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Review Article

Pediatric clear cell meningioma involving the middle cranial fossa in the context of NF2 and SMARCE1 mutations

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ABSTRACT

Meningiomas are an uncommon entity in children and adolescents. < 30 cases of pediatric clear cell meningioma (CCM), a World Health Organization (WHO) Grade II tumor, have been reported in the literature. These tumors are more likely to recur than the more common WHO Grade I meningiomas, especially with incomplete surgical resection. CCMs are most commonly found in the spine and posterior cranial fossa. Recently, SMARCE1 mutations have been linked to the development of CCM. To evaluate the progression of pediatric CCM in the context of emerging genetic knowledge, we reviewed all 45 cases of CCM at our institution for a 23 year period (1997–2019) to identify pediatric cases. Forty-four of the tumors arose in adults from age 34–81 years. The one pediatric case originally presented at age 4 years; the patient was found to have a CCM in the left cavernous sinus projecting into the posterior fossa, associated with a novel germline SMARCE1 mutation and somatic NF1 and DMD mutations. After two years, the patient had a recurrence of the tumor and underwent a second resection. This is the 5th reported case of CCM in the middle cranial fossa, and the only recurrent case, as well as the only reported case of recurrent pediatric CCM associated with a germline SMARCE1 mutation. Further study of the natural history of tumors associated with germline SMARCE1 loss could potentially inform prognosis.

1. Introduction

Meningiomas are the most common non-glial brain tumors in adults, accounting for approximately 1/3 of brain tumors in this population [1]. They are significantly less common in the pediatric age group, accounting for 2.8% of brain tumors in children and adolescents based on analysis of the Central Brain Tumor Registry of the US (CBTRUS) from 2007 to 2011 [1,2]. Of the 15 subtypes of meningioma described by the World Health Organization (WHO) in 2016, clear cell meningioma (CCM) is a relatively rare and more aggressive variant [3]. CCM is designated as a WHO Grade II brain tumor because of its rapid growth and tendency to recur, especially after incomplete surgical resection [4-6]. CCM accounts for < 1% of all meningiomas and is particularly rare in children, mostly described in the literature in isolated case reports and small case series [7]. This tumor is usually found in the lumbar spine and posterior fossa [4,8]. The pathologic hallmark of this tumor is the presence of clear cytoplasm in the tumor cells due to glycogen accumulation. Pathologic identification remains essential for the diagnosis of CCM, though genetic alterations including NF2 and SMARCE1 mutations have recently been associated with this entity [9,10]. Herein, we reviewed our series of clear cell meningiomas looking for pediatric cases to assess for the presence of a SMARCE1 mutation and to evaluate prognosis.

2. Results

Institutional Review Board (IRB) approval was obtained prior to commencement of the study. The surgical pathology files at our institution were searched over a 23 year period of time (1997–2019) to identify tumors diagnosed as CCM. A total of 45 cases were identified. Forty-four of the cases were diagnosed in adults who ranged in age from 34 to 81 years. One pediatric-aged patient was noted.

The pediatric patient was an 8-year-old female who originally presented at age 4 years at another institution with left facial asymmetry and vomiting following several months of worsening appetite and fevers. Magnetic resonance imaging (MRI) showed a large extra-axial mass involving the left cavernous sinus and projecting into the posterior fossa. The spectroscopic pattern favored a schwannoma arising from the trigeminal nerve. She underwent a craniotomy and resection of the tumor in the posterior fossa via a left retromastoid approach. This was followed by a subtemporal decompression for resection of the residual tumor in the cavernous sinus. This latter resection was incomplete due

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to the fact that tumor was admixed with the nerves within the sinus. On gross inspection, the tumor was grayish-yellow and nonvascular. The tumor was reportedly classified as a clear cell meningioma, WHO grade II, with a MIB-1 labeling index up to 15–20% focally. Genomic testing of the tumor revealed alterations in the NF1, DMD, and SMARCE1 gene loci. Germline testing revealed that the patient was heterozygous for the c.454_455deIGCinsT mutation in SMARCE1, a novel mutation predicted to result in a frameshift and premature protein termination (p.A1a152Phefs*2). This patient had no germline alterations in DMD, NF1, or NF2. The patient's mother and grandmother also tested as positive for pathogenic SMARCE1 loss. The patient's sister did not have the mutation.

During the next several months, the tumor increased in size and the patient underwent proton beam therapy (59.4 Gy/33fx CGE). After this treatment, the patient was followed by MRI studies every 6 months and the residual tumor in the left cavernous sinus remained stable in size for 2 years before it began to grow. At this time, there were no new symptoms or worsening of her baseline neurological status, which consisted of left-sided hearing loss and decreased eye and facial sensation as well as mild dysarthria and subtle right-sided pronator drift. Treatment with surgical resection versus radiation was considered. She underwent a second left craniotomy with anterior clinoidectomy/superior orbitotomy for Simpson grade 1 resection of this residual growth. She is currently recovering well with improvement in her left-sided facial sensation.

