Clear cell meningioma in a child: Case report and systematic literature review

Meningioma de células claras en una niña: revisión sistemática de la literatura y reporte de caso

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Resumen

Antecedentes: El meningioma de células claras (MCC) consiste en una variante poco común de meningiomas que generalmente ocurren en niños. Este tumor poco común se comporta de manera agresiva y las tasas de recurrencia son altas. Las manifestaciones clínicas son atípicas y el tratamiento generalmente implica cirugía. Métodos y Objetivos: Realizamos una revisión sistemática con el fin de definir las características más comunes de este raro tumor. Pubmed y LILACS fueron las bases de datos utilizadas para la búsqueda bibliográfica. Se incluyeron 17 estudios que cumplieron con nuestros criterios. Para avanzar en nuestra investigación, incluimos el caso clínico de una niña de 3 años con CCM operada en nuestro servicio. Resultados: Los MCC fueron más frecuentes en la población pediátrica que en adultos, especialmente en el sexo femenino. La resección macroscópica del tumor y el índice MIB-1 ≤ 3 fueron los parámetros relacionados con una menor tasa de recurrencia. La resección subtotal del tumor fue seguida de radioterapia en la mayoría de los casos de adultos. La mutación SMARCE-1 se pudo encontrar en varios pacientes. Conclusión: Los MCC son meningiomas raros que ocurren especialmente en niños. La agresividad y las altas tasas de recurrencia dificultan el manejo de esta enfermedad. Aún queda mucho por discutir sobre estos tumores raros, lo que exige más investigación.

Palabras clave: Tumor cerebral, meningioma de células claras, meningioma.

Abstract

Background: Clear Cell Meningioma (CCM) consists in a rare variant of meningiomas that generally occur in children. This uncommon tumor behaves aggressively and recurrence rates are high. Clinical manifestations are atypical, and the treatment generally involves surgery. Methods and Goals: We performed a systematic review in order to define the most common characteristics of this rare tumor. Pubmed and Lilacs were the databases used for the literature search. We included 17 studies that met our criteria. To further our research, we included the case report of a 3-year-old female child with CCM operated in our service. Results: CCMs were more frequent in the pediatric population than in adults, especially in females. Gross tumor resection and MIB-1 index ≤ 3 were the parameters related to a smaller recurrence rate. Subtotal tumor resection was followed by radiotherapy in most adult cases. SMARCE-1 mutation could be found in several patients. Conclusion: CCMs are rare...
meningiomas that occur especially in children. The aggressiveness and high recurrence rates difficult the management of this disease. There is still a lot to be discussed about these rare tumors, demanding further research.

Key words: Brain tumor, clear cell meningioma, meningioma.

Introduction

Cranial meningiomas are rarely found in children and teenagers. Cushing and Eisenhardt described an incidence in children of 1.9% among 313 patients with meningiomas in their famous 1938 monograph. A contemporary surgical series documented an incidence of 1.08% among children and teenagers operated over a 15-year period (1985 - 2000). Thus, the overall prevalence of pediatric cranial meningioma has not changed in over 50 years.

Clear Cell Meningioma (CCM) is an uncommon histological variant. It has been classified by World Health Organization (WHO) as a Grade II neoplasm. These tumors behave more aggressively than Grade I meningiomas, independently of their location and degree of excision. Most CCMs involve the spine and posterior fossa and the supratentorial location is relatively uncommon. CCMs involving the supratentorial area in children are extremely uncommon and to the best of our knowledge, only 5 such cases have been reported in the literature till date.

In this report, we present a case of a CCM in the temporal base with posterior extension in dumbbell shape in a child. Apart from this case, the authors presented a literature review.

Material and Methods

We conducted a systematic review based on the methodology outlined in the PRISMA (Preferred Reporting Project for Systematic Evaluation and Meta-Analysis) agreement. This study does not required ethical approval and patient consent.

Our literature search was based on PubMed and LILACS. We used various combinations of the following keywords: “clear cell meningiomas”, “meningiomas grade II” and “meningiomas in children”, “intracranial meningiomas” and “spine meningiomas”. We included clinical trials, comparative studies, observational studies, case reports and other systematical reviews. Only studies in humans and in English were selected for analysis. Studies in children and in adults were included. The evaluation period was from 1990 to 2021. The latest update was in May, 2020.

