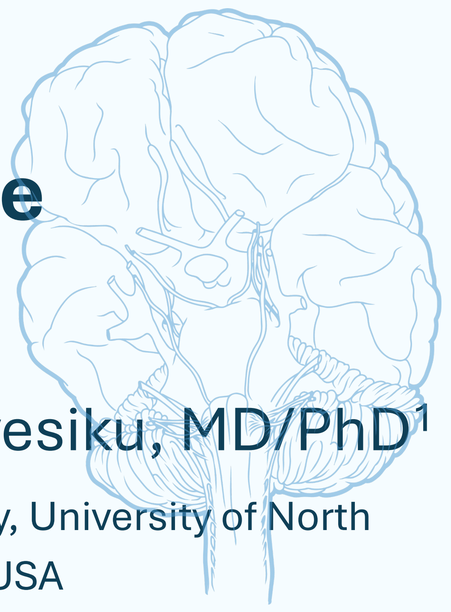
Expanding the Molecular Signature of Papillary Craniopharyngioma: FGFR2 Fusion in a BRAF-Wildtype Suprasellar Neoplasm



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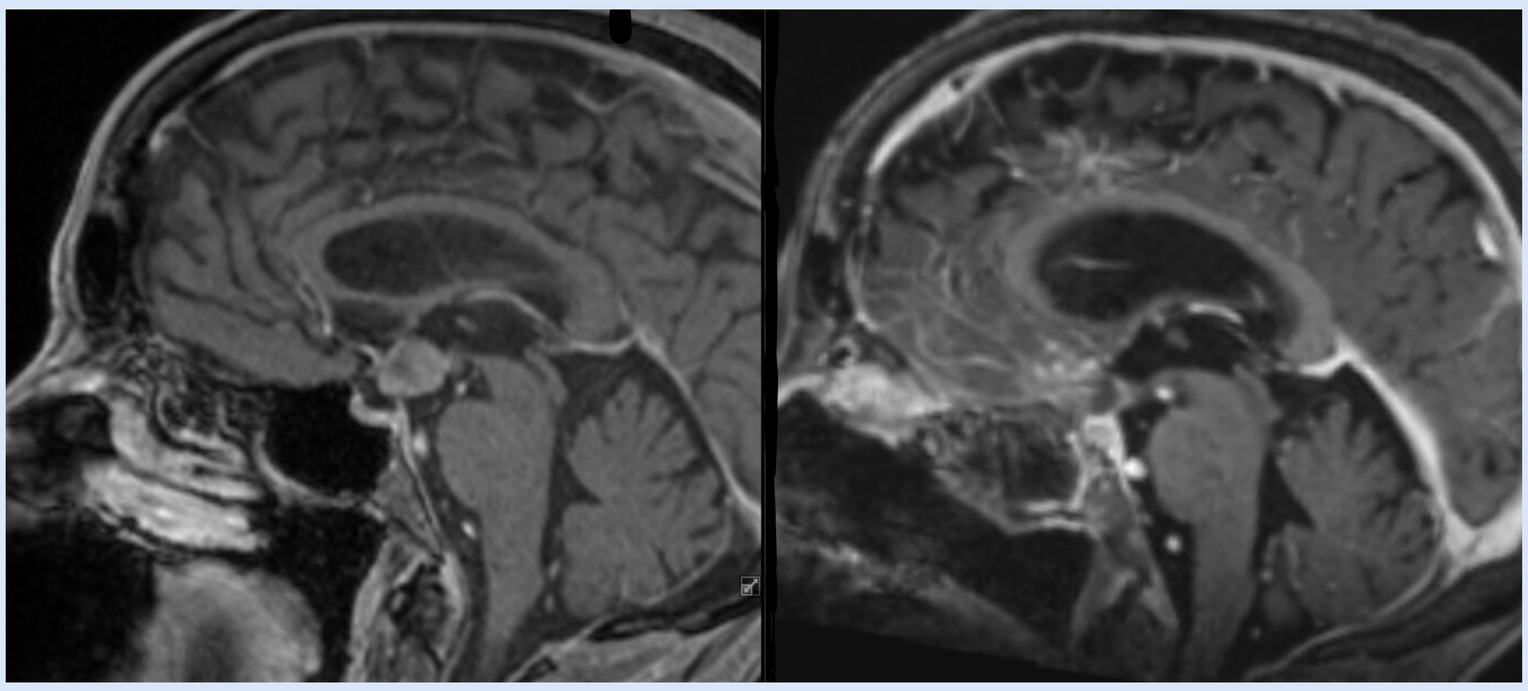
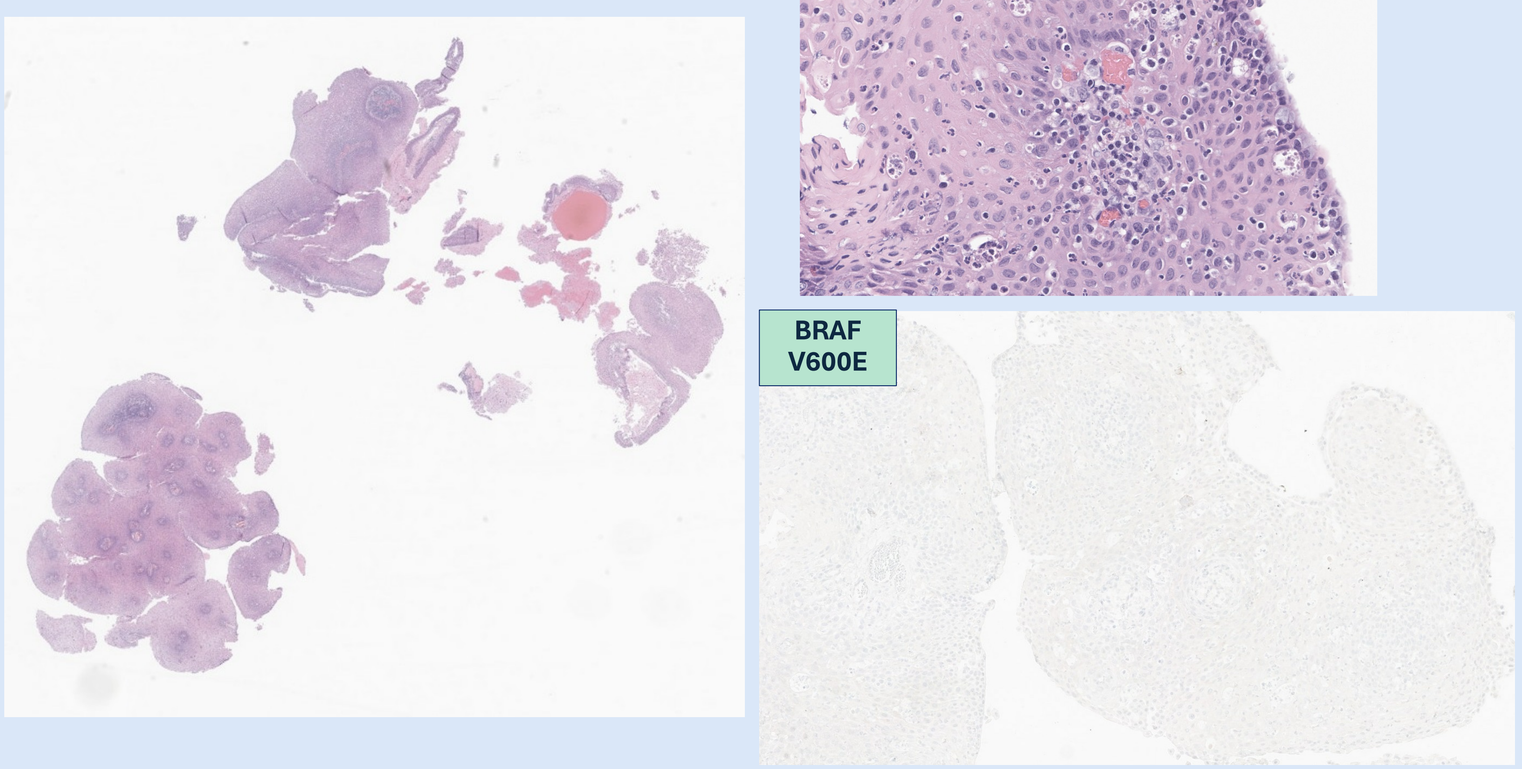
Illustrative Case

