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Case Report

Rapid Clinical Course of Multiple Metastatic Cerebral Angiosarcoma

Çoklu Metastatik Serebral Anjiyosarkomda Hızlı Klinik Seyir

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ABSTRACT

Central nervous system (CNS) angiosarcoma, both primary and secondary, is an exceptionally rare malignant tumor. The behaviour of angiosarcoma is one of rapid progression with early metastatic spread but as with all sarcomas, the primary site may not clinically evident by the time metastases develop. Identification of the primary site of origin is masked by the carpet-like growth pattern that may occur in the left atrium, the most frequently encountered primary site for angiosarcoma. This rare tumor presents many diagnostic challenges. We describe the clinical and neuropathologic features of two patients with angiosarcoma of the brain and review the previously published cases described to date.

KEYWORDS: Angiosarcoma, Cerebral angiosarcoma, Primary angiosarcoma

ÖZ

Merkez sinir sistemi (MSS) anjiyosarkomu hem primer hem sekonder tiplerde son derece nadir malign bir tümördür. Anjiyosarkomun davranışı erken metastatik yayılımla hızlı ilerleme şeklindedir ama tüm sarkomlarda olduğu gibi metastazların geliştiği zamanda primer bölge klinik olarak belli olmayabilir. Primer köken, anjiyosarkomun en sık görülen primer bölgesi olan sol atriumda oluşan halı tarzı büyüme paterniyle maskelenebilir. Bu nadir tümör birçok tanısal zorluğa yol açar. Beyin anjiyosarkomu olan iki hastada klinik ve nöropatolojik özellikleri tanımlıyor ve bugüne kadar yayınlanmış olguları gözden geçiriyoruz.

ANAHTAR SÖZCÜKLER: Anjiyosarkom, Serebral anjiyosarkom, Primer anjiyosarkom

INTRODUCTION

Central nervous system (CNS) angiosarcoma is considered a rare malignant tumor, most commonly metastatic and less likely to be primary in origin (12). The atrioventricular chambers are the most common primary sites of origin for angiosarcoma that spreads to brain. General risk factors for development of primary angiosarcoma include exposure to vinyl chloride, lymphedema following radical mastectomy, irradiation and the diagnostic use of thorium dioxide as a contrast dye for angiography (12, 16). Since 1984, two patients were found to have cerebral angiosarcomas in our department. We describe the clinical and pathologic features of multifocal angiosarcoma in brain and go on to show the insidious and occult nature of the angiosarcoma eventually confirmed in the left atrium in one patient.

CASE REPORTS

Patient 1

A 45-year-old lady with mitral stenosis and atrial fibrillation presented in 1986 with a 2-week history of confusion. Examination revealed left hemiparesis and upper motor neuron facial palsy. GCS was 14 with intermittent confusion. Computed Tomography (CT) (Figure 1A) and magnetic resonance imaging (MRI) of brain showed multiple cerebral lesions with associate edema. Initial investigation including thoracic-abdominal-pelvic CT with contrast, hematological, renal and inflammatory profiles were normal. Further work-up was postponed as she rapidly fell to GCS of 10 (E3,V2,M5). Radiotherapy was offered but the patient's health followed a progressively declining course and she died after three weeks in hospital. Postmortem examination showed multiple discrete hemorrhage lesions throughout the cerebral hemisphere with organizing thrombus (Figure 1B). Metastacic angiosarcoma was confirmed on histopathological examination with primary lesion from left atrium (Figure 1C, D).

