

Gliosarcoma with multiple extracranial metastases: case report and review of the literature

Thomas L. Beaumont · William J. Kupsky ·
Geoffrey R. Barger · Andrew E. Sloan

Received: 21 July 2006 / Accepted: 10 November 2006 / Published online: 14 December 2006
© Springer Science+Business Media B.V. 2006

Abstract Gliosarcoma is a rare malignant neoplasm of the central nervous system with a propensity for metastasis. There are fewer than 20 reported cases of extracranial metastases of gliosarcoma with the majority of cases reflecting a tendency for hematogenous dissemination. Here we describe the case of a 47-year-old man who developed pervasive extracranial metastases from a temporal gliosarcoma following radio- and chemotherapy for a primary glioblastoma. The patient initially presented with progressively worsening headaches, left-sided weakness and numbness associated with right temporo-parietal mass for which he underwent craniotomy with stereotactic gross-total excision. Two months postoperatively, interstitial brachytherapy and external beam radiotherapy were initiated. The patient initially declined chemotherapy. The tumor recurred twice and the patient underwent

re-operation and multiple courses of chemotherapy; histopathological diagnosis remained glioblastoma multiforme. Nineteen months following initial resection the patient's clinical status deteriorated and CT scan demonstrated multiple intrathoracic, hepatic and splenic lesions. Postmortem examination revealed widespread, infiltrating gliosarcoma with intravascular gliomatosis and extensive visceral metastases. This is the first report of pervasive extracranial metastases to numerous sites, several of which have not been previously reported. The histogenesis and the potential role of therapeutic irradiation in the development of gliosarcoma are briefly reviewed.

Keywords Extracranial · Glioma · Gliosarcoma · Metastasis · Sarcoma

Introduction

Gliosarcoma is a rare malignant neoplasm of the central nervous system estimated to comprise 1.8–2.4% of glioblastomas [13, 23]. Formerly referred to as “glioblastoma with sarcomatous component,” it was renamed in the current World Health Organization (WHO) classification scheme [20]. Gliosarcoma is presently defined as a glioblastoma consisting of an admixture of gliomatous and sarcomatous components. It has a predilection for the temporal lobe, is often located superficially, and presents surgically as a firm lesion adherent to the meninges where it has occasionally been mistaken for meningioma at surgery [24]. Although cerebral gliomas rarely exhibit extracranial metastases, it is well established that gliosarcomas have a propensity for such behavior. Indeed, there are

T. L. Beaumont · A. E. Sloan
Department of Neurosurgery, Karmanos Cancer Institute,
Wayne State University School of Medicine,
Detroit, MI 48201, USA

W. J. Kupsky · G. R. Barger
Department of Neurology, Karmanos Cancer Institute,
Wayne State University School of Medicine,
Detroit, MI 48201, USA

W. J. Kupsky
Department of Pathology, Karmanos Cancer Institute,
Wayne State University School of Medicine,
Detroit, MI 48201, USA

A. E. Sloan (✉)
Department of Neurosurgery Case,
Western University School of medicine,
11100 Euclid Avenue, Cleveland, OH 44106, USA
e-mail: SloanAE@moffitt.usf.edu

several reports of extracranial metastases to numerous sites, most commonly the lungs, liver and lymph nodes [8–10, 14, 15, 22, 25, 31, 33, 36, 38, 40]. Intra-axial metastases to the cervical spinal cord have also been documented [39]. The present case illustrates the first report of gliosarcoma with pervasive metastasis to at least 14 extracranial sites including the upper lip mucosa, chest wall, pleura, lung, liver, spleen, kidney, gastric mucosa, thyroid gland, pericardium, myocardium, diaphragm, and pancreas. The six latter sites have not been previously reported.