Pathology again confirmed the diagnosis of clear cell meningioma, WHO grade II. The tumor was marked by a proliferation of cells with clear cytoplasm; tumor cells were generally arranged in a sheet-like pattern (Fig. 1). Focal areas of the tumor demonstrated prominent sclerosis and fibrosis (Fig. 2). There was no evidence of brain invasion. Only rare mitotic figures were noted. Small cell change, hypercellularity, necrosis and prominent nucleoli were not observed. The tumor demonstrated positive immunostaining with antibody to epithelial membrane antigen (EMA) (dilution 1:50; Dako, Santa Clara, CA) (Fig. 3). The tumor also demonstrated evidence of nuclear staining with progesterone receptor antibody (prediluted; VMS, Indianapolis, IN) (Fig. 4). A Ki-67 (prediluted; Ventana, Tucson, AZ) labeling index of 7.4% was noted in the area of the tumor that had the most staining (Fig. 5).

3. Discussion

The majority of pediatric meningiomas are WHO Grade I tumors,

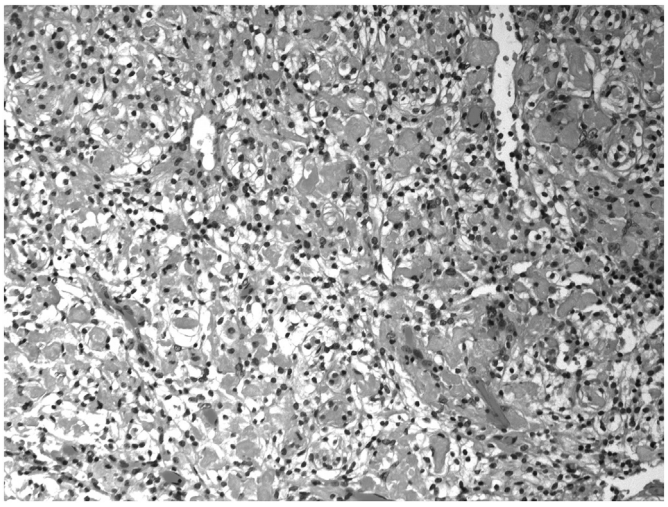

Fig. 1. The tumor is marked by a proliferation of rounded cells with clear cytoplasm arranged in a sheet-like configuration (hematoxylin and eosin, original magnification 200×).

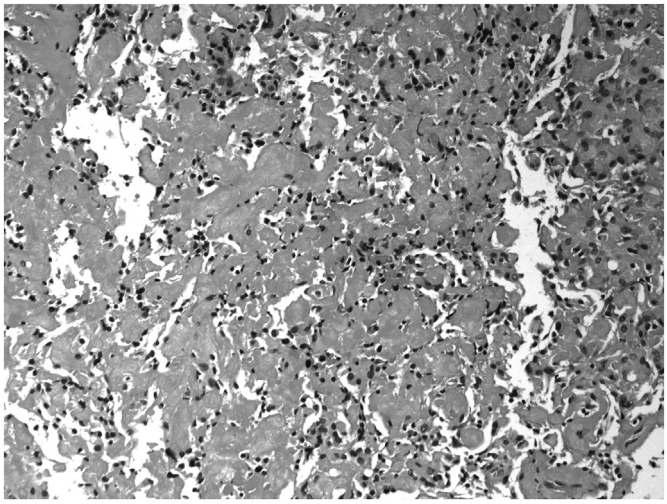

Fig. 2. Areas of the tumor were marked by prominent sclerosis and fibrosis (hematoxylin and eosin, original magnification 200×).

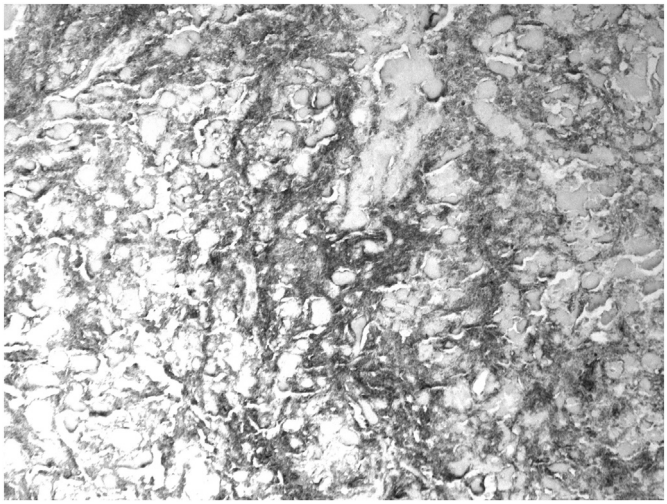

Fig. 3. The tumor demonstrated positive staining with antibody to epithelial membrane antigen (EMA) (original magnification 200×).