Patient 2

A 68-year-old lady with no significant medical history or known genetic syndrome presented to her local hospital with a 3-week history of occipital headache, ataxia and left arm weakness. Examination confirmed mild left hemiparesis, left homonymous hemianopia and ataxic gait. GCS was 14 with intermittent confusion. Imaging revealed hemorrhagic lesions in the left cerebellar, right occipital and parietal periventricular region (Figure 2A-C). Thoracic-abdominal-pelvic CT with contrast, echocardiography, hematological, renal and inflammatory profiles were normal. A right occipital

craniotomy and biopsy of the lesion was performed. On postoperative day two, she rapidly fell to GCS of 6 (E1,V2,M3) over 2 hour with left hemiplegia. CT revealed increasing size of the two remaining lesions with hydrocephalus (Figure 2D). An external ventricular drain was inserted followed by an excision of the left cerebellar lesion (Figure 2E-F). Further work-up e.g. positron emission tomography (PET) was postponed. Histology specimen showed complex anastomosing vascular channels lined by plump atypical endothelial cells, appearances of angiosarcoma (Figure 3A-F). Radiation oncology was sought but given the patient's poor performance status, the family decided to withhold active treatment. The patient died six weeks later.

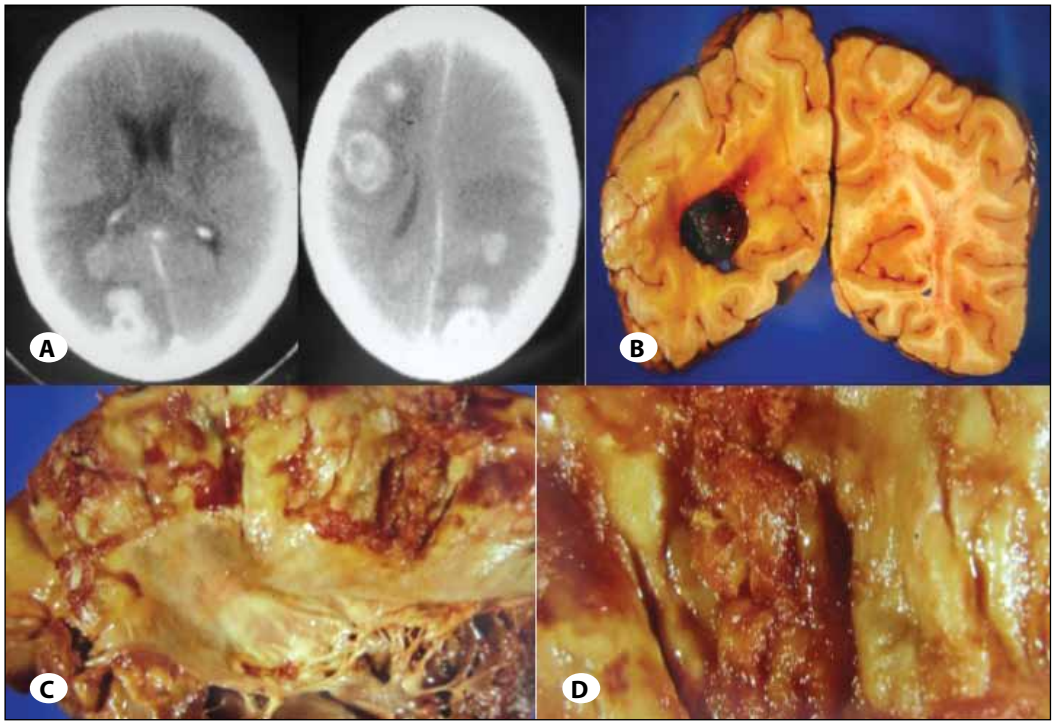

Figure 1: A) CT with contrast shows multiple cerebral hemorrhagic lesions. **B)** Brain autopsy shows multiple discrete hemorrhagic lesions throughout the cerebral hemispheres, largest being 1.3 cm x 1 cm. These were associated with surrounding edema and yellow discoloration of the brain substance. **C, D)** The mitral valve measures 9.5 cm and deformed. The cusps were thickened. The left atrium was vegetated.

