Editorial

High grade spinal meningiomas: a rare but formidable challenge

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Meningiomas are tumors arising from the arachnoid cap cells in the leptomeninges surrounding the brain and spinal cord. Spinal meningiomas (SMs) only make up a small fraction of all meningiomas. Albeit the most common spinal intradural tumor, they are 10 to 50 times less prevalent than their intracranial counterparts. The World Health Organization (WHO) classification of tumors of the central nervous system recognizes three grades of meningiomas based on their histopathological features: grade 1 (benign), 2 (atypical), and 3 (malignant) (1).

The absolute majority of SMs are slow growing, benign WHO grade 1, with typically low proliferation (MIB-1) indices (2). With a peak incidence falling between the seventh and eighth decades of life, these tumors are well-known to have a predilection for elderly females. Higher grade SMs (WHO grades 2 and 3) are considerably rarer and have been poorly studied. To date, excluding case reports, there are no more than 10 studies addressing this rare entity (3,4). In a recent systematic review and pooled analysis, only 267 cases of higher grade SMs were reported among a total of 5,641 tumors (5%), with WHO grade 2 SMs (n=243) being 10 times as frequent as grade 3 SMs (n=24). In an analysis of histological subtypes, it was found that atypical SMs accounted for the majority (66.7%), while clear cell and choroid SMs constituted a minority of WHO grade 2 SMs (29.4% and 3.9%, respectively). For WHO grade 3 SMs, the anaplastic (71%) and papillary subtypes (29%) were the only ones reported.

High grade SMs are more frequent in younger individuals compared to lower grade SMs that are more frequent in the elderly (3). Pooled data from two pediatric studies showed that 8 of 24 SMs were WHO grade 2, making up a significantly higher ratio than observed among all patients with SMs (33.3% *vs.* 5%) (5,6). In comparison, two studies on the elderly population (>65 and >70 years) reported three WHO grade 2 SMs in a total of 95 tumors (3.2%) (7,8). In two other reports where 70 younger patients (<50 years) were compared to 127 older ones (>50 years), they demonstrated a relative predisposition of WHO grade 2 tumors among the younger patients (5.7% *vs.* 0.8%) (9,10). Other studies on WHO grade 2 and 3 SMs, have reported significantly lower patients ages compared to the whole patient group of SMs. For instance, in one report, the average age among 12 patients with WHO grade 2 Clear cell SMs, was 28.8 years (11) and in two other reports of mixed WHO grade 2 and 3 tumors, the reported mean age among 16 and 25 patients were 52.8 (12) and 46.6 years (13), respectively. This is in contrast to the average age among the general population of patients with SM, which was estimated at 62.6 years (3). In a recent meta-analysis, high grade SMs were found to be associated with a tenfold increase in the odds of recurrence, when

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compared to WHO grade 1 tumors [odds ratio (OR) =11.1; 95% confidence interval (CI): 4.8–25.0; P<0.001]. In comparison, the likelihood of recurrence in patients with WHO grade 1 SMs is estimated at about 5–6%. Moreover, on survival analysis, these tumors were also found to have a significantly shorter recurrence-free survival as opposed to WHO grade 1 SMs (P<0.001) (14). The same meta-analysis also found a significantly shorter recurrence-free survival among male patients. One explanation may reside in the overrepresentation of high grade SMs among this patient group (14).

A recent article by Wu *et al.* documented the largest known series of WHO grade 3 SMs with six cases. The authors describe the clinical features, management, and outcomes of this extremely rare tumor, considering other similar cases found within the literature (4).

As expected, the average age at diagnosis was low (29 years), and patients of male sex, making up 50% of the cohort, were overrepresented as compared to the general population of patients with SMs (3). Histopathological analyses of tumor samples revealed high mitotic activities, cellular pleomorphism, and necrosis in all specimens. MIB-1 indices ranged from 20% to 60%. On radiology, the tumors mainly demonstrated isointensity on T1-weighted imaging and hyperintensity on T2-weighted imaging. Hetero- or homogenous gadolinium contrast enhancement was detected in all cases. Spinal cord infiltration was seen in one case, illustrating the potential for infiltrative and locally invasive growth of these high-grade tumors. Surgery with Simpson grades 2 (50%), 4 (33.3%), and 5 (16.6%), followed by adjuvant radiotherapy were offered to all patients in the study. Despite this treatment, three of the patients later experienced local recurrence (50%), two developed distant metastases (33.3%), and four ultimately died at an average of 9 months from diagnosis (66.7%). Two patients were still alive after 9 and 11 years.

High grade SMs are rare tumors with little coverage in the literature. Despite the limited sample sizes and the inherent limitations of the studies, detailed reports like the one by Wu *et al.* are of great value to characterize the clinical course and outcomes of this rare tumor subtype. The current literature finds that high grade SMs are aggressive tumors that pose a formidable clinical challenge. Their predilection for younger male patients, potential for high proliferation, locally invasive growth, and high recurrence rates sets them apart from low grade SMs.

Although little is known about the optimal management for these tumors, a multidisciplinary approach involving neurosurgical, neuroradiological, and oncological specialties is often required. Regardless of the treatment approach, high grade SMs, especially WHO grade 3 ones, tend to carry a dismal prognosis with a relatively high risk of local recurrence, distant metastasis, and death. Given the lack of evidence for the utility of different adjuvant therapies in the treatment of these tumors, solid recommendations cannot be presented. Currently, maximizing the extent of tumor resection remains paramount. However, based on the evidence pertaining to intracranial high grade meningiomas, we believe that radiation therapy should be offered (15), especially when Simpson grade 1 or 2 resection is not possible. While the evidence behind the use of chemotherapy for the treatment of high-grade meningiomas is weak or even absent, the improved understanding of molecular mechanisms driving meningioma tumorigenesis has prompted several targeted therapy trials (16).

Although primarily addressing high grade intracranial meningiomas, results of these trials may impact our approach towards high grade SMs, since separate studies on these tumors alone are hardly feasible due to their scarcity. In addition, regardless of the treatment regimen, we argue for the adoption of a thorough watchful waiting strategy with frequent magnetic resonance imaging (MRI) workups, for a timely detection of tumor regrowth or recurrence.

Further investigations are needed to improve our understanding of the outcomes of this rare tumor subtype as well as to develop more effective treatment strategies. Collaborative efforts between clinicians and researchers are pivotal to achieve these objectives and improve the care of patients with high grade SMs.

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