LETTER TO THE EDITOR

Brain
Pathology

Temporal lobe myxoid glioneuronal tumor, *PDGFRA* p.K385L-mutant with DNA methylation confirmation

Myxoid glioneuronal tumor (MGNT) is a newly recognized tumor type in the fifth edition of the WHO Classification of CNS tumors (CNS WHO 2021) (1). Histologically similar to dysembryoplastic neuroepithelial tumor (DNT) or, less commonly, to rosette-forming glioneuronal tumor, MGNT is currently defined by the presence of specific mutation in the platelet-derived growth factor receptor α (*PDGFRA*) gene, namely, p.K385 mutation (changing K385 from a basic amino acid to a hydrophobic amino acid, usually L or I). MGNT was initially described in the septum pellucidum, septal nuclei, corpus callosum and lateral ventricle/periventricular white matter (2–4), but has recently been reported in the midbrain tectum by our group (5). We now add to the literature a second example of a non-septum pellucidum location for this tumor in the temporal lobe, with both the mutation and confirmation by DNA methylation testing.

This 10-year-old female was managed for seizures for 9 months before presenting to our pediatric specialty hospital. Magnetic resonance imaging demonstrated a non-enhancing T2-hyperintense lesion in the anterior right temporal lobe measuring up to 2.0 × 2.7 × 1.5 cm (Figures 1A and S1). The tumor was cortically based, extending anteriorly to the periphery of the anterior mesial temporal cortex and superiorly into the amygdala. The tumor extended superficially into the periventricular white matter with thin septations pointing toward the ventricle but showed no intraventricular extension and did not involve the septum verum. The tumor manifested no surrounding edema or mass effect. Radiologic features were considered classic for DNT, although the multicystic/bubbly appearance that is often seen in DNT was not present. The lesion was stable on serial imaging over the next several months. However, seizure frequency and intensity increased despite antiepileptic drug treatment, prompting the decision to resect the tumor. A right temporal lobectomy was performed.

Histologic examination showed a mucin-rich tumor containing columns of uniform small round oligodendroglia-like cells with delicate chromatin (Figure 1B,C). Scant floating neurons were present (Figure 1C, inset), with typical larger nuclei, prominent nucleoli, and modest cytoplasm; neuronal origin of the floating neurons was confirmed on NeuN immunohistochemical stain (Millipore) (Figure 1D). Mitotic activity was absent and MIB1 was less than 1%. Although diagnostic consideration was given to several low-grade epilepsy associated tumors, CD34 immunohistochemical stain (Ventana) was negative, Rosenthal fibers or eosinophilic granular bodies were absent, and dysmorphic neurons/ganglion cells were not present, ruling out polymorphous low-grade neuroepithelial tumor of the young (PLNTY), pilocytic astrocytoma or ganglioglioma, respectively. Given the histology, tumor location and the radiologic findings, the initial histologic diagnosis was DNT. Location within the temporal lobe allowed assessment for possible focal cortical dysplasia in the adjacent cortex of this seizure-producing lesion. The associated cortical resection specimen showed abnormal cortical architecture with disruption of tangential neuronal lamination on hematoxylin and eosin (Figure 1E), with better appreciation on NeuN immunostain (Figure 1F). There were no radial architectural abnormality, dysmorphic neurons, or balloon cells.

Next-generation sequencing (NGS) mutation panel demonstrated a dinucleotide *PDGFRA* somatic mutation, resulting in *PDGFRA* p.K385L alteration. The tumor was negative for clinically significant mutations or gene fusions reported in diffuse gliomas, including *IDH1/2*, histone genes *H3F3A*, *H3F3B*, *HIST1H1C*, *HIST1H3B*, or *HIST1H3C*. NGS was further negative for alterations in *BRAF*, *FGFR1*, *2*, *3*, *NF1*, *PIK3CA*, *and PIK3R1*, genetic alterations often found in low-grade glial or glioneuronal tumors such as pilocytic astrocytoma, ganglioglioma, PLNTY or DNT; the complete list of genes covered in our 300+ gene fusion and mutation panels have been reported in our previous publication (5). *PDGFRA* p.K385L alteration was the sole genetic alteration identified and is likely to result in an oncogenic, gain-of-function mutation that causes constitutive activation of the kinase domain in the absence of ligand (4,6).

