IDH1/IDH2 **mutation** (Non-core)

Reason/Evidentiary Support

IDH1/IDH2 Mutation and IDH1 R132H Expression (Immunohistochemistry)

Isocitrate dehydrogenase (IDH) is an enzyme that exists in five isoforms, each of which catalyses the reaction of isocitrate to α-ketoglutarate.[1] Mutations in *IDH1/IDH2* are frequent (greater than 80%) in WHO grades II and III astrocytomas but are found in only about 10% of the glioblastomas. Most glioblastomas that have progressed from lower-grade astrocytomas ('secondary glioblastomas) are IDH-mutant tumours.[2] The finding of IDH mutations in an infiltrating astrocytoma is associated with better prognosis, grade for grade. The 2016 CNS WHO divides diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma into classes that are IDH-mutant and IDH-wildtype. Oligodendrogliomas are now defined as diffuse gliomas with *IDH1/IDH2* mutations and whole arm deletions of chromosomes 1p and 19q. The mutant forms of *IDH1* and *IDH2* lead to the production of the oncometabolite 2-hydroxyglutarate, which inhibits the function of numerous α-ketoglutarate–dependent enzymes.[3] Inhibition of the family of histone demethylases and the ten-eleven translocation (TET) family of 5-methylcytosine hydroxylases has profound effects on the epigenetic status of mutated cells and leads directly to a hypermethylator phenotype that has been referred to as the glioma CpG island methylator phenotype (G-CIMP).[4]

IDH1 and *IDH2* mutations target the enzyme's active site and result in a substitution for a key arginine at codons R132 and R172, respectively.[2,5,6] The most frequent mutation, representing 92.7%, occurs at codon 132 of the IDH1 gene, and results in the substitution of arginine for histidine (R132H).[5] Less frequent *IDH1* mutations include R132C (4.2%), R132S (1.5%), R132G (1.4%), and R132L (0.2%).[5] Residue R172 in exon 4 of the *IDH2* gene is homologous to R132 in the *IDH1* gene, with R172K representing 64.5% of all *IDH2* mutations followed by R172M (19.3%), and R172W (16.2%).[5] *IDH2* mutations are much less frequent than *IDH1* mutations among diffuse gliomas (approximately 3%), but are slightly more common in oligodendrogliomas than astrocytomas.[5]

A monoclonal antibody has been developed to the mutant IDH1 R132H protein, allowing its use in FFPE specimens (mIDH1 R132H).[7] The ability of the antibody to detect a small number of cells as mutant makes this method more sensitive than sequencing for identifying R132H-mutant gliomas.[8,9] However, mutations in *IDH2* and other *IDH1* mutations will not be detected using immunohistochemistry with this antibody, and in the proper clinical setting, it may be necessary to test for other *IDH1* or *IDH2* mutations by sequencing analysis. It has been suggested that sequencing may not be warranted in the setting of a negative R132H immunostain in glioblastomas arising in patients older than 55 years due to the rarity of non-R132H *IDH1* and *IDH2* mutations in patients in this age group.[10,11] On the other hand, all diffusely infiltrating gliomas of WHO grade II and III that lack IDH1 R132H positivity by immunohistochemistry should be assessed for less common *IDH1* or *IDH2* mutations by sequencing or other appropriate methods.

References

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