BRAF-V600E mutation in pediatric and adult glioblastoma

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With the recent identification of the BRAF rearrangement/duplication in pediatric pilocytic astrocytomas (PA), there has been renewed interest in the contribution of the BRAF gene to brain tumorigenesis. While the signature KIAA1549:BRAF fusion represents a common alteration in PA, activating mutations in the BRAF kinase gene (V600E) are more commonly observed in other glioma histological subtypes and malignancy grades. In this regard, we and others have previously found relatively few BRAF-V600E mutations in PA (<10% cases), whereas BRAF-V600E mutations are frequently identified in pleomorphic xanthoastrocytomas (WHO grades II and III; 50%–65% cases),8–10 gangliogliomas (20%–75% cases),6–10 and to a lesser frequency in diffuse gliomas,1,5,11 dysembryoplastic neuroepithelial tumors,10 desmoplastic infantile astrocytoma/ganglioglioma,10 and atypical teratoid/rhabdoid tumors arising in a background of either ganglioglioma or pleomorphic xanthoastrocytoma.7 In contrast, approximately 5% of adult high-grade gliomas, as well as a distinctive subset of adult diffuse low-grade gliomas, harbor BRAF-V600E mutations.6,11,12 Since most BRAF-V600E-positive glial neoplasms are encountered in young persons, we investigated the frequency of this mutation in pediatric high-grade gliomas.

Immunohistochemical analyses were conducted using a BRAF-V600E-specific antibody on tissue microarrays containing pediatric gliomas from 2 different institutions (Washington University and University of California, San Francisco) (clone VE1; Spring Bioscience; dilution 1:100). Using this method, none of the low-grade pediatric gliomas (n = 75; 67 WHO grade I PAs, 6 WHO grade II astrocytomas, 1 WHO grade II oligodendroglioma, and 1 WHO grade II mixed oligoastrocytoma) harbored a BRAF-V600E mutation. Of note, 23 of the PA tumors (34%) arose outside of the cerebellum. In contrast, 3 of 11 WHO grade III anaplastic astrocytomas (27%) and 3 of 25 (12%) WHO grade IV glioblastomas (GBMs) were BRAF-V600E immunoreactive. All of the BRAF-V600E-immunopositive glioblastomas were primary GBM.

To determine whether the low frequency of BRAF-V600E mutation observed in pediatric GBM was comparable to that observed in their adult counterparts, we examined 39 adult GBMs by immunohistochemistry. Three of these adult GBM tumors (7.7%) were BRAF-V600E immunoreactive: Two of these were giant-cell variants, and the expression appeared to be limited to the “monstrous cells”. Similar to their pediatric counterparts, all of these BRAF-V600E-immunopositive tumors were primary glioblastoma. Of note, these BRAF mutant tumors were generally found in younger patients (35–43 years with a mean age of 39 years compared to 27–79 years with a median age of 55.4 years for BRAF-V600E-immunonegative tumors; P = .0495). None of the BRAF-V600E-immunopositive tumors harbored the isocitrate dehydrogenase-1 (IDH1) R132H mutation. In addition, 2 of these tumors arose in women, despite a slight overall male preponderance in our series (25 males:14 females). The results of our series are comparable to the documented frequencies reported in the literature for adults (9/152 cases; 5.9%).6,12–14

While there were few BRAF-V600E-positive adult GBMs in our series, one of these patients is currently alive at 4.5 years. This finding is intriguing because at least 2 of the previously reported adult GBMs also exhibited prolonged survival (3 years).11,12 It is possible that BRAF-V600E mutations are either encountered in rarer, more favorable subtypes of GBM or that they confer different biological properties to these glial neoplasms, translating to improved clinical outcomes. In this regard, BRAF-V600E mutations have been reported to occur in over 50% of epithelioid GBM.12 This uncommon histologic variant appears to be more common in young adults,12 and is equally represented in males and females in one series as opposed to the male predominance typically seen in rhabdoid GBM.15 However, whether or not adult patients carrying BRAF-V600E mutations have a survival advantage remains to be established using additional patient cohorts.

Coupled with encouraging therapeutic studies demonstrating that BRAF and MEK inhibitors exhibit therapeutic efficacy in BRAF-V600E; Ink4a-deficient murine malignant glioma preclinical studies,16 the potential preselection of patients with GBM by BRAF-V600E mutation for BRAF/MEK inhibitor treatment may prove beneficial in combination with other therapies.
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