H3K27M-mutant pineal parenchymal tumor

Fomchenko et al. reported the clinical presentation, surgical management, whole-exome sequencing (WES), and clonality analysis of a patient with a radically resected H3K27M-mutant pineal parenchymal tumor (PPT) and spine metastases consistent with Pineal parenchymal tumor of intermediate differentiation (PPTID). They identified somatic mutations in H3F3A (H3K27M), FGFR1, and NF1 both in the original PPT and in the PPTID metastases. They also found chromosome 12q amplification containing CDK4/MDM2 and chromosome 17 loss of heterozygosity overlapping with NF1 that resulted in biallelic NF1 loss. They noted a hypermutated phenotype with increased C>T transitions within the PPTID metastases and 2p amplification overlapping with the MYCN locus. Clonality analysis detected three founder clones maintained during progression and metastasis. Tumor clones present within the PPTID metastases but not the pineal midline tumor harbored mutations in APC and TIMP2. While the majority of H3K27M mutations are found in pediatric midline gliomas, it is increasingly recognized that this mutation is present in a wider range of lesions with a varied morphological appearance. The present case appears to be the first description of H3K27M mutation in PPTID. Somatic mutations in H3F3A, FGFR1, and NF1 have been suggested to be driver mutations in pediatric midline gliomas. Their clonality and presence in over 80% of tumor cells in our patient's PPTID are consistent with similarly crucial roles in early tumorigenesis, with progression mediated by copy number variations and chromosomal aberrations involving known oncogenes and tumor suppressors. The roles of APC and TIMP2 mutations in progression and metastasis remain to be investigated [1)].

1)
Fomchenko EI, Erson-Omay EZ, Kundishora AJ, Hong CS, Daniel AA, Allocco A, Duy PQ, Darbinyan A, Marks AM, DiLuna ML, Kahle KT, Huttner A. Genomic alterations underlying spinal metastases in pediatric H3K27M-mutant pineal parenchymal tumor of intermediate differentiation: case report. J Neurosurg Pediatr. 2019 Oct 25:1-10. doi: 10.3171/2019.8.PEDS18664. [Epub ahead of print] PubMed PMID: 31653819.