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CLINICAL ARTICLE

Intracranial clear cell meningioma: a clinicopathologic study of 15 cases

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Abstract
Object Clear cell meningioma (CCM) is a rare histological variant of meningioma. CCM has a high recurrence rate and aggressiveness. In this study, we reviewed our experience in the treatment of the lesion.
Methods Here we present a series of 15 patients with intracranial CCM. The clinical data were retrieved from the records of our Neurosurgery Department and the patients' prognoses were attained by clinic service and telephone. Immunohistochemistry for epithelial membrane antigen (EMA), vimentin, glial fibrillary acidic protein (GFAP), CD10, and S-100 was done, and the MIB-1 labeling index was calculated in all cases.
Results The 15 patients included eight males and seven females; the mean age was 34.8 years. The most frequent initial symptoms were headache and hearing loss. The most common location was the cerebellopontine angle (CPA) zone. Eleven patients had total removal and four patients underwent subtotal removal. Histological features of atypia were present in different proportions, from 6.7% to 100%, and six cases accorded with atypia. Three tumors showed brain invasion. EMA and vimentin were 100% positive, and CD10 was 100% negative. GFAP was 87% negative and S-100 was 93% negative. The mean follow-up period was 36.7 months. Three patients with brain invasion all recurred and five cases with atypia recurred. In 11 patients with total removal, six patients recurred. In four patients with subtotal removal, three patients recurred. Kaplan-Maier analysis showed that incomplete surgical resection was significantly associated with recurrence ($p=0.001$). The MIB-1 labeling index for recurrence was $5.7\pm2.7\%$ versus $2.8\pm1.5\%$ for no recurrence ($p=0.036$).
Conclusions CCM is a rare subtype of meningioma, with a tendency to present in younger patients and a propensity to recur. Immunohistochemistry plays a vital role in differentiating CCM from other tumors. Brain invasion, atypia and MIB-1 labeling index are likely to predict the recurrence. The extent of resection might be connected with the prognosis.

Keywords Brain tumors · Clear cell meningioma · Glycogen rich meningioma · Intracranial · MIB-1 · Atypia

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Introduction

Meningiomas are common intracranial tumors that originate from the arachnoidal cap cell of the meninges and have a

large variety of histopathologic appearances. There are 15 subtypes in the 2007 WHO classification of meningioma of the central nervous system (CNS). Some subtypes, such as clear cell meningioma (CCM), have unique clinical associations and prognostic implications. CCM constitutes a rare variant of grade II meningiomas with distinctive histological features. It represents only 0.2% of all meningiomas, and may behave aggressively with local recurrence and cerebrospinal fluid metastasis [35]. It is histologically similar to other tumors such as clear cell ependymoma, microcystic meningioma, oligodendroglioma, metastases of clear cell carcinoma, metastasis of clear cell sarcoma of the kidney and so on. However, these tumors have a different choice of treatment and prognosis. Until now, only 48 intracranial CCM cases have been reported in the English literature since 1991 and most of them were described as isolated case reports, except for one series of seven cases and one series of eight cases [14, 35]. Here we studied the clinical, radiological and histopathologic features of 15 intracranial cases and evaluate the potential use of certain immunomarkers—such as epithelial membrane antigen (EMA), vimentin, glial fibrillary acidic protein (GFAP), S-100 and CD10—in discriminating CCM from other tumors, as well as reviewing the relevant literature. Also, we evaluate the relationship of prognosis with histopathologic features and different choice of treatment. To the best of our knowledge, this is the largest series of intracranial CCM in the existing literature.

Materials and methods

Search methods and case definition

All patients received surgical treatment at Huashan Hospital during the period from January 2000 to December 2009. Clinical data, including age, sex, presenting symptoms, duration of symptoms, location of tumor, neuroradiological data, and operative findings, were extracted from medical records. The diagnosis was verified by two pathologists (H.C. and Y.W.), who had no prior knowledge of the clinical status of the patients by re-examination of the tumor samples using the 2007 WHO classification [20].

Histological re-examination and immunostaining

Tissue specimens were fixed in 10% buffered formaldehyde solution, embedded in paraffin wax, and stained using hematoxylin-eosin according to standard protocol. Sections were cut to 3 μm thick. Special stains for periodic acid-Schiff (PAS) with and without diastase, mucicarmine, and alcian blue at pH 2.5 were applied to all cases.

Immunohistochemical staining was carried out by the Envision technique using monoclonal antibodies to EMA (1:50), vimentin (1:100), GFAP (1:100), CD-10 (1:50), S-100 (1:300) and MIB-1 (1:100). All antibodies were obtained from M/S Dako Patts, Denmark. The MIB-1 labeling index was calculated in regions of maximal activity and expressed as percentage of nuclear area stained. Atypia was defined as mitotic index≥4/10 high-power fields (HPF) or the presence of at least three of the following variables: increased cellularity, small cells with high nuclear/cytoplasmic (N/C) ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, foci of spontaneous or geographic necrosis. The mitotic index was defined as the maximal number of mitotic cells relative to all cells in ten consecutive HPF (each=0.16 mm^2).

Follow-up and ethical committee approval

The patients' prognoses were attained by clinic service and telephone. The surgical procedures were conducted under guidelines and the terms of all relevant local legislation.

Statistical analysis

Student's *t*-test was used to compare the difference of MIB-1 labeling index among the CCM patients with or without recurrence. Distributions of time to progression and time to recurrence were estimated using the Kaplan-Meier method and compared using the log-rank test. Data were presented as mean±SE, and the accepted significance was considered at 0.05. All these analysis were performed using Statistical Package for Social Sciences (SPSS, USA).

Results

During a period from January 2000 to December 2009, 5,423 cases of intracranial meningiomas were diagnosed at Huashan Hospital. Among these cases, 15 were CCMs. Thus, CCM constituted 0.28% of all intracranial meningiomas.

Demographics

This series included eight males and seven females, with a mean age of 34.8 years (range: 8–63 years; three at <18) upon initial diagnosis.

Lesion location

The cerebellopontine angle (CPA) zone was the most affected area (n=6). Other areas included petroclival, foramen magnum, hypoglossal canal, tuberculum sellae, middle basilar region, cerebellum tentorium, and cerebellum convexity (n=1 for each). The tumors were located in the ventricular system in remaining two cases: one in the lateral ventricle and the other in the fourth ventricle. The tumors

ranged from 2.0 cm to 6.5 cm in diameter, and the mean diameter was 3.8 cm.