Case report

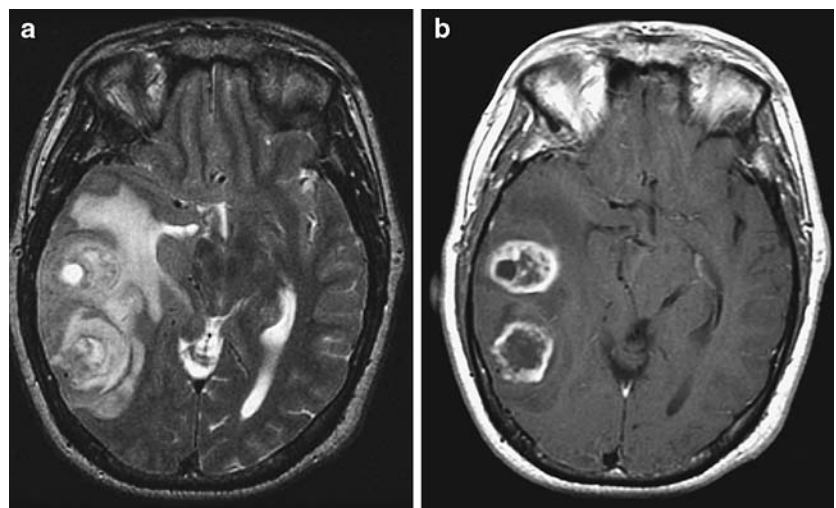
C.A. a 47-year-old, Caucasian, male presented to an outside institution with a 2-week history of progressively worsening headaches with weakness and numbness of the left extremities culminating in a fall. Past medical history was unremarkable while social history was notable for 30 pack-year history of smoking and family history was notable for carcinoma of the breast in the patient's mother. Neuroimaging demonstrated two distinct 2 × 3 cm ring-enhancing lesions in the right fronto-temporal and temporo-parietal lobes with irregular margins, central necrosis and vasogenic edema (Fig. 1). The following day, the patient underwent a right fronto-temporal-parietal craniotomy with stereotactic volumetric gross-total resection of the lesion. Final histopathologic diagnosis was glioblastoma multiforme (Fig. 2). The hemiparesis and hemianesthesia improved and 3-weeks postoperatively, the patient underwent stereotactic placement of low dose-rate ^{125}I catheters for interstitial brachytherapy delivering a total dose of 104 Gy to the periphery of the lesion over 12 months. Two months postoperatively, he received

standard external beam radiotherapy with a total dose of 54 Gy in 30 fractions. BCNU chemotherapy was declined.

Three months after the initial resection, severe headaches and left-sided hemiparesis recurred and MRI revealed tumor recurrence (Fig. 3a). Right temporo-parietal craniotomy was performed with resection of the enhancing masses and placement of BCNU wafers (Gliadel®). The resected tissue contained only rare infiltrating glial tumor cells but showed areas of necrosis and sclerotic vascular changes consistent with treatment effect. Routine follow-up MRI at 6 months revealed increased interval edema and tumor size (data not shown). Concurrent 3-deoxy-3[18F]fluoro-L-thymidine-PET (FLT-PET) confirmed recurrent tumor activity (Fig. 3b). Repeat MRI at 8 months indicated progressive enhancement despite the absence of neurological signs or symptoms (Fig. 3c). The patient continued to do well neurologically but experienced worsening headaches. Imaging studies demonstrated continued progression of the contrast-enhancing mass in the right anterior temporal lobe. The patient underwent right temporal lobectomy with partial resection of the hippocampus and removal of the ^{125}I implants 9½ months after initial resection. The resected tissue contained infiltrative glial tumor of low cellularity as well as areas of necrosis and vasculopathy consistent with treatment effect. A chemotherapy regimen consisting of Temozolomide and Thalidomide was then instituted.

The tumor continued to progress, and at 18 months, the patient was started on Irinotecan, 230 mg/week for four consecutive weeks [12]. Three weeks later, he was seen in clinic complaining of tonic-clonic seizures followed by progressive left-sided hemiparesis. MRI showed continued tumor growth and infiltration with

Fig. 1 Axial FLAIR (a) and T1-weighted postcontrast MRI (b) obtained upon initial presentation demonstrated two 2 × 3 cm ring-enhancing lesions in the right temporal lobe with irregular margins, central necrosis and vasogenic edema



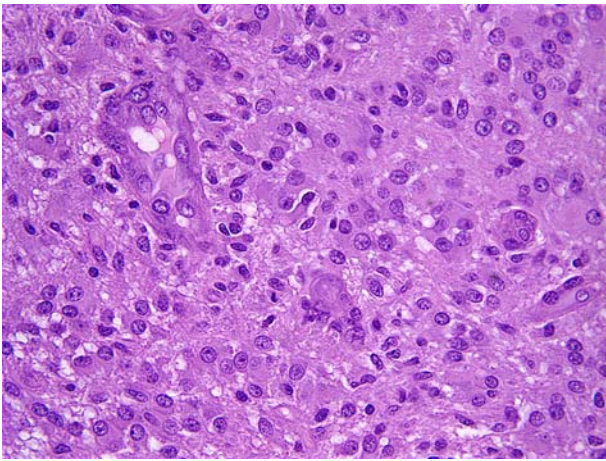


Fig. 2 Photomicrograph from primary resection demonstrated moderately cellular tumor with gemistocytes, occasional mitoses and microvascular proliferation consistent with high-grade glioma. No evidence of a connective tissue (sarcomatous) component was noted. H&E, 100× original magnification

edema and midline shift. Concurrently, a chest roentgenogram indicated an ill-defined mass over the right upper lobe with additional smaller nodules in the lower fields and CT scans of the thorax, abdomen and pelvis revealed multiple intrathoracic, hepatic and splenic metastases. The patient had also developed a painful, ulcerating mass in his upper lip mucosa. At this time, therapeutic intervention was discontinued and the patient was transferred to hospice where supportive measures were instituted. The patient expired 19.5 months following initial diagnosis. Postmortem histologic examination revealed widespread infiltrating gliosarcoma.