The selection criteria focused on design, reporting standards, clarity of results, and tumor classification. Considering the small number of papers found, we decided to also include case reports in our review.

In order to avoid human interference, the analysis was conducted independently. All authors have selected articles for comprehensive screening. The final selected articles have been read and approved by all authors.

Tumor location, sample size, tumor resection (gross or subtotal), recurrence rate, clinical results and conclusion were the parameters evaluated. Data extraction was performed using Microsoft Excel. Due to the small number of studies and subjects, there was no intention to do a quantitative analysis (meta-analysis).

Results

Seventeen papers written between 1998 and 2019 were included, totaling 349 patients. The tumor location, results and conclusion were summarized in Table 1.

Between the 346 patients, 191 were female (55.7%) and 152 male (44.3%). The mean age was 35.04 (age range 6-86). Recurrence after surgery was found in 147 patients (43.2%). All the data results can be found in Table 2.

Most studies found that CCMs occur in younger patients, especially pediatric age. Females had a higher incidence than males. CCMs showed a more aggressive behavior and higher rates of recurrence than other types of meningioma. Younger patients had a shorter progression-free survival.

Clinical presentation was atypical, including cranial nerve palsies, headache, vomiting, fevers and seizures.

The location of CMMs varied depending on the case series. The most frequent one was the spine (cervical, thoracic, lumbar or sacral). Other locations were: cerebellopontine angle (CPA), frontal lobe, parietal lobe, petroclival, middle and posterior fossa, basal ganglia, foramen magnum, cerebellar tentorium and convexity region.

Most cases underwent surgical treatment. When a gross tumor resection (GTR) could be achieved, recurrence rates were significantly lower. If a subtotal tumor resection (STR) was done, most authors complemented the treatment in adults with radiotherapy.

Cases with a MIB-1 index ≥ 3% had a shorter progression-free survival (PFS). Ki-67 index did not affect PFS. SMARCE-1 mutation was found in several cases.

