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Angiocentric glioma with *MYB-QKI* fusion located in the brainstem, rather than cerebral cortex

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Angiocentric glioma is defined in the 2016 WHO Classification as “an epilepsy-associated, stable or slow-growing cerebral tumor primarily affecting children and young adults; histologically characterized by an angiocentric pattern of growth, monomorphous bipolar cells, and features of ependymal differentiation” [5]. Since its initial description by Wang et al. [8], fewer than 100 cases have been reported, nearly all of which were epilepsy-associated tumors located in the cerebral cortex [1, 8]. Recently, an in-frame *MYB-QKI* gene fusion was identified as the defining genetic alteration in the majority of tumors pathologically classified as angiocentric gliomas [2, 6]. To date, only rare examples of angiocentric glioma-like tumors located outside of the cerebral hemispheres have been reported, but none have been genetically characterized [3, 7]. Here we report the case of a young child with 6th cranial nerve palsy due to an angiocentric glioma with *MYB-QKI* fusion centered in the pons; as such, the definition of this tumor type should not be restricted to

a location in the cerebral cortex or to seizures as the clinical presentation.

A 7-year-old boy in otherwise good health presented with several months of altered vision, described by his parents as difficulty fixating on objects and intermittent squinting, as well as problems with depth perception causing him to trip or stumble. He had not experienced any symptoms suggestive of seizure activity. Neurologic exam revealed a right 6th cranial nerve palsy but was otherwise intact. Magnetic resonance imaging revealed a well-circumscribed, T2-hyperintense, non-enhancing, 2.5-cm ovoid mass in the inferior pons (Fig. 1a; Supplemental Fig. 1). Stereotactic biopsy of the mass was performed. Intraoperative cytologic preparation and histologic sections revealed a low-grade glial neoplasm consisting of bland bipolar tumor cells with oval nuclei embedded in a myxoid stroma; a prominent angiocentric growth pattern was noted (Fig. 1b; Supplemental Figs. 2 and 3). No appreciable mitotic activity, necrosis, or microvascular proliferation were identified. Rosenthal fibers and eosinophilic granular bodies were not seen. Immunostaining for glial fibrillary acidic protein (GFAP) was positive in the tumor cells with accentuated perivascular staining. The Ki-67 labeling index was estimated at 2%. Immunostaining for IDH1-R132H and histone H3-K27M mutant proteins was negative. While the histologic features were considered most suggestive of pilomyxoid astrocytoma, targeted next-generation sequencing was performed on the UCSF500 Cancer Panel as previously described to help clarify the diagnosis [4]. This revealed an interstitial deletion on chromosome 6q with 5' breakpoint in the *MYB* gene and 3' breakpoint in the *QKI* gene (Fig. 1c), resulting in an *MYB-QKI* gene fusion. Sequencing reads demonstrated a fusion junction between intron 15–16 of *MYB* and intron 4–5 of *QKI* (Fig. 1d, e), predicted to result in an in-frame fusion protein where the N-terminal portion is composed