Global DNA methylation has been shown to reduce interobserver variability and improve diagnostic precision in CNS tumor diagnosis (7,8). We, therefore, performed DNA methylation profiling using standard methods, described in detail in our prior publication (5). The output .idat files were uploaded to the German Cancer Research Center (DKFZ) web interface (https://www.molecularneuropathology.org/
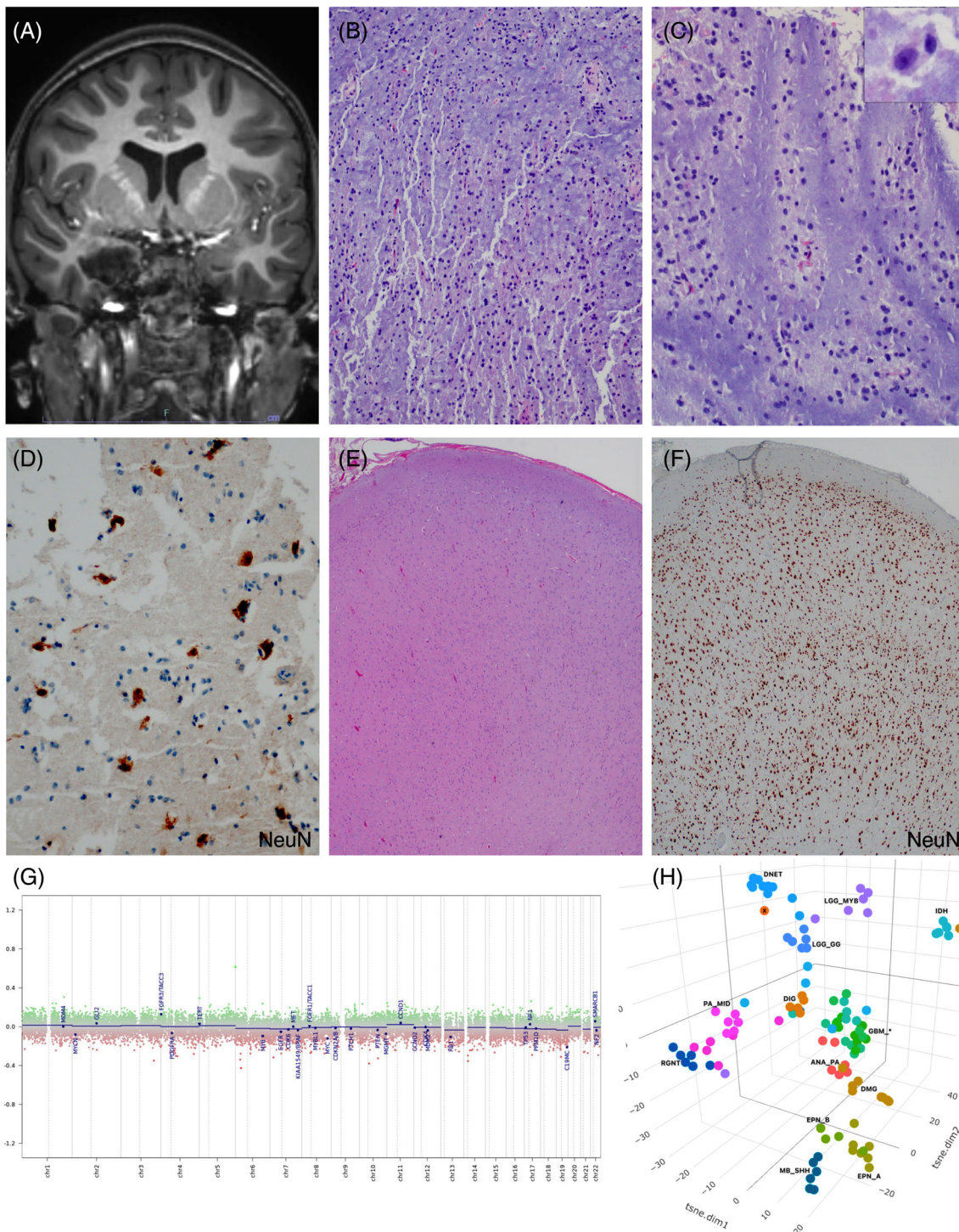
FIGURE 1 (A) Coronal T1-weighted MRI demonstrates a T1-hypointense right temporal mass. (B and C) (Hematoxylin and eosin) Low and medium power view of the small oligodendroglial-like cells embedded in a copious mucinous background. (C) (Inset) Occasional neurons floating in pools of mucin showed neuronal histology with somewhat larger neurons and prominent nucleoli. (D) Occasional cells were positive for NeuN confirming the neuronal nature of cells ("floating neurons"). (E and F) H&E and NeuN immunostained sections showing disruption of the hexa-laminar cortical architecture in the temporal neocortex adjacent to the tumor. (G) Copy number variation profile obtained from methylation analysis shows absence chromosomal copy number gains, losses, or focal amplifications or deletions. Important brain tumor-relevant gene regions are highlighted for easier assessment. (H) Methylome profile of the case on the t-SNE plot along with a reference cohort of CNS tumors. The case (denoted by circle marked with x) showed clustering close to dysembryoplastic neuroepithelial tumor (DNET). Abbreviations: ANA_PA, anaplastic astrocytoma with piloid features; DMG, diffuse midline glioma; *H3 K27M* mutant; EPN_a, ependymoma, posterior fossa-A, EPN_B, ependymoma, posterior fossa-B; IDH, IDH-mutant diffuse astrocytoma; GBM_*, adult IDH-wild-type glioblastoma; LGG_GG, ganglioglioma, LGG_MYB, low-grade glioma, *MYB* altered; PA_MID, pilocytic astrocytoma -midline; RGNT, rosette-forming glioneuronal tumor