Clinical presentation and treatment

Presenting symptoms included headache, dizziness, vomiting, sensory loss (hearing, vision or smell), raucitas, bucking, sialosis, swallowing difficulty, seizure, and hemiparesis. Headache and hearing loss were the most common symptoms. The duration from the appearance of the initial symptom(s) to diagnosis varied from 3 weeks to 7 years (mean 8.3 months).

Eleven patients received complete resection. For the remaining four cases, complete resection was not possible; the patients received subtotal resection. Two patients receiving subtotal resection were also treated with radiotherapy after the first craniotomy. No patient was treated with any antineoplastic agent.

Survival analysis

Prognosis was assessed by clinic service and telephone interview and no patient was lost to connection. The mean follow-up period was 36.5 months (range, 8–108 months). Tumor recurrence or progression occurred in nine patients (60%), with a mean recurrence time of 44.6 months. Tumor recurred in six out of the 11 patients receiving complete resection upon the initial episode and the estimated recurrence time was 69.9±13.4 months. Tumor recurred in three out of the four patients receiving subtotal resection and the estimated recurrence time was 10.8±1.2 months. The log-rank test showed that the incomplete surgical resection was significantly associated with recurrence (p=0.001). (Fig. 1). A summary of the 15 case is presented in Table 1.

Radiological findings

Computed tomography (CT) data were available in 13 cases. CT scan showed isodense (n=8) or slightly hyperdense (n=5) masses with homogenous or heterogenouse enhancement after administration of the contrast agent. Bone destruction was noted in three cases. Intratumoral cystic change and amorphous calcification were seen in one case each.

Magnetic resonance imaging (MRI) data were available in all 15 cases. Most of the tumors were hypointense on T1-weighted imaging and isointense to hyperintense on T2-weighted imaging. All the tumors showed strongly homogenous enhancement after administration of gadolinium. Marked peritumoral edema was noted in two cases (Figs. 2, 3).

Microscopic findings

Microscopic examination of the tumor revealed sheets of polygonal cells with abundant clear cytoplasm and distinct cellular outlines. The sheets of tumor cells were separated by hyalinized vascular stroma and bands of collagen.

The tumor cells were mostly euchromatic. Clear cell change occurred in between 30% and 80% of the tumors. Vague whorl formation was found in four cases. Scattered psammoma bodies were present in three cases. Microcalcification was noted in two cases. Increased cellularity was observed in nine cases. Small cell change was observed in six cases. Prominent nucleoli were seen in tumor cells in seven cases. Mitotic index≥4/10 HPF and necrosis of the tumor tissue were apparent in one case, respectively. Tumor invasion into the brain tissue was apparent in three cases. Embolization was not observed. Tumor cells were positive for periodic acid-Schiff (PAS) staining in all 15 cases. Six cases (cases 2, 6, 7, 11, 13, and 14) accord with atypia according to the above standard (Table 2).

Immunohistochemical findings

Tumors were positive for vimentin and EMA in all 15 cases. None of the 15 samples was positive for CD10. One tumor was positive for S-100. GFAP was positive in tumor cells in two cases, but positive in unaffected brain tissue in all 15 cases. The MIB-1 labeling index varied from 1% to 10% (mean 4.5%). The mean MIB-1 labeling index was 5.7 ±2.7% in the cases with recurrence, and 2.8±1.5% in cases without recurrence. The MIB-1 index was significantly higher in patients with recurrence than in patients without recurrence (p=0.036) (Figs. 4, 5).

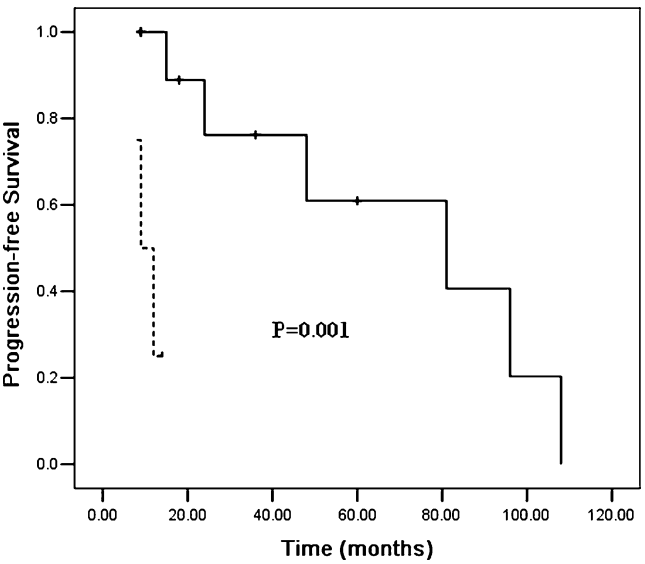

Fig. 1 Progression-free survival in patients with (*solid line*) or without (*dotted line*) complete tumor resection. Gross total resection is associated with a significantly longer progression-free survival

Table 1 Summary of the 15 patients with intracranial CCM in the present series

Case#	Sex/age (year)	Duration of symptoms	Pathology location	Clinical features	Treatment	Recurrence (Y/N)	Time to relapse
1	F/41	4 months	Tentorium of cerebellum	Headache	TR	N	60 months
2	M/39	3 months	Right petroclival	Headache, right hearing loss	TR	Y	108 months
2nd operation			Right petroclival	Headache	gamma knife	Y	60 months
3rd operation			Right petroclival		STR	Y	36 months
4th operation			Right petroclival		STR	Y	7 months
3	M/23	2 months	Left CPA	Hearing loss	TR	N	36 months
4	F/13	3 months	Left CPA	Gait disturbance	STR	Y	8 months
5	M/27	3 weeks	Foramen magnum	Swallowing difficulty	TR	N	9 months
6	F/27	6 months	Left CPA	Tinnitus, hearing loss	TR	Y	24 months
7	M/62	7 years	Right parietal	Headache	TR	Y	15 months
8	F/56	6 months	Left hypoglossal canal	Swallowing difficulty	STR	Y	12 months
2nd operation			Left hypoglossal canal		STR	Y	12 months
3rd operation			Foramen magnum		STR	Y	Died 24 months later
9	F/40	3 months	Left CPA	Headache, hear loss	TR	Y	48 months
2nd operation			Left CPA	Headache	TR	N	6 months
10	F/40	5 months	Right lateral CV	Headache, dizziness visual disturbance	TR	N	18 months
11	M/63	2 months	Left tuberculum sellae	Vision loss	TR	Y	96 months
2nd operation			Anterior basilar region	Vision loss, osmesthesia decreasing	TR	N	18 months
12	M/31	1 month	Middle basilar region	Headache	TR	Y	81 months
2nd operation			Middle basilar region		TR	Y	45 months
3rd operation			Middle basilar region		TR	Y	57 months
4th operation			Middle basilar region		STR	Y	6 months
5th operation			Anterior basilar region		STR	Y	6 months
13	M/8	2 months	Left CPA	Raucitas, bucking, gait disturbance	STR+RT	Y	9 months
14	F/43	2 months	Fourth CV	Nausea, vomiting	TR	N	9 months
15	M/9	6 weeks	Right CPA	Right eye esotropia	STR+RT	N	14 months

