a CT scan but died before the appointment due to respiratory failure as a result of a seizure.

Patient 4
A 51-year-old man presented in 2004 with complex partial seizures for 3 weeks. CT scan and magnetic resonance imaging of the brain revealed a contrast enhancing mass in the right temporal region and extensive vasogenic oedema.

The patient underwent surgical resection of the tumour. The pathology results were compatible with gliosarcoma. The tissue had a typical biphasic pattern, with glial and sarcomatous components. Staining with GFAP and epidermal growth factor (EGFR) confirmed collagen deposition in streaming areas and abundant reticulin. Actin and factor VIII were confined to the blood vessels. GFAP immunopositivity was restricted to the patternless areas and there was strong EGFR positivity, corresponding to the GFAP positive areas. p53 Mutation was not detected.

The patient was planned for adjuvant external beam radiation to a total dose of 60 Gy in 30 fractions, but had completed only 42 Gy in 21 fractions when treatment was stopped due to the patients’ rapidly deteriorating condition. CT scan showed disease progression. The patient underwent resection of a recurrent mass. The pathology results showed radiation-induced changes and a tumour compatible with astrocytoma grade III. The sarcomatous component seen in the previous specimen was not evident in the recurrence. GFAP was strongly positive, but reticulin and Ki-67 staining was non-contributory. CT scan of the brain after 2 months showed radiation-induced changes in the white matter and questionable tumour recurrence in the surgical bed.

The patient remained well for 11 months, but he represented with severe abdominal pain in late 2004. CT scan of the abdomen showed multiple metastases in the liver. CT scan of the brain showed either a tumour recurrence in the surgical bed or an inflammatory process. The other staging investigations of CT scan of the chest, abdomen, and pelvis, and bone scan to exclude a second primary tumour were negative. However, the patient died 1 month later.
**Patient 5**

A 34-year-old man presented in 2000 with sudden onset of headaches and difficulty in speech. CT scan showed a large left temporal lobe lesion with oedema causing left to right shift.

The patient underwent left frontotemporal craniotomy. Postoperatively, he remained neurologically intact and showed some improvement in speech. The pathology results showed a high-grade gemistocytic astrocytoma with angiosarcoma appearing near vessels in some sections. Immunohistochemistry showed positive GFAP and ulex europaeus. The diagnosis was gliosarcoma.

The patient received postoperative adjuvant radiation to a total dose of 56 Gy in 28 fractions. He remained disease free for 24 months, when he had a recurrence in the surgical bed in 2002. Resection was done and pathology showed glioblastoma multiforme (grade IV). Factor VIII, MIB-1, Ki-67, vimentin, and p53 were positive on immunostaining.

The pathology results of the recurrence were compared with the primary specimen. The astrocytic component had changed little, but showed enlarged cells with atypical mitotic figures. The mesenchymal component had less atypia, and did not have sufficient malignant features to warrant the designation of a sarcoma, although the possibility of a selective effect of radiation on the mesenchymal component could not be excluded.

The patient received 5 cycles of procarbazine, lomustine, and vincristine chemotherapy. He had ongoing issues with mentation and coordination, which were either related to radiation-induced toxicities or disease recurrence. He died 6 months after the last chemotherapy cycle.

**DISCUSSION**

According to the new WHO classification, gliosarcoma is defined as a glioblastoma variant, characterised by a biphasic tissue pattern with alternating areas displaying glial and mesenchymal differentiation. Gliosarcoma is a relatively rare malignant neoplasm accounting for approximately 2% of glioblastomas. Gliosarcoma occurs most commonly in adults in the fourth to sixth decades of life, and men are more commonly affected than women (ratio 1.8:1). Anatomically, gliosarcomas are usually located in the cerebral cortex, and involve the temporal, frontal, parietal, and occipital lobes in decreasing frequency. The presenting symptoms depend on the location of the tumour.

The aetiology of gliosarcoma remains uncertain, although it is recognised that gliomas can induce sarcomatous transformation in the supporting mesenchymal elements, and irradiation of the central nervous system can induce malignant transformation of the brain parenchyma and the meninges, predominantly to fibrosarcoma. The appearance of gross gliosarcoma may be a poorly delineated peripheral greyish tumour mass, with central yellowish necrosis stippled with red and brown from haemorrhage, and with the sarcomatous component producing a firm discrete mass.