mnp/classifier/1, accessed: 06/15/2021). While the prior version of the classifier (version: 11b2) identified the current temporal lobe tumor as LGG_DNT (confidence score 0.79), the most recent version (version 12.3) identified the tumor as an MGNT (with a confidence score of 0.88). This highlights the improving discriminatory power of the newer version of the classifier, possibly resulting from an increasing repertoire of cases in the database.

Thus, both NGS and DNA methylation analysis using the most recent Heidelberg/DKFZ classifier cemented the diagnosis of MGNT, not DNT for our temporal lobe tumor, despite our original histological diagnosis of DNT. There is well-known histological overlap of MGNT with DNT. Indeed MGNT had initially been described as a "septal region DNT," but those in the septum were subsequently shown to share *PDGFRA* p.K385- (L or I) mutation in over 3/4th of case (3) with the rest showing *FGFR1* or *NF1* alterations. The differing genetics prompted inclusion in the current CNS WHO 2021 of MGNT as a separate entity from DNT based on molecular characterization.

Morphologic features of DNT include the "specific glioneuronal element" that typically includes oligodendroglial-like cells within the cortex, neurons "floating" in myxoid matrix, and intracortical mucin-rich nodules. As demonstrated by our case, MGNT often shows similar or identical histologic features (3,4), although it has been suggested that the multi-nodularity and the specific glioneuronal element typical of cortically based DNT is absent in MGNT (3) and "floating neurons" are rare (3,6). Unlike DNT, well-formed neurocytic rosettes, composed of tumor cells surrounding central areas of neuropil have also been reported in MGNT (4). A thorough systematic review of histologic differences/similarities between the two entities has not been performed. Clinical outcome so far is similar between the two lesions: similar to DNT, all patients of MGNT have had an indolent disease course, despite metastasis within the neuraxis in a few cases (3).

In addition to differing mutations in MGNT compared to DNT, the DNA methylation clustering differs in many studies (9). In the study by Chiang et al., all 8/11 septal DNT cases harboring *PDGFRA* p.K385L/I mutation formed a distinct methylation cluster separate from other known CNS tumor entities, while the remaining few cases harboring *NF1* or *FGFR1* alterations and those instead clustered with other low-grade neuroepithelial tumors (3). Subsequently, Lucas et al. reported a DNT-like epigenomic profile in their series (6) similar to what is report here (Figure 1H).

It is worth noting that the recent most version of the Heidelberg classifier (version 12.3) features s separate category for MGNT and was able to identify our current temporal lobe case as an MGNT, while the previous version (version 11b2) was unable to do so. In fact, when we revisited the methylation-based classification for our previously reported midbrain MGNT (5), we obtained a score of 0.58 on the v12.3 of the classifier and DNT on version 11b2 (confidence score 0.12296). Thus, prospective DNA methylation clustering for the current temporal lobe MGNT as well as retrospective analysis of our first nonseptal MGNT in the midbrain, using the most recent version of the Heidelberg classifier (version 12.3) shows identity between the two and with other MGNTs, not DNTs.

In conclusion, we report another example of an MGNT in a non-septum pellucidum location, namely, a temporal lobe MGNT with *PDGFRA* p.K385L alteration, further validated by DNA methylation score using the newer version of the Heidelberg CNS tumor classifier. Although the more common septum pellucidum location for most MGNTs, as well as the unique midbrain location for the MGNT that we previously reported (5) did not offer the opportunity to assess possible adjacent focal cortical dysplasia, we did assess this feature in the current tumor in the temporal lobe. As reported previously for DNT, we show evidence of cortical neuronal tangential architectural abnormalities, that is, focal cortical dysplasia type 1b like change, associated with a case of temporal lobe MGNT.

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