Turkish Journal of Pathology 2007;23(1):5-15

Primary sarcomas of the central nervous system: UCSF experience (1985-2005)

Merkezi sinir sistemi primer sarkomları: UCSF deneyimi (1985-2005)

Tarık TİHAN[1], Ann GRİFFİN[2], Sema ÖZUYSAL[3]

University of California, San Francisco, Department of Pathology, Neuropathology Unit[1], University of California, San Francisco, Cancer Center Tumor Registry[2], Uludağ University, School of Medicine, Department of Pathology[3], SAN FRANSİSCO

ABSTRACT

Sarcomas constitute less than 2% of all cancers, and are a highly diverse group of neoplasms. Primary sarcomas of the central nervous system (CNS) are even less common, and our experience is limited by lack of studies with sufficient size that can address the challenges in predicting behavior or management. It is critical to recognize the characteristics of these uncommon neoplasms and to develop better predictors for prognosis and behavior.We have conducted a search of the UCSF Department of Pathology and UCSF Cancer Center Registry databases for all primary CNS sarcomas that were diagnosed and treated between 1985 and 2005. Hemangiopericytomas were included, so were the solitary fibrous tumors due to their close association with the former. We excluded all cases of metastatic sarcomas, chordomas, sarcomatoid variants of all neuroepithelial neoplasms, Ewing's sarcomas and other embryonal tumors. In addition, we have identified all soft tissue sarcomas diagnosed and treated during the same period. There were 43 primary CNS neoplasms that fulfilled the inclusion criteria. At the same time, we identified 1706 sarcomas primary to the soft tissue. Primary CNS sarcomas included 16 hemangiopericytomas, 15 chondrosarcomas, 3 solitary fibrous tumors, 3 osteosarcomas, 2 leiomyosarcomas, 2 undifferentiated sarcomas, 1 histiocytic sarcoma, and 1 fibrosarcoma. There was a distinctly higher frequency of hemangiopericytoma in the CNS compared to soft tissue. In addition, a group of low grade, parasagittal chondrosarcomas were noted for their highly indolent biological behavior. Unlike some previous series, our cohort was devoid of angiosarcoma and malignant fibrous histiocytoma. This study underscores the limitations of single institutional series, and highlights the value of multi-institutional studies to understand and better treat primary CNS sarcomas.

Key words: Sarcoma, primary, central nervous system, hemangiopericytoma, chondrosarcoma

ÖZET

Sarkomlar tüm kanserlerin %2'sinden azını oluşturur ve çok sayıda histolojik tipi içerir. Bu grupta bulunan merkezi sinir sistemi (MSS) primer sarkomları daha da ender tümörlerdir. Primer MSS sarkomlarının klinik özelliklerini irdeleyen yeterli sayıda olgu içeren çalışmanın azlığı nedeniyle, bu konularda deneyim sınırlıdır. Nadir görülen bu tümörlerin özelliklerinin daha iyi tanınması davranışlarının daha iyi belirlenmesinde kritik önem taşımaktadır. Bu çalışmada UCSF Patoloji Anabilim Dalı ve Kanser Bilgi İşlem Merkezi arşivleri taranarak, 1985-2005 yılları arasında tanı konulan veya tedavi edilen tüm primer MSS sarkoma olguları tespit edildi. Metastatik sarkom, kordoma, nöroepitelyal tümörlerin sarkomatoid formları, Ewing sarkomu ve diğer embriyonal sarkomlar çalışma dışı bırakıldı. Çalışmaya hemanjiyoperisitom ve bu tümöre yakınlığı dolayısıyla soliter fibröz tümör olguları da dahil edildi. Karşılaştırma amacı ile aynı dönemde tanı konan ve tedavi edilen tüm kemik ve yumuşak doku sarkomları da saptandı. Patoloji ve klinik verilerin incelenmesi sonucunda, çalışma kriterlerine uyan 43 adet primer MSS sarkomu saptandı. Aynı dönemde tanı ve tedavi gören 1706 primer yumuşak doku sarkomu olgusu tespit edildi. Primer MSS sarkomları içinde 16 hemanjiyoperisitom, 15 kondrosarkom, 3 soliter fibröz tümör, 3 osteosarkom, 2 leiomiyosarkom, 2 başkalaşım göstermeyen sarkom, 1 histiyositik sarkom ve 1 fibrosarkom olgusu bulundu.Bu çalışmada MSS hemanjiyoperisitomu sıklığının yumuşak dokudaki hemangiyoperisitomlara oranla belirgin biçimde fazlalığı dikkati çekti. Ayrıca parasagittal bölgede rastlanan düşük dereceli kondrosarkomların çok yavaş seyirli ve selim davranışları dikkate değer bir gözlem olarak kaydedildi. Sonuç olarak çalışmamız, MSS sarkomlarının daha kapsamlı anlaşılmasında tek merkez kaynaklı serilerin sınırlılığını, çok merkezli ve uzun vadeli çalışmaların gerekliliğini ortaya koymaktadır.

Anahtar sözcükler: Sarkom, primer, santral sinir sistemi, hemanjiyoperisitom, kondrosarkom

Corresponding Author: Tarık Tihan, UCSF School of Medicine Department of Pathology Neuropathology Unit, Room M551, 505 Parnassus Avenue San Fransisco, CA 94143-0102

INTRODUCTION

Sarcomas are a heterogeneous group of uncommon neoplasms with a broad range of differentiation, often interpreted as an indication of their etiological and pathogenetic diversity (1). Rarity of sarcomas and the difficulties in their nosology present major challenges in diagnosis, management and prognosis (2). Soft tissue is the most common location for sarcomas, accounting for more than half of all sarcomas, followed by skin and solid organs (3). Sarcomas in the central nervous system (CNS) are extremely rare (4). Most sarcomas in the CNS are either metastatic from elsewhere, or extend into brain parenchyma through direct spread. In addition, radiation therapy has been associated with an increased risk of developing sarcoma especially among younger patients (5). There is little information about the incidence and demographic characteristics of primary CNS sarcomas. Typically, CNS sarcomas are classified using similar diagnostic criteria as those in the soft tissue (6,7).

