



Pediatric primary intracranial angiosarcoma with epithelioid differentiation: a surgeon's dilemma

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Abstract

Angiosarcoma is a rare form of soft tissue sarcoma originating from endothelial tissue, accounting for < 1% of all sarcomas. Primary epithelioid angiosarcomas of the central nervous system (CNS) are even more elusive, with only four reports described in the literature. In this article, we describe the first case in pediatric population, with a brief literature review regarding this entity. A 13-year-old girl presented to emergency services with raised intracranial pressure. MRI demonstrated a heterogenous lesion in the temporal lobe. She underwent emergency craniotomy and subtotal excision of the tumor. Eventually the patient developed multiple infarcts and succumbed post operatively. Pre-operative diagnosis on radiology is difficult considering the rarity of this entity and heterogeneity in radiological appearance. One needs to have a high degree of suspicion to consider angiosarcoma as a radiological differential. Overall prognosis remains poor. Early adjuvant treatment may improve overall survival.

Keywords Pediatric primary intracranial angiosarcoma · Epithelioid Angiosarcoma · Endothelial tumor

Introduction

Angiosarcoma is a rare form of soft tissue sarcoma originating from endothelial tissue, accounting for < 1% of all sarcomas [1]. Primary epithelioid angiosarcomas of the central

nervous system (CNS) are even more elusive, with only four reports described in the literature [2–5]. In this article, we describe the first case in pediatric population, with a brief literature review regarding this entity.

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Case report

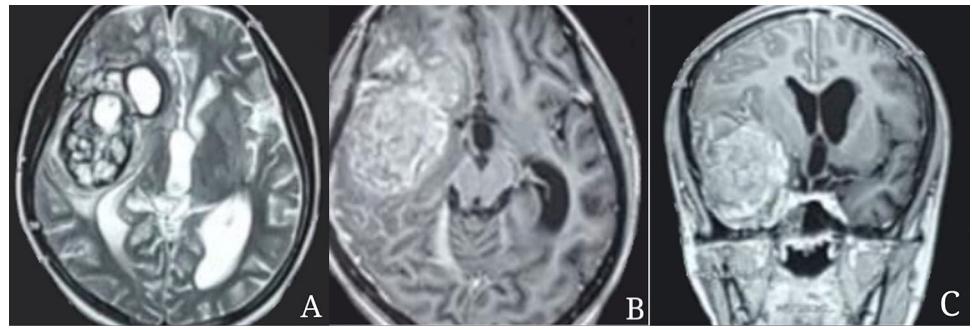
A 13-year-old girl presented to emergency department with symptoms of increased intracranial pressure (ICP) with no focal neurological deficit. Radiological evaluation revealed an intraaxial, irregular solid cystic, heterogeneously contrast-enhancing lesion in right temporal lobe, with mass effect on the brainstem and midline shift toward the opposite side (Fig. 1). There was no perilesional edema. The patient underwent emergency right temporal craniotomy with subtotal excision of the lesion. Intraoperatively, an intraaxial infiltrative tumor with heterogenous consistency containing fibrous and hemorrhagic areas was noted extending from the temporal lobe towards the insula. The tumor was seen involving the middle cerebral artery branches. Many branches of the middle cerebral artery were seen to be shriveled and had no flow. There were multiple thrombosed vessels inside the tumor. Tumor was not vascular and

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Fig. 1 **A** T2 axial, **B** T1 contrast axial, and **C** coronal images reveal intraaxial, irregular solid cystic, heterogeneously contrast-enhancing lesion in right temporal lobe, with mass effect on the brainstem and midline shift toward the left side



there was minimal blood loss during the surgery. In view of the less vascularity of the lesion, a possibility of fungal lesion was also evaluated. The poor vascularity of the lesion did not favor the diagnosis of a high-grade glioma. Post-operative course was complicated with multiple infarcts and the patient eventually succumbed.

The histopathology examination revealed a cellular tumor with large areas of hemorrhage and necrosis (Fig. 2). The individual tumor cells were oval to epithelioid shaped with the presence of intracytoplasmic vacuoles. Focally, immature vasculature formations by the tumor cells were noted. Few eosinophilic hyaline globules were also present. The

