ORIGINAL ARTICLE

Clear-cell meningioma: An uncommon aggressive variant of meningioma

Shilpa P. Tathe, Kirti N. Jaiswal

Department of Pathology, Super Speciality Hospital and Government Medical College, Nagpur, Maharashtra, India

Address for correspondence:
Dr. Shilpa P. Tathe, 72, Jaiprakash Nagar, Khamla - Nagpur - 440 025, Maharashtra, India.
E-mail: tatheshilpa@gmail.com

ABSTRACT

Background: Clear-cell meningioma is a rare subtype, representing 0.2–0.8% of all meningiomas. It is classified as grade 2 according to World Health Organization (WHO) classification due to its aggressive clinical course. Morphologically, it can mimic other clear-cell tumors arising in the central nervous system, each having different clinical behavior, therapeutic protocol, and prognostic outcome. **Aim:** This study aims to describe clinicopathological characteristics of clear-cell meningioma and to discuss the histomorphological features and differential diagnosis. **Materials and Methods:** The demographic, clinical, radiological, histopathological features, and follow-up of the patients were recorded and analyzed. **Results:** Clear-cell meningioma constituted 1.3% of all meningiomas. The age of the patients ranged from 16–46 years (mean age – 27 years), with a slight female predominance. Follow-up varied from six months to six years. Recurrence was noted in four patients while three patients died. Histopathology revealed sheets of clear cells with prominent blocky interstitial and perivascular collagen deposition. Focal vague whorl formation and occasional intranuclear inclusions could be identified on careful search. Conventional meningothelial areas or typical psammoma bodies were not seen. **Conclusion:** Clear-cell meningioma is a rare subtype of meningioma with aggressive behavior. The presence of blocky collagen, a careful search for whorl formation, and intranuclear inclusions are helpful in approaching the correct diagnosis. An interdisciplinary approach by correlating the clinical, radiological, and histological features can enhance the accuracy of diagnosis.

KEY WORDS: Aggressive variant, blocky collagen, clear-cell meningioma

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INTRODUCTION

Meningiomas are slow-growing, extra-axial tumors exhibiting a wide variety of morphological patterns due to the pluripotent nature of archnoid cap cells, which are the cell of origin of meningiomas. World Health Organization (WHO) has described 15 subtypes of meningiomas and has stratified them into three grades according to their biological behavior.[1] Clear-cell meningioma (CCM) is a rare subset, representing about 0.2–0.8% of all meningiomas.[2,3] These are graded as WHO grade 2 tumors and are associated with a high likelihood of recurrence. It usually affects young females with a predilection for spinal and cerebello-pontine angles.[4,5]

Histologically CCM is characterized by patternless sheets of polygonal cells with abundant clear cytoplasm and bland-looking round to oval centrally placed nuclei with fine chromatin. Prominent blocky perivascular and interstitial collagen are common. Histopathological diagnosis of CCM is challenging because the defining meningothelial features are usually focal or ill-defined.[1,2] Due to its aggressive behavior, it is important to differentiate it from other meningioma variants and clear-cell tumors occurring in the central nervous system. Due to its rarity, most of the descriptions of CCM are limited to single case reports and few case series.[2-6] Here, we report the clinicopathological characteristics of 10 cases of CCM and discuss its histopathological features and differential diagnosis.

MATERIALS AND METHODS

A total of ten cases diagnosed as CCM over a

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period of 20 years (2004–2023) were reviewed. Clinical details and immunohistochemistry reports were retrieved. The clinical data collected included age, gender, location of the tumor, symptoms, radiological features, and follow-up. Immunohistochemistry (IHC) was conducted only in six cases. IHC markers studied were epithelial membrane antigen (EMA), glial fibrillary acidic protein (GFAP), S-100, vimentin, and Ki-67. The study was approved by the medical ethics committee of the institution.

RESULTS

During the period of 20 years (2004–2023), 720 cases of meningiomas were diagnosed in the department, of which 10 were CCMs, thus constituting 1.3% of all meningiomas.

Clinical data

Age and sex ratio

The age ranged from 16–46 years (mean age – 27 years]. There was a slight female predominance with an M:F ratio of 1:1.5.

Site

The most common location was the spine (40%) and posterior fossa (40%) and one case each of the parasagittal, basifrontal region.