F male, *M* male, *Y* yes, *N* no, *CV* cerebral ventricle, *CPA* cerebellopontine angle, *TR* total removal, *STR* subtotal removal, *RT* radiotherapy

Discussion

The biological behaviour of intracranial CCM is poorly understood, partly due to a limited number of reported cases. From the results above, we know that CCM accounts for 0.28% of all intracranial meningiomas in our department, which is similar to Zorludemir et al.'s 0.2% report [35]. We also performed a systematic review of literature using the PubMed database with the key words 'clear cell' AND 'meningioma' without time limit, and 53 articles in the English language were reviewed. Only 48 cases had locations in the cerebrum and other cases were in the spine. However, from the data of our 15 cases plus previous 48 cases (Tables 3, 4), we found the age of onset ranged from 2 years to 84 years and the average age was 33.4 years and the male/female ratio is 28:35, which shows a slight female bias. The data indicate that CCM tends to occur in young patients, although the elderly population is also affected. Lee et al. [19] reported that the mean age of CCM was 29.8 years and Zorludemir et al. [35] also reported 29 years. However, neither of them distinguished cerebral CCM from spinal CCM. Zorludemir et al. [35] and Jain et al. [14] reported that the male/female ratio was approximately 0.86:1 or 0.75:1 respectively. Our series included three cases under 18 years of age. The literature identifies 16 cases of childhood CCM [1, 5, 14, 16, 19, 21, 22, 29, 32, 34, 35]. The 19 childhood cases (pooled) include eight females and 11 males, with an average age at 11 years, indicating a slightly higher incidence in males as opposed to the slight female predominance in adults. So the data show that intracra-

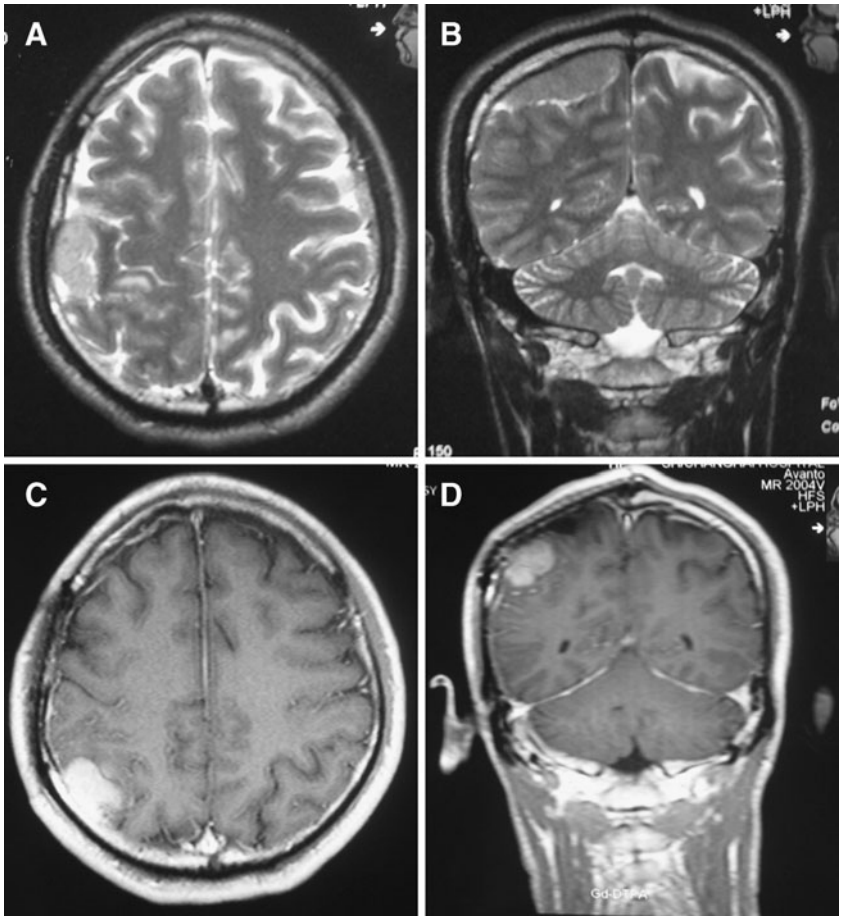

Fig. 2 Case 7. **a** Preoperative axial T2-weighted MRI showing a well-defined isodense elliptical mass in the convexity of right parietal lobe. **b** Preoperative coronal T2-weighted MRI showing a well-defined isodense elliptical mass in the convexity of right parietal lobe. **c** Postoperative axial T1-weighted contrast-enhanced MRI at 15 months showing the recurrence of tumors in the right parietal lobe. **d** Postoperative coronal T1-weighted contrast-enhanced MRI at 15 months showing the recurrence of tumors in the right parietal lobe

nial CCM has a female bias in adults, but a male bias in children.

It is generally believed that CCM is predominantly located in the intraspinal region [7, 23]. However, a recent study suggests that the cranium and spinal column are equally affected [10, 33]. In our series, the CPA zone is the most frequently affected area (n=6, out of 15 cases), followed by basilar region (n=5), intraventricular (n=2), tentorium of cerebellum and convexity (n=1, respectively). In the 48 cases reported in the literature, the most commonly affected areas are: basilar region (n=17) [1–3, 5, 10, 11, 14, 16–18, 22, 24, 25, 32, 35], convexity (n=12) [9, 15, 18, 19, 21, 24, 30, 31, 33, 35], and CPA (n=10) [13, 14, 28, 29, 34, 35]. Only six cases are in cerebral falx and tentorium of cerebellum [12, 14, 31, 35], and some cases (n=3) are intraventricular [4, 6], which is a very rare location for meningioma. This distribution pattern differs significantly from conventional meningioma, which occurs most frequently in the convexity and cerebral falx, and seldom seen in CPA zone and basilar region [27]. Consistent with the anatomical localization, the most common presenting symptoms in our series are headache, vomiting, hearing loss and cranial nerve palsies. In the two reported cases of CCM in cerebral ventricle, the patients presented with Castleman syndrome [6, 28]. However, our two intraventricular CCM cases did not have Castleman syndrome.