Pathology

Postmortem examination of the head revealed a firm $13 \times 8 \times 6$ cm mass underlying the right temporal craniotomy site and involving bone, dura and subjacent brain which, upon microscopic examination, showed biphasic tumor. The extraparenchymal firm mass consisted of densely cellular solid tumor composed of pleomorphic, spindle-shaped cells in a diffuse collagenous matrix (Fig. 4a). The intraparenchymal component consisted of infiltrative tumor of medium to high cellularity composed of pleomorphic glial cells (Fig. 4b) resembling the original tumor specimen. There were areas of necrosis and high mitotic activity, but microvascular proliferation was limited and focal. The glial component showed strong immunoreactivity to glial fibrillary acidic protein (GFAP) (Dako, Carpinteria CA) and S-100 (Ventana medical, Tucson, AZ), with variable immunoreactivity to vimentin (Ventana Medical, Tucson, AZ). The sarcomatous component was unstained with GFAP or S-100 but showed immunoreactivity to vimentin. Both components were negative for smooth muscle actin and factor VIII (Dako, Carpinteria CA). A sharp interface between the sarcomatous and glial components was noted at the tumor bed underlying the craniotomy site (Fig. 4c).

The glial component extensively infiltrated the brain parenchyma of the frontal and temporal lobes and extended into the deep brain structures. Small foci of sarcoma were present microscopically in the leptomeninges and extended along penetrating blood vessels into the underlying cortex. A separate discrete nodule of sarcoma measuring 1.3 cm in diameter was present

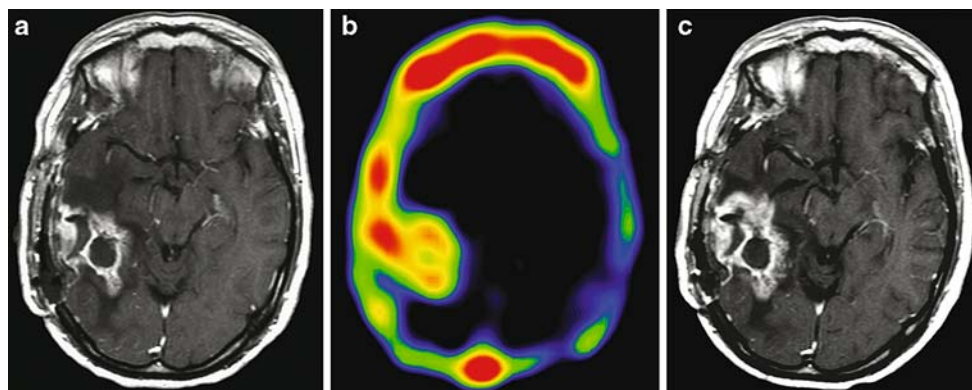


Fig. 3 Neuroimaging studies showing recurrent tumor activity. **(a)** T1-weighted postcontrast axial MRI obtained 3 months following resection of the primary tumor showed enhancement around the resection cavity with edema and midline shift. **(b)** Proliferation imaging with 3-deoxy-3[18F]fluoro-L-thymidine positron emission tomography (FLT-PET) conducted 2 weeks

following craniotomy for recurrent glioblastoma demonstrated intense signal around the resection cavity, overlying dura and surrounding bone. **(c)** T1-weighted postcontrast axial MRI at 8 months demonstrated progressive enhancement in the right temporoparietal region extending posteromedially