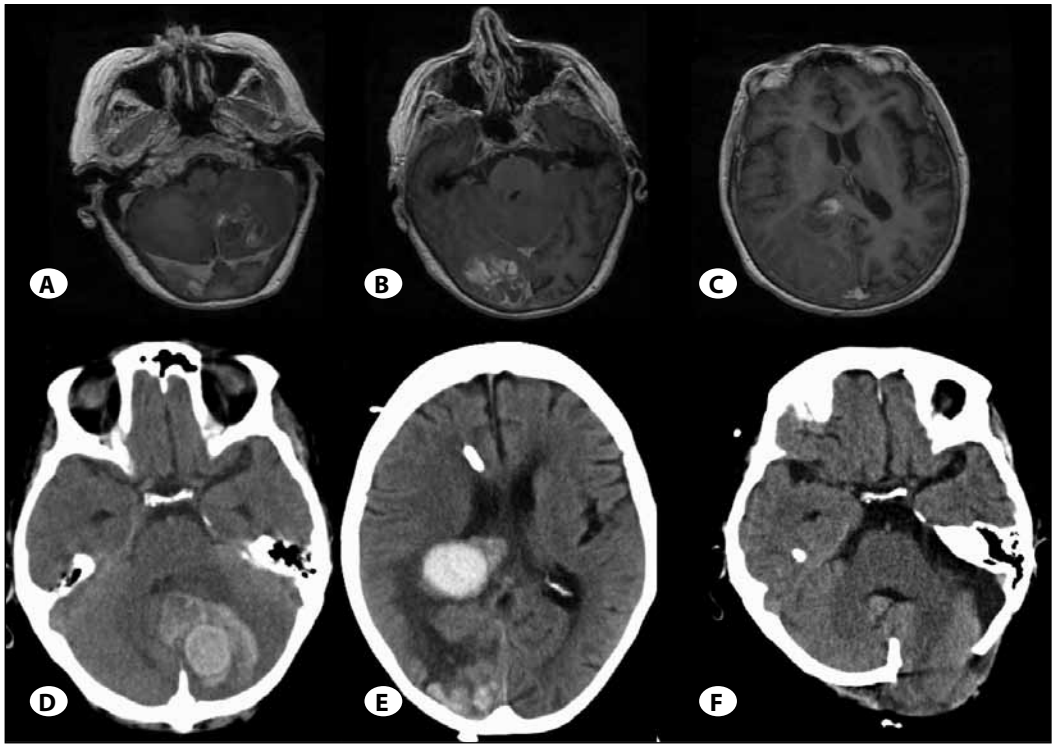

Figure 2: A-C) Gd-enhanced T1W MRI shows hemorrhagic lesions identified in the left cerebellar, right occipital lobe and splenium. **D)** Non-contrast CT shows an increase in hemorrhagic lesion with mass effect and distortion of fourth ventricle. **E-F)** Following an interval resection of cerebellar lesion, there is persistent increased hyperdense area within the right parietal periventricular region.

Table I: 26 Reported Cases of Angiosarcoma Originating in the Central Nervous System. (The First 17 Cases Tabulated were from Matsuno et al. (18)).

Case	Author and year	Age (year)/ Sex	Location	Management	Survival
1	Ziegler, 1975 (18)	17 /M	Right parietal	-	-
2	Mena and Garcia, 1978 (18)	15 /F	Left frontal	-	-
3	Charman et al., 1988 (18)	65 /M	Right parieto- occipital	-	-
4	Cookston et al., 1991 (18)	32 /F	Right occipital	-	-
5-12	Mena et al., 1991 (18)	2 weeks- 75; M5, F3	6 cerebral, I meninges, 1 unknown	-	-
13	Paulus et al. 1991 (18)	24/ M	Temporal	-	-
14	Paulus et al., 1991 (18)	26 /M	Frontal	-	-
15	Kirk et al., 1992 (18)	Neonate	Right temporal	-	-
16	Fuse et al., 1995 (18)	39 /M	Right temporal	-	-
17	Antoniadis et al., 1996 (18)	41 /F	Left parietal	-	-
18	Suzuki et al., 2000 (25)	30-day-old/M	Left fronto-temporal	OP	Alive at 1 year
19	Merimsky et al., 2000 (20)	27/M	Parietal	RTX	Two-and-a-half month
20	Merimsky et al., 2000 (20)	18/M	Parieto- occipital	OP	5 month
21	Lach and Benoit, 2000 (14)	37/M	Fronto-parietal	OP	18 month
22	Ito et al., 2007 (11)	66 /M	Left parieto-occipital	OP+RTX	6 month
23	Lach et al., 2008 (15)	9 /M	Left parieto-occipital	OP+RTX	4 month
24	Balamurali et al., 2009 (2)	68 /M	Right parietal	OP	1 year
25	Hackney et al., 2012 (9)	35 /F	Left middle fossa	OP+RTX+CTX	Alive at one-and-half years
26	Hackney et al., 2012 (9)	47 /M	Left middle fossa	OP+planned RTX+CTX	Alive