Case report

Female, 3-year-old with complains of sudden onset of holocranial headache associated with vomiting and ataxic gait. Upon neurological examination, the patient presented paresis of the left lateral rectus muscle, vestibular syndrome on the left side and intracranial hypertension syndrome. Magnetic resonance imaging revealed a contrast enhanced well-defined extra-axial mass lesion in left middle cranial fossa with extension into the posterior fossa and cavernous sinus (Figures 1a, 1b and 1c). We opted to remove the mass in two stages: middle fossa approach with anterior petrosectomy and...
| Author / year       | Tumor Location                                                                 | Patients           | Results                                                                                                                                                                                                 | Conclusion                                                                                                                                                                                                 |
|---------------------|-------------------------------------------------------------------------------|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Wu, L. et al., 2019  | Cervical, thoracic, thoracolumbar, lumbosacral spine                           | 10 patients 3      | GTR was achieved in 9 patients. STR was achieved in 1 patient. Postoperative follow-up magnetic resonance imaging showed no recurrence/regrowth in the 9 patients with total removal and 1 patient with subtotal removal during the mean follow-up periods of 68.4 months and 56.0 months, respectively. |
|                     |                                                                                | male / 7 females   | Mean age: 25.5                                                                                                                                                                                        | A good clinical outcome after GTR can be expected, and the risk of long-term recurrence is low.                                                                                                           |
| Li, J. et al. 2018   | Fronto-parietal-temporo convexity, petrous ridge and petroclival, skull base, posterior fossa, parasagittal and falx cerebri, basal ganglia, third ventricle and hypothalamus | 24 patients 7 males / 17 females | During the average follow-up of 61.1 months, four patients (19.0%) suffered from tumor recurrence. Patients with STR or a MIB-1 index ≥3% had significantly shorter progression-free survival (PFS) compared to gross total resection GTR and MIB-1 index < 3%.  | CCMs have a predilection to affect younger patients and have a high rate of recurrence and metastasis. Surgery resection is the first treatment choice. For patients underwent STR or with MIB-1 index ≥3%, further radiotherapy is necessary. |
| Wang, X.Q. et al., 2014 | Cerebellopontine angle (CPA), spine, anterior basalis, foramen magnum, cerebellar convexity, cerebral ventricle, petroclival and cerebellar tentorium | 23 patients 12 male / 11 female | 17 patients underwent GTR and 5 patients underwent STR. Eleven patients had recurrence and 2 eventually died.                                                                                          | CPA was the most affected area in this series. The extent of initial surgical resection is the most important prognostic factor                                                                                         |
| Ma, L. et al., 2009  | Occipital parietal Lobe                                                        | 1 patient 1 male   | CT showed total resection of the tumor on the second week after the operation. There was no evidence of tumor recurrence during follow-up.                                                               | Total resection was related to no tumor recurrence in the follow-up period                                                                                                                                 |
| Li, J. et al., 2019  | Lumbar, cervical, sacral and thoracic spine                                   | 12 patients 5 male / 7 female | The mean age at diagnosis was significantly younger than that of patients with spinal meningiomas (28.8 13.4 years vs. 54.0 14.4 years) 5 patients (41.7%) experienced tumor recurrence. Younger patients had a significantly shorter progression-free survival time than older patients. | Spinal CCMs tend to affect younger patients and have a high recurrence rate. GTR is considered the optimal treatment. Radiotherapy could be considered for patients who had subtotal resection or for younger patients, regardless of the extent of removal. |
| Kuzeyli, K. et al., 2003 | Frontal lobe, temporal fossa                                             | 2 patients 1 male / 1 female | After 6 months of follow-up, the first patient is in good condition and neurological examination is within normal limits except for a slight left hemiparesis. A right frontotemporal craniotomy was performed on the the second patient, with subtotal excision of the mass. He died 45 days later due to congestive heart failure. | Although the differential diagnosis of CCM with the other clear cell tumours of the CNS is possible, the diagnosis of CCM might be kept in mind in meningioma cases and close follow-up is required due to the high risk of recurrence. |
| Author(s)                | Location/Details                                                                 | Number of Patients | Gender Details               | Recurrence/Mortality Details                                                                 |
|-------------------------|----------------------------------------------------------------------------------|--------------------|------------------------------|---------------------------------------------------------------------------------------------|
| Li, P. et al., 2016¹⁶    | Lumbosacral spine, supratentorial, CPA or petrous apex, infratentorial           | 36 patients       | 13 male / 23 female         | 15 patients suffered from tumor recurrence. Patients after GTR had significantly longer PFS time than those after STR. Age, gender, postoperative, radiotherapy, progesterone receptor staining and Ki-67 index did not have significant effects on patients’ PFS time. The frequency of spinal CCMs is higher than intracranial ones. They should be totally resected when possible to decrease the risk of recurrence and prolong patient’s PFS time. |
| Epstein, N.E. et al., 2005¹³ | Spinal canal at the L3-L4 level                                                  | 1 patient         | 1 female 41 years old       | GTR was performed in the intradural lesion. Radiation and chemotherapy following surgery was not recommended. The patient remains disease-free 1 year postoperatively. In adults, radiation therapy following GTR should be reserved for secondary recurrences. |
| Zhang, H. et al., 2017³³ | Skull base                                                                       | 146 patients      | 73 females / 73 males       | 67.8% patients underwent GTR and 32.2% underwent STR. 50.7% patients had tumor recurrence during the follow-up. Recurrence-free survival rates at 1 and 5 years after resection were 86% and 37%. CCM behaves differently from the other types of grade II meningiomas. GTR should be the primary goal in the surgical management of intracranial CCMs. |
| Rousselot, C. et al., 2010⁴⁷ | Medullary, sphenoid wing, pontocerebellar angle and tentorium                    | 7 patients        | 5 females / 2 males         | Three patients underwent GTR. Recurrence occurred in four patients, three of them died from the disease. CCM course is less favourable than meningioma WHO grade I, even in the absence of anaplastic area, high mitotic activity or necrosis. |
| Ito, T. et al., 1998¹⁸    | Cerebellar tentorium                                                             | 1 patient         | 1 female 67 years old       | The occipital transtentorial approach was used. Some tumor cells infiltrated into the cerebellar cortex. Gamma knife radiosurgery was performed for regrowing tumor 6 months after surgery. CCM may be clinicopathologically malignant so careful follow-up will be necessary. |
| Lee, W. et al., 2000²⁴    | Left parietal convexity                                                          | 1 patient         | 1 male 17 years old         | MR imaging showed leptomeningeal enhancement that progressed into the entire subarachnoid space after surgical resection of the primary tumor (dural-based mass in the left parietal convexity). The patient underwent lumbar surgery and radiation therapy to the whole brain. CCMs are related to clinical aggressiveness despite its benign histologic nature. Metastasis and recurrence are frequent. Patients are younger than those in other subtypes of meningioma. |
| Libert, D.M. & Prayson, R.A., 2020²⁵ | Left cavernous sinus                                                             | 1 patient         | 1 female 8 years old        | The tumor was 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. Evaluation of the pathologic interaction of SMARCE1 loss with other somatic mutations may help define the tumorigenesis and progression of CCM. |
| Prayson, R.A et al., 2010⁴⁴ | Frontal lobe, cavernous sinus and CPA/posterior fossa                            | 18 patients       | 9 females / 9 males         | Seven tumors showed CA9 immunoreactivity, 5 tumors (27.8%) CD10 staining, and 0 cases showed RCC staining. 10 patients (62.5%) developed at least 1 recurrence requiring surgical intervention. Meningiomas with at least a 10% clear cell component tend to behave in a more aggressive fashion with increased risk of recurrence. Immunohistochemical staining with antibodies to CA9, CD10, and RCC are potentially useful in differentiating CCM from metastatic renal cell carcinoma. |
retrosigmoid approach.

