BRAF V600E mutation

Mutational analysis of the BRAF gene (BRAF), especially BRAF V600E, is gaining much importance in neurooncology practice due to its diagnostic, prognostic and therapeutic implications. This genetic alteration has been described in a wide morphological spectrum of central nervous system tumors. In a report Purkait et al., describe a BRAF V600E-mutated tumor with divergent morphological appearance comprising of anaplastic pleomorphic xanthoastrocytoma and astroblastoma. Both of these tumor entities are extremely rare and a combined morphology has not been described till now [1)].

The efficacy of vemurafenib is variable in different organs with CNS being particularly prone to resistance. Extrinsic factors, such as ERK- and PI3K-activating factors in CSF, may mediate BRAF inhibitor resistance in the CNS [2)].

Combined pleomorphic xanthoastrocytoma (PXA) and ganglioglioma (GG) is an extremely rare tumor, with fewer than 20 cases reported. Cicuendez et al report a case of combined PXA-GG in an 18-year-old man with a history of seizures. The tumor showed necrosis and the BRAF V600E mutation on histological examination, with no evidence of tumor recurrence 1 year after gross-total resection. The BRAF V600E mutation was present, which suggests that both cell lineages may share a common cellular origin [3)].

Case series

2016

Data from 35 patients diagnosed with glioneuronal tumors (GNTs), including 24 gangliogliomas and 11 dysembryoplastic neuroepithelial tumors, were retrospectively collected. DNA was extracted from GNTs tissues and BRAF V600E mutation was examined by DNA sequencing. The correlations between BRAF V600E mutation and clinical features were analyzed.

Totally, BRAF V600E mutations were detected in 11 patients with GNTs, the rate of mutation were 33.3% and 27.3% in GGs (8/24) and DNTs (3/11), respectively. The probability of BRAF V600E mutation in females (7/12, 58.3%) was significantly higher than that in males (4/23, 17.4%) (P=0.022). Moreover, patients with BRAF-mutated GNTs had a significantly wider variety of seizure types compared to GNTs with BRAF wild-type status (P=0.027). However, no significant correlation between the BRAF status and certain clinical features, such as age of seizure onset, duration of epilepsy, age at surgery, location of the tumor and postoperative seizure free, were observed.

Zhang et al., demonstrated the presence of BRAF V600E mutation in Chinese epileptic patients with GNTs, which was significantly correlated with gender and multiple seizure types. Large sample studies and long-term follow-up are required for further confirmation [4)].

A single institution, retrospective cohort of 225 melanoma patients was analyzed to determine if BRAF-V600 mutational status was associated with brain metastases. Eighty-three of the 225 patients (37%) had BRAF-V600 mutations. At initial diagnosis, BRAF-V600 mutations were associated with younger age (P ≤ 0.001), higher proportion of females (P = 0.0037), higher AJCC stage (P = 0.030), regional lymph node involvement (P = 0.047), and family history of cancer (P = 0.044). Compared to BRAF-WT, BRAF-V600 patients had an increased risk of brain metastases in multivariate analysis (OR = 2.24; 95% CL = 1.10-4.58; P = 0.027). However, BRAF-V600 patients treated with a selective BRAF inhibitor (BRAFi) had a similar risk of brain metastases compared to BRAF-WT patients (OR = 1.00; 95% CL = 0.37-2.65; P = 0.98). Moreover, treatment with BRAFi significantly prolonged the time from initial diagnosis to brain metastases diagnosis (HR = 0.30; 95% CL = 0.11-0.79; P = 0.015). Compared to other tissues, the brain was the most frequent site of metastases in BRAF-V600 patients without BRAFi (42±7%). The frequency of brain metastases was lower in BRAF-WT and BRAF-V600 patients with BRAFi (25±4% and 25±8%, respectively). The proportion of patients with brain metastases as the only site was 40%, 60%, and 0% in the BRAF-WT, BRAF-V600 without BRAFi, and BRAF-V600 with BRAFi groups, respectively. This study provides evidence on the clinical importance of BRAF-V600 mutations and BRAF inhibition in the progression to melanoma brain metastases [5].

2014

To evaluate the expression of the BRAF V600E mutated protein and its association with activation of the mammalian target of rapamycin (mTOR) pathway, immunophenotype and clinical characteristics in GNTs, Prabowo et al., investigated a cohort of 174 GNTs. The presence of BRAF V600E mutations was detected by direct DNA sequencing and BRAF V600E immunohistochemical detection. Expression of BRAF-mutated protein was detected in 38/93 (40.8%) gangliogliomas (GGs), 2/4 (50%) desmoplastic infantile gangliogliomas (DIGs) and 23/77 (29.8%) dysembryoplastic neuroepithelial tumors (DNTs) by immunohistochemistry. In both GGs and DNTs, the presence of BRAF V600E mutation was significantly associated with the expression of CD34, phosphorylated ribosomal S6 protein (pS6; marker of mTOR pathway activation) in dysplastic neurons and synaptophysin (P < 0.05). In GGs, the presence of lymphocytic cuffs was more frequent in BRAF-mutated cases (31 vs. 15.8%; P=0.001). The expression of both BRAF V600E and pS6 was associated with a worse postoperative seizure outcome in GNT (P < 0.001). Immunohistochemical detection of BRAF V600E-mutated protein may be valuable in the diagnostic evaluation of these glioneuronal lesions and the observed association with mTOR activation may aid in the development of targeted treatment involving specific pathogenic pathways [6].

BRAF V600 mutation in melanoma

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