Unusual low-grade neuroepithelial tumour with novel PDGFRA mutation
Yan Yuen Lo,1 Denise Malicki,2 Michael Levy,3 John Ross Crawford4

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, dyssembryoplastic 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. Immunohistochemistry 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 p.R2431W. 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

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.3 PDGFRA gene mutation in brain tumours is novel at large. Specifically, the PDGFRA p.K385S-mutant is a novel tumour entity of the central nervous system (CNS) with the PDGFRA p.K385R-mutant. Molecularly, the PDGFRA p.K385R-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.K385S-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...
polymorphous low-grade neuroepithelial tumour of the young.\textsuperscript{7} Given the novelty in the genetic mutation, the role and significance the \textit{PDGFRA} p.K385-mutant plays in tumour growth is unknown.

\textbf{Learning points}

\begin{itemize}
\item Platelet-derived growth factor receptor $\alpha$ (\textit{PDGFRA}) gene mutations are commonly associated with tumours in the gastrointestinal tract and are less commonly associated with paediatric brain tumours.
\item We present a case of low-grade glioma with novel mutation in the \textit{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.
\item Next generation sequencing and microarray can provide important tumour characterisation in paediatric low-grade glioma and guide future studies in phenotype-genotype correlations.
\end{itemize}

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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.

\textbf{REFERENCES}


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