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CORRESPONDENCE

Circumscribed/non-diffuse histology confers a better prognosis in H3K27M-mutant gliomas

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Diffuse midline gliomas harboring a recurrent H3 lysine 27-to-methionine (p.Lys27Met, H3K27M) constitute a recently defined pathologic entity with a particularly poor prognosis. They mainly occur in midline structures, such as the pons and thalamus of children and young adults, and are highly infiltrative [2]. More recently, case reports have described the H3K27M mutation in circumscribed (non-diffuse) gliomas, many of which are low-grade (e.g., pilocytic astrocytoma, ganglioglioma) [1, 3–5] (additional references are provided in Online Resource 1). Because of the rarity of these tumors, it is unknown whether they carry the poor clinical outcome ascribed to H3K27M-mutant infiltrating gliomas of the midline. Here, we address this gap in our knowledge by performing an integrated meta-analysis on collated clinical and pathologic data from published studies, data repositories, and collaborative efforts.

A systematic search of the literature was performed from 2012 to November, 2017. Tumors were categorized based on diagnosis, location, histologic grade, growth pattern, and H3K27M mutation status. IDH 1/2-mutant diffuse gliomas were excluded to avoid bias arising from the good prognosis attributed to this mutation. Circumscribed gliomas included pilocytic astrocytoma, ganglioglioma/glioneuronal tumor/ganglion cell tumor, pleomorphic xanthoastrocytoma, and ependymoma. Data from The Cancer Genome Atlas (TCGA) (http://cancergenome.nih.gov/) were obtained through the cBioPortal and PedcBioPortal for Cancer Genomics. Factors extracted included age, sex, overall survival, tumor location, histopathologic diagnosis, and WHO grade. Patient samples were then cross-referenced across studies to filter out duplicate data. Cases were also acquired from our in-house sequencing efforts and through collaboration with the Mayo Clinic in Rochester, Minnesota. Co-occurring mutations were also documented. The endpoint extracted from all data sources was overall survival (OS). Survival functions were estimated using the Kaplan–Meier method and differences analyzed with the log-rank (Mantel–Cox) test using GraphPad Prism software (version 7). The Cox-proportional hazards model was used to calculate hazard ratios (HR) using SPSS (version 24, IBM). All studies were approved by ethics committees at the respective institutions (see Online Resource 1 for further details of the methods).

Among published studies and through institutional collaboration, we identified 28 cases of H3K27M-mutant circumscribed gliomas (grade I: $n = 19$; grade III, $n = 9$). Histopathology included pilocytic astrocytoma ($n = 7$), ganglioglioma ($n = 10$), anaplastic ganglioglioma ($n = 3$), glioneuronal tumor ($n = 1$), anaplastic glioneuronal tumor ($n = 1$), ganglion cell tumor ($n = 1$; Fig. 1a–d), anaplastic ependymoma ($n = 3$), and circumscribed glioma, not further specified ($n = 2$) (see Online Resource 2 for references and case details). Strikingly, more than 96% ($n = 26/27$ cases with location provided) of H3K27M-mutant circumscribed gliomas occurred within the midline, including the brainstem ($n = 7$), thalamus ($n = 5$), cerebellum ($n = 2$), spinal cord ($n = 8$), and other midline regions (peduncle, posterior fossa, and midline-not further specified; $n = 4$) (Fig. 1g). Of the remaining two cases, one was reported in the cerebrum, while the location was not specified for the other. H3K27M mutations occurred in *H3F3A* ($n = 21$), *HIST1H3B* ($n = 1$),