The patient progressed well during surgery and in the postoperative period. She was discharged from the hospital feeling well and with no neurological deficits. Histopathology was suggestive of clear cell meningioma (CCM) (Figure 3a).

Tumor cells were positive for vimentin, S-100 and focally positive for epithelial membrane antigen. The proliferation index measured by means of MIB-1 was 13% suggestive of aggressive variant.

After 1 month, she was again submitted to surgery. A new approach was performed to remove the residual tumor in the petroclival area. The postoperative MRI showed total resection.

Two weeks later the patient developed subarachnoid hemorrhage due to a pseudoaneurysm bleeding of the basilar trunk. An emergency surgery with clipping to control the hemorrhage was necessary. After the episode, she developed hemiplegia, lesion of left ocular motor nerve and impairment of swallow. She developed hypertonia and spasticity, the verbal contact was also extremely difficult. Three years later, a very small local recurrence was treated by radiosurgery of dural extension.

Discussion

Epidemiology

Pediatric meningiomas account for 1.52% of total meningiomas (15/983) according to large series of Hui et al. The mentioned author showed that the mean age at presentation was 12 years, with male to female ratio of 1.5:1.

Zorludemir et al., first described clear cell meningiomas in 1995 and since then <50 cases have been reported. It was subsequently listed as a distinct entity in the current WHO classification of brain tumors in 2000. Most cases were single case reports.

Pediatric CCM

CCM is reported to occur more frequently in the pediatric age group. Most patients of CCM are young, usually in
the first three decades of life, although occasional cases in older patients have also been reported. Slight female predominance has been noted. These tumors may recur, spread locally, and even metastasize despite their rather innocuous histological appearance. Our patient was a 3-year-old girl and the tumor was located in middle cranial fossa with cavernous sinus as well as posterior fossa extension.

Usual sites of occurrence are the spinal canal (intrudural, 48%), the cerebellopontine angle, tentorium, skull base and...
The supratentorial location in pediatric CCMs is rare. Only 6 cases of supratentorial pediatric CCM have been reported till date.\textsuperscript{19,31,54} In a review of 35 cases of intracranial CCM, Ma et al.\textsuperscript{31}, reported only two pediatric patients with supratentorial intraparenchymal CCM. They treated those patients with intracranial and spinal irradiation after surgical removal.

Pereira et al. reported a pediatric series with a case of clear cell meningioma\textsuperscript{37,41} and Oviedo et al., 2005 described a 7-year-old boy with a CCM of the cauda equine. Another author published a paper about CCM in the fourth ventricle of 14 year old patient\textsuperscript{8}.

