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Commentary

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Management of Craniopharyngiomas in the Era of Molecular Oncological Therapies: Not a Panacea

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Abbreviations: ACP, adamantinomatous; PCP, papillary craniopharyngioma.

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Papillary craniopharyngiomas (PCPs) in the pediatric population are vanishingly rare (see brief review by Borrill et al. [1]); the vast majority in this age group being of the adamantinomatous (ACP) subtype. As alluded to by the authors [2], the major difference between these 2 histologies are usually mutually exclusive mutations in *BRAF* (specifically V600E, activating signaling via the MEK/MAPK pathway) and *CTNNB1* (causing hyperactivation of the WNT signaling pathway) respectively [3]. Both of these pathways have been implicated in tumorigenesis of a vast spectrum of benign and malignant tumors. It is worth noting, however, that coexistence of both *BRAF* V600E and *CTNNB1* mutations have been described in some ACPs [4]. Unfortunately in this case it was not possible to reanalyze the original tissue specimens obtained in childhood to elucidate whether this patient had a PCP or mixed ACP/PCP from the start presenting in childhood (more likely), or an initial ACP followed by a metachronous PCP arising later in adulthood. Transformation of an ACP to a PCP has never been described.

Traditionally, both craniopharyngioma subtypes have been treated with neurosurgery with or without adjuvant or salvage radiotherapy, with the challenge being to achieve maximum tumor volume reduction while minimizing hypothalamic damage. As expected, this objective is often not met, with a significant majority of survivors faced with long-term hypothalamic morbidity, including panhypopituitarism, adipsia, obesity (and its ensuing cardiometabolic morbidity), sleep, behavioral and temperature dysregulation, none of which are easily treated. Both subtypes have the additional propensity for repeated episodes of progression or recurrence, thereby causing further hypothalamo-pituitary damage.

Upcoming evidence- and consensus-based guidelines developed in the UK for pediatric ACPs with the endorsement of the Royal College of Pediatrics and Child Health (RCPCH), UK Children's Cancer and Leukemia Group (CCLG), and the British Society for Pediatric Endocrinology and Diabetes (BSPED) will hopefully help address some of these issues, set standards of care, and minimize variation in practice. Importantly, these guidelines will recommend risk stratification by degree of hypothalamic involvement to determine the initial management strategy (particularly complete vs partial surgical resection) and subsequent follow-up of such tumors. Contrastingly and unsurprisingly, due to their extreme rarity, no such guidelines exist for pediatric or adult PCPs.

However, unlike ACPs, where no successful molecular treatments targeting the WNT/CTNNB1 pathway have as

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yet been successfully translated into clinical practice, the presence of the *BRAF* V600E mutation in PCPs provides a clear target for both BRAF (eg, vemurafenib, dabrafenib) and MEK inhibitors (eg, trametinib, selumetinib) [5]. Both of these molecular therapies, either alone or in combination, have the ability to inhibit growth of a wide range of tumors associated with the *BRAF* V600E mutation apart from PCPs, including metastatic melanoma, non–small cell lung cancer, papillary thyroid carcinoma, low-grade astrocytoma, Langerhans cell histiocytosis, and plexiform neurofibromas [6]. In children, the majority of experience in neuro-oncology has been in the treatment of the last 3 diagnoses, and there have been no previous case reports of using BRAF or MEK inhibitors to treat papillary craniopharyngiomas in the pediatric age group.

The aim of any molecular-based therapy is of course to minimize the short- and long-term side effects observed in less targeted treatments such as surgery and radiotherapy. Apart from the additional hypothalamo-pituitary morbidity arising from both tumor and treatment as discussed above, other adverse outcomes arising from the latter treatment modalities include local alopecia, fatigue, cerebrovascular events (from secondary moyamoya disease to full-blown strokes), and cognitive and neurological deficits. Theoretically, molecular treatments such as BRAF and MEK inhibitors should have fewer side effects, but, as alluded to by the range of tumors amenable to such treatments, these pathways affect a wide variety of biological processes.

As discussed by the authors, common side effects from BRAF and MEK inhibitors include rashes, dry skin, photosensitivity, fever, diarrhea, arthralgia, fatigue, and liver dysfunction [7]. Other less common side effects include cardiac dysfunction, hypertension, interstitial lung disease, and retinopathies. Of particular interest in patients with craniopharyngiomas are the side effects of hyperglycemia and hyponatremia. Although less common, the significance of hyperglycemia in patients with craniopharyngiomas, a group already significantly predisposed to hypothalamic obesity, insulin insensitivity, and type 2 diabetes, who may have additionally received prophylactic glucocorticoids for neurosurgery, should be given due consideration. The mechanism of the former is not elucidated as insulin, the primary glucose-regulating hormone, does not signal down the MEK/MAPK pathway. Similarly, the side effect of hyponatremia, thought to be secondary to renal toxicity [8], cannot be underestimated in a group of patients prone to central diabetes insipidus (with or without concomitant adrenocorticotropin deficiency) and hypothalamic dysfunction.

Lastly, the optimal regimen for treating PCPs with BRAF or MEK inhibitors remains unknown. As illustrated here, even in the presence of these treatments tumor progression can still occur, with the risk of further toxicities from other therapies. The duration of treatment required also remains to be determined, and experience from other tumors such as low-grade astrocytomas indicates that cessation of treatment may be followed by rebound regrowth of the tumor. Good quality data on the efficacy of such treatments for a rare clinical entity can only be obtained through international, collaborative trials, and it would be reasonable to include the vanishingly rare entity of pediatric papillary craniopharyngiomas in such studies given the existing experience in using such treatments for other pediatric tumors.

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Additional Information

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