Oligodendroglioma 1p/19q co-deletion

In the 2016 WHO classification of diffuse glioma, the diagnosis of an (anaplastic) oligodendroglioma requires the presence of both an IDH mutation (mt) and 1p/19q co-deletion. [1].

Complete deletion of both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) is pathognomonic for oligodendroglioma [2] [3] It is strongly associated with IDH mutation and is mutually exclusive of ATRX & TP53 mutations.

Codeletion of chromosomal arms 1p and 19q, in conjunction with a mutation in the isocitrate dehydrogenase 1 or 2 genes, is the molecular diagnostic criterion for oligodendroglioma, IDH-mutant and 1p/19q-codeleted. 1p/19q codeletion is a diagnostic marker and allows prognostication and prediction of the best drug response within IDH-mutant tumors.

TERT promoter mutations commonly occur concomitantly with 1p/19q co-deletion, [4] and are mutually exclusive in gliomas with TP53 mutations.

Loss of one arm of a hybrid chromosome is called loss of heterozygosity (LOH) for that chromosome region. LOH in 1p & 19q occurs as a result of unbalanced whole-arm translocations between chromosome 1 & chromosome 19, [5] which occurs early in the pathogenesis of oligodendrogliomas.

It is often sent out, results typically take 3–7 days. Cost for FISH is on the order of $200 U.S., PCR is $300–500 U.S.

Less invasive method for prediction of pathological type-even gene status-is desired.

11C methionine positron emission tomography/MRI based texture analysis and conventional features may be a promising noninvasive predictor for differentiating the varied gliomas [6].

In the revised 4th edition of the World Health Organization Classification of Tumors of the Central Nervous System 2016, classification of especially diffuse gliomas has fundamentally changed: for the first time a large subset of these tumours is now defined based on presence/absence of IDH mutation and 1p/19q co-deletion. Following this approach, the diagnosis of anaplastic oligoastrocytoma can be expected to largely disappear [7].

While in cases of histologically classical oligodendroglioma 1p/19q analysis is essential for making the final (integrated) diagnosis, this is less clear for cases with less pronounced oligodendroglial differentiation or even for histologically astrocytic tumors. The WHO Classification states that the presence of an astrocytic component is compatible with the diagnosis of oligodendroglioma when molecular testing reveals the entity-defining combination of IDH mutation and 1p/19q co-deletion.

This means that histologically pure astrocytomas do not need to be analyzed for 1p19q codeletion. On the other hand, in the review article written by the editors of the WHO Classification, it is stated that “genotype trumps histological phenotype”, i.e., a diffuse glioma that histologically appears astrocytic, but proves to have IDH mutation and 1p/19q co-deletion necessitates a diagnosis of oligodendroglioma, IDH-mutant, and 1p/19q-codeleted [8].

This means that 1p/19q analysis would be required in all cases of diffuse glioma. The most appropriate practical approach may depend on the amount/representativeness of the material in the individual case as well as on systematic studies revealing the actual frequency of this kind of constellation, i.e., completely disparate genotype versus histotype. Some clarification and ideally consensus appears useful.

Otani et al. analyzed 170 WHO grade II to IV gliomas resected in there institution. 1p/19q status was analyzed by microsatellite analysis, and genetic mutations were analyzed by next-generation sequencing and Sanger sequencing. For validation, the Brain Lower Grade Glioma dataset of the TCGA was analyzed. Of the 42 grade III IDH-mutated gliomas, 12 were 1p-intact/19q-intact (anaplastic astrocytomas: AA), 7 were 1p-intact/19q-loss (AA), and 23 showed 1p/19q-codeletion (anaplastic oligodendrogliomas: AO). Of the 88 IDH-wild type Glioblastomas, 14 showed 1p-intact/19q-loss status. All of the seven 1p-intact/19q-loss AAs harbored TP53 mutation, but no TERT promotor mutation. All 19q-loss AAs had regions presenting oligodendroglioma-like morphology, and were associated with significantly longer overall survival (OS) compared to 19q-intact AAs (p=0.001). This tendency was observed in the TCGA Lower Grade Glioma dataset. In contrast, there was no difference in OS between the 19q-loss Glioblastoma and 19q-intact Glioblastoma (p=0.4). In a case of 19q-loss AA, both oligodendroglial morphology and 19q-loss disappeared after recurrence, possibly indicating correlation between 19q-loss and oligodendroglial morphology. We showed that there was a subgroup, although small, of IDH-mutated astrocytomas harboring 19q-loss that present oligodendroglial morphology, and also were associated with significantly better prognosis compared to other 19q-intact astrocytomas [9].