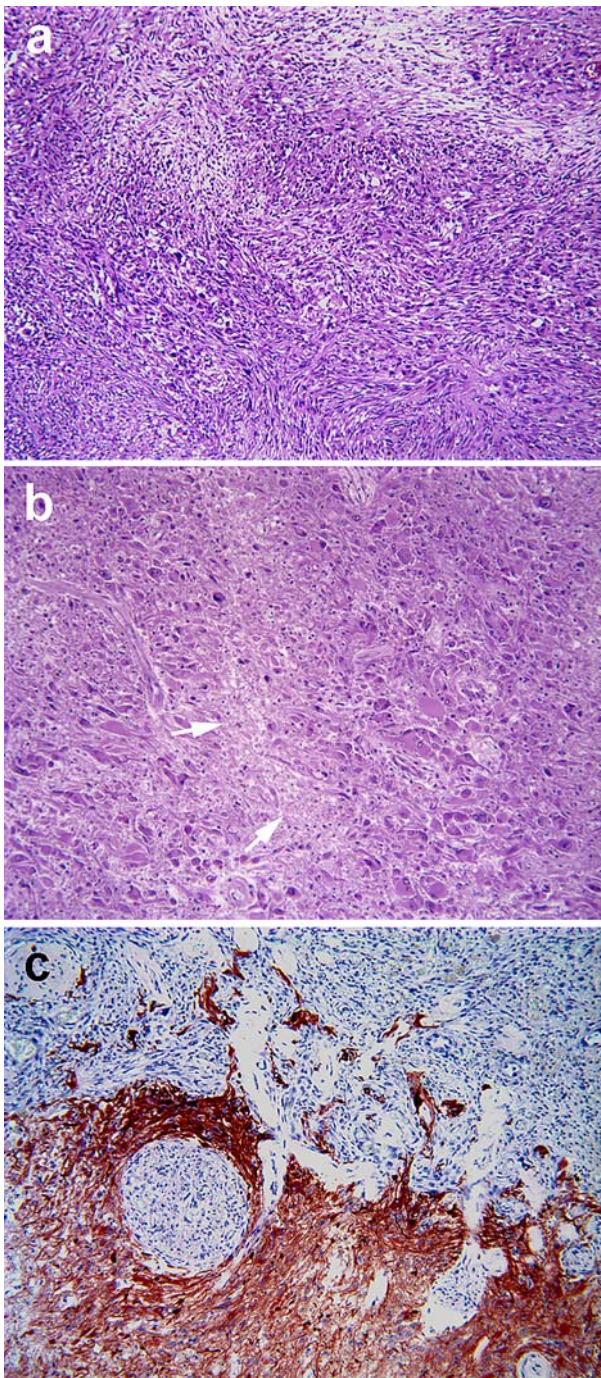


Fig. 4 Photomicrographs. **(a)** Densely cellular tumor composed of interweaving fascicles of spindle cells is typical of sarcomatous component occurring at craniotomy site. H&E, 50× original magnification. **(b)** Intra-axial glial tumor composed of pleomorphic fibrillated astrocyte-like cells. A focus of necrosis is seen (arrows). Other areas of tumor showed different patterns ranging from small anaplastic cells to giant cells. H&E, 50× original magnification. **(c)** Interface between glial and sarcomatous components in the tumor bed using immunohistochemical staining with antibody to GFAP. Avidin–biotin method, 25× original magnification. The glial component (below) is strongly immunoreactive to GFAP; the sarcomatous component (above) is unstained

in the left cerebellar hemisphere (Fig. 5a). Several small nodules of spindle-cell tumor were also present on nerve roots of the cauda equina. In addition, intravascular clusters of sarcoma were seen, particularly in the body of the left caudate nucleus (Fig. 5b).

The general postmortem examination demonstrated numerous nodules of metastatic sarcoma involving the scalp adjacent to the craniotomy site, the lip mucosa, chest wall, pleura, lungs, pericardium, myocardium, peritoneum, diaphragm, liver, pancreas, gastric mucosa, spleen, thyroid gland, and kidney. Intravascular tumor cell clusters, consistent with tumor emboli were abundant, particularly in the spleen, liver, kidney and lung, and were associated with parenchymal infarcts in the latter two sites. There was no evidence of a second primary neoplasm.