Clinical features

The symptoms in patients with the intracranial location were headache, vomiting, vertigo, and unilateral weakness of the body. In patients with spinal location, back pain and lower limb weakness were the common symptoms.

Radiology

Computed tomography (CT) and magnetic resonance imaging (MRI) showed variably sized extra-axial and extra-medullary dural-based lesions [Figure 1]. The largest dimensions noted on imaging were 8 × 5.3 × 5.5 cm. The clinical and radiological details of all the cases are shown in Table 1.

Histopathology

On gross inspection, the specimen comprised irregular grayish-white tissue pieces of size ranging from 1.5 to 8 cm. All the tumors showed similar histomorphology. On microscopic examination, the tumors were composed of sheets of clear cells with prominent blocky interstitial and perivascular collagen deposition [Figure 2a]. Focal vague whorl formation was noted in almost all the cases [Figure 2b]. Individual cell showed round to oval centrally placed nuclei with fine chromatin and moderate to abundant clear cytoplasm with distinct cytoplasmic borders [Figure 2c]. Occasional intranuclear inclusions could be identified on careful search. Calcification was noted in two cases, but typical psammoma bodies were not seen [Figure 2d]. In all the cases, the tumor occurred in pure clear-cell form, and admixed conventional meningothelial areas were not seen.

Table 1: Clinicoradiological details of the patients

Case no.	*Age*	*Gender*	*Site*	*Size*	*Follow-up*
1	16	Female	Posterior fossa	4.6 × 2.4 × 4 cm	Recurrence after six months followed by death
2	22	Female	Spinal IDEM (D12)	1.3 × 1.2 × 1.6 cm	No recurrence
3	23	Female	Spinal IDEM (L3–5)	1.5 × 1.5 × 1.2 cm	No recurrence
4	30	Male	Spinal IDEM (D12–L1)	2 × 1.6 × 1.2 cm	No recurrence
5	24	Male	Parasagittal	8 × 5.3 × 5.5 cm	Recurred two times 1st recurrence after three years 2nd recurrence after six years, followed by death
6	42	Female	Basifrontal	5.6 × 4.6 × 4.5 cm	Lost to follow up
7	46	Male	Posterior fossa	4.7 × 2.1 × 3.3 cm	Lost to follow up
8	18	Female	Cervicomedullary junction	3.7 × 2.5 × 3.8 cm	Recurred after 1.5 years
9	30	Male	Posterior fossa	4.5 × 3.5 × 4 cm	Recurred after one year followed by death
10	20	Female	Spinal (c2–c4)	2.1 × 1.5 × 1.6 cm	No recurrence

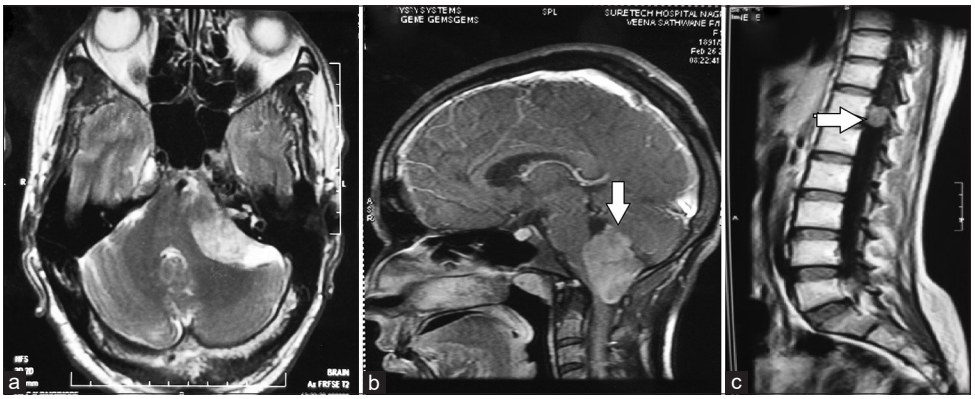

Figure 1: MRI IMAGES – (a) – well-defined lesion arising from tentorium (b) – extra-axial space-occupying lesion at cervicomedullary junction. (c) – intradural extramedullary lesion involving thoracolumbar junction

Nuclear pleomorphism or tumor necrosis was not seen, and mitoses were infrequent. Immunohistochemistry was conducted in six cases. Vimentin showed diffuse positivity [Figure 3b]. Focal positivity was seen with S-100 [Figure 3c]. EMA was negative or showed focal positivity, while GFAP was negative [Figure 3a and 3d].