***M**= Male; **F**= Female; **OP**= Operation, **CTX**= Chemotherapy; **RTX**= Radiation therapy.*

DISCUSSION

Clinical course of cerebral angiosarcoma is one of rapid progression (1, 2, 4, 8, 12, 21). Clinical presentation may mimic cardio- and cerebro-vascular syndromes in adult (4, 5, 16). In children, signs of raised intracranial pressure and increasing head circumference are the typical features (13, 15, 25). Matsuno et al. (18) presented the most comprehensive review and to date, a total of twenty-six primary cases originating within the CNS and twenty-four cases metastasizing to brain have been reported. The clinical and pathologic findings are summarized in Table I and II.

The typical primary site for metastatic cerebral angiosarcoma is the heart, especially the right atrium [57% - 71.4%] (4, 5, 12, 18). Primary cardiac angiosarcoma is difficult to diagnose clinically and can be misdiagnosed at initial stage. Donsbeck et al. (5) reviewed 24 cases of primary cardiac sarcoma over 18 year period. Angiosarcoma was the second most frequent histological type of cardiac sarcoma (25%). Two of the cases metastasized to brain but they are not specifically angiosarcoma. Of the tabulated result, 16 cases (63%) of metastatic cerebral angiosarcoma were cardiac origin. Seven patients had cardiac angiosarcoma diagnosed prior to metastases. The rest had the primary lesion diagnosed concurrently or at autopsy.

Skin or cutaneous angiosarcoma is part of anatomic sites and 50% of cases occur on the head and neck, particularly the scalp (20). The most common location of metastases is lung and rarely cases of brain metastases have been reported (3, 6, 17, 21, 23). Analysis by Naka et al. (23) reported only 5 out of 99 cases had brain metastases with 3 of them accounted from head area. Both skull and dura mater is a natural barrier from metastases to the brain from the overlying scalp (3). However, the vascular density of the scalp or the anastomotic arrangement of the vessels in this anatomic area should be considered as they may play a role in the invasion of angiosarcoma (21).

