Multiple meningioma

Although meningiomas are common intracranial tumors, multiple meningiomas (MMs) are rare entities in patients without neurofibromatosis type 2. Previous studies suggest most sporadic MMs are of monoclonal origin. ¹

Multiple meningiomas with synchronous tumor lesions represent only 1-9% of all meningiomas and usually show a uniform histology. The simultaneous occurrence of different grades of malignancy in these nodules is observed in only one third of multiple meningiomas ².

Usually occurs in one compartment of the neuraxis. Multiple meningiomas in different neuraxial compartments are an even rarer condition with only a few cases reported in the literature ³.

Tumor growth rates in patients with multiple meningiomas did not appear to be higher than reported rates for incidentally found solitary meningiomas. As such, asymptomatic multiple meningioma patients should be managed with clinical and radiographic follow-up ⁴.

Etiology

Multiple meningiomas were initially reported to be related to the NF2 gene mutation with a clonal spread across the meninges ⁵, but might also correspond to mosaic NF2 cases ⁶ ⁷ ⁸.

It can occur as familial multiple meningioma.

Development of multiple meningiomas in the setting of neurofibromatosis involves inactivation of the NF2 gene on chromosome 22, which affects the merlin tumor suppressor protein. Familial multiple meningioma demonstrates autosomal dominant inheritance, but does not typically involve the NF2 gene.

Many sporadic cases are also related to merlin inactivation and exhibit loss of one copy of chromosome 22.

Genomic profiling can provide an unbiased adjunct to traditional meningioma classification and provides a basis for exploring the different genetic underpinnings of tumor initiation and progression. Most importantly, the striking difference observed between sporadic and familial multiple meningiomas indicates that genomic profiling can provide valuable information for differential diagnosis of subjects with multiple meningiomas and for considering the risk for tumor occurrence in their family members ⁹.

Differential diagnosis

After reviewing the literature, Tian et al. concluded that Rosai-Dorfman disease should be considered as a differential diagnosis for lesions mimicking multiple meningiomas, especially in children ¹⁰.

IgG4-related disease is an emerging clinicopathologic entity. Hypophysitis, diffuse thickening of dura, and enlargement of the trigeminal nerve are well-known intracranial involvements of IgG4-related disease. This report of a case of systemic IgG4-related disease is the first to present neuroimaging of apparent supratentorial meningioma-like lesions and thickening and contrast enhancement of the walls of the intracranial internal carotid arteries. It is important to recognize IgG4-related intracranial pseudotumors so that patients do not undergo unnecessary surgical procedures ¹¹.
Outcome

Regression of multiple meningiomas has been observed in patients following cessation of estrogen agonist therapy. However, most cases of meningioma regression after cessation of hormone therapy were reported in patients under high-dose treatments, while doses of estrogen-progestin hormones in Turner syndrome patients aim at reproducing physiologic serum levels.

In the cases of Amelot et al., stopping substitutive hormone therapy did not lead to a decrease in meningioma size. Among the five tumors, three remained stable in size during follow-up, and two increased in size, leading to the resection of one of them after 4 years of follow-up. While they cannot establish the growth pattern of meningiomas during hormone replacement therapy, it is unlikely that cessation of hormone therapy subsequently modified the natural history of those tumors.

Case reports

Two MMs, located frontally and parietaIy on the right side, were surgically removed from a 52-year-old male. Pathological examinations and whole exome sequencing were performed on tumor samples, followed by Sanger sequencing validation.

MMs were diagnosed as secretory and fibrous subtypes, respectively, on histology (WHO grade I) and tumor DNA exhibited distinctive somatic mutation patterns. Specifically, the secretory subtype carried more single nucleotide variant while the fibrous subtype had much higher copy number variation. Besides, the two tumors demonstrated different mutation profiles in predisposing genes and known driver mutations. For example, the secretory subtype had missense mutations in TRAF7 and KLF4, while the fibrous subtype had frameshift deletion of NF2 gene in addition to copy number loss of NF2 and SMARCB1, genetic events that have already been associated with the development of meningiomas. Significantly mutated gene analysis revealed novel mutations of LOC729159 in the secretory subtype and RPGRIP1L and DPP6 in the fibrous subtype. Sanger sequencing validated important point mutations in TRAF7 (c.1678G>A, p.G560S), KLF4 (c.1225A>C, p.K409Q) and CDH11 (c.169T>G, p.W57G). This data suggest the two meningiomas might develop independently in this patient and molecular subtyping by NGS is a valuable supplement to conventional pathology. Further study is needed to ascertain whether these novel genetic events are tumorigenic or simply passenger mutations, as well as their clinical implications.

References

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