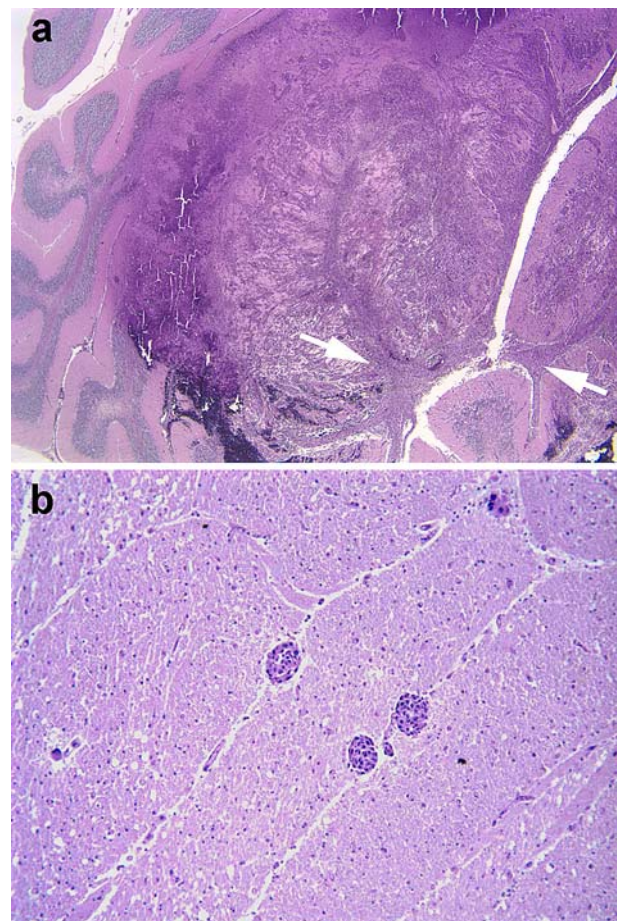


Fig. 5 Photomicrographs. **(a)** Metastatic sarcomatous nodule in cerebellum. Tumor is centered in white matter but is focally extending through cerebellar cortex into subarachnoid space (arrows). H&E, 2.5× original magnification. **(b)** Intravascular clusters of tumor cells (arrows) in white matter adjacent to caudate nucleus most likely represent emboli (H&E, 25× original magnification)

Discussion

Gliosarcoma has been historically reported to comprise 2–8% of all cases of glioblastoma multiforme (GBM) [10, 24]. More recent reports within the last decade suggest an incidence from 1.8 to 2.4% [13, 23]. Specific epidemiologic trends remain unclear, as multicenter prospective studies of this rare neoplasm have not been undertaken. Of the 162 reported cases of gliosarcoma, the age and sex distribution is similar to that of primary glioblastoma with mean age of 53 years and males being affected nearly twice as frequently as females (M:F 1.9:1). Among the 19 cases with extracranial metastases reported in the English language literature (including the present case), all have been supratentorial with 12 (63%) presenting in the temporal lobe, three cases each in the frontal and parietal lobes (16%) and a single tumor in the occipital lobe (Table 1).

Histogenesis

Although Gliosarcoma was first described by Stroebe in 1895 as a brain neoplasm consisting of both glial and mesenchymal components, the proposed biphasic histogenesis of this intriguing tumor was not accepted until the latter 1950s when Feigin defined gliosarcoma as a glioblastoma in which the vascular elements had become sarcomatous [10, 34]. Histologic evidence supporting this theory includes immunoreactivity to factor VIII-related antigen and the endothelial markers CD-34 and Ulex europaeus I agglutinin (UEA-1), as well as predominant perivascular distribution [18, 32, 38]. In the present case, the tumor lacked immunoreactivity for Factor VIII and neither smooth-muscle actin nor predominant perivascular distribution was observed in the intracranial component. Interestingly, recent molecular studies have demonstrated identical *p53* and *PTEN* mutations, *p16* deletions as well as amplification of *MDM2* and *CDK4* in both the glial and mesenchymal components [1, 6, 28]. Common cytogenetic alterations including trisomy 7, deletion of 9p, and monosomy 10 and 17, as well as nonrandom X chromosome inactivation have also been reported [7, 18, 26]. These observations refute the “collision tumor” concept in strong support of a clonal hypothesis wherein the sarcomatous component arises from metaplastic transformation of neoplastic glial cells, as opposed to the transformation of the vascular elements. The sarcomatous component may thus, result from a phenotypic shift of the neoplastic glial cells due to advanced genomic instability, whereby GFAP expression is lost with the acquisition of the sarcomatous phenotype.

Metastases

The criteria for establishing extracranial metastasis of a primary CNS neoplasm have been established by Weiss [37]. Extracranial metastases have been described in 18 (11%) of previously reported cases of gliosarcoma, most commonly involving the lungs (72%), liver (41%) and lymph nodes (18%) (Table 1). The present case exhibited metastases to at least 14 different sites, 6 of which have not been reported previously. These include the thyroid, pericardium, myocardium, diaphragm, pancreas and stomach. This pattern of spread throughout the thorax and abdomen, bone and skin reflects the well-established propensity of sarcomatous neoplasms to disseminate hematogenously. The observation of intravascular tumor emboli in the current case, with corresponding parenchymal necrosis in the striatum (Fig. 5b), liver and kidney is consistent with this concept. Intra-axial dissemination to the cerebrum, cerebellum and nerve roots of the cauda equina was noted, but widespread meningeal gliomatosis was not observed.

