Acta Neuropathologica (2019) 137:179–181
https://doi.org/10.1007/s00401-018-1940-x

CORRESPONDENCE

Chromosome arm 1q gain is an adverse prognostic factor in localized and diffuse leptomeningeal glioneuronal tumors with *BRAF* gene fusion and 1p deletion

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Received: 17 October 2018 / Revised: 15 November 2018 / Accepted: 15 November 2018 / Published online: 21 November 2018

We previously described a series of localized intramedullary glioneuronal tumors limited to the spinal cord with histomorphologic, immunophenotypic, and molecular characteristics of diffuse leptomeningeal glioneuronal tumor (DLGNT), a newly added provisional entry in the current World Health Organization classification of central nervous system tumors [1, 3]. These localized spinal tumors and DLGNTs are characterized by the concomitant presence of *KIAA1549–BRAF* fusion and chromosome arm 1p deletion [6]. Both have OLIG2-expressing oligodendrocyte-like tumor cells that are positive for synaptophysin and negative for GFAP [5]. Neuropil-like islands surrounded by neurocytic cells and variable amounts of ganglion cell differentiation are additional distinct features of both diseases [1]. However, despite this histomorphologic, immunophenotypic, and molecular resemblance, it remains uncertain whether the localized spinal *BRAF*-fused and 1p-deleted glioneuronal tumors are nosologically related to DLGNT, in which predominant and widespread leptomeningeal dissemination at presentation, often without a recognizable parenchymal component, is a defining feature [3].

To answer this question, we have been closely following cases of localized spinal *BRAF*-fused and 1p-deleted glioneuronal tumors at St. Jude Children's Research Hospital (St. Jude) by using serial magnetic resonance imaging of the brain and spinal cord, even when none of them showed evidence of detectable leptomeningeal dissemination at presentation and during a follow-up of up to 9.25 years. Herein, we report that one of the patients, who is now a 15-year-old boy, developed diffuse leptomeningeal dissemination ("sugarcoating") involving supratentorial, posterior fossa, and spinal compartments, accompanied by non-resorptive (communicating) hydrocephalus, after 25 months of follow-up (Fig. 1a–e). The primary T10–12 intramedullary lesion, on the other hand, showed minimal volumetric increase at the time of leptomeningeal progression. The patient had not received any chemotherapy or radiation after the biopsy at diagnosis and was closely followed with periodic surveillance imaging and physical examination. This finding confirms that localized spinal tumors with *KIAA1549–BRAF* fusion and chromosome arm 1p deletion have the ability to develop diffuse leptomeningeal dissemination, which affirms the nosologic relationship between these localized spinal tumors and DLGNT and has significant clinical implications.

Next, we sought to identify the risk factors that may predict disease progression and hence help guide clinical management and decision making of these patients upfront, since the prognosis of DLGNT is highly variable [1, 5]. However, next-generation sequencing analysis of 143 cancer-related genes by using the ClearSeq Cancer Panel (Agilent), and

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00401-018-1940-x) contains supplementary material, which is available to authorized users.

