

Pitfalls in the Histopathologic Diagnosis of Meningioma: Report of Three Rare Variants of Meningioma and Literature Review



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ABSTRACT

Meningioma is a common primary tumor of the central nervous system and one of the most encountered brain tumors. Although classic histopathologic features of meningioma are relatively common and make its diagnosis straightforward, certain variants possess unusual histologic features causing diagnostic challenges. We reported three cases of clear cell meningioma, microcystic meningioma, and angiomatous meningioma report, variants with potential deceptive morphologies, and discuss their distinguishing morphologic features.

Introduction

M

eningioma is well-known for its vast variety of histologic appearances and approximately, 15 histologic subtypes have been reported according to the World

Health Organization (WHO) meningioma classification [1]. The most common subtypes are meningothelial, fibroblastic, and transitional meningiomas. These classic variants usually show typical meningothelial differentiation features, such as syncytial growth pattern, whorl structures, and psammoma bodies in different extents.

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Among other variants, particular tumors with morphologic features far from those of the classic type can be mentioned that obscure their meningotheial identity. This can mislead the pathologist in rendering the correct diagnosis. What makes matters worse is that clinical and radiologic data are not always provided or are given when they are not useful for the diagnosis of the tumor nature. We presented and reviewed three rare cases of clear cell, microcystic, and angiomatous meningiomas, in an attempt to highlight characteristics that can be used in separating these challenging subtypes from their possible mimickers.

Case Presentation

Case 1

A 19-year-old female came to our center in March 2019 with facial hypoesthesia and right ear total hearing loss. On neurological examination, the right-sided facial sensory deficit was found, particularly involving the maxillary (V2) nerve distribution. Reduced corneal sensation was also identified. Brain Magnetic Resonance Imaging (MRI) revealed a large tumor located at the right Cerebellopontine Angle (CPA). The tumor was hypointense on a T1-weighted image (Figure 1A), slightly iso- to hyperintense on T2, and showed a weak T1 enhancement after contrast administration. The patient underwent suboccipital retrosigmoid craniotomy. Intra-operatively, the tumor adhered immensely to the trigeminal nerve involving the Meckel's cave with no typical petrous dural attachment and gross total resection was achieved. Postoperatively, the facial sensation was fully restored and hearing loss surprisingly recovered.

Histologically, the tumor showed sheets of cells with clear cytoplasm, traversed by hyalinized collagen bands (Figure 1B). The tumor cells had well-defined cellular borders and round to oval nuclei with no pleomorphism. Areas of thick acellular eosinophilic collagen were evident (Figure 1C). Mitoses and necrosis were not identified. The performed immunohistochemistry demonstrated positivity for vimentin and Neuron-Specific Enolase (NSE). However, Epithelial Membrane Antigen (EMA) immunostain was only focally and weakly positive (Figure 1D). CD56, EMA, S100, GFAP, CKAE1/AE3, and inhibin markers showed negative reactivity. The final diagnosis was Clear Cell Meningioma (CCM). On post-surgery evaluation, the patient has had no tumor progression or recurrence.

Case 2

A 54-year-old woman was admitted to our hospital in December 2016, with a history of headaches. Brain MRI revealed a right occipital falx cerebri mass, demonstrating low intensity on T1-weighted images and high intensity on T2-weighted images with mild T1 contrast enhancement (Figure 2A). The patient underwent craniotomy for mass resection. On histologic examination, microcystic spaces admixed with a vascular hyalinized stroma were observed (Figure 2C). Cytoplasmic processes of the tumor cells surrounded round to oval empty clear spaces creating a lace-like appearance. The tumor cells had small, oval nuclei, with an eosinophilic and some with vacuolated cytoplasm (Figure 2D). Recognizable meningotheial nests were also found. Mitoses and necrosis were not identified. The tumor was diagnosed as microcystic meningioma. Two years after surgery, the patient showed tumor recurrence, and due to the small size of the tumor, she has been clinically followed (Figure 2B).

