Secretory Meningiomas
Characteristic Features and Clinical Management of a Unique Subgroup

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KEYWORDS

• Meningioma • Secretory • Edema • Management

KEY POINTS

- Secretory meningiomas (SM) frequently present with extensive and disproportional peritumoral edema, which can complicate the clinical course and have a direct impact on prognosis and outcome.
- SM represent a benign histologic subgroup defined by a glandular transformation and the appearance of periodic-acidic Schiff–positive pseudopsammomas.
- This subgroup is characterized by an exclusive mutation in the KLF4 gene (K409Q) and a presumably interdependent mutation in the *TRAF7* gene.

INTRODUCTION

Secretory meningiomas (SM) represent a rare variant of the most common benign intracranial brain tumor. Defined by the histologic appearance of eosinophilic glandular formations and periodic-acidic Schiff (PAS)-positive pseudopsammoma bodies, SM are characterized by unique molecular alterations, a disproportional occurrence of reactive peritumoral brain edema (PTBE), and a clinical course that demands for increased awareness for perioperative complications. The frequent presence of extensive peritumoral edema has become a hallmark of SM and can be associated with life-threatening complications.[1] Although the exact pathophysiology of edema formation in SM is still unknown, the study of larger case series and the recent discovery of exclusive molecular alteration have helped to gain new insights into the unique clinical presentation of this distinct meningioma subgroup.

CLINICAL PRESENTATION AND IMAGING

SM are predominantly seen in female patients in the fifth decade. Interestingly, with a female-to-male ratio of 3:1 up to 11:1,[1–6] the prevalence of SM in women significantly exceeds the ratio of 2:1 described for meningiomas in general.[7] Similar to other benign meningioma subtypes, SM exhibit slow extra-axial growth. Usually this slow growth pattern results in the compression of adjacent structures, like cranial nerves or brain parenchyma, which consecutively leads to the clinical presentation depending on the location of the tumor. Besides unspecific headache, symptoms of cranial nerve compression, vertigo, focal seizures, diplopia, or other focal neurologic deficits are observed. Extremely rarely, SM can present with unusual symptoms like a transformed migraine or otitis media-like syndrome.[8,9] The pronounced edema leads to a shorter time to diagnosis and an increased likelihood of symptoms,

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which in turn is associated with higher rate of post-surgical complications (13.6% in asymptomatic vs 21.7% in symptomatic patients), as demonstrated by a study from Zeng and colleagues.[10,11]

On MRI, SM present as an extra-axial mass of dural origin, which appears isointense or hypointense in T1-, and hyperintense or isointense on T2-weighted images, with homogenous enhancement after application of contrasting agents such as gadolinium (**Fig. 1**).[12] SM can cause hyperostosis of the adjacent bone (13%), are frequently located at the skull base, and had intratumoral calcifications in 8.3% of cases.[3] Although other benign meningioma subgroups usually provoke reactive changes in a moderate extent or no changes in the adjacent brain parenchyma, SM are different in this regard. Extensive or even severe hemispheric PTBE was observed in 13% to 64% of all patients (**Fig. 2**, **Table 1**).[1–5] Exceeding the size of its originating tumor, this edema frequently resulted in a significant midline shift of greater than 10 mm and can be made responsible for an increased prevalence of perioperative and intraoperative complications, including progressive neurologic symptoms or loss of consciousness during the postoperative period.[1,3] Interestingly, more severe PTBE was observed in SM presenting with irregular margins, absence of peritumoral rim, and non-skull-base location.[3]

HISTOPATHOLOGY AND GENETICS

Meningiomas are slow-growing extra-axial tumors of the central nervous system, originating from arachnoidal cap cells. Among the 15 different meningioma variants, SM represent a benign subgroup with a prevalence of 1.1% to 4.4% and a unique epithelial and secretory transformation.[1,6,7,13–15] Only in extremely rare cases, an anaplastic variant or a progression to a higher grade (World Health Organization [WHO] II) has been documented.[16,17]

First described by Harvey Cushing and Louise Eisenhardt,[18] SM are defined by glandlike eosinophilic hyaline inclusions within intracytoplasmic lumina, which are lined by microvilli, also called pseudopsammomas.[2] These PAS-positive globules are pathognomonic for the SM subtype and show strong correlation to the characteristic PTBE formation.[1,2] Labeling with carcinoembryonic antigen (CEA) and broad-spectrum cytokeratin (CK) shows characteristic focal CEA and CK positivity surrounding the pseudopsammomas (**Fig. 3**). The secretory characteristics do not correlate to MIB-1 proliferation index.[1] Additional studies further report positivity for the epithelial membrane antigen (EMA), CK7, CK8, as well as certain mucin epitopes, including sialyl-Tn, Tn, CA19.9, CA125, while staining for CK20, CD15, and BerEP4 are negative.[19,20] Because the histologic glandular formation of SM can impose a histopathological characteristic similar to metastatic adenocarcinoma, the differential expression of CK7 and CK20 can aid in the differential diagnosis (CK7+/CK20− for SM, CK7−/CK20+ for adenocarcinoma).[20]

SM exhibit high rates of progesterone and estrogen receptor positivity (33%–100%),[1,4,15] which is in concordance with the female preponderance in the prevalence rate. First, histologic evidence for the unique pathophysiology of SM was described by Paek and colleagues,[21] who demonstrated a link between vascular endothelial growth factor (VEGF) and matrix metalloproteinase -9 expression to the peritumoral edema. Furthermore, additional evidence was found in an increased frequency of CD117-positive mast cells as well as the pronounced pericytic proliferation patterns within the vessel walls (83%–92% of SM) compared with meningotheliomatous meningiomas.[4,5]

Complementing histopathological investigations in unraveling the pathogenesis of SM, a recently published whole-exome sequencing analysis of 16 SM for the first time described that SM are defined by the combination of Kruppel-like factor-4 (*KLF4*) and *Tumor necrosis factor Receptor-Associated Factor 7* (*TRAF7*) mutations.[22] Again emphasizing the unique role of the secretory subgroup, identical heterozygous *KLF4* mutations (K409Q in exon 4 on chromosome 9q) were found in 100% of SM tumors, while were absent in other meningioma subgroups or other types of intracranial tumors. *KLF4* is supposed to play a role in oncogenic activation, tumor suppression, and stem-cell maintenance.[22] The second mutation was described in the *TRAF7* gene. Although *KLF4* was exclusive to SM, *TRAF7* mutations could be detected in 93% of SM and 8% of non-SM (meningotheliomatous and atypical). Influencing signal transduction, *TRAF7* inhibits NF-κB activation and serves as an agonist for the JNK-AP1 pathway. Interestingly, supporting an *NF2*-independent pathogenesis in SM,[23] *NF2* mutations could only be detected in meningiomas with no *KLF4* or *TRAF7* mutations.[22,24] The tight linkage of these 2 mutations highlights the interplay of interdependent mutational incidents in SM cancerogenesis.[22] Furthermore, the discovery of the exclusiveness of the *KLF4* K409Q mutations supports the notion to consider SM as a separate meningioma entity.