LETTER TO THE EDITOR

Pineal Region High-Grade Glioneuronal Tumor With a Novel ZBTB10-NTRK3 Fusion

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To the Editor:

Tumors of the pineal region constitute <1% of all central nervous system tumors. Due to their rarity, their histopathologic features and genomic alterations are poorly understood. Here, we report a 47-year-old man with a high-grade pineal glioneuronal tumor treated with gross total resection and external beam radiation, but who died 2 months after initial presentation due to an aspiration event. Histologic examination of the tumor revealed cords, nests and sheets of cells with eosinophilic cytoplasm, multinuclear processes and ovoid nuclei. Tumor cells were variably immunoreactive for glial and neuronal markers. Next generation sequencing revealed a novel, in-frame fusion of the first 2 exons of zinc finger and BTB domain-containing protein 10 (ZBTB10) with exon 13 of neurotrophic kinase receptor 3 (NTRK3). This novel fusion is predicted to result in activation of NTRK3 signaling. In summary, this study describes a rare high-grade glioneuronal tumor in the pineal region and represents the first report of a NTRK3 fusion or alteration in glioneuronal tumors.

Pineal region tumors are rare, accounting for 0.2% of all central nervous system tumors in the United States Central Brain Tumor Registry from 2011 to 2015 (1). While germ cell tumors, pineal parenchymal tumors, and gliomas comprise the most common tumor types arising within the pineal region, many other entities including glioneuronal tumors have been reported but are poorly characterized (2). To the best of our knowledge, only 4 high-grade glioneuronal tumors have ever been identified in the pineal region (3–6), and their genomic alterations are not known. Over the past few years, rare glioneuronal tumors have been found to harbor neurotrophic kinase receptor (NTRK) fusions. The NTRK gene family consists of 3 members, NTRK1–3, that encode tropomyosin receptor kinases A–C (TRKA, TRKB, and TRKC) that are highly expressed in the central and peripheral nervous systems during development. Tumorigenic gene fusions involving NTRKs result from chromosomal rearrangements that contain the 3′ end of the NTRK gene, with the tyrosine kinase domain, fused to a 5′ sequence of another gene that frequently contains a dimerization domain. Several TRK kinase inhibitors are emerging as therapeutic options, under-scoring the importance of identifying tumors with high NTRK activity (reviewed in [7]). Here we describe a case of a high-grade pineal glioneuronal tumor with a novel ZBTB10-NTRK3 fusion.

The patient was a 47-year-old man with Marfanoid habitus, Crohn’s disease, dysphagia, hypertension, and mitral valve prolapse who began to experience headache, memory loss, nausea, and decreased balance 2 months before admission. MRI showed a heterogeneously enhancing mass, measuring up to 28 mm, that was centered in the pineal and projected into the left thalamus and third ventricle (Fig. 1A, B). The patient underwent a suboccipital craniotomy with a gross total resection. He received 2400 cGy external beam radiation therapy between postoperative weeks 4 and 6. While being treated, the patient aspirated leading to a cardiac arrest, and he died.

Hematoxylin and eosin-stained sections of the resection specimen show cords, nests and sheets of cells with multipolar processes, oval nuclei and eosinophilic to clear cytoplasm (Fig. 1C, D). Brisk mitotic activity, microvascular proliferation and confluent areas of necrosis are present (not shown). No rosettes or papillary structures are seen. GFAp expression is variable, with most areas of tumor strongly positive (Fig. 1E). Neurofilament (Fig. 1F), NeuN, and synaptophysin are more focally positive (not shown). Olig2, CD56, NSE, S100, and vimentin are more uniformly positive (not shown). Mutated IDH1 (R132H), mutated histone H3 (K27M), chromogranin, epithelial membrane antigen, smooth muscle actin, pan-cytokeratin, CAM5.2, HMB45, and CD10 are negative.
in the tumor cells, and ATRX is retained (not shown). A Ki-67 stain shows a markedly elevated proliferation index, focally up to ~50% (not shown). Based on these histologic properties, a diagnosis of high-grade glioneuronal tumor was rendered.

RNA fusion analysis was performed using an anchored multiplex PCR approach with a custom 17-gene panel. A novel ZBTB10-NTRK3 fusion, involving the first 2 exons of ZBTB10 fused in frame to exon 13 of NTRK3, was identified (Fig. 1I). The fusion transcript contains the amino terminus of ZBTB10, with its BTB domain intact, and the carboxyl terminus of NTRK3 with its PTK domain. The zinc fingers of ZBTB10 are absent. Interrogation of COSMIC, the St. Jude PeCan Data Portal, and the Jackson Laboratory Tumor Fusion Gene Data Portal did not reveal this fusion in any neoplasms. In potential support of a role for this fusion, the tumor cells are strongly and diffusely positive with a pan-NTRK antibody (Fig. 1G). Furthermore, break-apart fluorescence in situ hybridization (FISH) probes showed rearrangement with gains in the NTRK3 region (Fig. 1H). FISH with other DNA probes showed deletions within chromosome 1p36 and chromosome 19q13 in this tumor (not shown). At least 2 cases of pineal tumors with similar morphology, immunophenotype (including synaptophysin expression), and chromosome 1p and chromosome 19q alterations have been reported (8, 9).

The adult pineal consists of lobules, with pinealocytes and astrocytes, separated by fibrovascular septae (10). During human fetal development, 2 cell types can be distinguished, with smaller cells temporarily positive for S100 becoming progressively replaced by larger cells positive for NSE and morphologically identifiable as pinealocytes (11). Pinealocytes are neuroepithelial cells with endocrine and sensory receptor cell specializations (12). Pineal parenchymal tumors exhibit neuroendocrine differentiation, but may exhibit focal glial or neuronal differentiation (13). This underscores the phenotypic plasticity of pinealocytes. The pineal tumor described in this report consists of primitive cells with both glial and neurocytic features, suggesting that this tumor may have arisen from a less differentiated progenitor. Although the majority of the tumor was located in the pineal and appeared to infiltrate adjacent thalamus, the possibility remains that the tumor has an extrapineal origin and invaded the pineal.

In a large, multi-institutional cohort of pediatric gliomas, NTRK fusions were found in high-grade, hemispheric gliomas that lacked histone H3 (K27M or G34R/V) and IDH1/2 mutations (14). Over the past few years, glioneuronal tumors with BCAN-NTRK1, STRN3-NTRK2, WNK2-NTRK2, ARHGEF2-NTRK1, TLE4-NTRK2, SLMAP-NTRK2 fusions have been reported (reviewed in [7]). The current case is the first report of an NTRK3 fusion in a glioneuronal tumor. Interestingly, NT-3 and TRKC are expressed in the pineal during rodent development (15), and NT-3 is required for the sympathetic innervation of the pineal that is essential for regulation of melatonin synthesis and release (16). Although oncogenic fusions involving ZBTB proteins have rarely been reported, the BTB domain may provide a sub-
strate underlying a mechanism of oncogenesis in this tumor (17).

In summary, we present a case of a novel pineal region high-grade glioneuronal tumor in an adult man that does not fit into the 2016 WHO classification system. Review of our large institutional cohort of 227 pineal region tumors, resected over 25 years, reveals 2 additional high-grade glioneuronal tumors with similar morphological features (not shown). Additional studies are needed to determine if the ZBTB10-NTRK3 fusion is recurrent in these tumors. Given the wide array of 5’ partners for NTRK fusions, the possibility exists that other fusion partners may be present. Future studies are also warranted to delineate the cell of origin and the contributions of these genomic alterations in the pathogenesis of this pineal neoplasm.

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