CT and MRI results do not differ between CCM and other types of meningiomas, indicating that imaging analysis is not sufficient for establishing diagnosis. Histologically, CCM consists of polygonal cells with clear, glycogen-rich cytoplasm and prominent perivascular and interstitial collagen. Tumor cells typically have bland-appearing nuclei. Mitotic and anaplastic features are rare. A distinctive feature of CCM is hyalinized stroma with intermixed and bland tumor cells. Psammoma bodies and whorl formations are present in a minority but significant proportion of the cases.

In our series, we found conventional meningothelial features, such as psammoma bodies and whorl formations, present in four tumors and three tumors, respectively. Histological features of atypia, such as more than four mitoses per 10 HPF, increased cellularity, small cell change, prominent nucleoli, sheet-like growth, and foci of geographic necrosis, are present at differing proportions from 6.7% to 100%. Sheet-like architecture is the frequent index of atypia for CCM, which is observed in all 15 cases. Six cases accord with atypia according to the above standard. Clear cell change is one character of the CCM, which

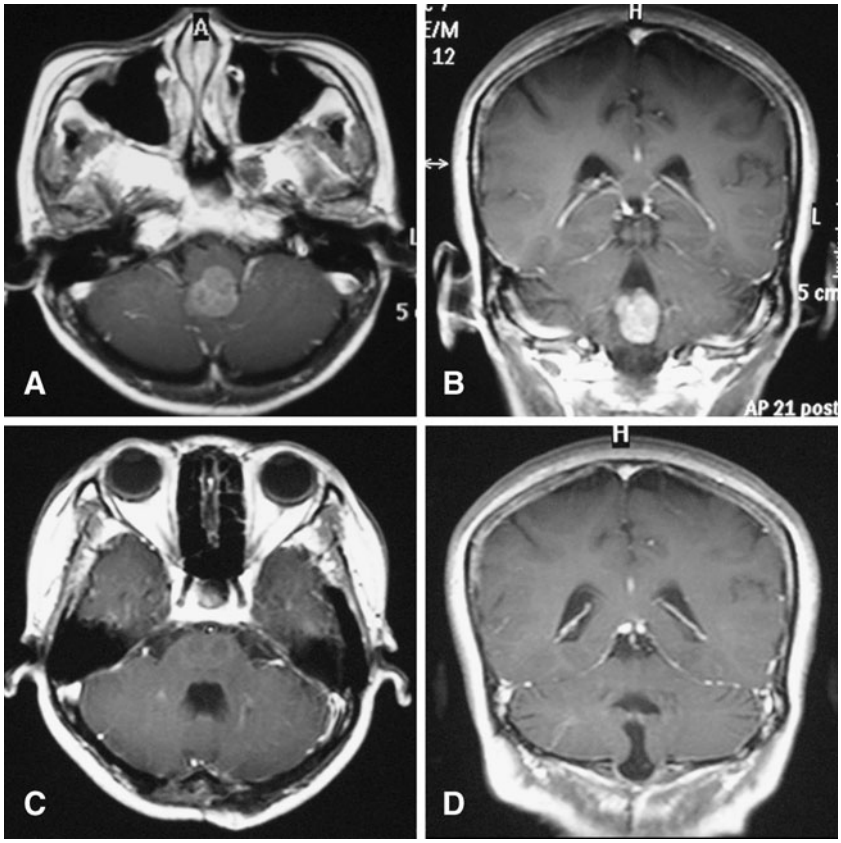

Fig. 3 Case 14. **a** Preoperative axial T1-weighted contrast-enhanced MRI showing an intense enhancement of a well-defined rounded mass in the fourth ventricle. **b** Preoperative coronal T1-weighted contrast-enhanced MRI showing an intense enhancement of a well-defined rounded mass in the fourth ventricle. **c** Postoperative axial T1-weighted contrast-enhanced MRI at 9 months showing deformity of the fourth ventricle without any sign of tumor recurrence. **d** Postoperative coronal T1-weighted contrast-enhanced MRI at 9 months showing deformity of the fourth ventricle without any sign of tumor recurrence

Table 2 Summary of the histological features of intracranial CCM in the present series

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Percent clear cell change	60	80	50	50	40	80	50	40	80	40	30	60	70	50	70
Sheet-like architecture	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Whorls meningothelial cell	+	-	-	+	+	-	-	-	-	+	-	-	-	-	-
Psammoma bodies	-	+	-	-	-	-	-	-	-	-	-	+	-	+	-
Microcalcifications	+	-	-	-	-	+	-	-	-	-	-	-	-	-	-
Increased cellularity	-	+	+	-	-	+	+	+	-	+	+	-	+	+	-
Small cell change	+	+	-	+	-	+	+	-	-	-	-	-	-	+	-
Prominent nucleoli	-	+	-	-	-	+	+	-	-	-	+	-	+	+	+
Mitotic figures/10HPF	2	2	1	0	0	0	3	2	1	0	0	1	5	2	3
Necrosis	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
Embolization	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Brain invasion	-	-	-	-	-	-	+	+	-	-	-	-	+	-	-
MIB-1	5	2	2	10	3	4	5	5	6	4	4	5	10	1	2
EMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vimentin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GFAP	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-
PAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CD10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
S100	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-