Follow-up

The postoperative follow-up period varied from six months to six years. Out of 10, two patients lost to follow up. Recurrence was noted in four cases (40%) after six months to six years. Recurrent tumors were noted in patients with intracranial location. None of the patients with spinal tumors had recurrence. Three patients (30%) died after being operated for recurrence.

DISCUSSION

CCM is a rare variant of meningioma which is potentially aggressive despite its bland histological appearance. Zorludemir *et al*.[2] first described this neoplasm in 1995 and were subsequently listed as a distinct entity in the WHO classification of brain tumors in 2000. Till date, more than 100 cases of CCM have been reported in English literature.[3] Most of these are single case reports with few case series.[2-6]

CCM constitutes 0.2–0.8% of all meningiomas.[2,3] A higher incidence accounting for 1.3% was noted in our study. CCM exhibits a predilection for the posterior fossa and spinal cord[2,4,5] as also seen in eight of 10 cases in the present study. Most patients of CCM are young usually in the first three decades of life, although occasional cases in older patients have also been reported. In this study, eight patients were in the first three decades of life except two who were 46 and 48 years old. A slight female predominance was noted in the study as described by other authors.[2-4] The aggressive nature of this tumor has been confirmed by various studies which warrant an accurate diagnosis of this tumor. In the current study, four of 10 cases (40%) had recurrence at the interval of six months to six years. Three patients (30%) died after being operated for recurrence. Previous studies have reported a recurrence rate from 22.2% to as high as 62%.[2-6] Intracranial CCMs are associated with a higher recurrence rate than the spinal ones, following resection.[2,4,5] In our series, also none of the spinal CCM recurred, while four of the six cases of intracranial CCMs had recurrence.

Most of the CCMs are dura-based but a few non-dura-based CCMs are also reported in the literature.[2,3,7,8] In our study, all the tumors were dura-based. On MRI, CCMs have similar features to other types of meningioma. Wang *et al*.[6] reported that CCMs tended to have marked heterogenous enhancement, apparent dural tail sign, prominent peritumoral edema, cystic components, and bone involvement. However, the definitive diagnosis of CCM can only be made by histopathology. Histologically CCM is characterized by patternless sheets of polygonal cells with clear glycogen-rich cytoplasm and prominent blocky perivascular and interstitial collagen.[1,2] Similar histological features were observed in our cases. Although few, recognizable whorl formation and occasional intranuclear inclusions were seen in all the cases. Calcification was noted in two cases; however, typical psammoma bodies were not seen. Another important observation was that in all cases, CCM occurred in pure form and was not admixed with areas of conventional meningioma, further accentuating the diagnostic challenge. The presence of blocky collagen, a careful search for whorl formation, and intranuclear inclusions were helpful in the diagnosis of CCM. Immunohistochemically CCM shows diffuse or focal membranous EMA positivity. Vimentin and S-100 are also positive.[1,9] Cytokeratin, synaptophysin, and GFAP negativity are helpful in excluding other tumors in the differential diagnosis. IHC can play a major role in the diagnosis of non-dura-based CCMs.

An accurate diagnosis of CCM can pose a diagnostic challenge because clear cells can be encountered in other intracranial

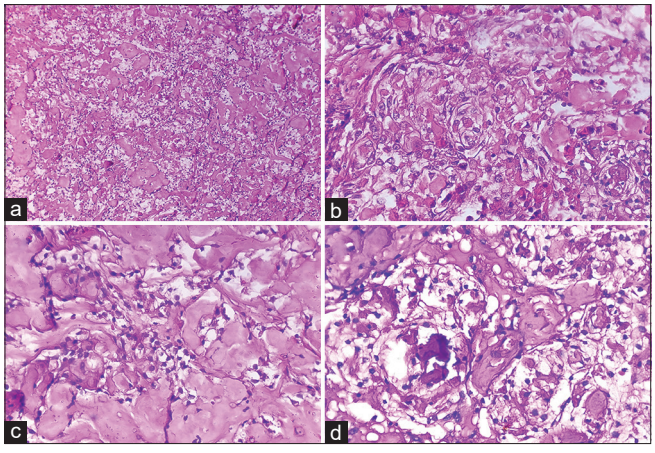

Figure 2: (a) – Section showing prominent blocky collagen with sheets of clear cells (H and E, 100X). (b) – Section showing clear cells with vague whorl formation (H and E 400X). (c) – Section showing clear cells with well-defined cell borders. (H and E 400X). (d) – Section showing non-psammomatous calcification. (H and E 400X)