Most common histologic type of sarcomas is the so-called malignant fibrous histiocytoma, followed by liposarcoma, leiomyosarcoma. A significant percentage of sarcomas cannot be further classified, and are considered under unclassified sarcomas (3). CNS sarcomas constitute 0.7% of all sarcomas and the incidence rate was estimated at 3 per 10 million person-years (3). In recent series of CNS sarcomas, undifferentiated sarcoma, fibrosarcoma, and malignant fibrous histiocytoma have been reported as the most common entities (4,6,8). Interestingly, no large study includes all possible histological subtypes, and the majority of the information in the literature is in the form of case reports.

Hemangiopericytomas (HPCs) have not been included in most of the reports of CNS sarcomas in earlier studies (4,6,8-10). This is partially due to misrecognition of CNS hemangiopericytomas as angioblastic meningiomas (for earlier studies), and partially due to unique status given to this tumor within the CNS tumor classification (11-13). Furthermore, there is much controversy on the actual incidence of HPC in soft tissue. In recent years, many tumors previously classified as HPCs have been re-classified as solitary fibrous tumor and other categories (1). Currently, it is not clear whether this paradigm shift will be readily accepted for tumors considered as HPC in the CNS. It appears, at least in the soft tissue literature, that the distinction between solitary fibrous tumor and HPC is becoming more subjective with every new publication, while examples in the CNS still seem to harbor differences (14).

We have undertaken a UCSF Cancer Registry and Pathology Database search and a pathological review of the cases to determine the frequency and histological diversity of primary CNS sarcomas in relation to bone and soft tissue sarcomas. Specific emphasis was placed on the so-called hemangiopericytomas and unusual tumors that may show unique biological properties within the CNS. The study also included solitary fibrous tumors due to their nosological proximity to HPCs (15).

MATERIALS AND METHODS

Pathology and Cancer Center Database Review:

We have used a search algorithm including ICD-O and SNOMED codes as well as a text-based search algorithm to identify all sarcomas registered at the UCSF Department of Pathology between the dates 1/1/1985 and 1/1/2005. We included all cases treated during this period, even though many patients had been diagnosed earlier in other institutions. We also searched the UCSF Cancer Center Registry Database for all sarcoma cases diagnosed and/or treated at UCSF during the same period. Separate pathology database searches were conducted using a text based algorithm that included all terms related to HPC (e.g. angiomatous meningioma) and solitary fibrous tumor (e.g. fibrous mesothelioma). HPCs and solitary fibrous tumors invol-

ving the pleura and the mediastinum were also included in the soft tissue cohort. Patient age, sex, tumor location, histological diagnosis, other coexisting diseases, and metastatic state were recorded for all patients. Each entry was reviewed to exclude tumor diagnoses other than sarcomas in bone/soft tissue database as well as in the CNS database. Both search lists were then compared with each other to exclude duplicate patients, second specimens and unrelated pathology material. Primary site for all tumors were verified through electronic chart review. Soft tissue sarcomas that were metastatic to the central nervous system were excluded from the CNS database, and were retained in the bone/soft tissue database. Detailed clinical information for the primary intracranial sarcomas were obtained from patients' records and physicians' notes.

Pathological Evaluation:

All available slides and paraffin blocks from primary intracranial sarcoma patients were retrieved and reviewed, and appropriate sections were selected for immunohistochemical studies.

Table 1. Antibodies used in the diagnosis of intracranial sarcomas.

Antibody	Dilution	Source
Actin (HHF35)	1:2	ENZO Labs
Actin (SMA)	1:800	DakoCytomation
Bcl-2	1:500	DakoCytomation
CAM5.2	1:100	Becton-Dickinson
CD1a	1:4	Immunotech
CD117	1:50	DakoCytomation
CD20	1:600	DakoCytomation
CD21	1:15	Novocastra
CD3	1:400	DakoCytomation
CD30	1:50	DakoCytomation
CD31	1:4	DakoCytomation
CD34	1:400	Novocastra
CD68	1:2000	DakoCytomation
Collagen Type IV	1:150	DakoCytomation
CK7	1:160	Novocastra
CK20	1:200	DakoCytomation
Cytokeratin cocktail	1:100	DakoCytomation
EMA	1:240	DakoCytomation
Myogenin	1:200	DakoCytomation
NSE	1:2	DakoCytomation
S100	1:1000	DakoCytomation
Myosin (SMM)	1:200	DakoCytomation
Vimentin	1:1600	Zymed

Immunohistochemical studies were performed at the UCSF Department of Pathology Immunohistochemistry Laboratory with commercially available antibodies, and appropriate positive and negative controls. Each run was accompanied by a positive and negative control and a normal brain section. Stains used, sources and dilutions are presented in Table 1. Electron microscopic evaluation, whereever available were performed in tissue fixed in 2% glutaraldehyde, postfixed in osmium tetroxide, embedded in epoxy for thick and thin sections.

Statistical Evaluation:

The collated data was analyzed using SPSS Advanced Statistical Package for Windows, release 11.0.1. Clinical and pathological features were compared using crosstabs, and the conditional survival probability, median survival time and 95% confidence intervals were estimated using the Kaplan-Meier model.

