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Biomarker-driven diagnosis of diffuse gliomas

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ABSTRACT

The diffuse gliomas are primary central nervous system tumors that arise most frequently in the cerebral hemispheres of adults. They are currently classified as astrocytomas, oligodendrogliomas or oligoastrocytomas and range in grade from II to IV. Glioblastoma (GBM), grade IV, is the highest grade and most common form. The diagnosis of diffuse gliomas has historically been based primarily on histopathologic features, yet these tumors have a wide range of biological behaviors that are only partially explained by morphology. Biomarkers have now become an established component of the neuropathologic diagnosis of gliomas, since molecular alterations aid in classification, prognostication and prediction of therapeutic response. *Isocitrate dehydrogenase (IDH)* mutations are frequent in grades II and III infiltrating gliomas of adults, as well as secondary GBMs, and are a major discriminate of biologic class. *IDH* mutant infiltrating astrocytomas (grades II and III), as well as secondary GBMs, are characterized by *TP53* and *ATRX* mutations. Oligodendrogliomas are also *IDH* mutant, but instead are characterized by 1p/19q co-deletion and mutations of *CIC, FUBP1*, *Notch1* and the *TERT* promoter. Primary GBMs typically lack *IDH* mutations and demonstrate *EGFR, PTEN, TP53, PDGFRA, NF1* and *CDKN2A/B* alterations and *TERT* promoter mutations. Pediatric gliomas differ in their spectrum of disease from those in adults; high grade gliomas occurring in children frequently have mutations in *H3F3A*, *ATRX* and *DAXX*, but not *IDH*. Circumscribed, low grade gliomas, such as pilocytic astrocytoma, pleomorphic xanthoastrocytoma and ganglioglioma, need to be distinguished from diffuse gliomas in the pediatric population. These gliomas often harbor mutations or activating gene rearrangements in *BRAF*.

Contents

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1. Introduction

Among primary brain tumors, gliomas are the largest and most diverse group (Louis et al., 2007; Ostrom et al., 2013). For purposes of pathologic diagnosis and patient management, they are subdivided into distinct classes according to clinical, neuroimaging, histopathologic and molecular genetic characteristics (Appin and Brat, 2014; Bourne and Schiff, 2010). The diffuse gliomas are a subset defined by their widely infiltrative properties, which make them impossible to completely resect, and their tendency toward biologically progression, which makes them ultimately fatal, yet with highly variable survival periods. Although they can occur throughout the neuraxis and at any age, they most frequently arise within the cerebral hemispheres of adults. The primary classes of diffuse gliomas are astrocytomas, oligodendrogliomas and oligoastrocytomas, and these are graded according to World Health Organization (WHO) criteria as grades II–IV (Louis et al., 2007). Glioblastoma (GBM) WHO grade IV is the highest grade and most frequent astrocytoma and has a dismal prognosis, with median survivals of one year (Ohgaki and Kleihues, 2013). Another class of gliomas are low grade, better circumscribed and associated with a more indolent clinical course (Rodriguez et al., 2013). These typically occur in children and adolescents, and include pilocytic astrocytomas, WHO grade I; pleomorphic xanthoastrocytomas (PXA), WHO grade II; and ganglioglioma, WHO grade I.

The diagnosis of glial neoplasms has been established primarily by histopathological examination since the early 1900s, when Bailey and Cushing first classified them based on their presumed histogenesis (Bailey and Cushing, 1926; Perry and Brat, 2010). This method is an inexpensive and efficient means for classifying and prognosticating based on morphologic features noted under the microscope. In these histologic schemes, diffuse astrocytomas are recognized by their irregular, elongated hyperchromatic nuclei and high degree of fibrillarity (Louis et al., 2007). Mitotic activity is associated with a shorter survival and is used as a grading criterion to distinguish infiltrating astrocytoma, WHO grade II, from anaplastic astrocytoma, WHO grade III. Likewise, necrosis and microvascular proliferation signal even more aggressive behavior and serve as criteria for GBM, WHO grade IV (Brat et al., 2008). By contrast, oligodendrogliomas have round, regular nuclei, perinuclear halos and a delicate branching ("chicken-wire") vasculature. Increased mitoses (≥6 per 10 high power fields), necrosis and microvascular proliferation are used as criteria to distinguish oligodendroglioma, WHO grade II, from anaplastic oligodendroglioma, WHO grade III (Giannini et al., 2001). The WHO has also recognized oligoastrocytomas, which show both astrocytic and oligodendroglial morphology, and grading schemes for this class have largely followed those of oligodendroglioma.

Though histologically classic cases of diffuse astrocytomas and oligodendrogliomas rarely cause diagnostic difficulty, examples with ambiguous morphology are common and criteria for diagnosing oligoastrocytoma vary considerably. Because of this, many studies have demonstrated low reproducibility and interobserver concordance in the diagnosis of diffuse gliomas, leading to confusion in clinical management. Similarly, correlations of histologic class with molecular markers, clinical behavior and response to therapies have been highly variable (Brat et al., 2008; Coons et al., 1997). Pilocytic astrocytomas, gangliogliomas and PXAs can also occasionally pose diagnostic challenges, yet their proper recognition is critical, since the treatment and prognosis differ from those of diffuse gliomas. Over the past 20 years, investigations of genomic alterations, gene expression and epigenetic changes of glial neoplasms have greatly informed our understanding of molecular classes of disease and have led to our current use of biomarker-driven glioma classification (Brat et al., 2015; Brennan et al., 2013; Rodriguez et al., 2013; Theeler et al., 2012).

2. *IDH* mutations subdivide infiltrating gliomas in adults into distinct subsets

The mutational status of *isocitrate dehydrogenase 1* and *2* (*IDH1* and *IDH2*) is now recognized as a major discriminator of biological classes among the diffuse gliomas (Fig. 1) (Parsons et al., 2008; The Cancer Genome Atlas Research Network, 2015; Yan et al., 2009). IDH normally catalyzes the oxidative decarboxylation of isocitrate, producing alpha-ketoglutarate and CO2. This enzyme has 3 isoforms: IDH1, IDH2 and IDH3. IDH3 catalyzes the third step of the citric acid cycle within the mitochondria. IDH1 and IDH2 catalyze this same reaction, but outside of the context of the citric acid cycle. Whereas IDH3 reduces NAD+ to NADH in this process, IDH1 and IDH2 use NADP+ instead. IDH1 is the only isoform localized to the cytoplasm (Xu et al., 2004). When mutations occur in *IDH1* or *IDH2*, the mutant enzyme develops a preferential affinity for alpha-ketoglutarate instead of isocitrate, which leads to the production and accumulation of the oncometabolite 2-hydroxyglutarate (Dang et al., 2009). Both *IDH1* and *IDH2* mutations occur in infiltrating gliomas, though *IDH2* mutations are much less common than *IDH1* (Hartmann et al., 2009; Yan et al., 2009). *IDH1* mutations are found in approximately 70–80% of histologic grades II and III infiltrating gliomas and secondary GBMs, yet are much less frequent in primary GBMs (~5%) (Liu et al., 2012; Ohgaki and Kleihues, 2011; Parsons et al., 2008; Watanabe et al., 2009; Yan et al., 2009). The most frequent *IDH1* mutation is R132H, which occurs at codon 132 and leads to exchange of the amino acid arginine for histidine (Balss et al., 2008; Mellai et al., 2011; Metellus et al., 2010; Watanabe et al., 2009; Yan et al., 2009). Infiltrating gliomas occurring in young adults are more likely to harbor an *IDH1* mutation than those in the elderly (Mellai et al., 2011; Metellus et al., 2010;