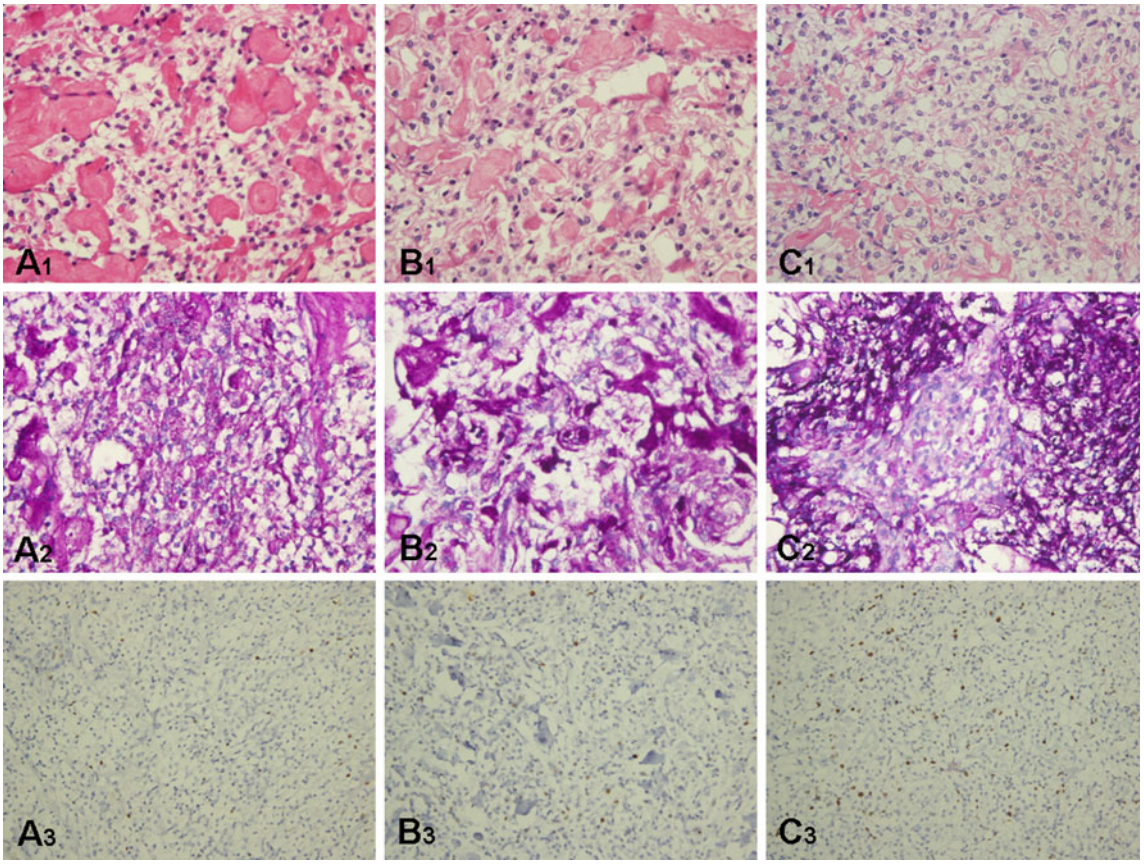

Fig. 4 Neuropathological findings. **a** Tumor tissue consisting largely of a sheet-like proliferation with wide fibrous connective tissue. Tumor cells have round nuclei with eosinophilic and clear cytoplasm in case 2 (**a***1*), case 10 (**b***1*), and case 13 (**c***1*) (H & E, original magnification×400). PAS-positive, material can be found in part of clear cytoplasm by special staining in case 2 (**a***2*), case 10 (**b***2*), and case 13 (**c***2*) (PAS, original magnification×400). MIB-1 labeling index in case 2 (**a***3*), case 10 (**b***3*), and case 13 (**c***3*) is 2%, 4% and 10% respectively (original magnification×200)

contributes to the diagnosis and occurs between 30% and 80% of the tumors.

Immunohistochemical staining is helpful in diagnosing CCM. CCM shows positive reactivity for vimentin and EMA, similarly to other meningioma subtypes [27]. Their staining for vimentin and EMA reflects their dual mesenchymal and epithelial properties. CCM contains more glycogen than the other subtypes of meningiomas, and it can be immunoreactive to GFAP, an atypical characteristic for meningiomas, and two cases were positive to GFAP in our series. S100 has been well established as a chondroid marker, and both chordomas and chondrosarcomas typically express this protein. Although a minority of our CCMs (one lesion) was positive for S100, the staining was mostly focal or patchy in nature. CD10, a common acute lymphoblasticleukemia antigen, is a cell surface neutral endopeptidase that inactivates bioactive peptides [26]. It has been shown to stain the vast majority of renal cell carcinomas and other neoplasms such as prostate carcinoma, pancreatic carcinoma, hepatocellular carcinoma, small cell lung carcinoma, and certain spindle cell sarcomas [8]. PAS-positive and diastase-sensitive material could also be found in clear cytoplasm either in the classical or the anaplastic component of tumor.

CCM is histologically unique but should be differentiated from other similar clear cell tumors of the CNS, such as microcystic meningioma, clear cell ependymoma, oligodendroglioma, metastases of clear cell carcinoma. Immunohistochemistry may be required to make the correct diagnosis. Although microcystic meningioma is similar to CCM on immunohistochemistry, with positive EMA and negative GFAP, it shows loose texture and microcystic formation, as well as sheets of tumor cells with vacuolated cytoplasm and is negative for PAS; and its clinical behavior is usually bland and different from that of CCM. All of these conduce to the differential diagnosis. Clear cell ependymoma is also similar to CCM histologically. However, it predominantly consists of round and clear cells with a honeycomb-like pattern, and shows abundant perivascular rosettes and ependymal canals. It is positive for GFAP, S-100 and only weak and dot-like positivity for EMA on immunohistochemistry, which is