RESULTS

The combined search results from the UCSF Cancer Registry and Pathology Databases identified 1706 soft tissue and bone sarcomas diagnosed or treated at UCSF between 1985 and 2005 (Table 2). During the same period, there were 43 primary CNS sarcomas (19 female, 24 male). The median age of the patients was 40 years (range 3-73). There were 16 HPCs, 15 chondrosarcomas, 3 osteosarcomas, 3 solitary fibrous tumors, 2 leiomyosarcomas, 2 undifferentiated sarcomas, a fibrosarcoma, and a histiocytic sarcoma. Demographic features of the primary intracranial sarcomas are presented in Table 3. The most common CNS sarcoma was the controversial HPC (37%, n=16), distinctly more frequent compared to HPCs in bone and soft tissue (1%, n=19). The frequency of chondrosarcomas was similar between CNS and bone. It was not possible to make a comparison on other sarcomas due to low numbers. The database did not include any angiosarcomas or

Table 2. Sarcomas diagnosed and treated at UCSF between 1985 and 2005.

	Bone and Soft Tissues			Primary Intracranial Sarcomas		
Histological Type	**N**	**%**	**Mean Age**	**N**	**%**	**Mean Age**
Alveolar Soft Part Sarcoma	13	1%	28.7	15	35%	44.0
Chondrosarcoma (All Types)	200	12%	47.1			
Clear Cell Sarcoma	19	1%	87.4			
Dermatofibrosarcoma	16	1%	30.1			
Epithelioid Sarcoma	19	1%	34.8			
Fibromyxosarcoma	35	2%	82.3			
Fibrosarcoma	33	2%	42.8	1	2%	72.0
Giant Cell Sarcoma, NOS	16	1%	58.1			
Gastrointestinal Stromal Sarcoma	5	0%	58.4			
Hemangiopericytoma	17	1%	55.6	16	37%	48.0
Hemangioendothelioma	2	0%	56.0			
(Hem)angiosarcoma	29	2%	60.1			
Histiocytic Sarcoma	1	0%	50.0	1	2%	47.0
Leiomyosarcoma (All Types)	146	9%	54.4	2	5%	35.0
Liposarcoma (All types)	185	11%	53.3			
Malignant Giant Cell Tumor	2	0%	37.0			
Malignant Mesenchymoma	8	0%	45.3			
Malignant Fibrous Histiocytoma	299	18%	67.5			
Osteosarcoma	301	18%	67.5	3	7%	8.0
Rhabdomyosarcoma (All Types)	90	5%	25.2			
Sarcoma, NOS	122	7%	48.3			
Small Cell Sarcoma (?)	11	1%	30.0			
Solitary Fibrous Tumor	30	2%	55.2	3	7%	36.0
Synovial Sarcoma	86	5%	31.4			
Undifferentiated Sarcoma	21	1%	47.0	2	5%	32.5
TOTAL	1706		50.1	43		40.3

malignant fibrous histiocytomas diagnosed or treated during the study period. There were a total of 22 patients who had recurrence during the follow-up period. At the end of a median follow up period of 58 months, 12 patients were dead due to progressive disease, 20 patients were alive with residual/persistent disease, 8 patients had no evidence of disease, and 3 were lost to follow-up. No statistically significant correlation could be found between clinical and pathological parameters. However, the sample size was often too small to detect a possible meaningful difference. Kaplan-Meier analysis for overall survival revealed a median survival of 170 months with a standard error of 53 months (95% CI 65.5-274.4). A Kaplan-Meier survival plot is presented in Figure 6. The values for overall survival probability did not change even after exclusion of three patients with solitary fibrous tumors.

Chondrosarcomas (Figure 1) occurred in 8 females and 7 males with a mean age of 44 years (range 19 and 73 years). The locations and histological grades are presented in Table 3. The tumors involving the skull base and clivus region often presented with 6th nerve palsy, vertigo and headaches. The mean follow-up period was 88 months (range 1-170 months). During a mean follow-up of 88 months, 2 patients with Grade III tumors (including the mesenchymal chondrosarcoma) died of progressive disease at 27 and 170 months, 7 were alive with residual tumor, and 4 patients had no evidence of disease. The remaining 2 patients were lost to follow-up at 1 an 91 months. All 3 patients with frontal lobe tumors had parasagittal grade I chondrosarcomas, and had undergone gross total resections, and were free of tumor at the end of follow-up. All tumors involving the skull base were partially resected, and most had persistent disease or were lost to follow-up. Histologically, the tumors were identical to their counterparts in soft tissue or bone. Immunohistochemical stains for S-100 protein and vimentin were diffusely positive, while EMA and cytokeratin were negative in all tumors.

Fibrosarcoma (Figure 2) occurred in a 72 year old male, who received external beam radiation for the treatment of a low grade oligodendroglioma. Six years later he developed multiple dura-based lesions as well as skull and scalp masses over the craniotomy site at within the radiation field. He underwent four separate surgical procedures and received multiple chemotherapy regimens as well as IMRT. He died of disseminated disease 28 months following first surgery for fibrosarcoma, and 8 years after radiation the-

Table 3. Distribution of intracranial sarcomas diagnosed at UCSF between 1985 and 2005.

