Case Lessons

What did we learn from methylation analysis for further prognostic information in treatment of Meningiomas

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Introduction: In the past few years, key genetic and epigenetic alterations that are strongly associated with clinicopathologic features, such as localization and prognosis, have been identified in meningiomas, and could represent targets for molecularly driven therapies[1,3]. The second most frequently reported genetic abnormalities in meningiomas after 22q loss are deletions of 1p and 14q[2]. They are highly associated with increasing histologic grade and play an important role in meningioma tumor progression.

Key words: DNA methylation; prognostic biomarkers; subtypes of meningioma

Case report: 73 years old, from Kosova, was admitted for left temporal-parietal lesion. The patient has no past medical history. Two years history of difficulty pronouncing words associated with short memory loss.
MRI: left temporal-parietal lesion, iso to hypointense on T1 and hyperintense T2/FLAIR sequence. The lesion enhances heterogeneously. Radiological features were in favor to Choroid plexus carcinoma.
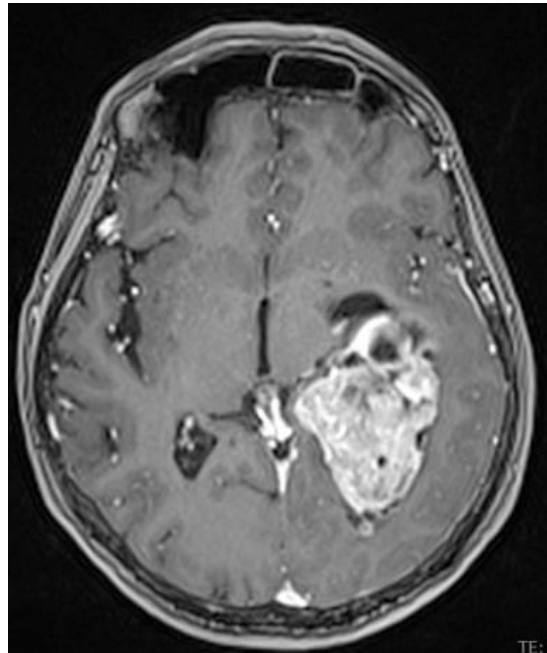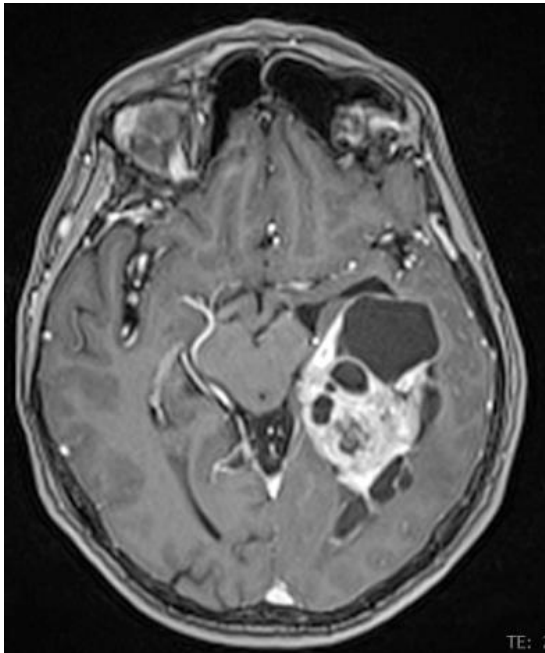
Figure1: MRI before the surgery

On June 2nd 2023, the patient underwent surgery; below the post-operative brain MRI
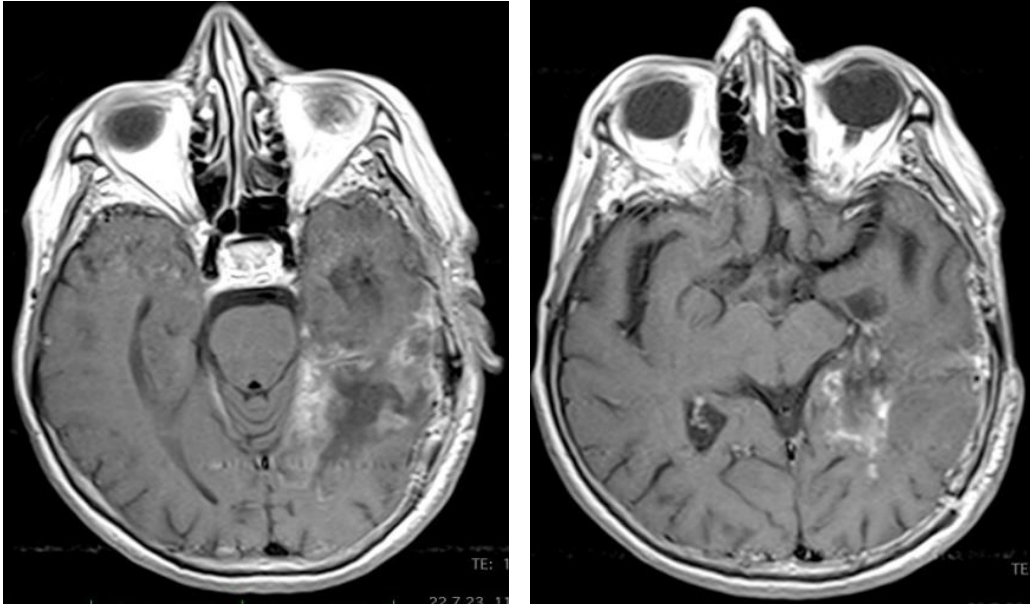
Figure 2: Postoperative MR image demonstrates surgery-related changes and GTR resection of tumor.

Intraoperative impression was of a Choroid plexus carcinoma versus HGG due to necrosis and brain invasion.