Histologically, the diagnosis of gliosarcoma is based on a biphasic tissue pattern comprising 2 distinct malignant cell populations, one component being gliomatous (fulfilling the criteria for glioblastoma) and the other with malignant mesenchymal differentiation (fulfilling the criteria for sarcoma). The glioblastoma part of the tumour forms heterogeneous infiltrative areas with haemorrhage and necrosis. The sarcomatous portion produces a firm discrete mass. At microscopy, the glial portions show the typical features of glioblastoma multiforme. The sarcomatous areas can resemble either a fibrosarcoma, with bundles of spindle cells in a herringbone pattern, or a malignant fibrous histiocytoma, with giant cells. Other mesenchymal tissues that can be seen are cartilage, bone, and smooth and striated muscle. Epithelial differentiation has also been noted. The sarcomatous portion demonstrates reticulin. The glial portion stains for GFAP. Many gliosarcomas stain for factor VIII-related antigen and ulex europaeus. Interestingly, the sarcomatous component can have varied histological features, ranging from the herringbone pattern of fibrosarcoma to the malignant bone of an osteosarcoma and cartilaginous differentiation of chondrosarcoma.

In the first patient, the sarcomatous component of the tumour showed features of spindle-cell morphology, with marked vascular proliferation. A diagnostic criterion to be fulfilled before a tumour is classified as a gliosarcoma is the demonstration of GFAP through immunohistochemistry in the gliomatous portion and reticulin in the sarcomatous component, preferably exhibiting a clear demarcation between the sarcomatous and glial components. Additional immunohistochemical staining, including actin, desmin, and cytokeratin, should be performed to further identify the mesenchymal differentiation. Although one component of gliosarcoma is clearly of astrocytic origin, the histogenesis of the sarcomatous component is still controversial. Papillary glioneuronal tumour is a recently described lesion
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of the brain parenchyma, which is not yet included as a separate entity in the WHO classification.

The second patient had a mixture of a glial and neuronal tumour, with notable papillary pattern with hyalised vessels, as seen by histology. This mixed glioneuronal tumour of the central nervous system is a papillary glioneuronal tumour. The pseudopapillae are made of hyaline covered by stratified GFAP-positive astrocytes. The cells forming the neuronal element often stain positive for synaptophysin.

In 1995, Feigin and Gross described gliosarcoma as a glioblastoma in which the proliferating tumour vessels acquired features of a sarcoma. This view has been widely accepted, given the prominent vascular proliferation found in glioblastoma. Several immunohistochemical studies supported this hypothesis by demonstrating the presence of factor VIII–related antigen and ulex europaeus I agglutinin in the sarcomatous component, while other studies have failed to confirm these findings. Another hypothesis suggested a process of dedifferentiation within the glioma, with secondary loss of GFAP expression and acquisition of mesenchymal characteristics. However, these views have not been supported by recent genetic analysis, which point to a monoclonal origin where p53 mutation, phosphatase and tensin homologue mutations, p16 cyclin-dependent kinase inhibitor 2A deletions, and coamplification of MDM2 and cyclic D kinase have been identified in both the gliomatous and sarcomatous components. Extensive immunohistochemical analyses and comparative genotypic analysis, using microdissection to secure representative glial and epithelial components, have been done. Loss of heterozygosity was analysed by a panel of 12 polymorphic microsatellite markers designed to indicate allelic loss and situated in proximity to known tumour suppressor genes located on chromosomes 1p, 9p, 10q, 17p and 19q. Ozolek et al found comparable patterns of acquired allelic loss between the glial and carcinomatous components, strongly supporting the monoclonal origin of this neoplasm, which represented an extreme form of phenotypic divergence in a malignant glioma. This heterogeneity reflects the potential for a range of phenotypic expressions in malignant gliomas that needs to be recognised. Boerman et al used comparative genomic hybridisation, fluorescence in situ hybridisation, cytogenetic analysis, and microsatellite analysis to describe genetic alterations shared by both tumour components. Reis et al, in their assessment of the genetic profile of 19 patients with gliosarcoma, found identical PTEN mutation, p53 nuclear accumulation, p16 deletion, and CDK4 amplification in both tumour areas. Recently, Actor et al have reported that 57% of all chromosomal imbalances detected by comparative genomic hybridisation of 8 gliosarcomas were shared by both components. These researchers also detected identical p53 mutations in both glial and sarcomatous areas in 13 of 38 patients. The authors speculated that sarcomatous differentiation in gliomas is probably facilitated by MDM2 and CDK4 gene amplification. Several studies confirm the hypothesis of similar cytogenetic abnormalities and identical p53 mutations between gliomatous and sarcomatous cells within gliosarcoma. The 2 components might be derived from a single precursor cell clone, progressing to 2 subclones with distinct morphology during cancer evolution.