Case 3

A 49-year-old woman presented to our center in August 2018, with a history of chronic headache and focal seizures. Radiological investigation revealed a left frontal parasagittal dural-based tumor surrounded by edema. The solid mass demonstrated low intensity on T1-weighted images and high intensity on T2-weighted images with avid T1 enhancement on contrast administration. Intra-operative findings showed a prominent vascular tumor with bone involvement. Also, gross total resection was achieved. Microscopically, numerous blood vessels of different sizes were identified, composed mostly of delicate and small-sized vessels, some exhibiting hyalinized walls. The tumor showed areas of meningotheial differentiation with tumor cells having indistinct cell borders, some forming whorl structures in the background of the vasculature (Figure 3A). Higher magnification also revealed foci of capillary-sized vascular spaces admixed with tumor cells showing a vacuolated cytoplasm (Figure 3B). EMA and vimentin were diffusely immunoreactive, but GFAP and inhibin markers were negative (Figure 3C). CD34 highlighted the vascular spaces but showed no reaction in the surrounding cells (Figure 3D). Weak positivity for CKAE1/AE3 was seen. Also, the proliferation index (Ki-67) was less than 5%. This case was diagnosed as angiomatous meningioma and in the follow-up after 2 years, no recurrence was encountered.

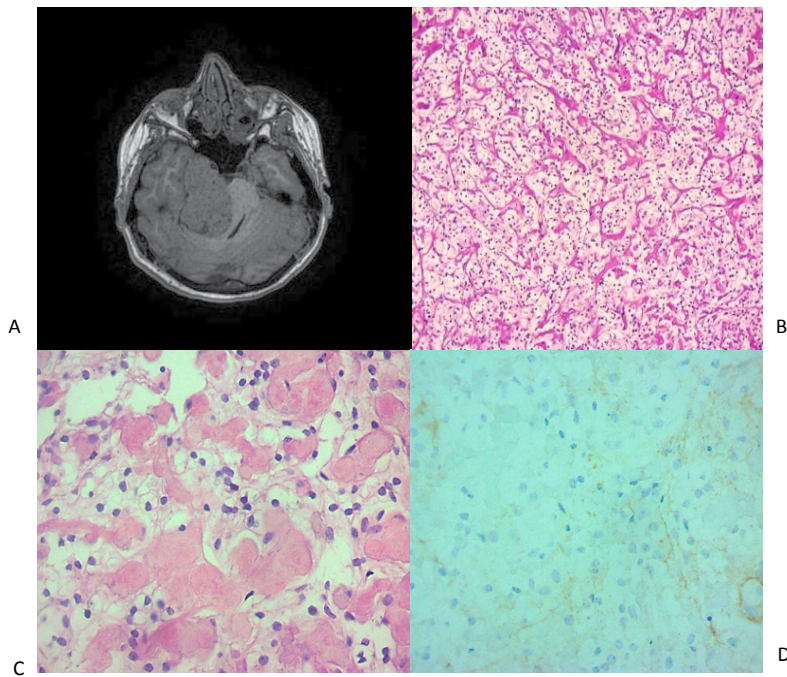


Figure 1. A) Pre-operative T1-weighted axial brain Magnetic Resonance Imaging (MRI). Note the right cerebellopontine angle tumor. B) Patternless growth of clear cells, interspersed by collagen bands (H&E x100). C) Higher magnification shows round and somewhat polygonal tumor cells with round to oval bland-looking nuclei and distinct cell borders. Thick acellular eosinophilic zones are also present (H&E x400). D) Epithelial Membrane Antigen (EMA) faintly stained tumor cells (x100).