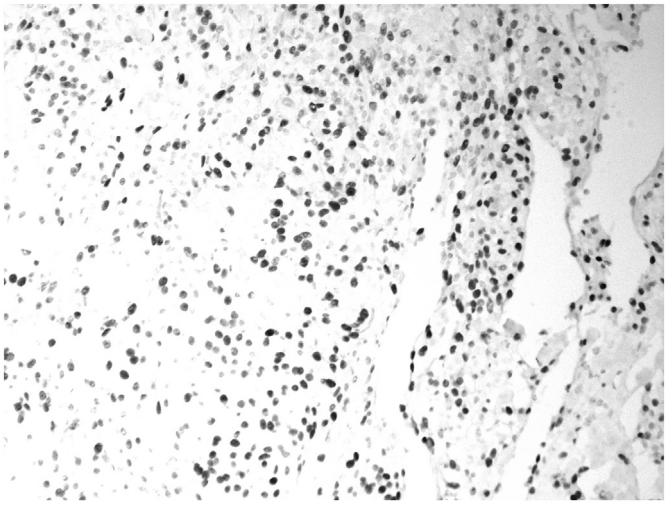

Fig. 4. Nuclear staining with antibody to progesterone receptor was noted in the tumor (original magnification 200×).

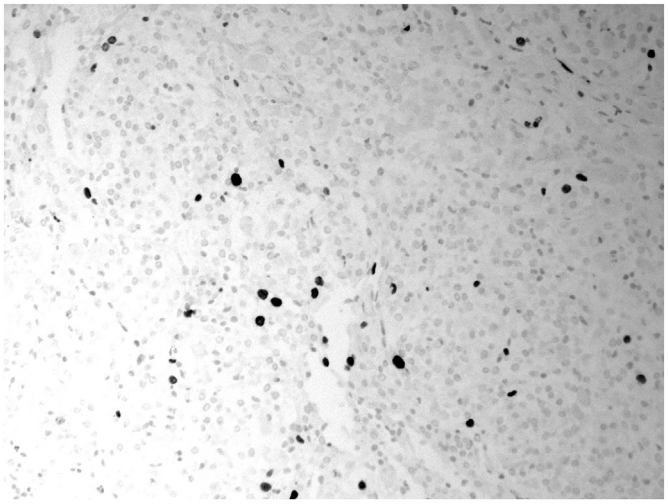

Fig. 5. A Ki-67 labeling index of 7.4% was observed in the neoplasm (original magnification 200×).

and the most common subtypes are transitional or mixed, meningothelial, and fibroblastic subtypes [11-13]. According to one large meta-analysis of 677 pediatric meningioma cases, only 9.9% of cases were grade II with the atypical subtype being the most common; 11 tumors in the series (1.6%) were clear cell type [13]. CCM typically arise in younger adults, with a mean age of approximately 30 years [6,7]. Though CCMs can occur in either intracranial or spinal locations in all ages, the relative frequency may differ between children and adults, with the spinal location possibly being more common in pediatrics [7,9,14,15]. This is difficult to evaluate because few cases of pediatric CCM have been described. Li et al. identified 23 cases of intracranial CCM in 2012 with several additional patients described since then [9,16-19]. The cerebellopontine angle (CPA) was the most common tumor location in this group [9]. There is an increased incidence in males, in contrast to the female predominance in adult CCMs [7,9]. The case presented here is only the 5th reported case of a CCM involving the middle fossa/parasellar region and the only recurrent case (Table 1).

Imaging features on MRI are similar to other meningiomas, namely, strongly contrast-enhancing on T1-weighted imaging as well as isointense and iso/hyperintense areas on T1- and T2-weighted imaging, respectively [8,20]. Histologically, CCM is usually marked by sheets of cells with clear, glycogen-rich cytoplasm and perivascular/interstitial collagen deposition and characteristic hyalinized stroma intermixed with tumor cells. Whorl formation and psammoma bodies are not prominent. The immunohistochemical profile of CCM has similarities to that of other meningiomas, including diffusely positive vimentin staining with focally positive and membranous epithelial membrane antigen (EMA) staining, as is seen in this case. Progesterone receptor positivity can also be observed [6]. Higher MIB-1 or Ki-67 labeling indices have trended with higher recurrence rates, though this is not a statistically significant finding in pediatric CCM cases [6,9]. At initial resection, this tumor's MIB-1 labeling index was as high as 15–20% and at recurrence, this patient's Ki-67 index was 7.4%.

