Anaplastic spheno-orbital meningioma: rapid growth after extensive exenteration

Spheno-orbital meningiomas (SOMs) arise from the sphenoid bone and extend into the orbit. These tumours account for approximately 2% of all orbital lesions.[1] Presenting symptoms typically include proptosis, diplopia, or optic neuropathy. Most SOMs are CNS World Health Organization (WHO) grade 1 lesions. These are generally considered benign and slow growing. A small proportion of SOMs consists of CNS WHO grade 2 lesions, whereas CNS WHO grade 3 SOMs are very rarely described. These are often called *malignant meningiomas*. Here we present a CNS WHO grade 3 anaplastic SOM with rhabdoid, sarcomatoid, and epitheloid features that was debulked by means of exenteration.

An 87-year-old male was referred for diplopia and anaesthesia along the left maxillary (V2) nerve. Past medical history included hypertension and benign prostatic hyperplasia. There was no personal history of cancer. Magnetic resonance imaging (MRI) revealed a left-sided sphenoid bone meningioma (Fig. 1A, B). The patient was deemed ineligible for neurosurgical intervention. Thus he was treated with external-beam radiation and hyperbaric oxygen therapy. Despite 2 rounds of treatment, left visual function deteriorated from 20/50 to no light perception by 5 months after initial presentation. He had progressive pain and proptosis, resulting in 6 mm of axial asymmetry. The right eye and orbit remained unaffected. Repeat MRI revealed expansion of the intraorbital soft tissue component of the tumour while the bony component remained stable (Fig. 1C, D). An incisional biopsy of the tumour was performed. Histopathology was significant for a pleomorphic tumour with increased mitotic activity and areas of necrosis. The sample was not diagnostic, however. Given continued expansion of the tumour (Fig. 1E, F) causing intractable pain, a left orbital exenteration was performed (Fig. 2).

Histopathologic analysis of the exenterated tissue showed a pleomorphic tumour. Approximately 25% of the tumour cells showed rhabdoid features including vesicular nuclei, variably prominent nucleoli, eccentrically placed eosinophilic cytoplasm, and globular paranuclear inclusions. In other parts, the tumour appeared cohesive, and some tumour cells showed epithelioid features or eccentric eosinophilic cytoplasm without paranuclear inclusions. Anaplastic foci contained 22 mitotic figures per 10 high-power fields (defined as 0.16 mm^2 each; Fig. 1C). Immunohistochemical analysis of the specimen showed positivity for SSTR2A (somatostatin receptor 2A), usually strongly positive in meningiomas, and AE1/AE3, a pan-cytokeratin stain that can be focally positive in meningiomas (Fig. 1D, F). A few tumour cells stained positive for epithelial membrane antigen (Fig. 1E). The tumour had lost expression of H3K27me3 (Fig. 1G). Nuclear expression of *BAP1* and *INI1* was retained, indicating the wild type of these genes. Based on histopathologic criteria, the final diagnosis was a CNS WHO grade 3 anaplastic SOM with rhabdoid, sarcomatoid, and epithelioid features.

Postoperatively, the patient was placed on daily oral steroids for pain control and inflammation. There was rapid new tumour growth along his infraorbital rim, and he died 3 months later.

We describe a case of a anaplastic SOM, CNS WHO grade 3, with rhabdoid, sarcomatoid, and epithelioid features as well as loss of H3K27me3 expression. The initial diagnosis of meningioma was inferred by the radiographic features on MRI. However, the diagnosis cannot be confirmed without pathologic specimens.

Meningiomas show a broad spectrum of histopathologic subtypes. The histochemical markers most often used in the diagnosis of meningiomas are SSTR2A and epithelial membrane antigen. The monoclonal antibody for SSTR2A is especially helpful in establishing the diagnosis of meningioma when there is poor cellular differentiation. SSTR2A is highly sensitivity and specific for meningiomas; nearly all meningiomas express this marker.