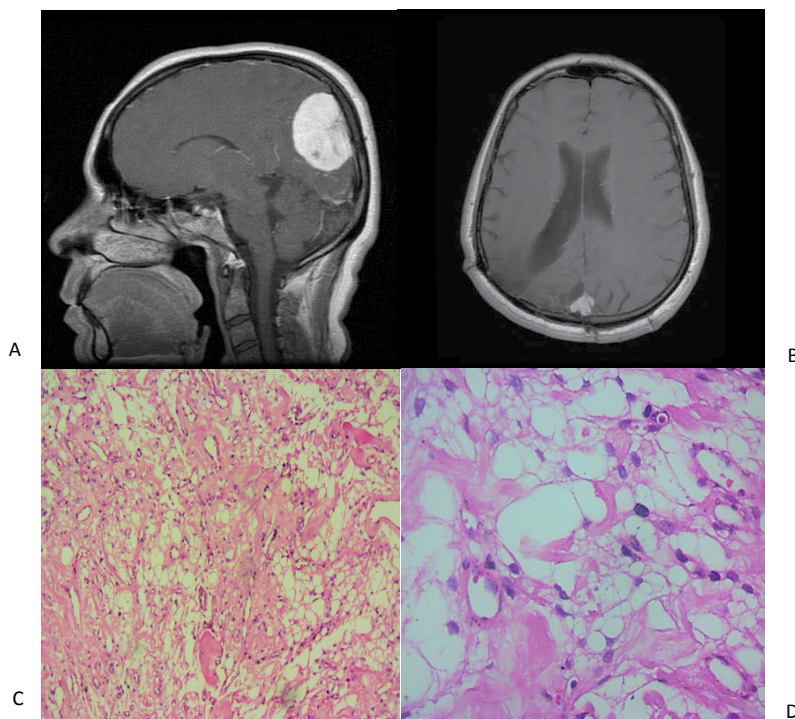


Figure 2. A) Pre-operative T1-weighted, post-contrast magnetic resonance imaging (MRI), sagittal view. B) Two-year postoperative MRI, axial view, showing tumor recurrence. C) A vascular hyalinized stroma admixed with microcystic spaces with a somewhat loose texture (H&E x 100). D) Numerous small cysts of different sizes. Tumor cells with eosinophilic cytoplasm and long delicate processes (H&E x 400).

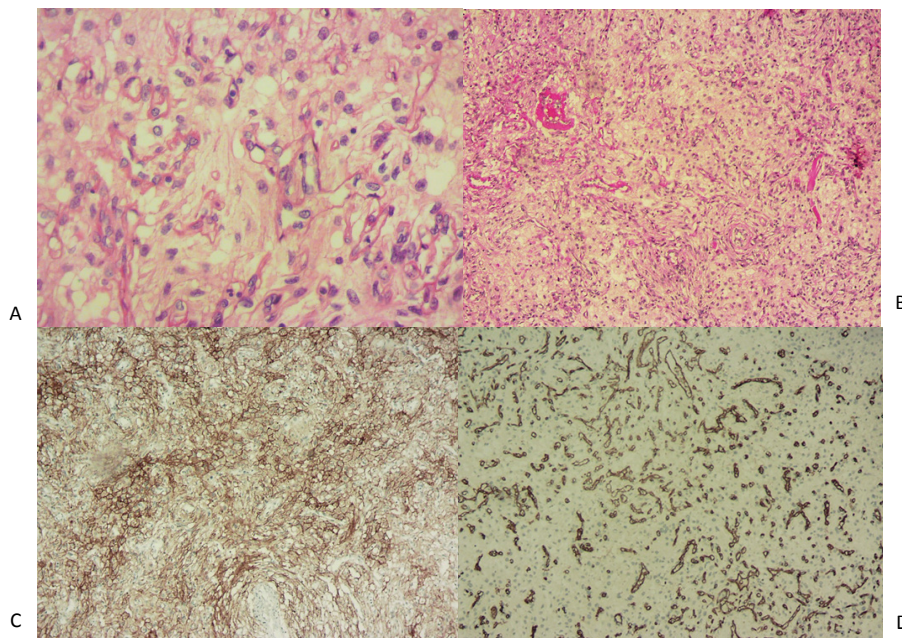


Figure 3. A) Many small vascular spaces intermixed with tumoral meningothelial cells. (H&E x 100). B) This picture illustrates vascular spaces surrounded by tumor cells, some with foamy-looking cytoplasm (H&E x400). C) Diffuse immunoreactivity for Epithelial Membrane Antigen (EMA) (x100). D) CD34 immunostain outlining the vessels, but negative in intervening tumor cells (x100).

