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CORRESPONDENCE

Subventricular spread of diffuse intrinsic pontine glioma

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Diffuse intrinsic pontine glioma (DIPG) is the second most common malignant pediatric brain tumor and the leading cause of brain tumor death in childhood [1]. 80 % of DIPG tumors exhibit a specific mutation (H3K27M) in the genes encoding histone 3.1 or 3.3 [2, 3]. Standard therapy consisting of local radiotherapy to a dosage of 54–60 Gy extends median survival from 5 months to ~9 months; 5-year survival remains less than 1 % [1]. The practice of focal radiotherapy to the brainstem is based in part on a 1982 autopsy study reporting DIPG to be relatively localized to the pons and adjacent structures [4]. In contrast, other neuroimaging and autopsy studies have identified widespread disease including supratentorial extension and leptomeningeal spread [5, 6].

Here, we report an autopsy series of 16 patients evaluated from 2009–2014 at Stanford ($n = 10$) and VU ($n = 6$) University Medical Centers [7]. Patient characteristics are listed in Table S1. Consistent with previous reports [5, 6], we found widespread dissemination of DIPG with extension to midbrain and medulla in 63 %, cerebellum in 56 %, thalamus in 56 %, frontal cortex in 25 % and supratentorial leptomeninges in 25 % (Fig. 1). The spinal cord was not consistently examined, but metastases were found in two of three cases examined; both had clinical evidence of spinal cord spread.

A previously under-recognized pattern of subventricular spread was noted in 10/16 cases, with infiltration of the subventricular zone (SVZ) and tumor nodules in the frontal horns of the lateral ventricles. In three cases lateral ventricular disease was noted on pre-mortem MRI (Fig. 2a), but subclinical tumor invasion in the SVZ of the lateral ventricles was found in six additional cases; subventricular spread was found in the third ventricle of one additional case (Fig. 2). The observed pattern of ventricular/subventricular

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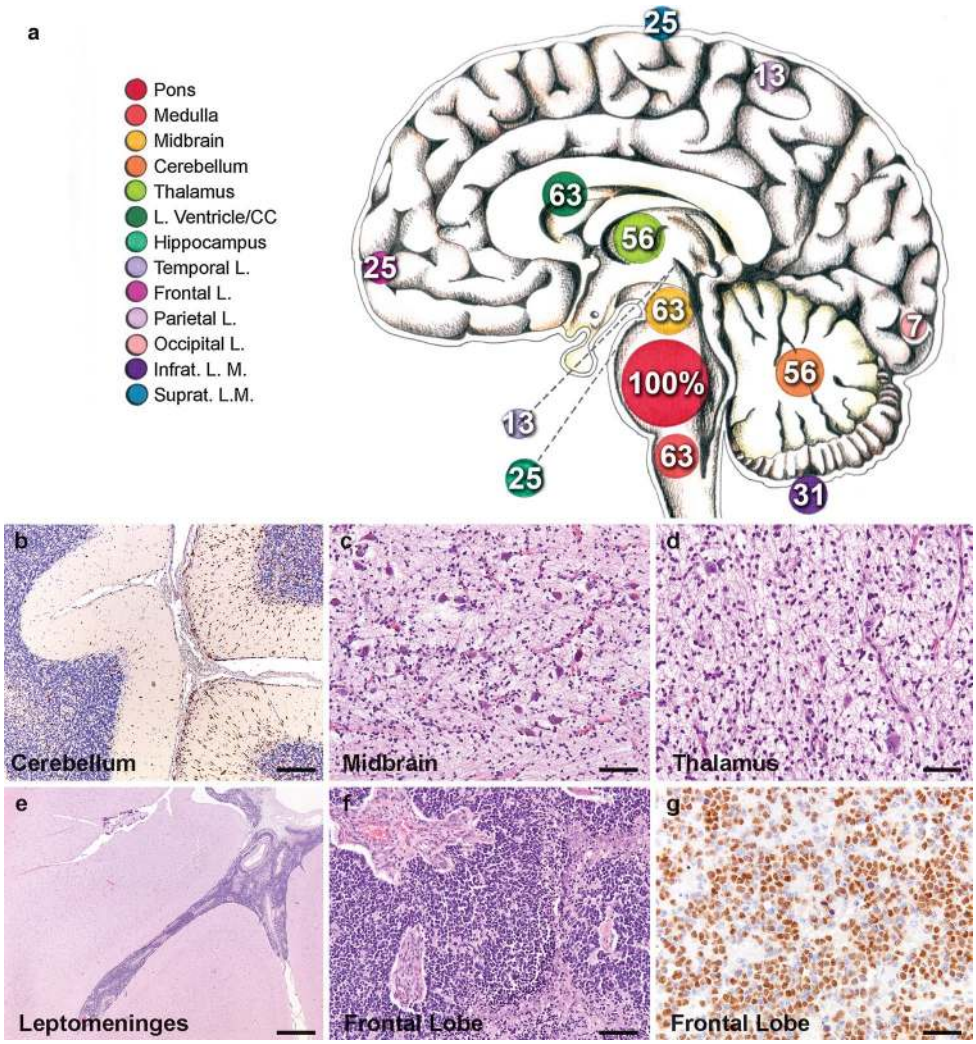