Since the first description by Ehrenreich and Devlin in 1958, there has been an increase in the extent of extracranial metastases (Table 1) [9]. Prolonged survival due to aggressive treatment including multiple craniotomies, radiation and new adjuvant therapies may play a role, and may have been a contributing factor in the present case. While on one hand cranial irradiation prolongs survival in glioblastoma, it may also facilitate sarcomatous metaplasia with the acquisition of an angioinvasive phenotype [8]. Our patient received 54 Gy external beam irradiation and 104 Gy delivered by interstitial brachytherapy, the highest overall dose of the 19 reported cases with extracranial metastases. The mean overall dose based on seven cases (including the present case) reporting specific dosing information was 70 Gy. Radiation dosage was not specified for the majority of the early cases.

Radiation-induction

It is well known that therapeutic cranial irradiation can induce astrocytic atypia and rarely, delayed neoplastic processes, most commonly meningioma, fibrosarcoma and other mesenchymal variants, and occasionally GBM [2–4, 16]. Several reports have estimated the relative risk of malignant glial tumors in patients receiving whole-brain irradiation for acute lymphoblastic leukemia from 3 to greater than 20, with one such report indicating statistically significant dose-dependence [11, 29, 35]. While most cases of gliosarcoma arise *de novo*, they have also been

Table 1 Reported cases of gliosarcoma with extracranial metastases

Author & Reference	Year	Age	Sex	Location & 1° Type Tumor	Sites of metastases	Character of metastases	Irradiation (Gy)	Chemotherapy	Survival (months)
Ehrenreich [9]	1958	44	M	P, GS	Lung	G, S ^a	Y		8 ^c
Feigin [10]	1958	6.5	M	T, GS	Lung	G, S			15
Garret [14]	1958	55	F	T, GS	Cervical lymph nodes	G ^a , S	30		9 ^c
Smith et al. [33]	1969	49	M	F, GS	Liver	S		MTX	8
Smith et al. [33]		44	M	T, GS	Liver	G, S ^a	Y		8
Smith et al. [33]		58	M	T, GS	Liver, lung	S	Y		8
Smith et al. [33]		63	M	T, GS	Lung, liver, rt. adrenal gland	G, S	Y		8
Smith et al. [33]		64	M	T, GS	Lung, liver	G, S			11
Smith et al. [33]		6.5	M	T, GS	Lung	G, S ^a	Y		13
Smith et al. [33]		63	F	F, GS	Lung, vertebra	G, S ^b			11
Slowik and Balogh [31]	1980	46	F	P, GBM	Lymph nodes; lungs, liver, kidney	G, S ^b	90		19 ^c
Ojeda and Sterret [25]	1984	83	F	F, GS	Lung	S			3
Weaver et al. [36]	1984	63	M	P, GBM	Lung, omentum	S	WB:50 Local: 12.5		7 ^c
Cerame et al. [8]	1985	11	F	T, GS	Lung	G, S	Y	PCV	1
Yokoyama et al. [40]	1985	22	F	O, GS	Lungs, pleura, liver, cervical & hilar lymph nodes, sternal bone marrow	G, S	40	VCR, 6MP Endoxan	4 ^c
Matsuyama et al. [22]	1989	68	M	T, GS	Liver, spleen spinal cord, scalp	G, S	50	MTX	5
Gjerdrum and Bojsen-Moller [15]	1999	61	M	T/P, GS	Oral mucosa, palpebra, lungs	S	Y		6 ^c
Wharton et al. [38]	2001	53	M	T, GS	Skull, ribs, vertebrae, liver, ileum	G, S, PNET ^a	60		5 ^c
Present Case	2002	47	M	T, GBM	Thyroid, chest wall, pleura, lung, pericardium, myocardium, diaphragm, pancreas, liver, spleen, kidney, stomach, upper lip mucosa, scalp	S	WB: 54 BTX: 103.7	Gliadel Temodar Thalidomide Irinotecan	20 ^c

P, Parietal lobe; T, Temporal lobe; O, Occipital lobe

BTX, brachytherapy; WB, whole brain; MTX, Methotrexate; PNET, primitive neuroectodermal tumor; PCV, Procarbazine, CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea), Vincristine (VCR); 6MP, 6-mercaptopurine

^a indicates predominant histological component

^b indicates predominant histological component is location-dependent

^c indicates postoperative survival following first resection

described at second surgery for a previously resected and irradiated GBM. In the series of 32 cases of gliosarcoma reported by Perry et al., 7 (28%) occurred following 50-Gy whole-brain irradiation for primary GBM [27]. Three additional cases of gliosarcoma which evolved following 59–90 Gy cranial irradiation for primary glioblastoma have also been reported [21, 31, 36].

In their review of radiation-induced gliosarcoma, Kaschten et al. noted that in contrast to glioma and meningioma, no radiation-induced sarcoma occurred

at doses lower than 20 Gy while gliosarcoma occurred following a mean dose of 37 Gy. The latency period from irradiation of the primary tumor to the appearance of radiation-induced tumor was 11 and 5.5 years, respectively, with a considerable range for gliosarcoma from 1 to 12 years [2, 17].