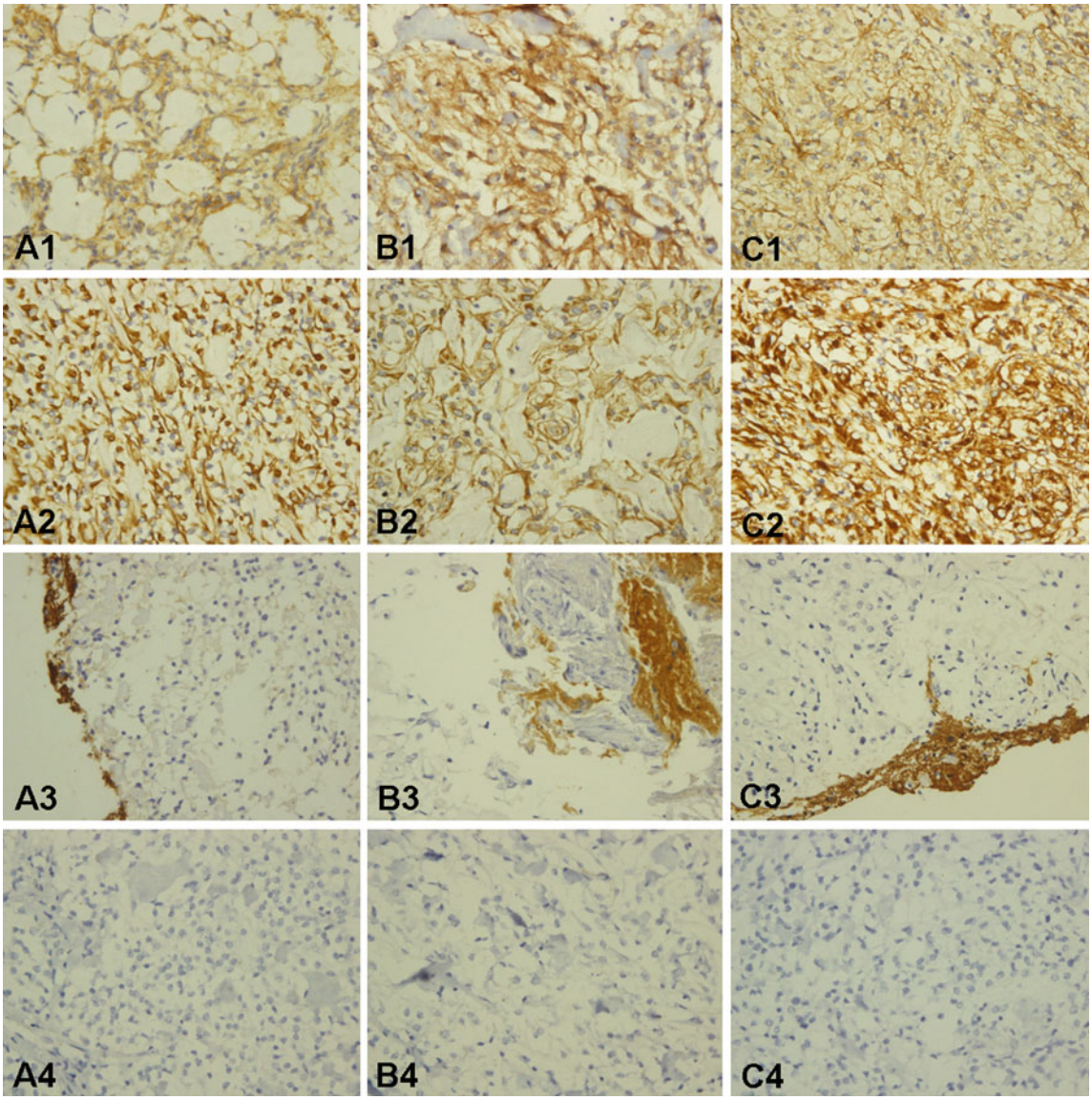

Fig. 5 Immunohistochemistry stain showing a positive immunoreactivity for EMA in case 2 (**a***1*), case 10 (**b***1*), and case 13 (**c***1*) (original magnification, ×400), vimentin in case 2 (**a***2*), case 10 (**b***2*), and case 13 (**c***2*) (original magnification, ×400), a negative immunoreactivity for CD10 in case 2 (**a***4*), case 10 (**b***4*), and case 13 (**c***4*) (original magnification, ×400). The neighbouring brain is positive for GFAP and, the tumor cell is negative in case 2 (**a***3*), case 10 (**b***3*), and case 13 (**c***3*) (original magnification, ×400). We can see the border between the brain and tumor is relatively clear

different from CCM. Anaplastic oligodendroglioma shows uniform cells with clear perinuclear halo. However, the tumor cells show nuclear pleomorphism, high mitotic activity and necrotic foci. And immunohistochemical staining for EMA and GFAP is useful to differentiate from CCM. Renal clear cell carcinoma is composed of clear cells with mild to moderate nuclear atypia, and nuclei are often arranged in lobules in vascular stroma. However, the tumor cells are positive for CD10, which is an immunohistochemical profile distinct from CCM. Recently, Prayson et al. [26] also reported that CA9, CD10, and RCC were potentially useful in differentiating CCM from metastatic renal cell carcinoma.

CCM has high rate of recurrence and/or CNS metastasis compared with other subtypes. In our series, the recurrence rate was 60%, with a mean recurrence time of 44.6 months. In 48 previously reported cases, the recurrence rate (including metastasis) was 49%, with a mean recurrence time of 37 months [1, 3, 9–14, 17, 19, 24, 33, 35]. In two large series of CCM, the recurrence rate of intracranial CCM is reported to be 71.4% and 25.0%, respectively [14, 35]. The clinical presentations and biological behavior of CCM may be inordinately aggressive despite its bland histological observation and may show conflicting correlation with MIB-1 proliferation. Previous reports suggested that MIB-1

Table 3 Summary of the clinicopathologic features observed in present and previous cases

Total number of cases	63
Age range (years)	2-84
Mean age (years)	33.4
Children (≤18 years)	19
Sex ratio (M:F)	28:35
Location	
CPA	16
basilar region	22
convexity	13
cerebral falx and tentorium of cerebellum	7
intraventricular	5
Duration of symptoms (months)	Sudden onset to 84
Treatment	
total removal	42
subtotal removal (no adjuvant treatment)	10
Subtotal removal plus radiotherapy or radiosurgery	7
unknown	4
Number of cases with available follow-up	56
Follow-up period (months)	1.5–156 (mean 33.3)
MIB-1 LI	
Recurring tumor	5.7% (present series)
Nonrecurring tumor	2.8% (present series)
Number or total removal	46
Total removal with follow-up	39
Recurrence rate of total removal	43.6% (17/39)
Recurrence time of total removal (months)	Median 24
Number of subtotal removal	17
Subtotal removal with follow-up	13
Recurrence rate of subtotal removal	84.6% (11/13)
Recurrence time of subtotal removal (months)	Median 12

labeling index could be used to predict the prognosis in patients with meningiomas [35]. For conventional meningioma, the mean MIB-1 labeling index is 4% for grade I, 7% for grade II, and 15% for grade III tumors. MIB-1 labeling index is appreciably higher among tumors that recurred than in those that do not. However, the MIB-1 labeling index in the series of Jain et al. [14] varied from 2 to 12% (mean 9%) with a noted 22% recurrence. Interestingly, in both the cases which recurred there was a low MIB-1 labeling index (2%). In reviewing the literature, we identify that the mean MIB-1 labeling index of the seven tumors that recurred is 7.7% [1, 3, 12, 14, 24, 33], and that of the 15 nonrecurrent tumors is 4.2% [4, 14, 16, 24, 25, 31]. There is significant difference in the recurrence between recurrent and nonrecurrent cases. In our study, the MIB-1 index is significantly higher in patients with recurrence (5.7±2.7%) than in patients without recurrence (2.8±1.5%) (p=0.036), thus confirming the use of MIB-1 index as a factor to predict prognosis. Moreover, in our series, the tumors with brain invasion (cases 7, 8, and 13) all recur in a shorter period (15, 12, 9 months, mean 12 months). However, the gross recurrence time in our study is 44.6 months. So the tumors with brain invasion have a higher recurrence rate and a shorter recurrence time. Maybe brain invasion is an important prognostic indicator. Six out of our 15 cases accord with atypia and five cases recured, except for the case 14, with a mean recurrence time of 50 months. However, case 14 did not recur but had a shorter follow-up of 9 months. The data show that atypia might likely be concerned with recurrence. No such difference is noted in percent clear cell change between the recurrence and no recurrence patients. Based on the limited data in this series and literature review, we believe that high MIB-1 labeling index, brain invasion and atypia are accountable for the high-recurrence rate of CCM, though CCM seems to be generally well excised surgically.

