Unusual low-grade neuroepithelial tumour with novel PDGFRA mutation

Yan Yuen Lo,[1] Denise Malicki,[2] Michael Levy,[3] John Ross Crawford[4]

[1]Department of Neurosciences, University of California San Diego, La Jolla, California, USA
[2]Department of Pathology, Rady Children's Hospital University of California San Diego, San Diego, California, USA
[3]Department of Neurosurgery, University of California San Diego, San Diego, California, USA
[4]Departments of Neurosciences and Pediatrics, University of California San Diego, La Jolla, California, USA

Correspondence to
Dr John Ross Crawford;
jrcrawford@ucsd.edu

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DESCRIPTION

An 8-year-old girl presented with precocious puberty and an otherwise normal examination. MRI of the pituitary was normal; however, an incidental oval, non-enhancing T2 hyperintense lesion in the right temporal subcortical white matter was identified (figure 1). The neuro-radiographic differential diagnosis included a low-grade glioma, dysembryoplastic neuroepithelial tumour or atypical cortical dysplasia. She underwent a robotic-guided biopsy where pathology revealed cortical areas with slightly increased cellularity, evenly distributed and containing scattered disoriented neurons, with some portions showing a loosely structured architecture and mildly myxoid background. Immunochemistry tested positive for glial fibrillary acidic protein and NeuN1, consistent with a histologic diagnosis of a low-grade neuroepithelial tumour (figure 2). Next general sequencing of the tumour revealed a mutation of *PDGFRA p.K385L* and variants of unknown mutations of *GRM3p.875s* and *NOTCH1 pR2431W*. Tumour microarray showed no copy number alterations. The patient is without progressive disease on follow-up MRIs 2 years after diagnosis.

Paediatric low-grade gliomas (pLGG) account for approximately 30% of paediatric brain tumours and encompass a wide range of histologic and molecular entities as defined by the WHO classification.[1 2] Although pLGG rarely transforms to higher grade tumours as seen in adults, the outcome and therapeutic response has been highly variable, making treatment challenging. Low-grade neuroepithelial tumour is a type of low-grade glioneuronal tumour with a wide spectrum of variable features in genetic variations, commonly associated with epilepsy in young adults and children. Molecular profiling of pLGG identified key genetic alteration in the RAS-mitogen-activated protein kinase (RAS/MAPK) pathway often involving somatic alterations of germline *NF1* or *BRAF*.[2 3] Rarer common pLGG alterations include RAS/MAPK alterations such as *FGFR1/2/3, NTRK2, RAF1, ALK* and *ROS1*, and non-RAS/MAPK alterations such as *MYB, MYBL1, IDH1* and *H3F3A*.[2 4] Recent work has characterised pLGG into a variety of molecular subgroups based on molecular signatures.[2] Even in patients who did not have identifiable mutations, single sample gene set enrichment analysis demonstrated increased activation signature in the RAS-MAPK pathway compared with normal brain controls, indicating pathway upregulation even in the absence of a clear molecular driver.[2]

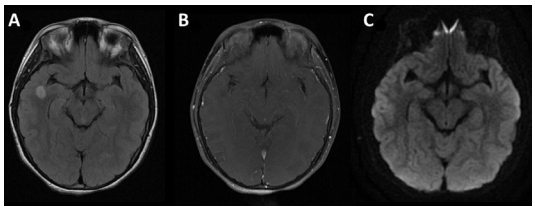

Figure 1 Neuroimaging features of low-grade neuroepithelial tumour. MRI reveals a hyperintense temporal lobe mass on fluid-attenuated inversion recovery sequences (A), without post-gadolinium enhancement (B) or reduced diffusivity (C).

Platelet-derived growth factor receptor α (*PDGFRA*) gene mutations are more commonly associated with gastrointestinal stromal tumours which occur in the gastrointestinal tract such as the stomach or the small intestine.[5] *PDGFRA* gene mutation in brain tumours is novel at large. Specifically, the *PDGFRA p.K385*-mutant is a novel tumour entity of the central nervous system (CNS) with the *PDGFRA p.K385*-mutant. Molecularly, the *PDGFRA p.K385*-mutant contains a defined dinucleotide mutation at codon 385 of the *PDGFRA* oncogene where lysine is replaced by either isoleucine or leucine. Optimal treatment and clinical outcome of the *PDGFRA p.K385*-mutant is yet to be defined.[6]

We present a low-grade neuroepithelial tumour with a unique *PDGFRA* mutation that may fit into the category of the recently described

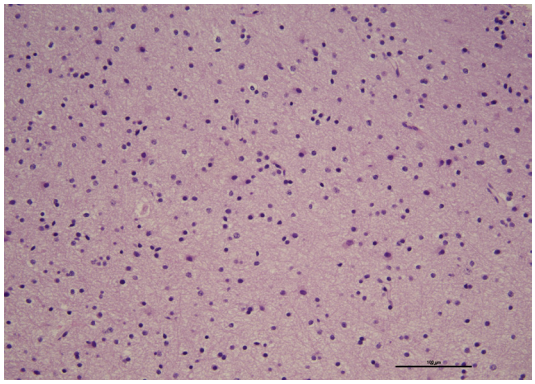

Figure 2 Neuropathologic features of low-grade neuroepithelial tumour. Haematoxylin eosin biopsy specimens reveal increased cellularity with scattered disoriented neurons in a mildly myxoid background. Immunohistochemistry (not shown) was diffusely positive for glial fibrillary acidic protein (GFAP) and scantly positive for NeuN1 positivity consistent with a histologic diagnosis of a low-grade neuroepithelial tumour.

polymorphous low-grade neuroepithelial tumour of the young.[7] Given the novelty in the genetic mutation, the role and significance the *PDGFRA p.K385*-mutant plays in tumour growth is unknown.

Learning points

- Platelet-derived growth factor receptor α (*PDGFRA*) gene mutations are commonly associated with tumours in the gastrointestinal tract and are less commonly associated with paediatric brain tumours.
- We present a case of low-grade glioma with novel mutation in the *PDGFRA p.K385L* gene and several variants of unknown significance that may fit into the spectrum of the recently described polymorphous low-grade neuroepithelial tumour of the young.
- Next generation sequencing and microarray can provide important tumour characterisation in paediatric low-grade glioma and guide future studies in phenotype-genotype correlations.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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