Criteria for establishing radiation induction have been defined by Schrantz and Araoz [30]. To date there are five reported cases of radiation-induced gliosarcoma [2, 5, 17, 19]; however, the precise role of irradiation in the development of the two cases reported by

Averback [2] is unclear. One patient received 58 Gy local irradiation following subtotal resection of a temporal meningioma; the second 54 Gy bilaterally following transsphenoidal subtotal resection of a pituitary adenoma. The radiation dosage in both cases was well above the 37 Gy threshold suggested by Kaschten et al. [17]. However, the lack of autopsy in the former case precludes definitive diagnosis, and the 1 year latency of the second case which unequivocally represents a true secondary neoplasm, would appear incompatible with the kinetics of carcinogenesis.

In the present case, whether the sarcomatous element arose de novo from the metaplastic transformation of an initial glioblastoma, perhaps facilitated by extensive irradiation, or whether the original neoplasm contained a sarcomatous component but was erroneously diagnosed as a glioblastoma due to sampling error cannot be definitively stated. In support of the former, however, several postoperative specimens were independently reviewed by a noted neuropathologist who concurred with the diagnosis of glioblastoma. Thus, 11 cases of gliosarcoma (includes present case) which putatively evolved following irradiation for primary glioblastoma have now been reported [21, 27, 31, 36].

Conclusion

Gliosarcoma is a rare CNS neoplasm which occurs most commonly in the temporal lobe with age and sex distribution similar to glioblastoma. It has a marked propensity for extracranial metastases which occur more frequently in younger males who have undergone adjuvant radiotherapy. Here we report a case of postirradiation gliosarcoma with pervasive extracranial metastases, that evolved following extensive chemo- and radiotherapy for primary glioblastoma.

Acknowledgements We thank Dr. Bradley McCollum for his assistance with the imaging of the pathological specimens and Drs. Marc Chamberlain and Richard Rhiew for their helpful discussions and critical review of the manuscript. We also thank Dr. Otto Muzik for compiling the PET data. AES was supported in part by a grant from the NCI (CA101954).

References

- Albrecht S, Connelly JH, Bruner JM (1993) Distribution of p53 protein expression in gliosarcomas: an immunohistochemical study. *Acta Neuropathol (Berl)* 85:222–226
- Averback P (1978) Mixed intracranial sarcomas: rare forms and a new association with previous radiation therapy. *Ann Neurol* 4:229–233
- Banerjee AK, Sharma BS, Kak VK et al (1989) Gliosarcoma with cartilage formation. *Cancer* 63:518–523
- Barnard RO, Bradford R, Scott T et al (1986) Gliomyosarcoma. Report of a case of rhabdomyosarcoma arising in a malignant glioma. *Acta Neuropathol (Berl)* 69:23–27
- Beute BJ, Fobben ES, Hubschmann O et al (1991) Cerebellar gliosarcoma: report of a probable radiation-induced neoplasm. *AJNR Am J Neuroradiol* 12:554–556
- Biernat W, Aguzzi A, Sure U et al (1995) Identical mutations of the p53 tumor suppressor gene in the gliomatous and the sarcomatous components of gliosarcomas suggest a common origin from glial cells. *J Neuropathol Exp Neurol* 54:651–656
- Boerman RH, Anderl K, Herath J et al (1996) The glial and mesenchymal elements of gliosarcomas share similar genetic alterations. *J Neuropathol Exp Neurol* 55:973–981
- Cerame MA, Guthikonda M, Kohli CM (1985) Extraneural metastases in gliosarcoma: a case report and review of the literature. *Neurosurgery* 17:413–418
- Ehrenreich T, Devlin JF (1958) A complex of glioblastoma and spindle-cell sarcoma with pulmonary metastases. *Arch Pathol* 66:536–549
- Feigin IH, Gross SW (1955) Sarcoma arising in glioblastoma of the brain. *Am J Pathol* 31:633–653
- Fontana M, Stanton C, Pompili A et al (1987) Late multifocal gliomas in adolescents previously treated for acute lymphoblastic leukemia. *Cancer* 60:1510–1518
- Friedman HS, Petros WP, Friedman AH et al (1999) Irinotecan therapy in adults with recurrent or progressive malignant glioma. *J Clin Oncol* 17:1516–1525
- Galanis E, Buckner JC, Dinapoli RP et al (1998) Clinical outcome of gliosarcoma compared with glioblastoma multiforme: North Central Cancer Treatment Group results. *J Neurosurg* 89:425–430
- Garret R (1958) Glioblastoma and fibrosarcoma of the brain with extracranial metaastases. *Cancer Phil* 11:888–894
- Gjerdrum LM, Bojsen-Moller M (1999) October 1998–61-year-old male with brain tumor and oral, lung, and palpebral masses. *Brain Pathol* 9:421–422
- Haddad SF, Moore SA, Schelper RL et al (1992) Smooth muscle can comprise the sarcomatous component of gliosarcomas. *J Neuropathol Exp Neurol* 51:493–498
- Kaschten B, Flandroy P, Reznik M et al (1995) Radiation-induced gliosarcoma. Case report and review of the literature. *J Neurosurg* 83:154–162
- Kattar MM, Kupsky WJ, Shimoyama RK et al (1997) Clonal analysis of gliomas. *Hum Pathol* 28:1166–1179
- Kepes JJ, Bastian FO, Weber ED (1996) Gliosarcoma developing from an irradiated ependymoma. *Acta Neuropathol (Berl)* 92:515–519
- Kleihues P, Burger PC, Scheithauer BW (1993) The new WHO classification of brain tumours. *Brain Pathol* 3:255–268
- Lieberman KA, Fuller CE, Caruso RD et al (2001) Postirradiation gliosarcoma with osteosarcomatous components. *Neuroradiology* 43:555–558
- Matsuyama J, Mori T, Hori S et al (1989) [Gliosarcoma with multiple extracranial metastases. Case report]. *Neurol Med Chir (Tokyo)* 29:938–943
- Meis JM, Martz KL, Nelson JS (1991) Mixed glioblastoma multiforme and sarcoma. A clinicopathologic study of 26 radiation therapy oncology group cases. *Cancer* 67:2342–2349
- Morantz RA, Feigin I, Ransohoff J III (1976) Clinical and pathological study of 24 cases of gliosarcoma. *J Neurosurg* 45:398–408
- Ojeda VJ, Sterrett GF (1984) Cerebral gliosarcoma, pulmonary adenoid-cystic carcinoma, and pulmonary metastatic gliosarcoma: report of an untreated case. *Pathology* 16:217–221