Of the 63 cases reported so far, including our 15 cases, the recurrence rate after gross total removal is 17/39(43.6%)

Table 4 Comparison of clinicopathologic features observed in present and previous series

	Previous case reports	Present study
Total number of cases	48	15
Age range (years)	2-84	8-64
Mean age (years)	33.0	34.8
Children (≤18 years)	16	3
Sex ratio (M:F)	20:28	8:7
Location		
CPA	10	6
basilar region	15	5
convexity	14	1
cerebral falx and tentorium of cerebellum	6	1
intraventricular	3	2
Duration of symptoms	Sudden onset to 3 years	3 weeks to 7 years
Treatment		
total removal	31	11
subtotal removal or partial removal(no adjuvant treatment)	8	2
subtotal removal or partial removal plus radiotherapy or radiosurgery	5	2
unknown	4	0
Number of cases with available follow-up	41	15
Follow-up period	6 weeks to 13 years (mean 32.1 months)	8 months to 9 years (mean 36.5 months)
MIB-1 LI		
Recurring tumor	UN	5.67%
Norecurring tumor	UN	2.83%
Recurrence rate of total removal	39.3% (11/28)	54.5%(6/11)
Recurrence time of total removal	29.2 months	62 months
Subtotal (partial) removal	13	4
Recurrence rate of subtotal (partial) removal	88.9% (8/9)	75% (3/4)
Recurrence time of subtotal (partial) removal	54.3 months	9.7 months

and the median recurrence time is 24 months; in contrast, the recurrence rate after subtotal removal or parital removal is 11/13 (84.6%) and the median recurrence time is 12 months. The results show that the recurrence rate of total removal is obviously lower than subtotal removal, and the recurrence time of total removal is longer also. The prognosis of intracranial CCM is related to the initial treatment and the extent of resection might be predictive for recurrence. Because the number of cases who had undergone radiotherapy and radiosurgery is insufficient, it is difficult for us to draw a conclusion whether radiotherapy has an influence on the recurrence of CCM. However, radiation therapy and radiosurgery might be important in the cases of cerebral CCM with incomplete resection and primarily treating recurrences. Postoperative regular MRI scans of the entire neuraxis should be performed to monitor for recurrence.

Conclusions

CCM is a rare subtype of meningioma with a tendency to present in younger patients and a propensity to recur and metastasize. The most commonly affected area is the CPA and basilar region. Immunohistochemistry is helpful to differentiate CCM from other primary and metastatic clear cell tumors. Brain invasion, atypia, MIB-1 labeling index and the extent of resection might likely predict the recurrence. Postoperative regular MRI scans of the entire neuraxis should be performed to monitor for recurrence.

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Conflicts of interest None.