Gliosarcoma has the same prognosis, overall survival, and pattern of relapse as glioblastoma multiforme, and should be treated in the same way. In rare instances, treatment of gliosarcoma may result in prolonged survival, as for patient 2, although the underlying pathogenetic mechanism for this clinical behaviour is not understood. The patients described in this report were recommended to have postoperative radiation at a mean dose of 60 Gy in 30 fractions; this was standard of practice before temozolomide became available. Patients are usually treated with external beam radiation and concurrent temozolomide-based chemotherapy, followed by 6 months of adjuvant chemotherapy, as for Stupp et al’s protocol. However, this study included only patients with glioblastoma multiforme. In the study by Galanis et al, disease-free survival and actual survival time was compared between patients with gliosarcoma (n = 18) and a matched and an unmatched group of patients with glioblastoma multiforme (n = 18 and n = 730, respectively). The control group of patients with glioblastoma multiforme were matched for known prognostic factors, including age, randomisation date, performance status, and extent of resection. Patients in all treatment groups received radiation and carmustine-/lomustine-based chemotherapy. The median time to progression and survival time for patients with gliosarcoma were 28.0 weeks and 35.1 weeks, respectively, compared with 24.7 weeks and 41.6 weeks, respectively, for the unmatched group of patients with glioblastoma multiforme (log rank test, p = 0.94 and p = 0.27, respectively) and 16.7 weeks and 34.4 weeks, respectively, for the control group (p = 0.20 and p = 0.84, respectively). Recently, stereotactic radiosurgery (SRS) has emerged as a potent
means of delivering precise high-dose radiation therapy. Studies involving the role of gamma knife radiosurgery for treatment of glioma have yielded conflicting results. Souhami et al were the first researchers to conduct a multicentre randomised trial to investigate the addition of SRS (including both gamma knife surgery and linear accelerator–based radiosurgical techniques) to standard external radiation for the treatment of glioblastoma multiforme. SRS was included in the initial management of patients with glioblastoma multiforme rather than as salvage therapy. The researchers randomised 203 patients to receive either postoperative SRS (prescription dose, 15 to 24 Gy) followed by external radiation and carmustine or to external radiation and carmustine without SRS. There was no difference between the 2 groups for the primary endpoint of survival. The patients receiving SRS had a mean survival time of 13.5 months and the control group had a mean survival time of 13.6 months. While no significant benefit was seen by including SRS in the initial treatment of glioblastoma multiforme, its role in the treatment of gliomas should not be excluded entirely. More prospective randomised studies are needed to validate the results.

Recently, dasatinib, an oral dual Philadelphia chromosome and Src family tyrosine kinase inhibitor, has been found to be effective for the treatment of gliosarcoma and glioblastoma multiforme. The Radiation Therapy Oncology Group is conducting a phase II trial of dasatinib in patients with recurrent glioblastoma multiforme or gliosarcoma.

Gliosarcoma is similar to glioblastoma multiforme in terms of clinical presentation, survival, pattern of relapse, and treatment. However, the evidence shows that gliosarcoma can metastasise out of the neural axis. Currently, the treatment for gliosarcoma is identical to that for glioblastoma multiforme but more trials of glioblastoma multiforme should include patients with gliosarcoma.

REFERENCES