NEUROPATHOLOGY REPORT

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Specimen(s) Received
1: Stained slides (x2 H&E) and paraffin block (x1) - APS-2332 A1
2: Stained slides x11 (S23-13127 A1)

MICROSCOPIC DESCRIPTION
The histology shows fragments of a moderately cellular tumor composed of tumor cells with round, oval nuclei, frequent pseudo inclusions and eosinophilic cytoplasm. There is mild to moderate nuclear pleomorphism. The tumor cells are arranged in lobules, papillae and show scattered pseudopsammoma bodies and numerous whorls around hyalinized vessels. In regions the tissue separates imparting a papillary pattern. There are focal microcystic changes and frequent blood vessels with hyalinized walls.

Mitosis are counted at 1 per 10 HPF. There are foci of necrosis. There are foamy macrophages with cholesterol clefts and areas of collagenization. CNS tissue is identified in the periphery of the tumour and it is affected by crushed artefacts and fragmentation in regions. No choroid plexus tissue or ependymal lining is appreciated

The immunohistochemical panel performed at the referral laboratory was reviewed. Immunostaining for GFAP is negative in the tumour cells and highlights the adjacent brain tissue: there is mainly a well-defined margin but areas of entrapped GFAP positive cells with in the tumour and nodules of tumour in brain tissue are seen supporting brain invasion. The tumour cells

are diffusely positive for EMA and focally positive for Desmin, SMA, s100 and AE1/AE3. The tumour cells are mainly negative for SOX10, Synaptophysin and CD99. Immunostaining CD34 highlights mainly the blood vessels. The Ki67 proliferation index is moderate.

HISTOLOGICAL DIAGNOSIS
Meningioma with brain invasion, WHO CNS Grade 2

COMMENT: The histological features with brain invasion qualify this as grade 2 meningioma. There is also a focal papillary architecture as well as necrosis although the mitotic activity is not elevated. In view of these features methylation array analysis for further prognostic information will be carried out this case.

REVISED FINAL DIAGNOSIS
Prof Maria Thom (Honorary Consultant Neuropathologist)

Integrated diagnosis: Atypical meningioma, CNS WHO grade 2, with intermediate risk of early recurrence
Histology: Atypical meningioma, CNS WHO grade 2
Methylation profile: Meningioma, intermediate
Integrated meningioma risk score: 5 (intermediate risk of recurrence)
MGMT promoter (Illumina array): Unmethylated
SUPPLEMENTARY COMMENT
The DNA methylation v12.6 classifier has classified the tumor as meningioma, intermediate. The chromosome copy number profile, derived from the Illumina array data, shows loss of chromosome 1p and 6q, but no evidence of chromosome 14q loss (several other alterations are noted). Histologically the tumor corresponds to a CNS WHO grade 2 atypical meningioma due to evidence of brain invasion and some cytoarchitecturally atypical features.
Based on a combination of histological and molecular features, predicted risk of early recurrence for this tumor is intermediate.
Layered three-tiered score for this meningioma:
Histological CNS WHO grade: score 1
Methylation class: score 2
Loss of chromosomes 1p, 6q, 14q: score 2
Integrated meningioma risk score: 5 (intermediate risk of recurrence)
Integrated meningioma risk score rationale: See appended documents below.

SUPPLEMENTARY MOLECULAR REPORT
Brain classifier v12b6 research report:
Super family: meningioma [Calibrated score: 0.99]
Family: meningioma [Calibrated score: 0.99]
Class: meningioma, intermediate [Calibrated score: 0.99]
Subclass: meningioma, intermediate B [Calibrated score: 0.98]
Methylation class description Brain Classifier 12.6:
The "mc Meningioma intermediate A/B" cases typically show 22q deletions/NF2 mutations and additional CNVs, mostly deletions of 1p and 10. Prognosis in this subclass is intermediate, similar to WHO grade 2. Integration of meningioma subclasses into the brain tumor classifier is under development, thus, the specific meningioma classifier should be consulted in parallel. Integration of histology, methylation and CNVs can further increase prognostic accuracy.
MGMT promoter status prediction (MGMT-STP27 logistic regression model):

unmethylated

Discussion: DNA methylation is an epigenetic modification that plays a crucial role in gene expression regulation. Methylation patterns in DNA have been shown to be associated with various subtypes of meningioma. DNA methylation markers have been identified as potential diagnostic and prognostic biomarkers.[1,2]

As had been noticed in our case Ki67 proliferation index is moderate, so on based on the study "Correlations between genomic subgroup and clinical features in a cohort of more than 3000 meningiomas " published on JNS is strong prognostic factors in worse prognosis and high recurrence of meningeomas[5]. This is the main study involving more than 3000 meningiomas and followed them according the genomic testing.[5]

In " Molecular diagnosis and treatment of meningiomas: an expert consensus (2022)' deletion of chromosome 1p is the second most common CNA identified after 22q loss and is mainly associated with higher WHO grade.

As shown in our case loss of chromosome 1p and 6 q without evidence of 14q associated with other histological and molecular features predicted intermediate risk for early recurrence and play an important role in meningioma tumor progression[5]. Meningiomas, according to the embryologic origin of their dural attachment, display differences in pathological diagnosis and genetic abnormalities.[2] Whereas in our case there is no dural attachment so DNA methylation analysis can be a useful tool as prognostic biomarker.

Follow-up of meningiomas with 1p loss could be done every 6 months within 5 years (Evidence 3; Grade III recommendation)[4].

Conclusion:

Using a rigorous and comprehensive approach, studies [expand] previously described correlations between genomic drivers and clinical features, enhancing our understanding of meningioma pathogenesis, and laying further groundwork for the use of targeted therapies [1,5]. Meningioma DNA methylation groups identify biological drivers and therapeutic vulnerabilities.[1,2]

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