Reference

1. Ahn ES, Chin LS, Gyure KA, Hudes RS, Ragheb J, DiPatri AJ Jr (2005) Long-term control after resection and gamma knife surgery of an intracranial clear cell meningioma: case report. J Neurosurg 102:303–306
2. Baxter DS, Smith P, Stewart K, Murphy M (2009) Clear cell meningioma presenting as rapidly deteriorating visual field and acuity during pregnancy. J Clin Neurosci 16:1502–1504
3. Benchetritt M, Hofman V, Long E, Odin G, Basc E, Pasquier B, Pedeutour F, Hofman P (2008) Primary clear cell meningioma of the orbit mimicking a metastatic carcinoma: usefulness of immunohistochemistry and cytogenetic analysis. Virchows Arch 452:209–213
4. Carlotti CG Jr, Neder L, Colli BO, dos Santos MB, Garcia AS, Elias J Jr, Chimelli LC (2003) Clear cell meningioma of the fourth ventricle. Am J Surg Pathol 27:131–135
5. Carra S, Drigo P, Gardiman M, Perilongo G, Rigobello L (2003) Clear cell meningioma in a 22-month-old male: update after five years. Pediatr Neurosurg 38:162–163
6. Cassereau J, Lavigne C, Michalak-Provost S, Ghali A, Dubas F, Fournier HD (2008) An intraventricular clear cell meningioma revealed by an inflammatory syndrome in a male adult: a case report. Clin Neurol Neurosurg 110:743–746
7. Chen MH, Chen SJ, Lin SM (2004) A lumbar clear cell meningioma with foraminal extension in a renal transplant recipient. J Clin Neurosci 11:665–667
8. Chu P, Arber DA (2000) Paraffin-section detection of CD10 in 505 nonhematopoietic neoplasms. Frequent expression in renal cell carcinoma and endometrial stromal sarcoma. Am J Clin Pathol 113:374–382
9. Deb P, Datta SG (2009) An unusual case of clear cell meningioma. J Cancer Res Ther 5:324–327
10. Dhall SS, Tumialan LM, Brat DJ, Barrow DL (2005) Spinal intradural clear cell meningioma following resection of a supra-sellar clear cell meningioma. Case report and recommendations for management. J Neurosurg 103:559–563
11. Heth JA, Kirby P, Menezes AH (2000) Intraspinal familial clear cell meningioma in a mother and child. Case report. J Neurosurg 93:317–321
12. Ide M, Yamamoto M, Hagiwara S, Tanaka N, Kawamura H (2004) Rapid regrowth of intracranial clear cell meningioma after craniotomy and gamma knife radiosurgery—case report. Neurol Med Chir (Tokyo) 44:321–325
13. Imlay SP, Snider TE, Raab SS (1998) Clear-cell meningioma: diagnosis by fine-needle aspiration biopsy. Diagn Cytopathol 18:131–136
14. Jain D, Sharma MC, Sarkar C, Suri V, Garg A, Singh M, Sharma BS, Mahapatra AK (2007) Clear cell meningioma, an uncommon variant of meningioma: a clinicopathologic study of nine cases. J Neurooncol 81:315–321
15. Kakita A, Takahashi H, Fusejima T, Konno K, Nakazawa T, Aoki K, Tanaka R, Ikuta F (1995) Clear cell variants of intracranial tumors: meningioma and ependymoma. Noshuyo Byori 12:111–116
16. King J, Cusimano M, Hawkins C, Dirks P (2009) Extradural middle fossa approach to a clear cell meningioma in a child. Can J Neurol Sci 36:257–261
17. Kubota T, Sato K, Kabuto M, Hasegawa M, Kitai R, Nakagawa T, Arai Y, Yamashita J (1995) Clear cell (glycogen-rich) meningioma with special reference to spherical collagen deposits. Noshuyo Byori 12:53–60
18. Kuzeyli K, Cakir E, Usul H, Karaarslan G, Kadir Reis A, Temiz C, Baykal S (2003) Clear cell meningioma: case report and literature review. J Clin Neurosci 10:264–266
19. Lee W, Chang KH, Choe G, Chi JG, Chung CK, Kim IH, Han MH, Park SW, Shin SJ, Koh YH (2000) MR imaging features of clear-cell meningioma with diffuse leptomeningeal seeding. AJNR Am J Neuroradiol 21:130–132
20. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97–109
21. Ma L, Liu WK, Wang K, Shrestha B, Zhang YK (2009) Intracranial clear-cell meningioma. Acta Neurochir (Wien) 151:373–378, discussion 378
22. Miranda P, Simal JA, Vila M, Hernandez M, Menor F, Alvarez-Garijo JA (2009) Posterior fossa clear cell meningioma without dural attachment in a child. Childs Nerv Syst 25:389–392
23. Park SH, Hwang SK, Park YM (2006) Intramedullary clear cell meningioma. Acta Neurochir (Wien) 148:463–466
24. Pimentel J, Fernandes A, Pinto AE, Fonseca I, Moura Nunes JF, Lobo Antunes J (1998) Clear cell meningioma variant and clinical aggressiveness. Clin Neuropathol 17:141–146
25. Pizzoni C, Sarandria C, Pierangeli E (2009) Clear-cell meningioma of the anterior cranial fossa. Case report and review of the literature. J Neurosurg Sci 53:113–117
26. Prayson RA, Chamberlain WA, Angelov L (2010) Clear cell meningioma: a clinicopathologic study of 18 tumors and examination of the use of CD10, CA9, and RCC antibodies to distinguish between clear cell meningioma and metastatic clear cell renal cell carcinoma. Appl Immunohistochem Mol Morphol 18:422–428
27. Rogers L, Gilbert M, Vogelbaum MA (2010) Intracranial meningiomas of atypical (WHO grade II) histology. J Neurooncol 99:393–405
28. Sato T, Sugiyama T, Kawataki T, Sato E, Horikoshi T, Sugita K, Kinouchi H (2010) Clear cell meningioma causing Castleman syndrome in a child. J Neurosurg Pediatr 5:622–625
29. Shih DF, Wang JS, Pan RG, Tseng HH (1996) Clear cell meningioma: a case report. Zhonghua Yi Xue Za Zhi (Taipei) 57:452–456
30. Shiraishi K (1991) Glycogen-rich meningioma. Case report and short review. Neurosurg Rev 14:61–64
31. Tena-Suck ML, Salinas-Lara C, Gomez C, Bojorquez DR (2007) Frontotemporal clear cell meningioma. Report of 3 cases. Ann Diagn Pathol 11:182–189
32. Teo JG, Goh KY, Rosenblum MK, Muszynski CA, Epstein FJ (1998) Intraparenchymal clear cell meningioma of the brainstem in a 2-year-old child. Case report and literature review. Pediatr Neurosurg 28:27–30
33. Tong-tong W, Li-juan B, Zhi L, Yang L, Bo-Ning L, Quan H (2010) Clear cell meningioma with anaplastic features: case report and review of literature. Pathol Res Pract 206:349–354
34. Yu KB, Lim MK, Kim HJ, Suh CH, Park HC, Kim EY, Han HS (2002) Clear-cell meningioma: CT and MR imaging findings in two cases involving the spinal canal and cerebellopontine angle. Korean J Radiol 3:125–129
35. Zorludemir S, Scheithauer BW, Hirose T, Van Houten C, Miller G, Meyer FB (1995) Clear cell meningioma. A clinicopathologic study of a potentially aggressive variant of meningioma. Am J Surg Pathol 19:493–505

Comment

An important part of neuro-oncology group practice is the recognition of unusual to very rare CNS tumors and the tailoring of optimal therapy and follow-up for their carriers—based on more or less scarce published data. The trouble of identifying and analyzing series of rare

CNS tumours from the last 30 years, i.e., the CT period, should be supported in the era of genomics. Never trust the previous histologic diagnosis but have it re-evaluated by your neuropathologist—more than one if in doubt.

In the authors' hospital in Shanghai, a staggering number of 5,423 intracranial meningiomas were diagnosed in a 10-year period, which allowed the compilation of the largest series of intracranial clear cell meningioma (CCM), a rare (0.28%) WHO grade II subtype of meningiomas. The authors, importantly, solidify the clinical spectrum of intracranial CCMs:

1. Younger average age at diagnosis, some 30 years.
2. Totally different intracranial distribution with the petroclival and CPA regions overrepresented.
3. MRI and CT not suggestive of subtype diagnosis.
4. Immunostaining helpful in the differentiation from other primary and metastatic clear cell tumors, such as microcystic meningioma, central neurocytoma, clear cell ependymoma, oligodendroglioma or renal clear cell carcinoma.
5. Recurrence rate of some 60% after seemingly complete removal.
6. Time to recurrence some 4 years.

So, regular MRI controls are mandatory, in our practice at 12-month intervals, as for other grade II meningiomas. But no one has produced convincing data on the impact of local or stereotactic radiotherapy on the recurrence/regrowth rate of CCMs.

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This is an interesting paper and it seems to be the largest series of clear cell meningiomas reported in the literature. The authors present 15 cases of this rare meningioma variant, which is associated with a more aggressive behaviour, including frequent recurrence and occasional cerebrospinal fluid seeding despite a bland cytology in most cases. They are different from other subtypes of meningiomas on clinical and histopathological manifestations, i.e they are composed of sheets of polygonal cells with clear cytoplasm and perivascular hyalinization without whorls formation and psammoma bodies. As stressed in this paper, it could be hard to diagnose them based only on hematoxylin and eosin examinations, and a definite diagnosis needs other specific immunohistochemical stains to permit their distinction from other subtypes of meningiomas with less aggressive behaviour.

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