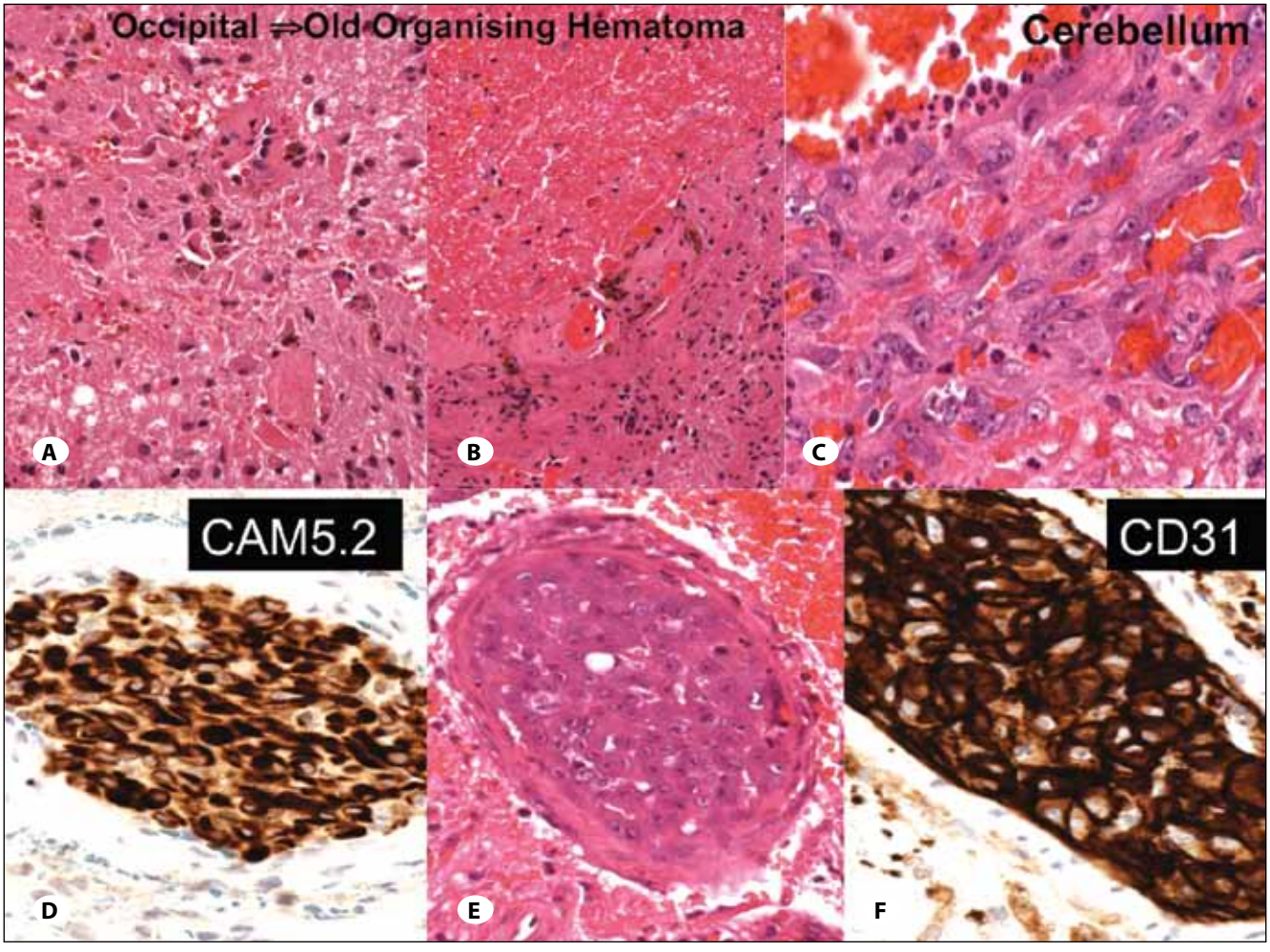

Figure 3: A) Microscopic examination shows occipital cortex with multiple large fragments of organizing hematoma surrounded by newly formed blood vessels together with light fibrocollagenous connective tissue and fibrin. **B)** These vessels are lined by prominent 'endothelial' cells which have large nuclei and multiple hypereosinophilic nucleoli. **C-E)** A blood vessel cut in cross section shows complete occlusion by endothelial cells. These atypical cells exhibit strong immunoreactivity for CAM5.2 and CD31. Intravascular cells express lymphoid markers (CD45, CD20) and CD34 are negative (data not shown).

Table II: 24 Reported Cases of Metastatic Angiosarcoma to the Brain. (The First Fifteen Cases were Tabulated by Matsuno et al. (18)).