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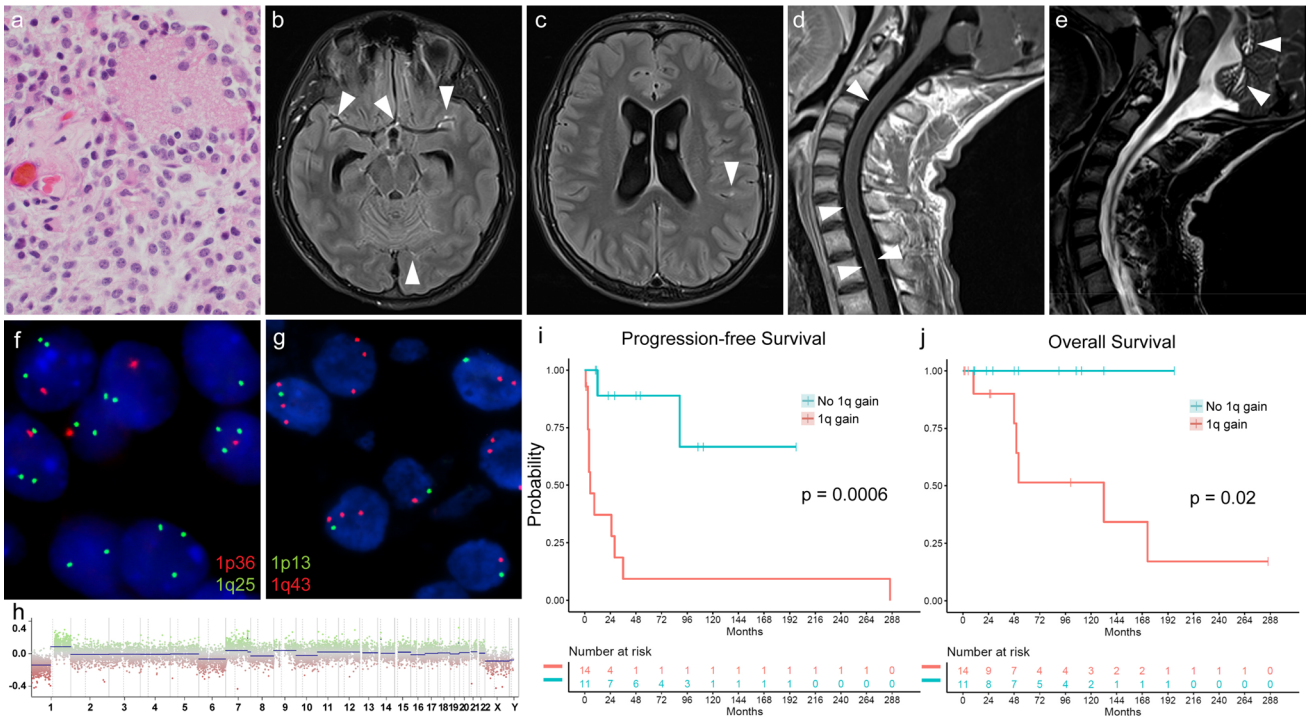

Fig. 1 **a** Hematoxylin and eosin-stained image of the primarily thoracic intramedullary *BRAF*-fused and 1p-deleted glioneuronal tumor from a patient who developed extensive leptomeningeal metastatic disease 25 months after the initial diagnosis. **b**, **c** Transverse post-contrast T2-weighted fluid attenuation inversion recovery images of the brain showing multifocal leptomeningeal metastatic dissemination (arrowheads). The enlarged supratentorial ventricular system corresponds to non-resorptive ("communicating") hydrocephalus. **d** Sagittal post-contrast T1-weighted image of the cervical spine showing fine "sugar coating" type of leptomeningeal spread (arrowheads). **e** The "cystic changes" (likely enlarged perivascular spaces) along the anterior vermis (arrowheads) are a characteristic imaging feature of DLGNT [4]. **f**, **g** Interphase fluorescence in situ hybridization using two different probe sets (Abbott Molecular # 07J73-001 and laboratory developed) showing gain of chromosome arm 1q, in addition to loss of chromosome arm 1p. **h** Whole-arm gain of chromosome arm 1q, in addition to whole-arm loss of chromosome arm 1p, was further confirmed by copy number variation (CNV) analysis, using the Infinium MethylationEPIC platform (Illumina). CNVs other than 1p and 1q are not recurrent. **i** Progression-free survival and **j** overall survival of patients with *BRAF*-fused and 1p-deleted glioneuronal tumors significantly correlate with chromosome arm 1q status (log-rank test)

whole genome, whole exome, and transcriptome analysis performed on this patient's tumor sample revealed no variants of pathologic or likely pathologic significance other than the known *KIAA1549–BRAF* fusion. While we performed interphase fluorescence in situ hybridization (iFISH) at the time of diagnosis in this case, gain of chromosome arm 1q was observed in addition to deletion of chromosome arm 1p (Fig. 1f). This finding was further confirmed by a different laboratory-developed iFISH probe set (Fig. 1g), and later by copy number variation (CNV) analysis and genome-wide DNA methylation profiling using the Infinium MethylationEPIC platform (Illumina) (Fig. 1h). A recent study reported that DLGNTs comprise two methylation classes (MCs), DLGNT MC-1 and MC-2, based on genomic DNA methylation profiles [2]. Patients with DLGNT MC-2 showed inferior progression-free survival (PFS) and overall survival (OS). Interestingly, gain of chromosome arm 1q was seen in all tumors of DLGNT MC-2 and less frequently (35%) in those of DLGNT MC-1. Large-scale CNVs other than loss of chromosome arm 1p and gain of chromosome arm 1q seen in the tumor of this patient are not recurrent, consistent with previous findings [2].

