LETTER TO THE EDITOR

Re-evaluation of nondiagnostic biopsies of suspected low-grade glioma using isocitrate dehydrogenase 1 mutation immunohistochemistry

Keywords: biopsy, glioma, IDH.

Mutations in the isocitrate dehydrogenase 1 (IDH1) or 2 (IDH2) genes, which involve the citric acid cycle, have been recently identified as common early mutations in low-grade glioma and are rarely found in primary glioblastoma. The IDH1 and IDH2 mutations are beginning to play a role in the classification of gliomas and to provide clues into gliomagenesis. This mutation is commonly present in low-grade, infiltrating glial tumors or tumors that had progressed secondarily from low-grade lesions, and is acquired early in development, before accumulating TP53 or 1p/19q mutations. This suggests an origin from a common glial progenitor cell for these tumors but a different molecular and genetic origin for primary glioblastomas. This mutation also is generally unique to malignant glial processes, with no evidence of this mutation being found in nonneoplastic conditions, which include gliosis, infectious changes, vascular changes, demyelinating changes, and radiation changes. However, mutations have also been shown to be present in cartilaginous tumors and some myeloproliferative neoplasms, and there have been rare mutations described in primary glioblastoma, primitive neuroepithelial tumors, and dysmyelinating neuroepithelial tumors (DNT). Low-grade glioma is likely to be underdiagnosed in circumstances in which cellularity is only mildly increased. The threshold for cellularity and atypia are highly subjective. IDH1 mutation immunohistochemistry may be helpful as a diagnostic tool in these borderline cases, because IDH1 mutant glioma cells have been detected in samples in areas distant from a patient’s known glioma that would not have been otherwise appreciated.

In this institutional review board–approved study, 6 cases were identified during 2006–2010 with T2 hyperintense lesions on MRI concerning low-grade glioma but with nondiagnostic pathology evaluations. Each case had minimal to mild hypercellularity present (Fig. 1A and B), and evaluations for mutant p53 and the MIB-1 proliferation index were unremarkable. An immunohistochemical (IHC) stain for the mutant IDH1 R132H protein was performed to assess the IDH1 status of the tissue.

For the 6 patients identified, median age at time of biopsy was 42 years (range, 26–48 years). Lesions were identified on imaging incidentally for symptoms, such as headache (83%) and vertigo (67%), and 1 patient had transient neurological symptoms that did not correlate with the location of the lesion. Five of the patients underwent stereotactic biopsy, and 1 patient underwent an open biopsy with nearly complete resection of the lesion. Length of follow-up after biopsy was 2–6 years. Locations of the lesions were variable, but all were anterior, either in the temporal or frontal lobe of either hemisphere.

Five samples had no expression of the IDH1 mutant protein by IHC (Fig. 1D). One sample had expression of the IDH1 mutant protein by IHC (Fig. 1C).

The current WHO diagnostic criteria for low-grade glioma are based on cellularity and nuclear atypia on H&E sections. These subjective measures create challenging diagnostic dilemmas, particularly in reactive conditions, such as gliosis. Occasionally, MIB-1 and P53 IHC can be helpful, but frequently in low-grade glioma, these tests are not definitive. Nondiagnostic histopathology from stereotactic biopsy can also result from sampling error because the limited scope of the biopsy can miss or obtain tissue from the edge of the lesion, which may not show obvious signs of malignancy. Even in completely resected tissue, cords of tumor can be missed in the sectioning for histochemical staining. Previous studies have shown that, even in biopsies in which the lesion was missed or the tissue was likely from the edge of a lesion, it is still possible to detect cells with IDH mutations with use of IHC staining.

Use of IDH1 IHC in an otherwise nondiagnostic sample could establish the diagnosis of low-grade, infiltrating glioma.

In the 6 samples identified during 2006–2010 (before the availability of IDH1 IHC), the biopsy specimens were considered to be abnormal because of hypercellularity. However, even with ancillary studies, such as p53 and MIB-1 IHC, a definitive diagnosis of glioma could not be reached. Five samples, when checked for the presence of an IDH1 mutation, were negative for the mutation. This tissue is not likely to be glioma, because of the lack of interval progression during follow-up surveillance imaging. However, this could represent tissue in which the biopsy failed to capture tumor cells despite the presence of a glioma. False-negative results might also arise if an IDH1 mutation is not recognized by the antibody used for IHC (R132C, p.R132S, and pR132G) or an IDH2 mutation is present and in the small percentage of low-grade glioma that are IDH1 wild-type.

The single case that did display IDH1 mutation with immunostaining involved an open procedure of an
enlarged gyrus, but with unclear histology. The lack of definitive histologic evidence of malignancy was not attributable to sampling error. Multiple pathologists examined the case and concluded that the findings were insufficient for the diagnosis of infiltrating glioma based on H&E and p53 and MIB-1 IHC. Indeed, some degree of cortical disorganization in the specimen prompted a differential diagnosis of developmental disorder, such as cortical dysplasia. Cortical dysplasia has not been investigated for IDH mutations, although cortical dysplasia may be associated with DNT, which have been shown to harbor IDH mutations. There was no evidence of DNT in this specimen, however. Therefore, in retrospect, given the presence of an IDH1 mutation in cells that resemble infiltrating tumor cells, this lesion was most likely a low-grade glioma.

IDH1 IHC testing in biopsies of suspected low-grade glioma may improve detection of infiltrating glioma.
In this small collection of initially nondiagnostic biopsies, a definitive diagnosis of glioma was established retrospectively by IDH1 IHC in 1 (17%) of 6 patients. None of the patients showed clinical or radiological progression after 2–6 years. The one patient whose specimen was positive for the IDH1 mutation showed only a minimal increase in the residual T2 abnormality after 4 years (Fig. 1E–H). This supports the notion that low-grade gliomas may remain stable for many years. Management for the resected IDH1 mutant low-grade glioma is to continue long-term imaging surveillance. IDH1 IHC testing in nondiagnostic biopsies does not eliminate the possibility of false-negative results from sampling error in suspected low-grade glial neoplasms when there is scant tissue present.

Funding

This research was funded by a grant from the Vanderbilt Institute for Clinical and Translational Research (VICTR).

Conflict of interest statement. None declared.

Mark D. Anderson, Ty W. Abel, and Paul L. Moots
Departments of Neurology (M.D.A., P.L.M.) and Pathology (T.W.A.), Vanderbilt University, Nashville, Tennessee

References


Corresponding Author: Mark D. Anderson, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 431, Houston, TX 77030 (mdanderson2@mdanderson.org).