Fig. 1 Extent of spread in DIPG. **a** Neuroanatomical sites and frequency of tumor invasion. *Numbers* indicate the percentage of cases that exhibit tumor invasion at the indicated anatomical location. The size of the circles marking each anatomical site (color key to the left) illustrates the frequency. *CC* corpus callosum, *infrat. L.M.* infratentorial leptomeninges, *Suprat. L.M.* supratentorial leptomeninges. Photomicrographs illustrating **b** Olig2 + tumor cells infiltrating the cerebellum, **c** tumor infiltrating the substantia nigra in the midbrain (H&E), **d** tumor infiltrating the thalamus (H&E), **e** leptomeningeal spread affecting the temporal lobe (H&E), **f** tumor in the frontal cortex (H&E) and **g** Olig2 + tumor cells in the frontal lobe. *Immunostains* DAB with hematoxylin counterstain. *Scale bars* 100 μm (**b**–**d**, **f**), 1 mm (**e**) and 50 μm (**g**)

involvement could be due to direct invasion along the SVZ corridor, intraventricular cerebrospinal fluid (CSF) seeding of the SVZ, or an as yet undescribed mechanism. The postnatal SVZ is a neural stem cell niche in the human brain [8] and DIPG cells express an immunophenotype reminiscent of neural precursor cells (Fig. S1 and [9]). Whether DIPG cells exhibit a particular tropism for this niche remains to be explored.

Following standard brainstem radiotherapy, disease progression typically occurs locally in the brainstem. However, in three of sixteen cases the subventricular frontal lobe disease contributed substantially to morbidity and mortality and preceded pontine recurrence in two cases. As therapies improve and patients survive longer in the natural history of their cancer, new patterns of regional relapse often appear (e.g. sanctuary disease in childhood leukemia). Our data show subventricular tumor spread in the majority of patients, typically later in the course of their disease. Thus as future therapies evolve to control local disease, strategies including extended or whole brain irradiation may become crucial. The patterns of widespread dissemination, including leptomeningeal, direct extension and subventricular spread, suggest that the extent of the optimal radiation field should be re-examined.

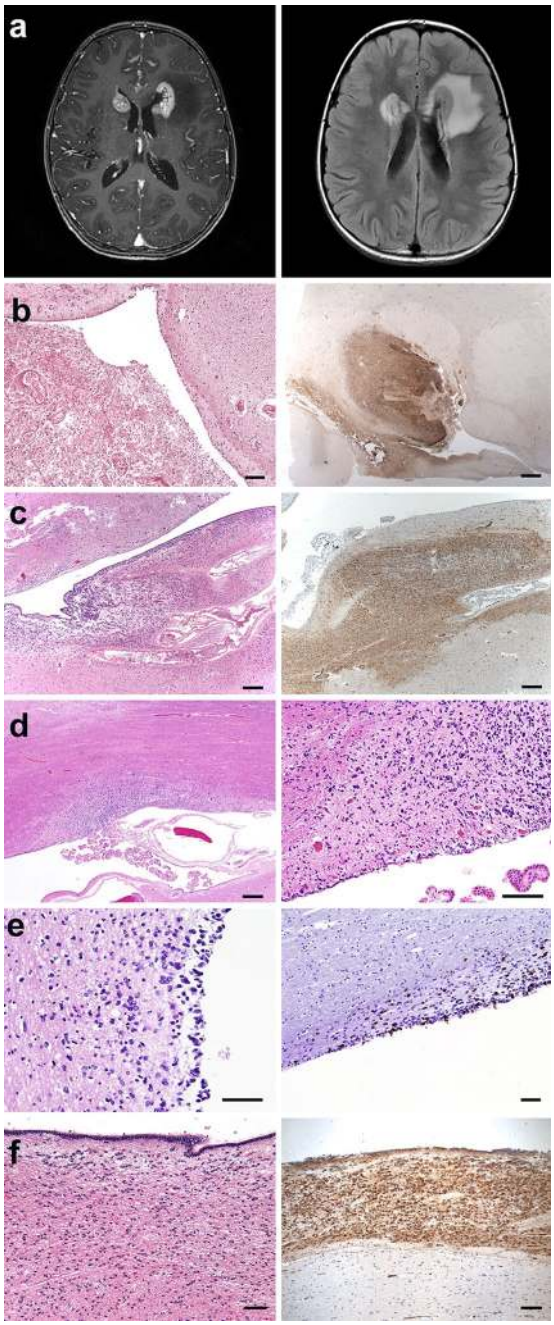

Fig. 2 Invasion of the subventricular zone in DIPG (**a**). MRI images illustrating enhancing lesions (T1 post gadolinium, *left image*) at the frontal horns of the lateral ventricles with associated edema (FLAIR, *right image*) in case SU-DIPG-XIII. **b** H&E (*left*) and nestin immunostaining (*right*) of DIPG tumor at the frontal horn of the lateral ventricle in case SU-DIPG-III. **c** Similar to **b** in SU-DIPG-V. **d** H&E demonstrating DIPG tumor at the frontal horn of the lateral ventricle in SU-DIPG-XIII. **e** H&E stain (*left*) and Ki67 immunostaining (*right image*) illustrating tumor infiltration in the lateral ventricle SVZ of SU-DIPG-VI. **f** H&E (*left*) and nestin immunostaining (*right*) of DIPG tumor in the third ventricle of SU-DIPG-IV. *Immunostains* DAB with hematoxylin counterstain. *Scale bars* 1.25 mm (**b**–**c**, **d**, *left panel*), 250 μm (**d**, *right panel*; **e**, **f**)

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Conflict of interest The authors declare that they have no conflict of interest.

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