A 74-year-old female with a history of hormone receptor-positive breast cancer in remission presented with progressive visual symptoms including bitemporal hemianopsia and worsened visual acuity.



Pre-operative (left) and post-operative (right) MRI brain, sagittal views, T1 post-contrast sequence. 1.7 x 1.4 x 1.2-centimeter cystic suprasellar mass with peripheral enhancement, mass effect on the posterior optic chiasm and optic tracts, as well as involvement of the pituitary stalk. No residual tumor post resection.

The patient underwent endoscopic transsphenoidal resection with a good radiographic outcome. Clinically, her vision slowly improved and she developed panhypopituitarism as largely expected with stalk manipulation and neoplasm origin. She did experience delayed cerebral vasospasm on postoperative day eight which improved after intraarterial verapamil treatment over the course of two sessions.



*Histopathologic examination of the tumor demonstrated **papillary architecture** (left), non-keratinizing squamous neoplasm with goblet cells and adjacent reactive gliosis (top right). Immunohistochemistry was **negative for BRAF V600E** (bottom right), nuclear β-catenin, and TTF-1. Next-generation sequencing identified a complex **FGFR2-USO1 and FGFR2-G3BP2 fusion**. No BRAF or CTNNB1 mutations were detected. Methylation profiling using the Heidelberg and NCI/Bethesda classifiers yielded a consensus match to papillary craniopharyngioma.*

Discussion

Papillary craniopharyngioma is defined by BRAF V600E mutation in nearly all cases, with large genomic studies reporting this alteration in >94% of tumors and no recurrent FGFR2 fusions identified. BRAF-wildtype papillary craniopharyngiomas are exceedingly rare, and the presence of an FGFR2 fusion in this context has not been previously reported. FGFR2 rearrangements have been described in other epithelial neoplasms and in rare BRAF-wildtype craniopharyngiomas, but not in the papillary subtype. The integrated histopathologic, molecular, and epigenomic findings in this case support a diagnosis of papillary craniopharyngioma, CNS WHO grade 1, with an atypical molecular profile.

Conclusions

This case highlights the importance of comprehensive molecular and epigenomic profiling in the diagnosis of sellar region tumors, particularly when canonical driver mutations are absent. The identification of an FGFR2 fusion in a BRAF-wildtype papillary craniopharyngioma expands the known molecular spectrum of these tumors and raises the possibility of a novel or unclassified entity. Further research is needed to clarify the clinical significance, prognostic implications, and potential for targeted therapy in craniopharyngiomas with noncanonical molecular alterations.

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