Low rate of R132H IDH1 mutation in infratentorial and spinal cord grade II and III diffuse gliomas

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Diffuse gliomas not only are more frequent in the cerebral hemispheres but also occur in the brainstem, cerebellum, and spinal cord. In adult populations, 5 % or less localize to the infratentorium [6, 14]. Primary tumors of the spinal cord are uncommon and only 2.5 % are
diffuse gliomas [6]. In the brainstem, many gliomas are diagnosed solely by radiology and even when a biopsy is obtained it tends to be of minute size, rendering interpretations challenging. Accurate diagnostic ancillary studies on such specimens would therefore be valuable.

Analysis of R132H mutant isocitrate dehydrogenase 1 (mIDH1), either by molecular methods or by immunohistochemistry (mIDH1-IHC) [4, 5, 13], has been shown to reliably distinguish diffuse astrocytomas from some of their most frequent mimickers, including pilocytic astrocytomas, gangliogliomas, or reactive gliosis [1, 3, 8, 9, 11], or likewise to distinguish oligodendroglioma from other brain tumors with clear cell morphology like neurocytomas or dysembryoplastic neuroepithelial tumors [2]. However, results from mIDH1-IHC are only diagnostically useful when positive and although prior reports have shown that about 75% of supratentorial grade II and III diffuse gliomas are mIDH1 positive [10], no such data are available in adult infratentorial and spinal cord diffuse gliomas.

We searched our surgical pathology archives (1990–2011) for infratentorial and spinal cord diffuse gliomas, excluding glioblastomas and patients under the age of 16, and selected all cases with paraffin-embedded tissue available. All sections were reexamined and cases were reclassified according to the WHO 2007 criteria. None of the cases had histologic features of ganglioglioma. Small biopsies initially designated “low grade astrocytoma” that showed contrast enhancement, incomplete features of pilocytic astrocytoma, and no recurrence after many years were excluded since they may have represented pilocytic astrocytomas.

A total of 44 cases were selected for mIDH1-IHC (clone H09, Dianova, Hamburg, Germany), including 23 brainstem, 12 cerebellar and 9 spinal cord tumors (Table 1). The median age at diagnosis was 36 years (range 16–90) and the male to female ratio was 1.75:1. Two patients had neurofibromatosis type 1 (case B18 and C12). Surprisingly, only 3/44 tumors (7%) were positive for the mutation, all localizing to the brainstem. None of the cerebellar or spinal cord tumors had the mutation. The median overall survival of this cohort (grade II, 43 months; grade III, 25 months) was similar to that previously reported for same grade supratentorial IDH wild-type tumors [12].

The vast majority of these infratentorial and spinal cord specimens were needle or small biopsies with insufficient tissue for DNA extraction and sequencing, as is often the case in routine clinical practice. In the nine cases in which DNA extraction was achieved (six cerebellar and three brainstem tumors), mass spectrometry array mutation profiling (MassARRAY system, Sequenom, San Diego, CA) or fluorescence melting curve PCR analysis [7] confirmed the absence of R132H IDH1 mutation. Testing for other rarer IDH1 mutations or mutations in IDH2 revealed one case with an IDH1 R132G mutation.

This low rate of R312H IDH1 mutation is in sharp contrast with the high rate seen in same grade diffuse gliomas in the supratentorial compartment and suggests mIDH1-IHC may only rarely be of diagnostic help in the context of small biopsies from infratentorial and spinal cord tumors.
Acknowledgments

We wish to thank Lindsey Heathcock and Alicia Ledoux and her team for technical assistance. This work was supported in part by the Gyorkey Endowed Chair for Research and Education in Pathology.

References


Table 1

Study cohort listed with patient age at first diagnosis, sex, location, current diagnosis, result of mIDH1-IHC, result of IDH genotyping, overall survival, and status at last follow-up

<table>
<thead>
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<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>Diagnosis</th>
<th>mIDH1 IHC</th>
<th>IDH genotyping</th>
<th>OS (months)</th>
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