Case No	Sex	Age	Location	Diagnosis	Recurrence	Outcome	Survival (months)	Extent of Surgery
15	F	19	Clivus	CHONDROSARCOMA Gr I	No	AWD	138	GTR
42	F	30	Parasellar	CHONDROSARCOMA Gr I	No	AWD	102	STR
2	F	37	Parasellar	CHONDROSARCOMA Gr I	No	AWD	150	STR
29	F	37	Clivus	CHONDROSARCOMA Gr III	Yes	DOD	170	GTR
30	F	45	Frontal	CHONDROSARCOMA Gr I	No	NED	60	GTR
27	F	45	Parasellar	CHONDROSARCOMA Gr I	No	LFU	91	STR
1	F	60	Skull base	CHONDROSARCOMA Gr I	No	LFU	1	STR
32	F	66	Parasellar	CHONDROSARCOMA Gr II	No	AWD	138	STR
23	M	26	Frontal	CHONDROSARCOMA Gr I	No	NED	18	GTR
39	M	33	Frontal	CHONDROSARCOMA Gr II	No	NED	169	GTR
12	M	38	Clivus	CHONDROSARCOMA Gr II	Yes	AWD	38	STR
6	M	43	Clivus	CHONDROSARCOMA Gr I	No	AWD	70	STR
9	M	52	Brainstem	CHONDROSARCOMA Gr I	No	NED	151	STR
34	M	61	Skull base	CHONDROSARCOMA Gr I	Yes	AWD	95	STR
37	M	73	Skull base	CHONDROSARCOMA Gr III*	Yes	DOD	27	STR
5	M	52	Skull base	FIBROSARCOMA	Yes	DOD	28	STR
4	F	19	Parasellar	HEMANGIOPERICYTOMA	No	AWD	18	STR
40	F	31	Temporal	HEMANGIOPERICYTOMA	No	AWD	58	STR
7	F	40	Skull base	HEMANGIOPERICYTOMA	Yes	AWD	47	STR
10	F	59	Pineal	HEMANGIOPERICYTOMA	No	AWD	24	GTR
25	F	66	Frontal	HEMANGIOPERICYTOMA	Yes	AWD	50	STR
17	F	75	Frontal	HEMANGIOPERICYTOMA	No	AWD	73	STR
13	M	38	Temporal	HEMANGIOPERICYTOMA	Yes	DOD	96	STR
14	M	39	Cerebellar	HEMANGIOPERICYTOMA	Yes	AWD	106	STR
43	M	40	Temporal	HEMANGIOPERICYTOMA	No	AWD	70	STR
3	M	43	Temporal	HEMANGIOPERICYTOMA	No	AWD	138	STR
18	M	44	Parietal	HEMANGIOPERICYTOMA	Yes	AWD	89	STR
31	M	46	Cerebellar	HEMANGIOPERICYTOMA	Yes	DOD	77	STR
36	M	53	Occipital	HEMANGIOPERICYTOMA	Yes	AWD	180	STR
21	M	54	Temporal	HEMANGIOPERICYTOMA	Yes	DOD	36	STR
38	M	62	Temporal	HEMANGIOPERICYTOMA	No	NED	41	GTR
35	M	68	Frontal	HEMANGIOPERICYTOMA	No	NED	58	GTR
16	F	47	Temporal	HISTIOCYTIC SARCOMA	Yes	AWD	25	GTR
8	M	32	Frontal	LEIOMYOSARCOMA	Yes	DOD	3	STR
22	M	38	bilateral	LEIOMYOSARCOMA	Yes	DOD	49	STR
41	F	3	Frontal	OSTEOSARCOMA	Yes	LFU	96	STR
20	F	8	Sphenoid	OSTEOSARCOMA	Yes	DOD	49	STR
33	M	11	Occipital	OSTEOSARCOMA	Yes	DOD	15	STR
11	M	27	Thalamus	PRIMITIVE SARCOMA, NOS	Yes	DOD	35	STR
19	M	38	Temporal	PRIMITIVE SARCOMA, NOS	Yes	DOD	32	STR
26	F	30	Cerebellar	SOLITARY FIBROUS TUMOR	Yes	AWD	49	GTR
24	F	34	Tentorium	SOLITARY FIBROUS TUMOR	No	NED	21	GTR
28	M	45	Frontal	SOLITARY FIBROUS TUMOR	No	NED	20	GTR

** This tumor was classified as a high grade mesenchymal chondrosarcoma.*
GTR=Gross total resection
STR=Subtotal resection
AWD=Alive with disease
DOD=Died of disease
NED=No evidence of disease
LFU=Lost to follow-up

rapy for oligodendroglioma. During the last four years of his life, and at the time of his death, there was no evidence of oligodendroglioma recurrence.

Hemangiopericytomas (Figure 3) occurred in 7 females and 9 males between ages 19 and 75. In all patients, the radiological differential diagnosis included meningioma, and two of the tumors had convincing "dural tail" in T1-weighted contrast enhanced MRI studies. All tumors were symptomatic, and while headache was the most common complaint, the symptoms varied considerably among patients. Extent of resection and

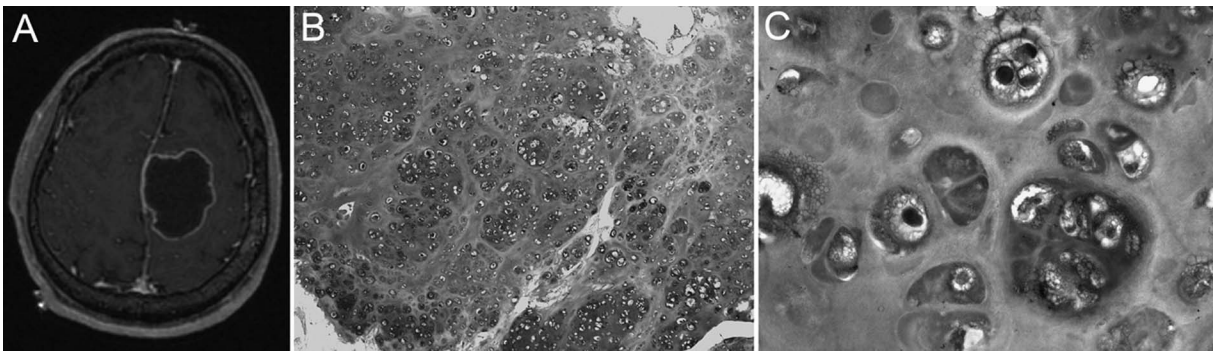

Figure 1. A) Axial contrast-enhanced T1-weighted image of a Grade I parasagittal chondrosarcoma. B,C) Histologically, the tumor is composed of mature-appearing, hyperchromatic plump nuclei with occasional binucleated cells.