Discussion

Meningiomas are common primary tumors of the Central Nervous System (CNS) accounting for about 20%-36% of intracranial tumors with an annual incidence rate of 7.61 per 100,000 individuals with a female preponderance [2, 3]. Brain meningiomas are extra-axial dural-based tumors mostly seen over the cerebral convexities, the superior sagittal sinus, and the flax cerebri. The typical meningioma is a well-circumscribed sessile or lentiform mass with broad-based attachment to the dura on neuroradiology images [4]. Clinical presentations are different based on the tumor location and include signs, such as headaches and seizures. Meningiomas are derived from the meningothelial cells lining the arachnoid mater covering the brain and spinal cord. They display a broad range of histologic patterns manifesting the divergent mesenchymal and epithelial differentiation of the arachnoid cap cells as expressed immunohistochemically by positivity for EMA and vimentin, respectively [5, 6].

In order to recognize a tumor as meningioma, certain histopathologic or immunophenotyping evidence of meningothelial differentiation must be met. Syncytial cells, whorl structures, concentric lamellated calcifications known as psammoma bodies, nuclear clearing, and pseudoinclusions are common histological features that describe a meningioma and are variably expressed in different subtypes. Yet, recognizing tumor cells as me-

ningothelial may not always be easy in all variants. EMA, Claudin-1, CK18, and SSTR2a are among the immunohistochemistry markers that help confirm the meningothelial nature of the tumor.

CCM is a rare and unusual subtype of meningioma categorized as a WHO grade II tumor [5] an unusual subset of meningioma has prominent, clear-cell morphology. It is a wolf in sheep's clothing characterized by benign histologic attributes, but tendency for recurrence (61% Few cases of CCM have been reported in the literature [7, 8] which affect younger patients, occur more often in spinal or cerebello pontine locations and shows a higher recurrence rate. Only few case reports have been described in the literature. The study has been undertaken to document the clinicopathological features of nine cases of CCM, operated at All India Institute of Medical Sciences during 1998 to December 2005. Methods: Clinical information was retrieved from the records of our Neurosurgery Department. The cases were stained with H&E, Periodic Acid Schiff (PAS) Despite having a benign histopathologic appearance, it shows aggressive behavior and a 60% recurrence rate [7]. Unlike classic meningioma, it has a preference for young adults and children but similarly affects females more than males [9, 10]. Most tumors are located in the skull base and a common site of involvement is the cerebellopontine angle of the posterior fossa [7, 8] which affect younger patients, occur more often in spinal or cerebello pon-

tine locations and shows a higher recurrence rate. Only few case reports have been described in the literature.

The study has been undertaken to document the clinicopathological features of nine cases of CCM, operated at All India Institute of Medical Sciences during 1998 to December 2005. Methods: Clinical information was retrieved from the records of our Neurosurgery Department. The cases were stained with H & E, Periodic Acid Schiff (PAS Foramen magnum, the spine, and the filum terminale are also common tumor locations. Among radiologic findings, intracranial CCMs display characteristics of peritumoral edema consistent with angiomatous and microcystic subtypes [10]. The histologic appearance of this variant can be quite deceptive because it usually shows little or no typical features of meningioma. Polygonal to round cells with clear cytoplasm and distinct cellular borders with a bland euchromatic round to oval nuclei with inconspicuous nucleoli form patternless sheets separated by prominent bands of interstitial and perivascular collagen. These bands can form acellular eosinophilic zones explaining why Harkin and Leonard described the first case of CCM as “abnormal amianthoid collagen fibers in meningioma” [11].

The clear cells contain glycogen, which can be shown by a positive Periodic Acid-Schiff (PAS) staining. Sometimes a vague whorl structure is seen, but maybe totally absent. Also, psammoma bodies are indistinct [1]. Features suggestive of malignant behavior, such as necrosis, nuclear pleomorphism, or significant mitosis are not observed. Unlike most meningiomas that express a diffuse positivity for EMA, this variant shows only a focal and faint reaction [9].