WHO grading of CNS tumours has traditionally been based exclusively on histologic features. A WHO grade 3 meningioma is defined by 20 or more mitotic figures in 10 consecutive high-power fields, wherein a high-power field measures 0.16 mm^2. Frank anaplastic features such as sarcomatous, carcinomatous, or melanomatous appearance also qualify as a WHO grade 3 lesion. But WHO grading of CNS tumours is no longer restricted to histologic grading. Molecular markers provide powerful prognostic and diagnostic information. The presence of a telomerase reverse transcriptase (*TERT*) gene promoter mutation and (or) a homozygous deletion of the *CDKN2A* or *B* gene also constitutes a tumour that is a WHO grade 3 meningioma.[2] This case was consistent with an anaplastic meningioma, WHO grade 3, given the high mitotic rate ($\geq$20 per high-power field) and the presence of carcinomatous and sarcomatous features. Thus no further molecular testing was performed for tumour grading.

Historically, rhabdoid and papillary morphology qualified a CNS meningioma as WHO grade 3. However, up to 50% of meningiomas with rhabdoid features lack aggressive histologic features.[3] Therefore, while papillary and rhabdoid features often are seen in combination with aggressive features, grading of these tumours is not done based on rhabdoid or papillary architecture alone. Meningiomas with rhabdoid morphology often harbour breast cancer 1 (*BRCA1*)-associated protein (BAP1) inactivation.[4] BAP1-negative meningiomas have reduced time to recurrence compared with those that retain BAP1 function. Further, a subset of

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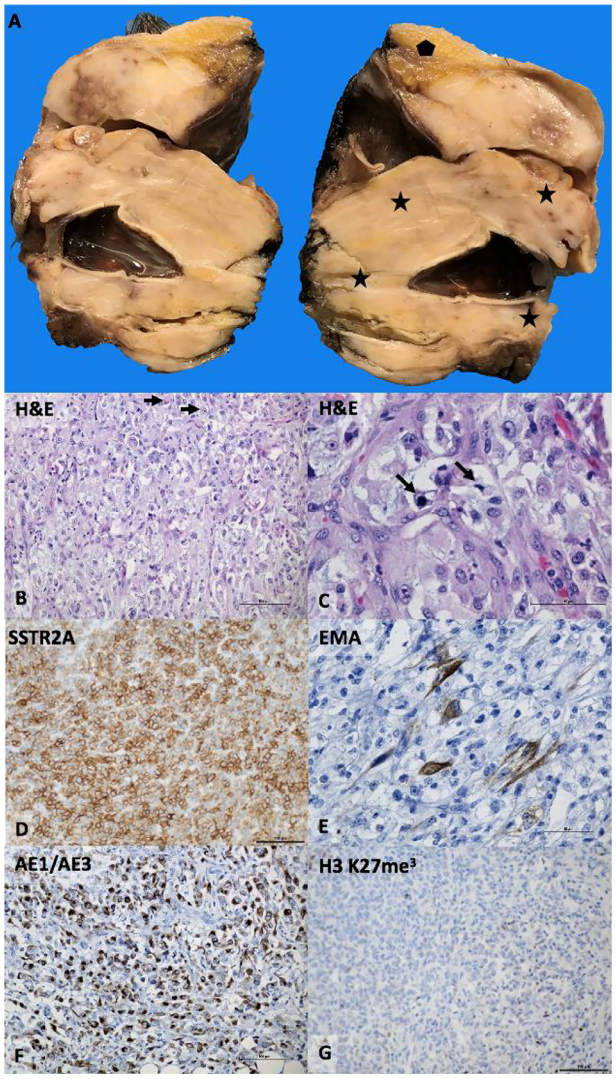