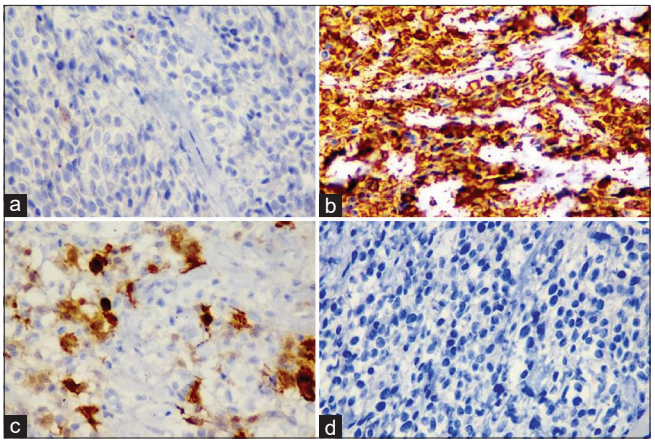

Figure 3: (a) – Epithelial membrane antigen (EMA) – Negative. (b) – Vimentin showing diffuse positivity. (c) – S-100 showing focal positivity. (d) – Glial fibrillary acidic protein (GFAP) – Negative

tumors. Morphologically CCM needs to be differentiated from oligodendroglioma, clear-cell ependymoma, central neurocytoma, and metastatic clear-cell carcinomas. Oligodendrogliomas are diffusely infiltrating tumors typically located in the cerebral hemispheres. Radiologically, it appears as an intra-axial space-occupying lesion located in the cortex and subcortical white matter. Calcification is common. Histologically, it shows sheets of clear cells with discrete cytoplasmic borders and uniform round nuclei.[1,10] In addition, delicate thin branching vasculature (chicken wire pattern) is seen; unlike CCM, which displays thick hyalinized blood vessels.

Another principle differential diagnosis is clear-cell ependymoma which commonly occurs in supratentorial locations in children and young adults. Clear-cell ependymomas have round to oval nuclei with fine chromatin and clear cytoplasm.[10,11] Identifying the presence of perivascular pseudorosettes or ependymal rosettes is instrumental in the diagnosis, which is not a feature of CCM. Moreover, clear-cell ependymomas are immunoreactive for GFAP, which differentiates it from clear-cell meningoma.

Posterior fossa being the common site for CCM, and cerebellar hemangioblastoma can be a differential diagnosis. Radiologically, hemangioblastoma is frequently cystic with a mural nodule. Histologically, it shows sheets of cells with vacuolated bubbly cytoplasm embedded in a rich anastomosing network of capillaries.[12]

Due to its clear-cell morphology, CCM may sometimes resemble metastatic clear-cell adenocarcinoma, particularly renal cell carcinoma. Prayson *et al*.[13] reported that IHC staining with antibodies to CA9, CD10, and RCC is potentially useful in differentiating CCM from metastatic renal cell carcinoma. An interdisciplinary approach by correlating clinical, radiological, and histological features can enhance the accuracy of the diagnosis and differentiate it from its mimics.

The pathogenesis of CCM is still unclear. SMARCE1 germline mutation has been implicated in the tumorigenesis of CCM.[14-17] NF2 mutation has also been reported in some cases of CCMs.[2,18] The mechanism underlying the aggressive behavior of CCM still needs to be elucidated.

Treatment of choice for CCM is maximal surgical resection with radiotherapy being reserved for the residual or recurrent cases. Long-term follow-up is essential in these patients considering their high propensity for recurrence.

CONCLUSION

CCM is a rare subtype of meningioma with aggressive behavior. It can morphologically mimic other clear-cell tumors in the central nervous system, each having distinctive biological behavior, therapeutic protocol, and prognostic outcome. The presence of blocky collagen, a careful search for whorl formation, and intranuclear inclusions are helpful in approaching the correct diagnosis. An interdisciplinary approach by correlating the clinical, radiological, and histological features can enhance the accuracy of diagnosis.