**Differential Diagnosis**

Prior to the acceptance of CCM as a distinct variant of meningioma, differential diagnosis of tumors with clear cell morphology were often reported as metastatic renal cell carcinoma, oligodendroglioma, hemangioblastoma, and clear cell ependymoma, without specific immunohistochemical (IHC) analysis. Diagnoses was based solely on histomorphology.\textsuperscript{19,35,54} It is known that the absence of IHC facility during the initial pathological analysis, compounded with the lack of sufficient data pertaining to CCM possibly attributed to misinterpretation of initial tumor as an oligodendroglioma\textsuperscript{11}. Tumor localization (axial or extra axial) can help the pathologist in this differential diagnosis.

**Molecular Biology**

The biological behavior of CCM may be inordinately aggressive, despite its benign histological appearance. It may also display inconsistent correlation with MIB-1 proliferation. Aspects of cell proliferation in CCM and its correlation with edema have been described before. Previous studies noticed that grade of edema and MIB-1 could be associated to malignancy and radiological tumor shape.\textsuperscript{1,2,15,32,36,48} Zorludemir et al.\textsuperscript{54}, noticed that high MIB-1 tumors (range: 3.3-25.7%, mean 13.3%) had a 61% recurrence rate, while Jain et al. noticed a 22% recurrence rate in low MIB-1 tumors\textsuperscript{19}.

Zorludemir et al.\textsuperscript{54}, in their series found a recurrence rate of 61%, but failed to note any definite correlation between tumor recurrence and mitotic activity, proliferating cell nuclear antigen proliferation indices, percent S-phase determination, or DNA ploidy status. Pimentel et al.\textsuperscript{43}, found that recurrent CCMs generally were in the intracranial location and had been treated with subtotal resection.

Now a days, molecular genetics and karyotypic studies have also found consistent correlation between meningioma recurrence and loss of heterozygosis 22q, 1p, and 14q, also presence of cyclin E\textsuperscript{20,42}.

Navalkele et al. reported a case of a 6 year-old girl and her 25 year-old mother harboring CCMs. The first one with MRI showing an enhancing tumor infiltrating the preponsine area, extending to cerebellopontine angle along the bainstem and middle fossa, similarly to our case, and the second one with multiple CCMs. Tumor cytogenetics of the child revealed 2 chromosome aberrations, a 95 Mb gain on 13q12.11-q34 and a 62 Mb gain on 20p13-q13.33, and 3 areas of absence of heterozygosis on chromosomes 5 and 17, encompassing the TERT and NF1 genes (including region for SMARCE 1 gene). Neurofibromatosis (NF) type 1 was ruled out clinically. Germline testing excluded NF type 2 and SMARCB1 was found in the mother analysis, but Germline testing excluded NF type 2 and SMARCB1. Germline SMARCE 1 testing revealed a pathogenic variant (c.525delT) in both\textsuperscript{34}.
Treatment

The gold standard treatment of CCM is surgery. Radiotherapy and radiotherapy (radiosurgery or stereotactic fractioned radiotherapy) should be reserved for residual/recurrent cases. Staged excision could be an option for children, considering the extensive nature of the procedure in large tumors like in our patient.

Possible complications are CSF leak, venous lesion, arterial lesion. Small tumors have a higher chance of total resection and smaller complication rates can be observed. Our patient presented a late complication in the postoperative period, a severe subarachnoid bleeding after a rupture of pseudoaneurysm in the basilar artery.

We shall mention that radiotherapy in children can produce neurocognitive complications and late malignancies. In our opinion we must remove residual or recurrent tumors whenever possible, leaving the modalities of irradiation for radiotherapy.

Conclusion

CCMs in childhood are indeed rare. They represent meningiomas with a high grade of recurrence, even when the satisfactory resection of the lesion is accomplished. Recurrence usually appears after subtotal resection. Its similarity to other neoplasias with clear cell aspect (clear cell renal carcinoma) makes the diagnosis sometimes a challenge. The goal of treatment is surgery with total resection of the tumor. In cases of relapse or in cases of residual tumor, it is necessary to use radio-therapeutic devices such as radiosurgery and stereotatic fractioned radiotherapy. A long-term follow-up is mandatory to truly decipher the natural course of disease in these patients.

Conflict of Interests

The authors have no conflict of interests to declare.

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