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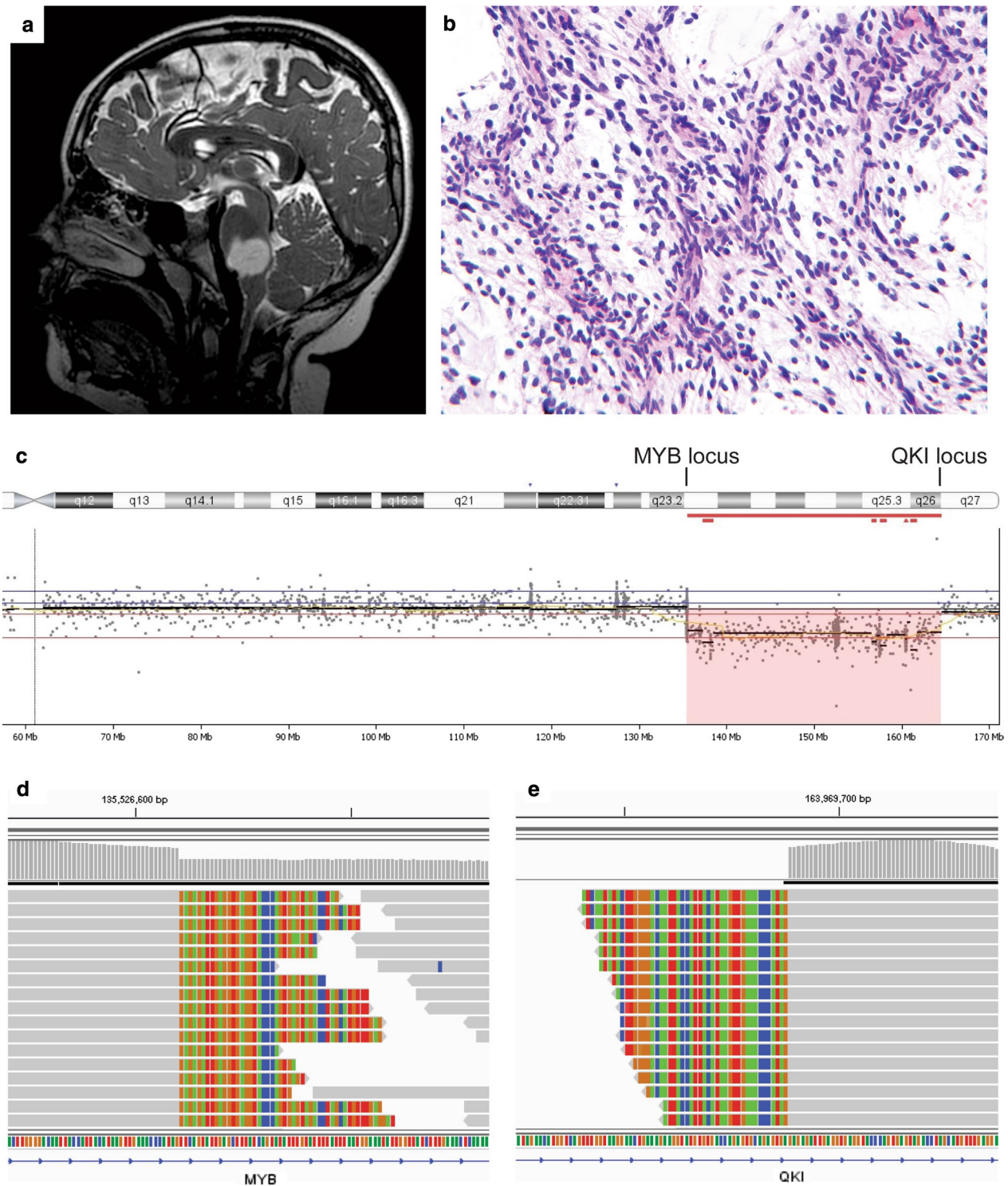


Fig. 1 Imaging, histologic, and genetic features of the angiocentric glioma located in the brainstem. **a** T2-weighted magnetic resonance image demonstrating a sharply demarcated mass within the pons. **b** H&E stained section of the tumor demonstrating a low-grade glial neoplasm with myxoid stroma and angiocentric growth pattern. **c**

Copy number scatter plot for chromosome 6q demonstrating an interstitial deletion with 5' breakpoint in the *MYB* gene and 3' breakpoint in the *QKI* gene. **d**, **e** Next-generation sequencing reads aligning to intron 15–16 of *MYB* (**d**) and intron 4–5 of *QKI* (**e**) showing the fusion breakpoints of the *MYB-QKI* gene fusion

of exons 1–15 of *MYB* and the C-terminal portion of exons 5–7 of *QKI*. No other chromosomal copy number alterations were seen (Supplemental Fig. 4), and no other pathogenic alterations were identified in genes known to be important in the pathogenesis of pediatric gliomas including those seen in pilocytic and pilomyxoid astrocytomas (e.g., *BRAF*, *RAF1*, *FGFR1*, *NTRK2*, *NF1*, and *KRAS*). Subsequent immunohistochemistry for epithelial membrane antigen (EMA) showed paranuclear dot-like staining in a subset of tumor cells (Supplemental Fig. 3f). An integrated diagnosis of angiocentric glioma with *MYB-QKI* fusion, WHO grade I, was rendered. The patient recovered well from the biopsy and is without additional deficits one month later. Given the potential risks of surgical resection for a tumor in this location, observation alone versus chemotherapy are currently being contemplated as therapy options.

To the best of our knowledge, a genetically confirmed angiocentric glioma arising outside of the cerebral cortex has not been previously reported prior to this case. While angiocentric gliomas in the cerebral cortex are generally benign and can be cured by surgical excision alone, the clinical behavior of angiocentric gliomas arising in structures that are not amenable to surgical resection, such as the brainstem, is uncertain. This case suggests the need to expand the operational definition of angiocentric glioma beyond those tumors which are epilepsy associated or located in the cerebral hemispheres.

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management. NG provided neurosurgical management. EC and DAS wrote the manuscript and created the figures. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests related to this case report.

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