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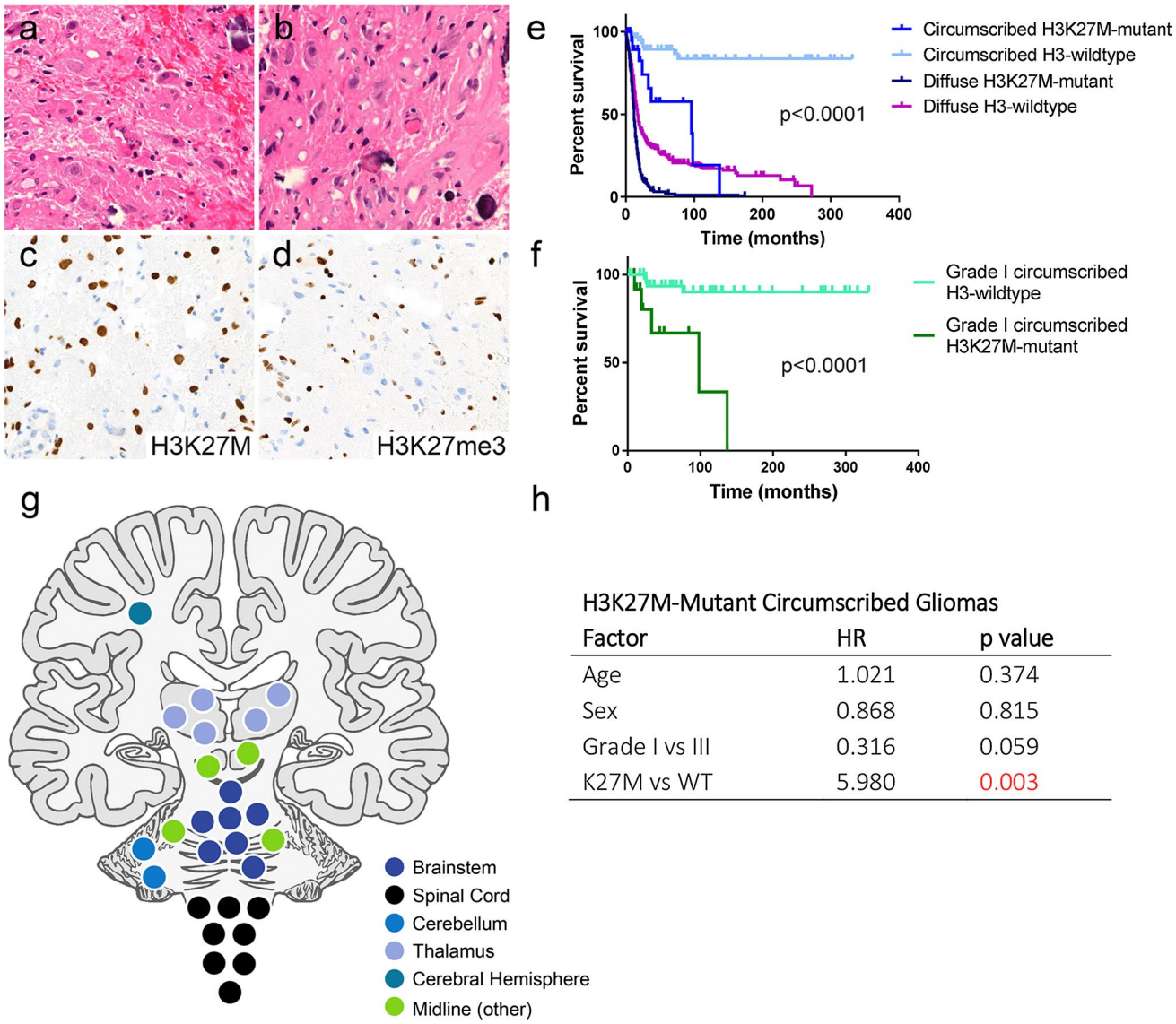

H3K27M-Mutant Circumscribed Gliomas

Factor	HR	p value
Age	1.021	0.374
Sex	0.868	0.815
Grade I vs III	0.316	0.059
K27M vs WT	5.980	0.003

Fig. 1 Histopathology, localization, and survival analyses in H3K27M-mutant circumscribed gliomas. **a**–**d** Representative histology of a ganglion cell tumor (**a**–**b**, H&E) with nuclear expression of the H3K27M mutant protein (**c**) and concurrent loss of H3K27me3 (**d**). **e** Kaplan–Meier estimation shows stratification of overall survival based on growth pattern and H3K27M mutation status (circumscribed glioma H3-wild-type, $n = 63$; circumscribed glioma H3K27M-mutant, $n = 21$; diffuse glioma H3/IDH-wild-type, $n = 550$; diffuse glioma H3K27 M-mutant, $n = 432$). **f** H3K27M mutation demonstrated a worse prognosis compared to H3-wild-type tumors in grade I-matched circumscribed gliomas. **g** Locations of H3K27M-mutant circumscribed gliomas. **h** Cox regression analysis

HIST1H3C ($n = 1$), and five cases were detected by immunohistochemistry. Information on co-occurring somatic mutations was available in 50% (14/28) of cases. The most frequent alteration was *BRAF* V600E ($n = 7$) mutations followed by *ATRX* ($n = 3$), *FGFR1* N546K ($n = 2$), and *NF1* ($n = 2$) (see Online Resource 2). Copy number alterations were reported in chromosomes 13 and 17 in two tumors.

Survival information was available for 21 cases (grade I: $n = 14$; grade III: $n = 7$). Univariate analysis of these tumors demonstrated poor OS compared to H3-wild-type circumscribed gliomas ($n = 59$; grade I: $n = 51$; grade III: $n = 8$) (log-rank, $p < 0.0001$), but a significantly improved OS compared to H3/IDH-wild-type (log-rank, $p = 0.025$) and H3K27M-mutant diffuse gliomas (log-rank, $p < 0.0001$) (Fig. 1e). This association remained significant after matching tumors for grade (grade I, log-rank, $p < 0.0001$; Fig. 1f) and treatment [chemotherapy and/or radiotherapy, log-rank, $p < 0.0001$; Supp. Fig. (Online Resource 3)]. Cox regression analysis with age, sex, grade, and mutation status included as covariates showed the H3K27M mutation remained an independent predictor of OS (HR, 5.980; 95% CI, 1.839–19.445; $p = 0.003$; Fig. 1h).

These results confirm that the poor prognosis of the H3K27M mutation also extends to circumscribed gliomas. While H3K27M-mutant circumscribed gliomas show poor survival compared to H3-wild-type circumscribed gliomas, prognosis remains significantly better than both H3K27M-mutant and H3-wild-type diffuse gliomas. This has important implications regarding the current WHO grading of H3K27M-mutant diffuse gliomas, which are uniformly labeled as grade IV. However, we note that an important limitation to our study is the relatively short follow-up duration, largely owing to the rarity of these tumors. We also show that H3K27M-mutant circumscribed gliomas show a similar predilection for midline regions. Our data suggest that midline circumscribed gliomas should be routinely tested for H3K27M mutations.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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