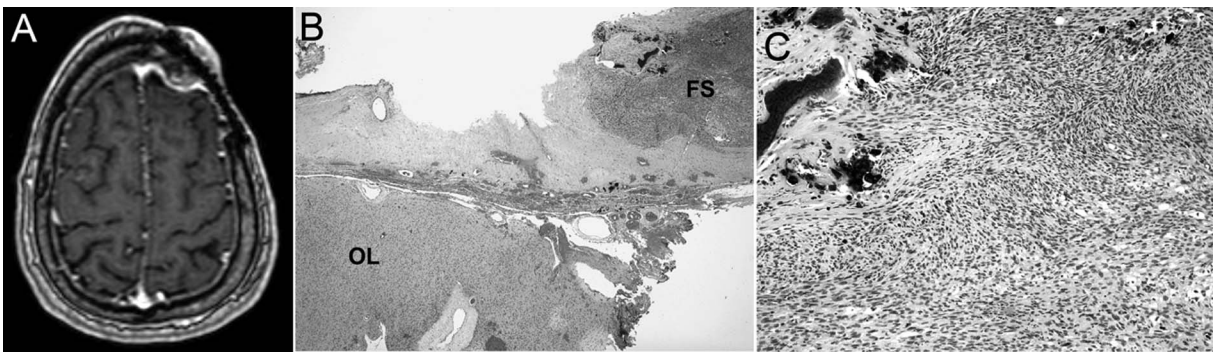

Figure 2. A) Axial contrast-enhanced T1-weighted image of frontal skull-based tumor at the site of prior craniotomy and radiotherapy. B) Low power image demonstrates residual infiltrating oligodendroglioma involving the cortex (OL) and fibrosarcoma involving the overlying dura and soft tissues (FS). C) High power magnification of the high grade fibrosarcoma.

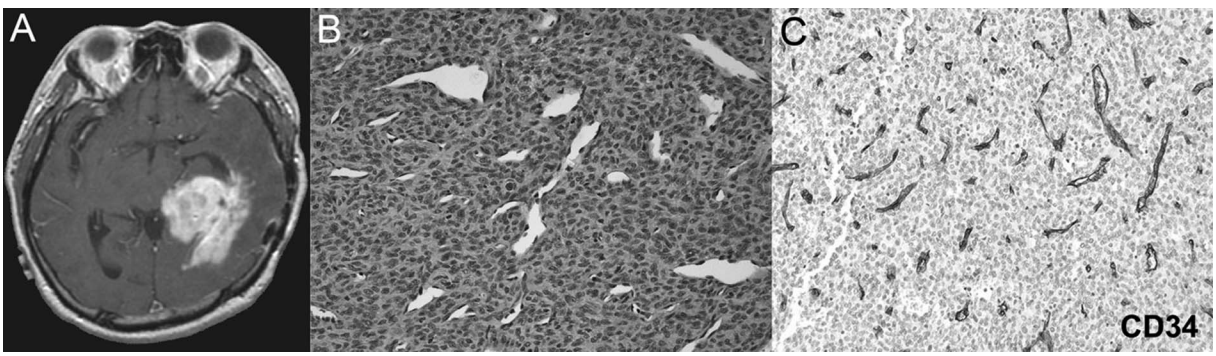

Figure 3. A) Axial contrast-enhanced T1-weighted image of an intracranial hemangiopericytoma, partially involving the lateral ventricle and causing peritumoral edema. B) Histologically, the tumor has a "typical" monomorphous, jumbled architecture with staghorn vasculature C) CD34 staining highlighting the vascular network, with almost no staining of tumor cells.

survival following initial surgery are presented in Table 3. The median follow-up time was 89 months for all patients (range 18-180 months). Recurrences were noted in 8 of the tumors, while 3 demonstrated extracranial metastases. All three tumors with extracranial metastases had high grade histological features, and were considered anaplastic HPCs according to the criteria of Mena et al. (13) During the follow-up period, 3 patients died of their disease. Eleven patients were alive at the end of the follow-up period with persistent or residual tumors. Only two pa-

