Clinical and molecular predictors of malignancy in meningiomas

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In 1990 a 25-year-old female underwent a complete exeresis of a grade I meningioma. 20 years later, a new MRI revealed a local recurrence, and a second resection was performed. A third resection was carried out in 2011. Despite RT and radiosurgery, a new local recurrence was diagnosed in 2012, with systemic metastases in the lung, kidney and spleen. In May 2014, after a neurological deterioration, patient died.

Although rarely, it is known that even a "benign" WHO grade I meningioma may have an aggressive behavior (Asioli et al., 2007), but predictors of malignant behavior are currently not clear.

Clinical predictors

The most important predictors of malignant behavior are tumor grade and histological features. Higher tumor grade (atypical or anaplastic) correlate with a worse prognosis. High cellularity, high mitosis rate, cellular heterogeneity and nuclear pleomorphism predict an aggressive behavior. Male gender, young age, some subtypes (papillary, clear cell, chordoid) and specific locations (convexity) are negative prognostic factors.

Molecular Markers & Cytogenetic

Monosomy of chr. 22 is the most common genetic alteration for sporadic meningiomas and more than half have alterations in neurofibromatosis type 2 (NF2) gene. NF2 gene alteration is a very early event; it encodes for merlin, a protein involved in inhibition of cell proliferation and cell motility. Other genes on chromosome 22 (as BCR) could be involved in meningioma progression.
Loss of 1p is the second most frequent chromosomal abnormality. This deletion is correlated with an increased risk of recurrence (Ketter et al., 2007). Genes involved are not actually known (Linsler et al., 2014). 1p- is often associated with other deletions in recurrent meningiomas, as 19q or 14q: altered genes are involved in cell proliferation (as NDGR2), cell cycle, IGF and WNT signaling, TGF pathway and apoptosis regulation. Rb pathway is also involved in meningioma malignancy: inactivation of p16 and p14 (encoded by CDKN2A, chr. 9) is a frequent event in anaplastic meningiomas and recurrences (Kim et al., 2014).
Finally, the loss of 6q and deletions on chromosome 10 (PTEN) are associated with a trend to recur.

In addition to the described alterations, other chromosomal abnormalities are involved in malignant evolution. These alterations (Fig.1) affect cell cycle genes (e.g. control of the G1/S-phase and p53-pathways). Others abnormalities are related to intracellular signaling pathways, such as downregulation of WNT pathways, upregulation of IGF (Wrobel et al., 2005) and loss of the inhibitory effect of TGF Beta. Other altered genes (eg. E-cadherin) are involved in cell adhesion. Even a disregulation in angiogenesis (eg. VEGF) or in metabolic ways (eg. GLUT1) may explain an aggressive behavior of a "benign" meningioma.

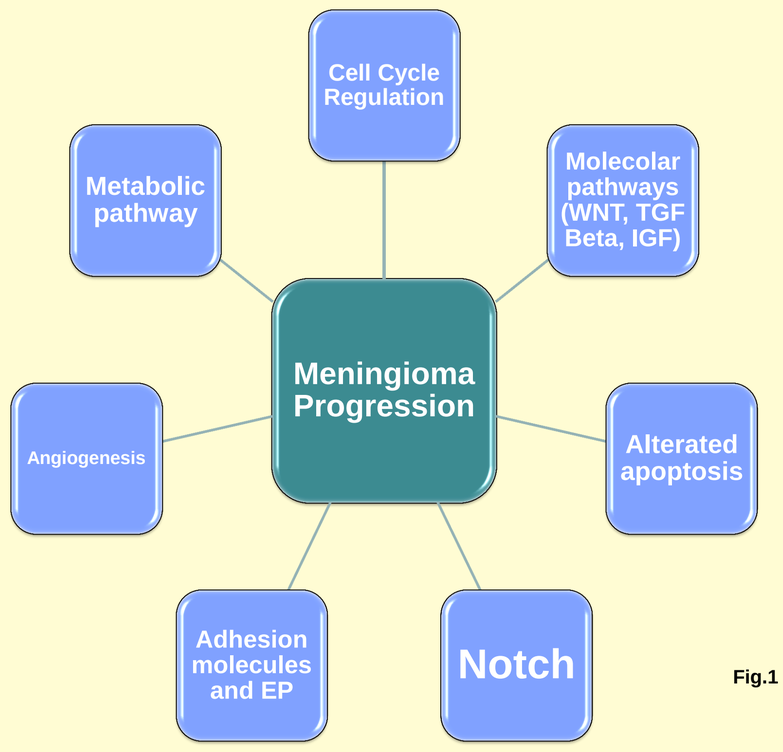

Fig.1

A genetic model of tumor progression

The development of an aggressive behavior could depend on the accumulation of mutations (Zang et al., 2001; Ketter et al., 2007).
Loss of chr. 22 is usually a primary event in both benign and malignant meningiomas. The main gene involved is NF2, but a second gene on chr. 22 was hypothesized by several authors (e.g. BAM2, MN1, LARGE). In some cases a primary mutation independent from chr 22 has to be considered. The progression to aggressive phenotypes is characterized by the loss of 1p and/or by deletions involving more chromosomes (chr.14, 18, 19, 10, 6).