In oligodendrogliomas, mutations in IDH1 and codeletion of chromosomes 1p and 19q are associated with improved survival with upfront use of combined chemotherapy and radiation, and these tumors also have unique mutations of CIC and FUBP1 genes

The 1p-/19q- combination appears to be an objective diagnosis marker of classic oligodendrogliomas, one that can be used, in combination with histological examination, to improve the diagnosis of oligodendroglioma. Fluorescence in situ hybridization on touch preparations is a simple way to obtain information on 1p-/19q- in 24 hours [10].

Chromosome 1p/19q deletion is an established prognostic and predictive marker in the WHO grade III oligodendroglial tumors (OT).

Oligodendroglioma patients with 1p/19q LOH and Sox17 protein expression had a better prognosis. Thus, analysis of 1p/19q LOH and Sox17 protein expression could significantly enhance diagnostic accuracy, guide treatment, and improve the prognosis [11].

The diagnosis and classification of diffusely infiltrative gliomas are based on their histopathological appearance; however, histopathological delineation of diffuse gliomas can be difficult because of vague and subjective histopathological criteria. Combined loss of chromosome arms 1p and 19q (denoted as 1p-/19q-) has proven to be a powerful predictor of chemotherapeutic response and survival in oligodendrogliomas.

Fluorescence in situ hybridization using probes specific for chromosomes 1 and 19 was performed on 22 paraffin-embedded tissues retrospectively; 15 touch-preparation smear samples were studied prospectively; and loss of heterozygosity (LOH) screening was performed on 11 samples with microsatellite markers specific to chromosome 1 and chromosome 19. Of the 37 cases, 24 had 1p-/19q-, 1 case had 1p- only, 2 cases had 19q- only, and 10 cases had no deletion. The length of the largest deletion was mapped between markers D1S2795 (1p36.31 locus) and D1S2722 (1p34.2 locus) and between markers D19S416 (19q13.11 locus) and D19S397 (19q13.14 locus), using LOH. All of the pure oligodendrogliomas (n=7) harbored 1p-/19q-. In light of previous findings, the 1p-/19q- combination appears to be an objective diagnosis marker of classic oligodendrogliomas, one that can be used, in combination with histological examination, to improve the diagnosis of oligodendroglioma. Fluorescence in situ hybridization on touch preparations is a simple way to obtain information on 1p-/19q- in 24 hours [12].

Adjuvant temozolomide chemotherapy was associated with a significant survival benefit in patients with newly diagnosed non-co-deleted anaplastic glioma. Further analysis of the role of concurrent temozolomide treatment and molecular factors is needed [13].

Determination

Brandner et al. performed a Cochrane review and simple economic analysis to establish the most sensitive, specific, and cost-effective techniques for determining 1p/19q co-deletion status. Fluorescence in situ hybridizations (FISH) and PCR-based loss of heterozygosity (LOH) test methods were considered as the reference standard. Most techniques (FISH, CISH, PCR, Real-time PCR, MLPA, SNP array, CGH, array CGH, next-generation sequencing, mass spectrometry, and NanoString) showed good sensitivity (few false negatives) for detection of 1p/19q codeletions in glioma, irrespective of whether FISH or PCR-based LOH was used as the reference standard. Both NGS and SNP arrays had a high specificity (fewer false positives) for 1p/19q codeletion when considered against FISH as the reference standard. Findings suggest that G-banding is not a suitable test for 1p/19q co-deletion analysis. Within these limits considering cost per diagnosis, and using FISH as a reference, Multiplex ligation-dependent probe amplification (MLPA) was marginally more cost-effective than other tests, although these economic analyses were limited by the range of available parameters, time horizon, and data from multiple health care organizations [14].

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