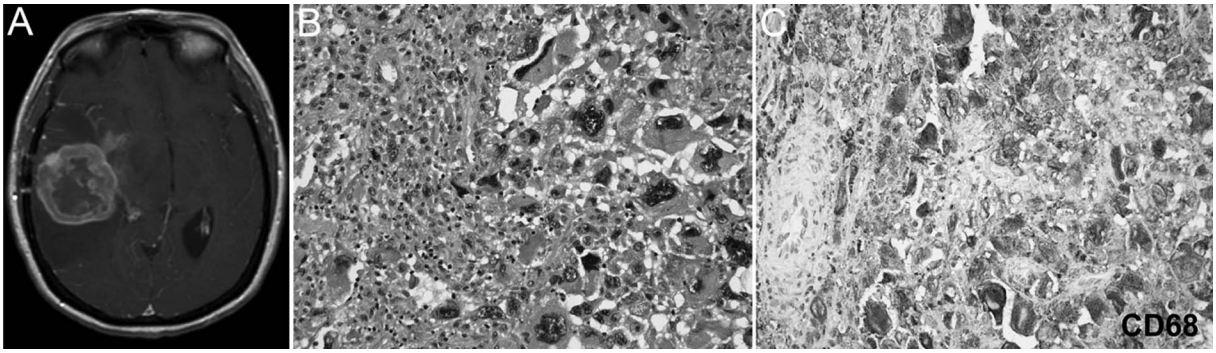

Figure 4. A) Axial contrast-enhanced T1-weighted image of an intracranial histiocytic sarcoma with heteregenous enhancement. The central dark area corresponded to the necrotic center. B) Histological appearance of highly pleomorphic bizarre cells admixed with numerous atypical histiocytic cells C) Immunohistochemical staining for CD68 demonstrating diffuse positive staining of both bizarre and small neoplastic cells.

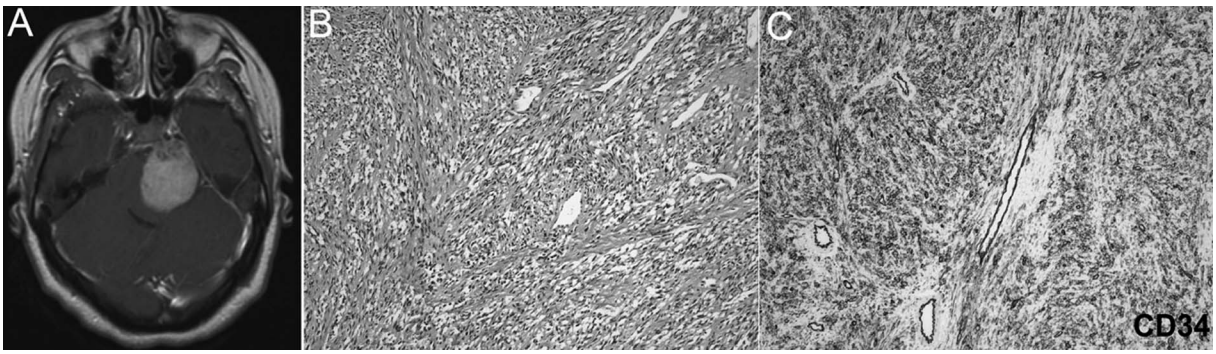

Figure 5. A) Axial contrast-enhanced T1-weighted image of a posterior fossa solitary fibrous tumor with typical homogenous enhancement. B) H&E image demonstrating a markedly spindled tumor cells in a rich collagenous background. C) Immunohistochemical staining for CD34 showing strong and diffuse positivity.

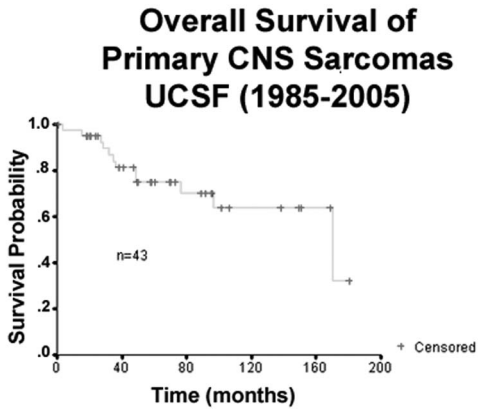

Figure 6. Kaplan-Meier analysis and plot for overall survival probability for all CNS sarcomas (n=43).

tients who underwent gross total resection had no evidence of tumor after 3 and 5 years. Histologically, all tumors were composed of tightly packed, randomly oriented (jumbled-up) tumor cells with little intervening collagen, elaborate, stag-horn-like branching vasculature with extensiveand delicate reticulin network. CD34 staining mostly highlighted the vascular background, but also stained a minor population of tumor cells in 4 of the cases. Staining for Vimentin and Collagen type IV was strongly and diffusely positive in all tumors. Bcl-2 was strongly positive in a variable percentage of tumor cells, while S-100 protein and EMA were negative in all tumors.

Histiocytic sarcoma (Figure 4) occurred in a 47 year old female who presented with dizziness, confusion, and difficulty in word finding. A CT and MRI evaluation demonstrated a well-defined, 3 cm lobulated mass in the right temporoparietal region. A stereotactic biopsy was per-

formed, and the pathology specimen was interpreted as malignant lymphoma elsewhere. A thorough work-up of the patient including bone marrow biopsy, thoracic, abdominal, and pelvic scans, whole-body PET scan, and series of laboratory testing revealed no evidence of disease elsewhere. She was treated with two rounds of chemotherapy followed by standard protocol for CNS lymphoma including methotrexate, leucovorin, temozolamide, and rituximab. Twelve days after the second cycle, she was re-admitted to emergency room with signs of intacranial hypertension and evidence of uncal herniation. She underwent a whole brain external beam radiation with a goal of 40 Gy in 15 fractions. She completed 11 of the fractions, when she suffered seizures and the emergency scan demonstrated a marked increase in tumor size. She underwent surgery the next day, and a gross total resection of the tumor was achieved. Microscopic analysis of the tissue revealed a solid highly pleomorphic neoplasm with numerous large, bizarre cells, with multinucleated forms, and the tumor showed an angiocentric distribution in most areas. Immunohistochemically, the tumor cells were strongly positive for CD68, Lysozyme, and Vimentin, and only weakly positive for S-100 protein (Figure 4). All other antibodies were negative. Ultrastructural studies were compatible with a histiocytic origin. A year after the resection, the patient developed T6 vertebral metastasis, and received radiation and chemotherapy followed by a resection of the metastatic tumor. She is currently alive with no apparent evidence of tumor 2 years after the resection of her cranial tumor.