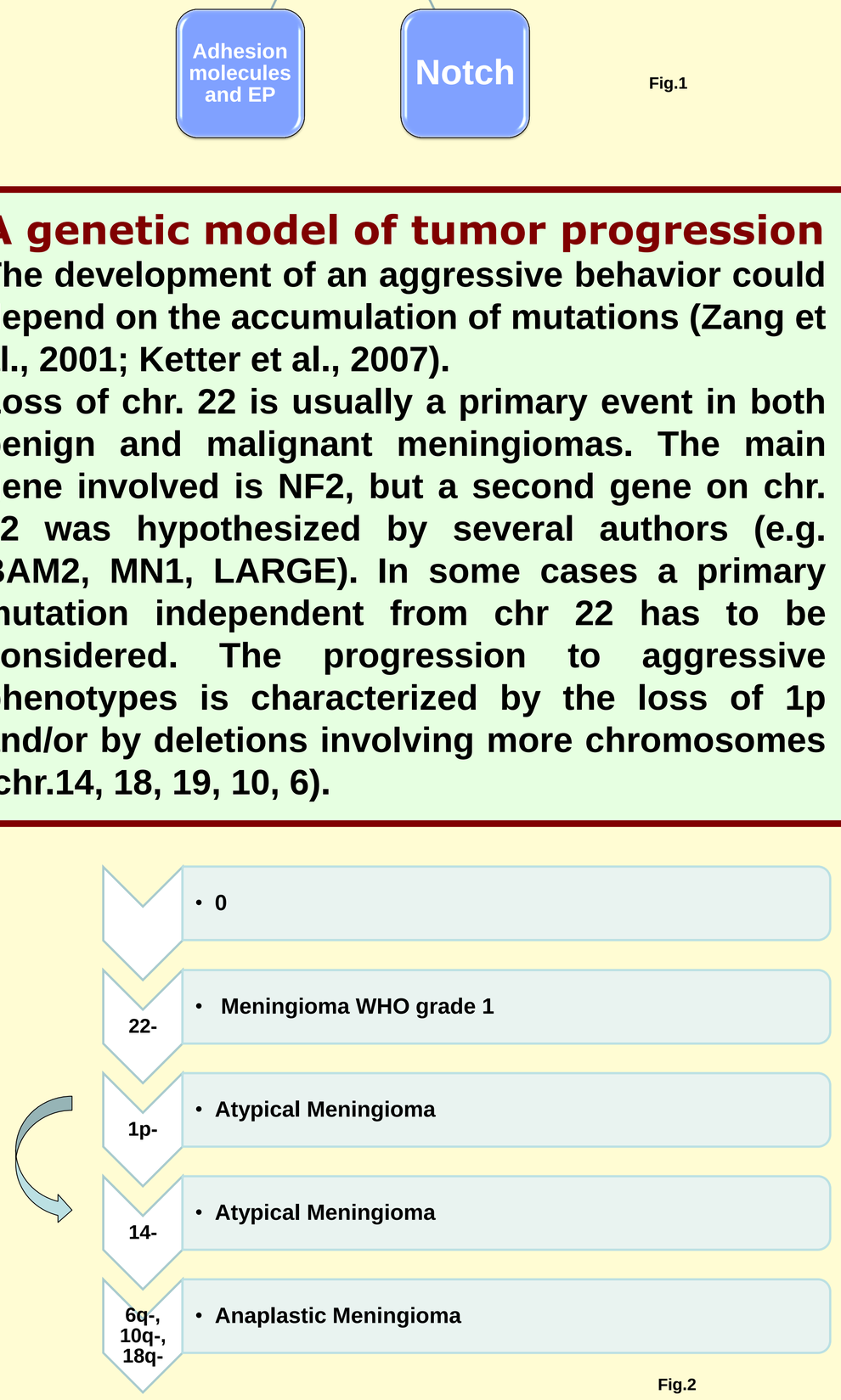

Fig.2

Conclusion

For some low grade meningiomas, histological grade does not match with the biological behavior. Grade I meningiomas with aggressive phenotype share molecular features with higher grade meningiomas, as loss of 1p and multiple chromosomal deletions, cell cycle genes dysregulation or alterations in intracellular signaling pathways. Considering this, some authors (Pfisterer et al., 2008, Aarhus et al., 2011) have proposed a meningioma classification based on molecular features. As it is happening for gliomas, meningioma classification should consider molecular features as well as histological characteristics.