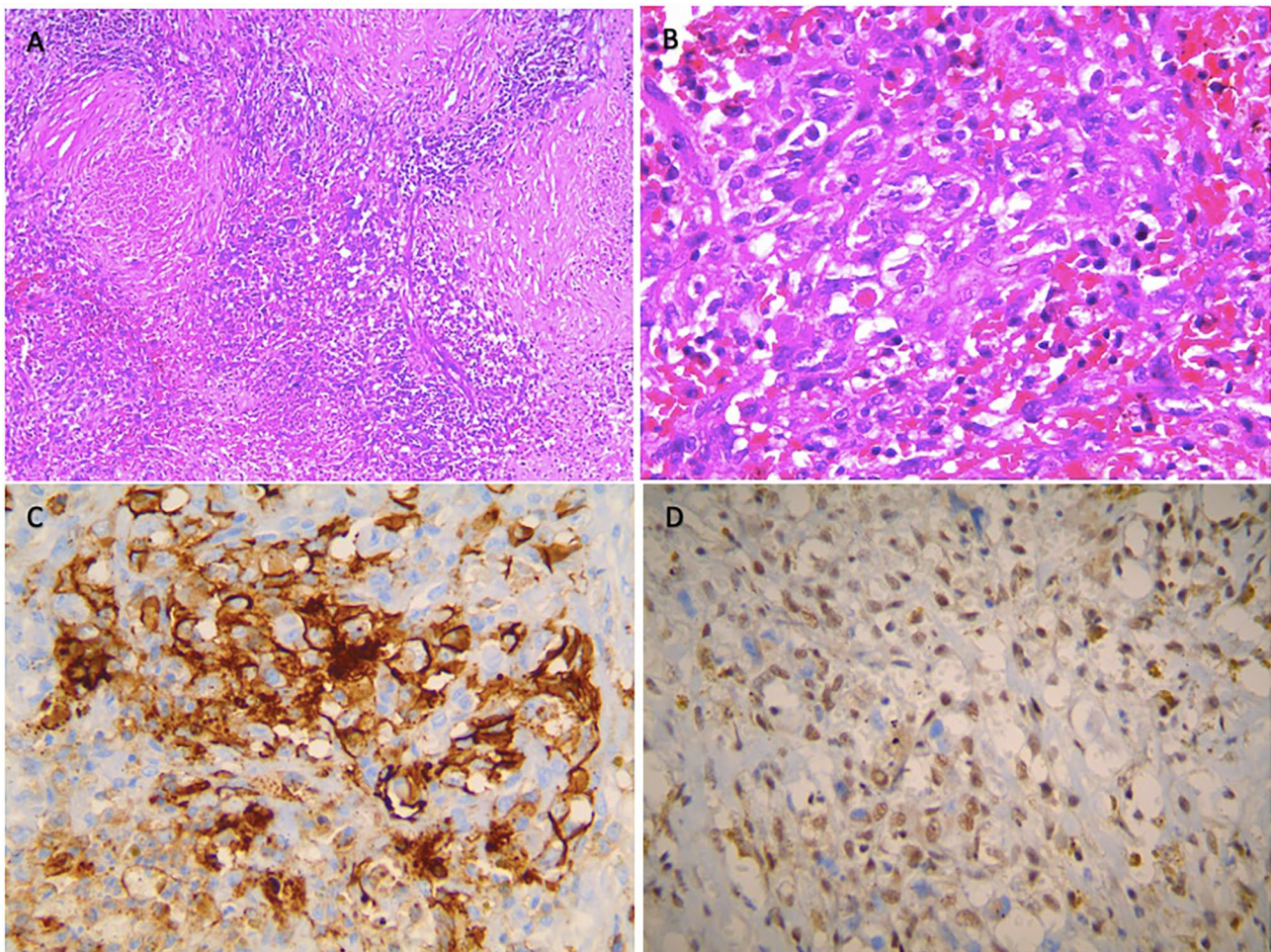


Fig. 2 **A** Section from tumor shows a cellular tumor with areas of necrosis (hematoxylin and eosin, $\times 100$). **B** The tumor cells are lining slit-like spaces containing red blood cells and show moderate nuclear atypia (hematoxylin and eosin, $\times 400$). **C** The tumor cells show strong

membranous CD34 positivity (immunohistochemistry, $\times 400$). **D** The tumor cells show strong nuclear ERG positivity (immunohistochemistry, $\times 400$)

tumor cells showed nuclear atypia and frequent mitosis. There was a sharp demarcation from the adjacent brain parenchyma with invasion into the underlying cortex along the Virchow-Robin spaces. Upon immunohistochemistry, strong and diffuse positivity was noted for CD31, ERG, and vimentin, with focal positivity for keratin. Tumor cells were negative for GFAP, EMA, desmin, myogenin, OCT-4, SALL-4, S-100, SATB2, and Melan A. INI-1 nuclear staining was retained. The final histological diagnosis was epithelioid angiosarcoma.

Discussion

Angiosarcoma is a highly malignant, rare type of sarcoma, originating from endothelial cells. These are known to occur in various soft tissue locations like muscle, skin, and bones. However, rarely are known to arise from skull bones, meninges, or brain [6]. These have been classified by World Health Organization (WHO) under malignant mesenchymal tumors of vascular origin. They are subdivided into classical and epithelioid variety based on histology. They may arise *de novo* and have a primary intracranial origin or may metastasize from a secondary location to brain. The exact underlying etiology is unknown; some studies have linked it to radiation therapy, thorotrast contrast use, and vinyl chloride exposure [7–9].

Angiosarcomas classically occur in the 5th to 7th decade of life. A few cases of pediatric and adolescent age have been reported in the literature [10]. However, no cases of primary pediatric intracranial epithelioid angiosarcoma have been reported in the literature. In the previous series including adults, around 30 cases of primary intracranial (brain and meninges) angiosarcoma have been previously documented, with 4 having epithelioid differentiation [11]. The majority of these lesions have been noted in supratentorial, lobar regions with few present in rare locations like septum pellucidum, pineal gland, and brainstem [3, 11, 12]. Clinical presentation may range from focal neurological deficit or raised ICP symptoms. Usually, rapid clinical worsening is noted, attributable to the rapid growth of the lesion or secondary to hemorrhage within the lesion.