Leiomyosarcomas occurred in two males ages 32 and 38, both of whom had evidence of immune suppression. Thirty-two year old male underwent renal transplantation, and the tumor was positive for EBV on in-situ hybridization. In-situ hybridization for EBV in the other patient with HIV/AIDS was equivocal. Both tumors had evidence of smooth muscle differentiation immunohistochemically (HHF35, SMA, Vimentin positive) and ultrastructurally. Both patients died of their disease 1 year and 2 years after their initial surgery on the tumors, respectively.

Osteosarcomas occurred in two girls and one boy, ages 3, 8 and 11 involving frontal lobe, skull base, and occipital lobe, respectively. Two patients, ages 8 and 11 had been treated earlier with radiation for bilateral retinoblastoma, and rhabdomyosarcoma, respectively. Both of these neoplasms were considered to be associated with radiation treatment. Two patients died 2 and 3 years after subtotal resections, multiple chemo and radiotherapy regimens. The 3 year old patient was lost to follow-up. All three tumors were histologically high grade tumors with marked hypercelluarity, abundant osteoid formation, identical to their counterparts in long bones.

Primitive (undifferentiated) sarcomas occurred in two male patients ages 27 and 38, in thalamus and temporal lobe respectively. Both had undergone subtotal resections and multimodal chemo- and radiotherapy. Both patients died of recurrent disease 1 year and 3 years following initial surgery. Histopathological studies failed to identify any particular architectural pattern, or any kind of differentiation on immunohistochemistry (see Table 1 for panel of antibodies) or by electron microscopy.

Solitary fibrous tumors (Figure 5) were considered in this category due to their recently suggested similarity to HPCs, and the uncertainty of their biological behavior in CNS. The tumors occurred in 2 females and 1 male. Two tumors in females involved the tentorium and the posterior fossa, while the third tumor was located in the frontal lobe. One of the tumors developed a recurrence 10 months after a gross total resection, and received local radiotherapy. The remaining two patients are free of disease 17 and 18 months following gross total resection. Histolo-

gically, all three tumors demonstrated markedly collagenous background with a vague storiform architecture, diffuse strong CD34 and bcl-2 staining, and variable Collagen type-IV staining with a coarse reticulin network.

DISCUSSION

Sarcomas are extremely rare, and comprise a very small percentage of all malignant neoplasms. CNS sarcomas are even less common, and comprise a fraction of primary brain tumors. In this study, primary intracranial sarcomas constituted only 2.5% of bone and soft tissue sarcomas diagnosed at UCSF during the same period. This finding is in keeping with the study of 18 primary sarcomas of the brain and spinal cord by Oliviera et al. (4), even though the authors did not include HPCs in their report. An earlier study by Paulus et al. (8) provided a much lower estimate of CNS sarcoma incidence, and similarly, these authors have not included HPCs in their group. The rarity of CNS sarcomas compounded by their histological diversity, precludes an objective assessment of demographic characteristics, treatment or management strategies even in largest studies. Nevertheless, our study underscores a number of interesting points.

First, there seems to be a distinctly higher prevalance of HPCs, or HPC-like neoplasms in the CNS. These tumors were disproportionally overrepresented in the CNS compared to soft tissue, even though we included mediastinal and pleural examples within the "soft-tissue/bone" category. It has been suggested that "most lesions formerly known as haemangiopericytoma show no evidence of pericytic differentiation and, instead, are fibroblastic in nature and form a morphological continuum with solitary fibrous tumour" (1). Nevertheless, the tumors categorized in the HPCgroup constitute a clinicopathological entity with a high rate of local recurrence and a substantial risk of distant metastases. This observation confirms our earlier studies comparing solitary fibrous tumors and hemangiopericytomas in the CNS (14). It is quite plausible to consider the tumors with the typical histological features of HPC at the more aggresive, or malignant end of this spectrum, and among bona fide sarcomas of the CNS. We may be able to answer this question better, if there is progress in identifying the "cell of origin" for HPCs, and the factors that lead to its neoplastic transformation or differentiation.

One possible reason for the discrepancy mentioned above is, therefore, the diagnostic criteria for HPC used in in the CNS. Recognizing this caveat, we have performed a vigorous review, and attempted to categorize the neoplasms under other and more specific entities using the panel of antibodies (Table 1), but were not able to do so in these 16 tumors. The discrepancy can also be explained by the fact that our institution is a highly specialized large referral center for brain tumors, and there is a well-developed program for treatment of meningiomas, for which HPCs are often mistaken. The series from our cancer registry cannot be considered population based data, and the lack of a referal center for soft tissue sarcomas may account for the rarity of such lesions. This argument, however, is far from being convincing given the number of soft tissue sarcomas analyzed in the study.

While we have observed a significant rate of recurrence, and few deaths among HPCs, the numbers are too small to calculate 5 year survival expectancy, effect of adjuvant therapy or features that imply higher recurrence/metastasis risk.

Second, among the second most common sarcomas, a distinct group of low grade chondrosarcomas is worth mentioning due to their clinical and pathological characteristics. These low neoplasms occurred in the parasagittal region of young adults, and demonstrated an excellent survival following surgery. Due to their parasagittal location, these tumors could often be resected in toto, and did not show recurrence or

metastasis on follow-up. Histologically, some of these neoplasms were indistinguishable from tumors reported in the literature under intracranial chondromas (16). Nevertheless, histological criteria along with radiological evidence were convincing for a low grade chondrosarcoma. These examples suggest that the neoplasms can be adequately treated with surgery alone if a gross total resection is achieved.