26. Paulus W, Bayas A, Ott G et al (1994) Interphase cytogenetics of glioblastoma and gliosarcoma. *Acta Neuropathol (Berl)* 88:420–425
27. Perry JR, Ang LC, Bilbao JM et al (1995) Clinicopathologic features of primary and postirradiation cerebral gliosarcoma. *Cancer* 75:2910–2918
28. Reis RM, Konu-Lebleblicioglu D, Lopes JM et al (2000) Genetic profile of gliosarcomas. *Am J Pathol* 156:425–432
29. Rimm IJ, Li FC, Tarbell NJ et al (1987) Brain tumors after cranial irradiation for childhood acute lymphoblastic leukemia. A 13-year experience from the Dana-Farber Cancer Institute and the Children's Hospital. *Cancer* 59:1506–1508
30. Schrantz JL, Araoz CA (1972) Radiation-induced meningeal fibrosarcoma. *Arch Pathol* 93:26–31
31. Slowik F, Balogh I (1980) Extracranial spreading of glioblastoma multiforme. *Zentralbl Neurochir* 41:57–68
32. Slowik F, Jellinger K, Gaszo L et al (1985) Gliosarcomas: histological, immunohistochemical, ultrastructural, and tissue culture studies. *Acta Neuropathol (Berl)* 67:201–210
33. Smith DR, Hardman JM, Earle KM (1969) Contiguous glioblastoma multiforme and fibrosarcoma with extracranial metastasis. *Cancer* 24:270–276
34. Strobe H (1895) Ueber entstehung und bau der gehirnglioma. *Beitr Pathol Anat Allg Pathol* 18:405–486
35. Walter AW, Hancock ML, Pui CH et al (1998) Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children's Research Hospital. *J Clin Oncol* 16:3761–3767
36. Weaver D, Vandenberg S, Park TS et al (1984) Selective peripancreatic sarcoma metastases from primary gliosarcoma. Case report. *J Neurosurg* 61:599–601
37. Weiss L (1955) A metastasizing ependymoma of the cauda equina. *Cancer* 8:161–171
38. Wharton SB, Whittle IR, Collie DA et al (2001) Gliosarcoma with areas of primitive neuroepithelial differentiation and extracranial metastasis. *Clin Neuropathol* 20:212–218
39. Witwer BP, Salamat MS, Resnick DK (2000) Gliosarcoma metastatic to the cervical spinal cord: case report and review of the literature. *Surg Neurol* 54:373–378; discussion 378–379
40. Yokoyama H, Ono H, Mori K et al (1985) Extracranial metastasis of glioblastoma with sarcomatous component. *Surg Neurol* 24:641–645