Fig. 1—(A) Macroscopic aspect of the left eye following midline section. Almost the whole orbit is invaded by tumour (stars); only small areas of orbital adipose tissue are still present (pentagon). The grey areas of solid tumour show small tan areas of hemorrhages and small yellow areas of necrosis. (B) Microscopic aspect of the anaplastic meningioma, CNS WHO grade 3. Many tumour cells have a clear cytoplasm and appear epithelioid, sarcomatous, or rhabdoid (arrows) (H&E stain, magnification × 20). (C). Prominent nucleoli are noted in almost all the tumour cells. Arrows indicate mitotic figures. The mitotic index was varying, being as high as 22 mitotic figures per 10 high-power fields (H&E stain, magnification × 40). (D) The vast majority of tumour cells is immunopositive for SSTR2A (magnification × 20). (E) A few of the tumour cells are immunopositive for epithelial membrane antigen (EMA, magnification × 40). (F) Many tumour cells can be seen that are immunopositive for cytokeratin (AE1/AE3, magnification × 40). (G) Lack of expression for H3K27me3 (magnification × 20).

patients with BAP1-deficient rhabdoid meningiomas harbour germ-line *BAP1* mutations.[4] Germ-line mutations in *BAP1* result in a tumour predisposition syndrome that confers a high risk for developing other tumours, including uveal melanomas, cutaneous melanomas, pleural or peritoneal malignant mesotheliomas, and renal cell carcinomas. Most patients with germ-line *BAP1* mutations develop malignancies earlier in life. Testing for *BAP1* inactivation in meningiomas displaying rhabdoid histomorphology provides prognostic information for the patient. Additionally, it can help guide genetic counselling and cancer surveillance for family members of affected individuals.

Histochemical and molecular markers are important in the diagnosis and prognosis of meningiomas. In this case, where the diagnosis was ascertained with the exenterated tissue and the prognosis was clinically evident, not all immunostains and genetic tests were performed. In retrospect, SSTR2A staining may have assisted in diagnosing the tumour at the time of incisional biopsy. We would encourage the use of SSTR2A stain during investigation of poorly differentiated CNS tumours. Further, in cases where the diagnosis is made but the prognosis is not clear, testing for a *TERT* mutation or *CDKN2A/B* homozygous deletion can offer additional clinical information by predicting an increased risk of recurrence and progression. Loss of H3K27me3 nuclear expression, as occurred in this case, is associated with a potentially worse prognosis.[2]

Spheno-orbital meningiomas are typically benign and slow growing. The triad of symptoms commonly seen in these tumours is proptosis, diplopia, and optic neuropathy. The average age at presentation is 51 years, and it does not, typically, alter life expectancy.[5] Approximately 90% of SOMs are CNS WHO grade 1. CNS WHO grade 2 lesions account for nearly the entire remaining 10% of SOMs and have relapse rates between 30%–50%.[5–7] CNS WHO grade 3, or anaplastic, SOMs are rare. Many published series find no cases. The case series citing the highest proportion of CNS WHO grade 3 SOMs found them to represent 10.5% of all SOMs, although this was from a large quaternary centre and only represented meningiomas that required resection.[7] These SOMs are a surgical challenge because of the presence of critical ophthalmologic and neurovascular structures within the spheno-orbital region. Anaplastic meningiomas are aggressive, have a poor prognosis, and have a median overall survival of 1.5 years.[8] Given their aggressive nature, they may require surgical debulking for curative or palliative reasons. Approximately half of CNS WHO grade 3 meningiomas arise de novo, whereas the other half are the result of anaplastic transformation of lower-grade meningiomas.[6]

The primary treatment for anaplastic meningiomas is gross total surgical resection and adjuvant radiation.[9] The literature on chemotherapy is not yet conclusive. Resection of the orbital component of SOMs necessitates a multidisciplinary team including both neurosurgeons and orbital surgeons. Radiographic studies to assess for recurrence should be considered postoperatively each 6 months for 2 years and yearly thereafter.[9] However, as was the case for our patient, CNS WHO grade 3 SOMs carry a poor prognosis for survival.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2022.07.004.

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Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.