Among CNS tumors with histologic features imitating, CCM is hemangioblastoma, microcystic meningioma, clear cell ependymoma, and metastatic carcinoma [8] which affect younger patients, occur more often in spinal or cerebello pontine locations and shows a higher recurrence rate. Only few case reports have been described in the literature. The study has been undertaken to document the clinicopathological features of nine cases of CCM, operated at All India Institute of Medical Sciences during 1998 to December 2005. Methods: Clinical information was retrieved from the records of our Neurosurgery Department. The cases were stained with H&E, Periodic Acid Schiff (PAS Hemangioblastoma, in particular, is sometimes a notorious mimicker. Large foamy stromal cells of this tumor can display a clear cell appearance as a result of lipid-containing cytoplasmic vacuoles, leading to confusion with CCM.

A network of numerous small vascular channels and the lack of transversing eosinophilic collagen help in distinguishing hemangioblastoma. Nuclear pleomorphism and atypia are also usually seen, unlike CCM, which usually shows bland nuclear features. Immunophenotyping helps their discrimination because the stromal cells of hemangioblastoma are reactive for S100, NSE, CD56/NCAM, aquaporin 1, Glut1, brachyury, and inhibin alpha with no immunorexpression for EMA or SSRT2 [9].

Microcystic meningioma is rare WHO grade I variant accounting for 1.6% of intracranial meningiomas with a female predominance [12]. Early terms used to describe microcystic meningioma were ‘Humid’ meningioma, due to its soft and glistening cut surface, and ‘myxomatous’ meningioma [6, 13]. Microcystic meningioma can be pure or may be seen together with angiomatous meningioma [13]. Classic meningiomas also occasionally show focal, but not extensive, microcystic changes [14]. Radiologically, it manifests as a cystic tumor with distinct peritumoral edema and may mimic a glial or metastatic tumor with cystic or necrotic changes [6]. Histologically, microcystic spaces of different sizes create a somewhat loose texture, admixed with a vascular hyalinized stroma, and occasionally show a myxoid background. A closer look shows stellate tumor cells with thin elongated delicate processes surrounding empty clear, eosinophilic, or mucin-containing spaces, resulting in a “spider web-like” appearance [9].

These tumor cells have eosinophilic cytoplasm with some degrees of xanthomatous and clear vacuolated appearance caused by glycogen or lipid accumulation [9]. The majority of neoplastic cells bear uniform nuclei with fine chromatin, but sometimes nuclear atypia is commonly seen without an increase in mitosis. Identification of this variant as meningioma is usually accomplished by a careful and thorough examination of the specimen for foci of recognizable meningotheial cells. The myxomatous changes seen in microcystic meningioma could be a source of the mistake, causing resemblance to chordoid meningioma, chordoma, or myxomatous schwannomas.

The cords of eosinophilic epithelioid cells or the lymphoplasmacytic infiltration seen in chordoid meningioma or chordoma are not found [14]. Key features separating myxomatous schwannomas are their location, along with positivity for S100 and negativity for EMA immunostains. Vacuolated stromal cells of hemangioblastoma sometimes contain large, lipid-containing cytoplasm mimicking microcysts. This feature next to occasional nuclear pleomorphism can emulate microcystic

meningioma; however, hemangioblastoma is negative for EMA. CCM can also have morphologic features overlapping with those of microcystic meningioma. In comparison, tumor cells of CCM have abundant PAS-positive cytoplasm, whereas those of the microcystic subtype have less cytoplasm and a weak PAS-positive extracellular fluid component [8] which affect younger patients, occur more often in spinal or cerebello pontine locations and shows a higher recurrence rate. Only few case reports have been described in the literature.

The study has been undertaken to document the clinicopathological features of nine cases of CCM, operated at All India Institute of Medical Sciences during 1998 to December 2005. Methods: Clinical information was retrieved from the records of our Neurosurgery Department. The cases were stained with H&E, Periodic Acid Schiff (PAS Nuclear pleomorphism and hyperchromasia that are observed in the microcystic subtype are absent in the clear cell variant. Angiomatous meningioma is also a rare grade I WHO tumor accounting for 2.1% of all variants with no aggressive behavior [15]. As its name implies, this variant is a hypervascular tumor. A meningioma with more than 50% vascular component is designated as an angiomatous meningioma [15].