Since genome-wide methylation profiling has not been widely available and its implementation is associated with higher technical and financial barriers, we tested whether gain of chromosome arm 1q, which can be easily detected with iFISH, could be used as an adverse prognostic indicator of *BRAF*-fused and 1p-deleted glioneuronal tumors, including DLGNT. We collected data on the chromosome arm 1q status of 11 cases followed or reviewed at St. Jude through central pathology review, and an additional 14 reported and well-characterized cases for which outcome data were available [2]. Chromosome arm 1q status was confirmed by iFISH and/or CNV analysis by genome-wide DNA methylation profiling (Supplementary Table 1). Progression was defined as confirmed volumetric increase of lesions, or leptomeningeal dissemination if the tumor was localized initially. Results of chromosome arm 1q status by iFISH showed 100% (7/7) concordance with those of CNV analysis by genome-wide DNA methylation profiling. Chromosome

arm 1q gain occurred in 14 (56%) cases. The gain was specific to chromosome arm 1q; non-specific global polysomy was not observed in our study cases. Kaplan–Meier analysis of PFS and OS confirmed that the presence of chromosome arm 1q gain significantly correlates with inferior PFS and OS in patients with *BRAF*-fused and 1p-deleted glioneuronal tumors, including DLGNT (Fig. 1i–j).

In summary, our findings affirm the nosologic relationship between DLGNT and localized spinal *BRAF*-fused and 1p-deleted glioneuronal tumors. More importantly, we demonstrate that gain of chromosome arm 1q is an adverse prognostic indicator of both DLGNT and localized glioneuronal tumors with *KIAA1549–BRAF* fusion and chromosome arm 1p deletion. Chromosome arms 1p and 1q status can be interrogated with one tissue section by iFISH, which is clearly beneficial in oftentimes minute leptomeningeal or spinal cord biopsy specimens. Clinical implementation of iFISH or equivalent tests can significantly facilitate the prognostication and management of this entity, especially in settings wherein genome-wide methylation profiling is not readily available. The putative gene(s) on chromosome arm 1q that, when acquiring additional copies, confers inferior prognosis in patients with DLGNT and localized spinal *BRAF*-fused and 1p-deleted glioneuronal tumors remain to be determined.

Acknowledgements We thank Emily Walker in the Hartwell Center at St. Jude for technical assistance in genome-wide DNA methylation profiling and Vani Shanker in the Department of Scientific Editing at St. Jude for editing this manuscript.

Funding JC receives funding from the American Lebanese Syrian Associated Charities (ALSAC) through St. Jude Children's Research Hospital Department of Pathology.

References

1. Chiang JCH, Harreld JH, Orr BA, Sharma S, Ismail A, Segura AD et al (2017) Low-grade spinal glioneuronal tumors with BRAF gene fusion and 1p deletion but without leptomeningeal dissemination. Acta Neuropathol 134:159–162. https://doi.org/10.1007/s00401-017-1728-4
2. Deng MY, Sill M, Chiang J, Schittenhelm J, Ebinger M, Schuhmann MU et al (2018) Molecularly defined diffuse leptomeningeal glioneuronal tumor (DLGNT) comprises two subgroups with distinct clinical and genetic features. Acta Neuropathol 136:239–253. https://doi.org/10.1007/s00401-018-1865-4
3. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK et al (2016) The 2016 world health organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131:803–820. https://doi.org/10.1007/s00401-016-1545-1
4. Lyle MR, Dolia JN, Fratkin J, Nichols TA, Herrington BL (2015) Newly identified characteristics and suggestions for diagnosis and treatment of diffuse leptomeningeal glioneuronal/neuroepithelial tumors: a case report and review of the literature. Child Neurol Open 2:2329048X14567531. https://doi.org/10.1177/2329048X14567531
5. Rodriguez FJ, Perry A, Rosenblum MK, Krawitz S, Cohen KJ, Lin D et al (2012) Disseminated oligodendroglial-like leptomeningeal tumor of childhood: a distinctive clinicopathologic entity. Acta Neuropathol 124:627–641. https://doi.org/10.1007/s00401-012-1037-x
6. Rodriguez FJ, Schniederjan MJ, Nicolaides T, Tihan T, Burger PC, Perry A (2015) High rate of concurrent BRAF-KIAA1549 gene fusion and 1p deletion in disseminated oligodendroglioma-like leptomeningeal neoplasms (DOLN). Acta Neuropathol 129:609–610. https://doi.org/10.1007/s00401-015-1400-9