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Conflicts of interest

There are no conflicts of interest.

REFERRENCES

1. Sahm F, Perry A, Brastianos PK, Santagata S, Claus EB, von Deimling A, *et al.* Meningioma. WHO Classification of Tumors Editorial Board. Central Nervous System Tumors. Vol 5. Lyon (France): International Agency for Research on Cancer; 2021. p. 283-97.
2. Zorludemir S, Scheithauer BW, Hirose T, Van Houten C, Miller G, Meyer FB. Clear cell meningioma. A clinicopathologic study of a potentially aggressive variant of meningioma. Am J Surg Pathol 1995;19:493-505.
3. Li P, Yang Z, Wang Z, Zhou Q, Li S, Wang X, *et al*. Clinical featuers of clear cell meningioma: A retrospective study of 36 cases among 10,529 patients in a single institution. Acta Neurochir 2016;158:67-76.
4. Jain D, Sharma MC, Sarkar C, Suri V, Garg A, Singh M, *et al.* Clear cell meningioma, an uncommon variant of meningioma: A clinicopathologic study of nine cases. J Neurooncol 2007;81:315-21.
5. Pimentel J, Fernandes A, Pinto AE, Fonseca I, Moura Nunes JF, Lobo Antunes J. Clear cell meningioma variant and clinical aggressiveness. Clin Neuropathol 1998;17:141-6.
6. Wang XQ, Huang MZ, Zhang H, Sun FB, Tao BB, Feng BH, *et al.* Clear cell meningioma: Clinical features, CT and MR imaging findings in 23 patients. J Comput Assist Tomogr 2014;38:200-8.
7. Teo JGC, Goh KYC, Rosenblum MK, Muszynski CA, Epstein FJ. Intraparenchyal clear cell meningioma of the brainstem in a 2 year old child. Pediatr Neurosurg1998;28:27-30.
8. Payano M, Kondo Y, Kashima K, Daa T, Yatsuka T, Kida H, *et al*. Two cases of non dura based clear cell meningioma of the cauda equine. APIMS 2004;112:141-7.
9. Chen H, Li XM, Chen YC, Wu JS, Dou YF, WAng Y, *et al.* Acta Neurochir (Wein) 2011;153:1769-80.
10. Sandra Camelo- Piragua. Clear cell tumors of the central nervous system: A case based review. Arch Pathol Lab Med 2012;136:915-26.
11. Fouladi M, Helton K, Dalton J, Gilger E, Gajjar A, Merchant T, *et al*. Clear cell ependymoma: A clinicop[athologic and radiologic analysis of 10 patients. Cancer 2003;98:2232-44.
12. Padhi S, Sarangi R, Challa S, Bussary P, Panigrahi MK, Purohit AK. A 10 year retrospective study of hemangioblastomas of the central nervous system with reference to von Hippel- Lindau (VHL) disease. J Clin Neurosci 2011;18:939-44.
13. Prayson RA, Chamberlain WA, Angelov L. 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 2010;18:422-8.
14. Smith MJ, Ahn S, Lee JI, Bulman M, Plessis DD, Suh YL. SMARCE1 mutation screening in classification of clear cell meningiomas. Histopathology 2017;70:814-20.
15. Smith MJ, Wallace AJ, Bennet C, Hasselblatt M, Elert-Dobkowska E, Evans LT, *et al*. Germline SMARCE1 mutations predispose

to both spinal and cranial clear cell meningiomas. J Pathol 2014;234:436-40.
16. Evans LT, van Hoff J, Hickey WF, Smith MJ, Evans DG, Newman WG, *et al.* SMARCE1 mutations in pediatric clear cell meningioma: Case report. J Neurosurg Pediatr 2015;16:296-300.
17. Tauziede-Espariat A, Parfait B, Besnard A, Lacombe J, Pallud J, Tazi S, *et al.* Loss of SMARCE1 expression is a specific diagnostic marker of clear cell meningioma: A comprehensive immunophenotypical and molecular analysis. Brain Pathol 2018;28:466-474.
18. Hartmann C, Sieberns J, Gehlhaar C, Simon M, Paulus W, von Deimling A. NF2 mutations in secretory and other rare variants of meningiomas. Brain Pathol 2006;16:15-9.