Compared to meningioma, in general, the male to female ratio is higher [15]. The location of origin is similar to classic meningioma usually arising in the cerebral convexities. It also shows distinct peritumoral edema not proportionate to the tumor size, causing clinical suspicion for more aggressive tumors, like anaplastic meningiomas, hemangiopericytoma, malignant gliomas, or metastatic carcinoma [16]. Histologically, the main portion of the tumor is composed of blood vessels in different sizes from small to medium, with thin or thick hyalinized walls.

The vascularity varies from tumor to tumor leading to different histological pictures. Scattered or clusters of meningothelial cells are seen at least focally in the background. Sometimes, foamy looking tumor cells are seen surrounding the blood vessels. Moderate to marked nuclear atypia is commonly present in this tumor. Notably, these are degenerative changes and are not indicative of malignant behavior [17]. The abundant blood vessels at times obscure the meningothelial nature of this tumor and the key distinguishing meningothelial component may not be seen, leading to diagnostic difficulties. Tumor vasculature composed of large and thickened markedly hyalinized vessel channels can simulate a vas-

Table 1. Comparison of the features of three meningioma variants

Features	Clear Cell Meningioma	Microcystic Meningioma	Angiomatous Meningioma
Age and sex	Young adults and children Female>Male	Adults Female>Male	Adults Male>Female
Location	Posterior fossa Cerebellopontine angle Foramen magnum Spine Cauda equina	Cerebral convexities Superior sagittal sinus Flax cerebri	Cerebral convexities Superior sagittal sinus Flax cerebri
Radiology features	Peritumoral edema	Cystic tumor with Peritumoral edema	Hypervascular tumor with peritumoral edema
Prominent Histopathologic features	Collagen bands transversing clear tumoral cells	Stellate tumor cells with thin elongated processes surrounding empty clear spaces	Numerous vessels in different sizes composing more than 50% of the tumor
EMA Immunoreactivity	Focal and faint EMA positivity	Positive EMA in meningothelial foci	Diffuse membranous EMA stain in the background
Histopathologic differential diagnosis	Hemangioblastoma Microcystic meningioma Clear cell ependymoma Metastatic carcinoma	Hemangioblastoma Chordoid meningioma Chordoma Myxomatous schwannoma Clear cell meningioma	Vascular malformation Hemangioblastoma Hemangiopericytomas
Behavior	WHO grade II Recurrence	WHO grade I	WHO grade I

EMA: Epithelial Membrane Antigen; WHO: World Health Organization

cular malformation. Sometimes the tumor vasculature is composed of delicate capillary-sized vessels. When these small vessels are surrounded by foamy-looking tumor cells, they resemble hemangioblastoma. Hemangioblastoma is considered the main histologic differential diagnosis of angiomatous meningioma [15].

Angiomatous meningioma exhibits a similar immunoreactivity pattern to classic meningioma and stains positive for EMA and vimentin, while stromal cells of hemangioblastoma show inhibin alpha and brachyury reactivity. Hemangiopericytomas is another hypervascular tumor that might resemble angiomatous meningioma; however, unlike hemangiopericytomas, its occurrence in the CPA is unusual [17]. Positivity for CD34 is also a feature of hemangiopericytomas but not angiomatous meningioma [18]. Table 1 summarizes the features of the discussed meningioma variants.

Conclusion

Meningioma is a common yet diverse tumor with distinct subtypes, some of which display features obscuring their meningotheial nature causing diagnostic challenges. Clear cell, microcystic, and angiomatous meningiomas are among rare variants with histopathologic characteristics different from classic meningioma. Although such variants may sometimes be hard to recognize as meningioma due to their different morphologic appearances, considering their unique histological characteristics and immunohistochemistry features help in their recognition as meningioma and distinction from tumors with overlapping morphology.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed about the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them.

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Conflict of interest

The authors declared no conflict of interest.

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