Preoperative diagnosis on radiology is difficult considering the rarity of this entity and heterogeneity in radiological appearance. One needs to have a high degree of suspicion to consider angiosarcoma as a radiological differential. In a review by Lee et al., no common radiological features could be identified among findings reported for over 30 primary intracranial angiosarcomas [11]. Most lesions are identified by heterogeneous contrast enhancement with areas

of necrosis and hemorrhage. Perilesional edema is seen in majority of cases on T2 weighted imaging; however, this was absent in our index case. Flow voids have also been observed in few cases.

Histopathological evaluation of epithelioid angiosarcoma reveals pleomorphic, polygonal epithelioid cells with atypia. These cells are arranged in sheets along irregular blood vessels. Hemorrhage and necrosis may also be present. They are strongly positive for vimentin, ERG, CD31, and CD34. Focal keratin expression may also be seen in epithelioid variant, which is not seen in classical variant [13]. Proliferative indices like Ki-67 may be used to further quantify the aggressive behavior of the tumor. The differential diagnosis of epithelioid tumors is wide, which include epithelioid sarcoma, epithelioid malignant peripheral nerve sheath tumor, epithelioid angiosarcoma, epithelioid malignant melanoma, epithelioid osteosarcoma, and epithelioid glioblastoma. However, the presence of vacuolated cytoplasm, vascular formations on morphology, and immunopositivity for CD31, CD34, and ERG1 established the diagnosis of epithelioid angiosarcoma in the index case.

Gross total excision with adjuvant therapy in the form of radiotherapy and chemotherapy is the treatment of choice for intracranial angiosarcomas [5]. Due to the rarity of epithelioid differentiation, no separate consensus is present in the literature. Adjuvant radiotherapy in the form of conventional or stereotactic is commonly used to prevent local recurrence [14].

Numerous chemotherapeutic agents like Paclitaxel, Temozolomide, and Bevacizumab have been used, but generally poor overall response has been noted with these [14–16]. Hence, role of chemotherapy is inconclusive and may be tailored to the individual case.

Long-term prognosis is variable with factors such as tumor size, location, and extent of resection having significant influence over it [17]. Intraparenchymal lesions have been noted to have a poor prognosis as compared to dural based lesions. In our patient, postoperative course was complicated with developed of multiple infarcts, and eventually, the patient succumbed. Our intraoperative impression ranged from intracranial aspergillosis to high-grade gliomas. Treatment and resection strategies vary widely for these possible etiologies and as surgeon is in a dilemma regarding the extent of resection in such cases. Survival may range from a few months to as high as 105 months, median survival of 1 year [6]. Due to a wide range of survival, additional parameters like proliferative indices should be used for better risk stratification (Table 1).

Table 1 Pediatric and adolescent cases of cerebral angiosarcoma (classic and epithelioid) reported in literature [8, 18–24]

Study	Age (years)	Location	Treatment	Surgery	Survival (months)	Epithelioid differentiation
Ziegler [18] (1975)	17	Right posterior frontal	Surgery + radiotherapy	Subtotal excision	2.5	No
Mena and Garcia [19] (1978)	15	Left frontal	Surgery	Subtotal excision	2	No
Mena et al. [20] (1991) (individual case details NA)	2 weeks to 72 years	6 supratentorial, 1 meningeal, 1 unknown	Surgery	Not known	< 4 ($n=4$), 30, > 39, > 102, unknown	Yes (in few cases, individual case details not available)
Kirk et al. [21] (1992)	2 weeks	Rt temporal	Surgery	Gross total excision	> 26	No
Merimsky et al. [22] (2000)	18	Parieto-occipital	Surgery	Subtotal excision	5	No
Suzuki et al. [23] (2000)	4 weeks	Left frontotemporal	Surgery	Gross total excision	> 11	No
Guode et al. [24] (2008)	16	Right cerebello-pontine angle	Surgery + radiotherapy	Gross total excision	> 6	No
Balamurali et al. [8] (2009)	9	Right parieto-occipital	Surgery	Subtotal excision	11	No
Present case	13	Rt temporal	Surgery	Subtotal excision	5 days	Yes

Conclusion

Primary intracranial angiosarcoma is a rare entity with its epithelioid variant being even rarer. A high index of suspicion is needed to establish its preoperative diagnosis, due to a wide heterogeneity of clinical and radiological presentation. Gross total excision with adjuvant treatment helps in improving overall survival. The intraoperative findings can be variable leading to a diagnostic dilemma in a surgeon's mind.

Author contributions Tejasvi Singh Randhawa and Mayur Gopichand Gharat wrote the manuscript draft. Debyajyoti Chatterjee and Chirag Ahuja prepared slides, radiology, figures. Ashish Aggarwal and Raghav Singla edited and finalised the manuscript. All authors reviewed and approved the manuscript.

Declarations

Conflict of interest The authors declare no competing interests.

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