Histiocytic sarcoma, albeit very rare, may easily be misrecognized as either malignant fibrous histiocytoma, lymphoma or gliosarcoma, and pose a significant challenge in the differential diagnosis of solid, pleomorphic malignant neoplasms. We believe that this neoplasm is most like underreported, and some have historically been considered malignant fibrous histiocytoma or histiocytic lymphoma or simply malignant lymphoma. Better recognition of the clinical characteristics of this highly unusual lesion will await larger studies and more experience with this neoplasm. This entity should be kept in mind especially when dealing with highly pleomorphic neoplasm resembling malignant fibrous histiocytoma, or a "bizarre" lymphoma.

Our series included distinctly fewer primitive or undifferentiated sarcomas compared to previous studies. This is typically due to recognizing the histological diversity and features of unique entities and developing larger arsenal of immunohistochemical as well as genetic markers. We should expect to see fewer such tumors with the advance of specialized analyses and more tumors reclassified as etiologically distinct lesions. The absence of malignant fibrous histiocytoma in our series also highlights the fact that most pleomorphic sarcomas can be further classified, and a significant number of such tumors may even represent high grade glial tumors previously misclassified as sarcomas (1).

Unlike the previously reported series, our series was distinctly devoid of some sarcomas known to occur in the CNS, such as angiosarcomas or inflammatory myofibroblastic tumors. This fact suggests that a series from a single institution, however large and referral-based, may not include all the spectrum of sarcomas, and this handicap can only be overcome with coordinated, large-scale, and long term studies involving multiple institutions or regions. Rare diseases such as CNS sarcomas demand multi-institutional studies that coordinate a relatively uniform analysis of patients to enable merging of data, comparison of clinical, pathological and specialized information in a prospective manner.

The implication of this study in our country is also critical. While in larger centers dealing with CNS tumor may have as many cases as in this study, it is far more valuable to develop nationwide consortia for such rare diseases in order to accumulate both experience and expertise in the diagnosis and the management of these unusual tumors. We hope that the extremely hopeful advances in the field of neuro-oncology and brain tumor epidemiology will result in the development of such multi-institutional studies.

REFERENCES

1. Fletcher CD. The evolving classification of soft tissue tumours: an update based on the new WHO classification. Histopathol 2006;48:3-12.
2. Palesty JA, Kraybill WG. Developments in the management of extremity soft tissue sarcomas. Cancer Invest 2005;23:692-699.
3. Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CD, Devesa SS. Incidence patterns of soft tissue sarcomas, regardless of primary site, in the surveillance, epidemiology and end results program, 1978-2001: An analysis of 26,758 cases. Int J Cancer 2006;119:2922-2930.
4. Oliveira AM, Scheithauer BW, Salomao DR, Parisi JE, Burger PC, Nascimento AG. Primary sarcomas of the brain and spinal cord: a study of 18 cases. Am J Surg Pathol 2002;26:1056-1063.
5. Virtanen A, Pukkala E, Auvinen A. Incidence of bone and soft tissue sarcoma after radiotherapy: a cohort study of 295,712 Finnish cancer patients. Int J Cancer 2006;118:1017-1021.
6. Ironside JW. Classification of primary intracranial sarcomas and other central nervous system neoplasms. Histopathol 1991;18:483-486.
8. Kleihues P, Cavenee WKe. Pathology and Genetics of Tumours of the Nervous System. World Health Organization Classification of Tumours. IARC Press: Lyon, 2000.
8. Paulus W, Slowik F, Jellinger K. Primary intracranial sarcomas: histopathological features of 19 cases. His-

topathol 1991;18:395-402.
9. Mena H, Garcia JH. Primary brain sarcomas: light and electron microscopic features. Cancer 1978;42:1298-1307.
10. Al-Gahtany M, Shroff M, Bouffet E, Dirks P, Drake J, Humphreys R, Laperriere N, Hawkins C, Rutka J. Primary central nervous system sarcomas in children: clinical, radiological, and pathological features. Child Nerv Syst 2003;19:808-817.
11. Ecker RD, Marsh WR, Pollock BE, Kurtkaya-Yapicier O, McClelland R, Scheithauer BW, Buckner JC. Hemangiopericytoma in the central nervous system: treatment, pathological features, and long-term follow up in 38 patients. J Neurosurg 2003;98:1182-1187.
12. Kabus D, Sidhu GS, Wieczorek RL, Choi HS. Metastatic meningioma. Hemangiopericytoma or angioblastic meningioma? Am J Surg Pathol 1993;17:1144-1150.
13. Mena H, Ribas JL, Pezeshkpour GH, Cowan DN, Parisi JE. Hemangiopericytoma of the central nervous system: a review of 94 cases. Hum Pathol 1991;22:84-91.
14. Tihan T, Viglione M, Rosenblum MK, Olivi A, Burger PC. Solitary fibrous tumors in the central nervous system. A clinicopathologic review of 18 cases and comparison to meningeal hemangiopericytomas. Arch Pathol Lab Med 2003;127:432-439.
15. Fletcher CDM, Unni KK, Mertens F. World Health Organization Classification of Tumors. Pathology and Genetics of Tumours of Soft Tissue and Bone. IARC Press: Lyon, 2002.
16. Luzardo-Small G, Mendez-Martinez O, Cardozo-Duran J. Cavitated (cystic) falcine chondroma: case report. Br J Neurosurg 1999;13:426-428.