There are a variety of genetic alterations in meningiomas [21]. NF2 mutations are the most common somatic changes found in sporadic meningiomas and patients with germline NF2 mutations are predisposed to develop these tumors as well as schwannomas and ependymomas [22]. However, most NF2-associated meningiomas have a fibroblastic or transitional histology [23]. Loss of function mutations in SMARCE1 (also called BAF57), a subunit of the SWI/SNF chromatin remodeling complex located on chromosome 17q21, predispose carriers to either spinal or cranial CCM [18,24]. SMARCE1 has many functions, including apoptotic induction by stimulating cylindromatosis tumor

Table 1
Reported cases of pediatric clear cell meningiomas in the middle cranial fossa.

Gender	Age (years)	Clinical presentation	Tumor location	Genetic analysis	MIB-1 (Ki-67) index	Treatment	Adjuvant therapy	Follow-up time	Recurrence (Yes/No)	Reference
M	11	Ptosis, recurrent headache and hemiparesis	Parasellar	N/A	2%	GTR	N/A	84 months	No	Jain et al. [5]
F	11	Headache, ataxia, bilateral horizontal nystagmus	Middle and posterior fossa	N/A	5%	GTR with residual	N/A	6 weeks	No	King et al. [34]
M	8	Gait disturbance, right month droop, hoarseness and dysphagia	Middle and posterior fossa	Somatic NF2 mutation	4%	STR	CKS	32 months	No	Li et al. [9]
M	11	Headache, vomiting, paranasal heaviness, facial palsy, subtle hemiparesis	Middle and infratemporal fossa	N/A	7%	GTR	N/A	9 months	No	Kumar et al. [19]
F	4	Left facial asymmetry, vomiting, fevers, decreased appetite	Middle and posterior fossa	Germline SMARCE1 loss, somatic NF1 and DMD mutations	15–20% initially; 7.4% at recurrence	GTR with residual	Proton beam therapy	48 months	Yes	Current case

Abbreviations: M: male; F: female; CKS: cyber-knife radiosurgery; GTR: gross total resection; STR: subtotal resection; N/A: not applicable or done.

suppressor (CYLD) expression; therefore, it acts as a tumor suppressor [25]. Including this case, 21 separate families with germline SMARCE1 mutations associated with CCM have been identified [10]. Interestingly, CCMs associated with germline SMARCE1 mutations appear to have incomplete penetrance in males [18]. In this case, the patient had a germline mutation in SMARCE1 as well as somatic mutations in the NF1 and DMD genes, which are located on chromosome 17q11.2 and Xp21.2–21.1 [26,27]. Table 1 summarizes the clinicopathologic features of other pediatric cases of clear cell meningioma that have been documented to arise in the parasellar and middle and posterior fossa regions. This is the only case of a CCM in the middle fossa with a known association with germline SMARCE1 loss (see Table 1). Patients with germline NF1 mutations appear to develop meningiomas at a rate similar to the general population [28]. NF1 encodes the neurofibromin protein, which can inhibit Ras-dependent growth and thus acts as a tumor suppressor [29]. It is possible that the dual loss of the tumor suppressor functions of NF1 and SMARCE1-encoded proteins promoted tumorigenesis, either independently or synergistically. DMD mutations have been linked to meningiomas which are progressive or have poor prognosis, implicating the role of dystrophin as a cytoskeletal structural protein and component of signaling for cell proliferation [30]. Future studies in genetics and molecular biology will help define how somatic mutations such as NF1 and/or DMD contribute to the pathogenesis of SMARCE1-associated meningiomas.

Patients with CCM are usually treated with surgical resection, though the frequent proximity of these tumors to vital structures such as the medulla, cranial nerves, and vertebral artery sometimes prevents safe total resection [31]. In these cases, adjuvant radiotherapy is used. Both adult and pediatric CCM have a substantial risk of recurrence, though the rate in adult CCM appears to be slightly higher at 46.4% in the largest case series to date, with some studies reporting over 60%, while that in pediatrics is reported as 30.4% [6,7,9]. In addition to high MIB-1 labeling, factors that have been accredited with the high recurrence rate of CCM include brain invasion, nuclear atypia, and anaplastic features on histology [14,32,33]. Though it has been noted that CCM associated with SMARCE1 mutations may be lower-risk for recurrence, this case shows that recurrence can occur in the context of these mutations.

Herein, we present a recurrent pediatric CCM case associated with a novel germline SMARCE1 mutation with somatic DMD and NF1 mutations. This is the only report of recurrence of a pediatric CCM in the middle fossa, and is currently the only tumor in this location and only relapsed pediatric CCM associated with a germline SMARCE1 mutation. As the association of pediatric CCM with SMARCE1 loss continues to be explored, it is essential to clarify its relationship with tumor location and prognosis. Furthermore, evaluation of the pathologic interaction of SMARCE1 loss with other somatic mutations may help define the tumorigenesis and progression of CCM.

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