Case	Author & Year	Age (yo) / Sex	Location in brain	Management	Survival	Primary Site	Other Metastases
1	Angrish et al., 1979 (18)	38 /M	Right temporal	-	-	Left atrium	None
2	Wasmer et al., 1981 (18)	61 /M	Brain	-	-	Penis	Liver, cheek, lung
3	Seto et al., 1988 (18)	17 /M	Pineal region	-	-	Liver	Lung
4	Potter et al., 1989 (18)	27 /F	Multiple	CTX	15 month	Right atrium	Lung, liver, bone, thyroid, pancreas
5	Grollier et al., 1990 (18)	70 /F	Brain	-	-	Right atrium	Liver
6	Vaquero et al., 1990 (18)	30 /M	Right frontal	OP	6 month	Heart (Right auricle)	Lung, bone
7	Kuratsu et al., 1991 (18)	17 /M	Pineal region	RTX	-	Liver	None
8	Kuratsu et al., 1991 (18)	31 /F	Left temporal, thalamus, vermis	OP /RTX	-	Femur	None
9	Crespo et al., 1993 (18)	31 /M	Multiple	-	-	Right atrium	Lung, bone, liver
10	Crespo et al., 1993 (18)	32 /M	Multiple	-	-	Right atrium	None
11	Rettmar et al., 1993 (18)	44 /M	Bilateral temporo-parietal	-	-	Right atrium	Lung
12	Watanabe et al.,1993 (18)	30 /M	Multiple	-	1 month	Right atrium	Lung
13	Chaudhuri et al.,1994 (18)	31 /F	Left fronto-parietal	-	-	Placenta	None
14	Hwang et al., 1996 (18)	17 /F	Left fronto-temporo-parietal	-	-	Pericardium	Multiple
15	Nitta et al., 18 (18)	50 /M	Not described	-	-	Right atrium	Lung
16	Gallo et al., 2001 (8)	33 /M	Left Temporal	OP	3 day	Right atrium	Lung
17	Mühlau et al., 2003 (22)	72 /M	Multiple	None	2 month	Left ventricle	Thyroid, peritoneum, suprarenal gland
18	Akutsu et al., 2004 (1)	52 /M	Right frontal	OP	6 month	Abdominal aorta	Bony metastasis
19	Liassides et al., 2004 (16)	24 /F	Left parietal & occipital	OP /CTX	6 month	Right atrium	Lung
20	Matsuno et al., 2005 (18)	79 /F	Left fronto-parietal, cerebellar	OP	-	Left atrium	Lung, adrenal, bone
21	Ikeya et al., 2006 (10)	49 /M	Right temporal	None	37 day	Right atrium	Subclavian artery, psoas muscle, bone
22	Plotnik et al., 2008 (24)	61 /F	Right occipital	OP	-	Spleen	Lung, sacral
23	Dea et al., 2009 (4)	64/M	Left frontal	OP	-	Carotid artery	None
24	Jung et al., 2012 (12)	36 /M	Right parietal	OP /RTX	9 month	Right atrium	Iliac bone

***M**= Male; **F**= Female; **yo**= year-old; **OP**= Operation; **CTX**= Chemotherapy; **RTX**= Radiotherapy.*

Sensitivity for detecting cardiac angiosarcoma using echocardiography increases from 74% to 90% with repetition and following aspiration of pericardial effusions. MRI precisely delineates tumor extension into the pericardium or along great vessels but CT usefully complement echocardiography (5). Metastatic or primary sarcomas of the brain have a great tendency to bleed. Gradient Echo T2W MRI is more sensitive and shows well-circumscribed areas of hemorrhage with surrounding oedema and increased signal intensity for multiple lesions (8, 12, 22). Interpretative MRI difficulties may be overcome by PET-CT, which further increase uptake in the lesions (12).

Primary CNS angiosarcoma(s) arise from mesenchymal elements of the brain and meninges (8, 13). Angiosarcoma can appear deceptively benign histologically and even metastases occasionally been diagnosed as cavernous angiomas (12, 18). Typically, constituent cells form an irregular vascular network (4, 5), as shown in our cases. The degree of cellular atypicality is considerably greater than might be expected in organising granulation tissue surrounding a resolving hematoma. High proliferation index as assessed by MIB-1, uniform homogeneous immunopositivity of atypical cells for CD31 and CD34 are supportive though not diagnostic of malignancy (4, 5).

Patients with primary CNS angiosarcoma who had a complete surgical excision can be disease free for more than two years even without adjuvant chemoradiation therapy (13). The prognosis is dismal in metastases with median life expectancy of eight months (14, 19). Once metastasized, chemotherapy may not be effective, because drugs useful for treatment of sarcomas, such as Adriamycin do not penetrate the CNS effectively (7). Recently, it has been proposed that radiation with concurrent chemotherapy with temozolomide and bevacizumab be employed after gross total tumour resection (9). There is also a renewed interest in stereotactic radiosurgery in that it may improve local control rate especially in treating a radioresistant tumor (12).

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