Significance of histopathological and molecular genetics investigations on the diagnosis and prognosis of astrocytic and oligodendrogial glioma

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INTRODUCTION

Gliomas represent the most common primary brain tumors. Despite their significant incidence their classification and grading remain controversial. For instance, there is a number of grading systems for glioma and the diagnosis of oligodendrogioma is highly subjective. To date, classification and grading has relied on histopathological and immunohistochemical findings. However, histological parameters have not explained differences in survival within this tumor group. The possibility of elucidating the molecular basis of glioma formation may impact both on diagnostic and therapeutic aspects of clinical neuro-oncology. The glioma of astrocytic and oligodendrogioma type are currently in the focus of molecular genetic analyses.

ASTROCYTIC GLIOMA

Diffuse astrocytic gliomas (low-grade astrocytoma - WHO grade II, anaplastic astrocytoma - WHO grade III and multiform glioblastoma - WHO grade IV) are the most common brain tumors. They have the tendency for malignant progression, with the multiform glioblastoma (GBM) as the most malignant phenotypic endpoint.

Histopathological diagnosis

The histopathological diagnosis of diffuse astrocytic glioma as well as WHO grade IV are made by applying the 2000 World Health Organization (WHO) criteria (1). These include: cell types (different forms of astrocytes, giant cells, small undifferentiated cells, spindle cells and oligodendrogioma cells); cell proliferation assessed by counting mitoses and by determining the fraction of Ki-67/MIB-1 positive nuclei; necrosis (not present, band-like with pseudopalsading, large ischaemic); microvascular proliferation (not present, moderate, extensive/glomeruloid); lymphocytic infiltration; thromboses; sarcomatous growth (not present, predominant - gliosarcoma) and expression of GFAP (glial fibrilar acidic protein).

Low-grade astrocytoma is predominantly manifested in young adults. It is characterized by high degree of cellular differentiation, slow growth, diffuse infiltration of neighboring structures and tendency for malignant progression to anaplastic astrocytoma and eventually to secondary glioblastoma. However, the majority of GBM develop de novo (primary GBM) without a recognizable less malignant precursor lesion (2,3). They manifest in older adult patients (mean 55 years) after a short clinical history of usually less than 3 months. Secondary GBM (the terms primary and secondary GBM were first used by Scherer in 1940) occur in younger age group (mean 39 years), show a slightly more favorable outcome and develop far less often than primary GBM. The time interval for progression from diffuse low-grade astrocytoma to secondary GBM varies considerably (mean 4-5 years). In regard to histopathological and immunohistochemical features there are no differences between primary and secondary GBM.

Molecular genetics

Molecular genetics of low-grade astrocytoma (WHO grade II) include point mutations in the p53 tumor suppressor gene. It was shown that the frequency of p53 mutations are very high (50%-80%) in low-grade astrocytomas which progress to GBM. Since approximately 25% of low-grade astrocytoma do not contain p53 mutation, other genetic alterations may be involved. These include loss of heterozygosity (LOH) on chromosomes 10p and 22q (17%) and chromosome 6 deletion (14%). Increased mRNA expression of PDGFRA is observed in astrocytic tumors of all stages, but gene amplification was only detected in a small subset of GBM.

Anaplastic astrocytoma (WHO grade III) has a high frequency of p53 mutations. Additional genetic changes found in some percentage of cases include p16 and p19 deletion, RB alterations, PTEN mutations, CDK4 amplification and LOH on chromosomes 10q (15-30%), 19q (40%) and 22q (30%) (4).

Recent studies have identified distinct molecular alterations in GBM, adding a novel set of parameters for evaluation of clinical course and therapeutic responses (5). The primary GBM are characterized by EGFR amplification (40% of cases) and/or overexpression (60%), CDKN2A, CDK4 and PTEN mutations (30%), RB alteration and p16 deletion (30-40%) (6). There is LOH on the entire chromosome 10 (50-80%) as well as on several chromosomal arms (1p, 9p, 13q, 17p, 19q, 22). The sequence in which gene alterations are acquired is not known since these neoplasms develop very rapidly, without a clinically or histopathologically identifiable precursor lesion (7). The p53 mutations are less common in primary GBM (>10%). Some of these cases have the phenotype of giant cell GBM. MDM2 overexpression/amplification is a genetic hallmark of primary GBM that lack a mutation.

Secondary GBM frequently contain p53 mutations of which >90% are already present in the first biopsy of low grade or anaplastic astrocytoma. Most likely, the p53 mutation is the initial gatekeeper lesion in astrocytic tumor which then, through genetic instability undergoes malignant progression (8). The pathway to secondary glioblastoma is further characterized by LOH on chromosome 17p and 10q (but not on the entire chromosome 10 as seen in primary GBM).

Pilocytic astrocytoma (WHO grade I) represents the most common glioma in children. In contrast to diffuse astrocytoma, this slow growing and circumscribed neoplasm is remarkable in maintaining WHO grade I status over years and even decades. The mutational inactivation of the p53 gene does not play a role in the evolution of this tumor (9).

Association between clinical and histopathological parameters and survival

The favorable parameters for GBM include younger age, good Karnofsky performance, lateral tumor localization, macroscopic complete resection, area of better histopathological differentiation and abundant presence of giant cells (gigantocellular GBM).

Association between molecular parameters and survival

Recent studies indicate that p53 mutations are a favorable prognostic factor independent of primary or secondary GBM. These mutations show the ten-
dency to occur more frequently in younger than in older GBM patients. This may explain the better survival associated with secondary GBM since these patients frequently combine 2 favorable parameters - younger age and p53 mutations. Some investigator reported that amplification and overexpression of EGFR gene is associated with poor prognosis, while others have not confirmed this finding (10). LOH10q is associated with poorer survival. High levels of expression of PTEN were found to be associated with longer survival. The genomic alterations of LOH1p and LOH19q, which are observed in the majority of oligodendroglioma, are also observed in GBM. However, in contrast to oligodendroglioma, in GBM loss of 19q is more likely to be partial than complete and loss of 1p is uncommon (approx. 10%). It was suggested that combined loss of chromosomal arms 1p and 19q might indicate the better prognosis and potential sensitivity to chemotherapy in GBM patients, while isolated loss of either 1p or 19q is of no prognostic significance. If this were to be confirmed, LOH analyses may allow identification of a subgroup of chemoresistive GBM patients that could not be distinguished by morphologic investigation (11).

OLIGODENDROGLIAL GLIOMA

Oligodendrogial glioma is moderately common brain tumor of adults that generally recur locally. Malignant progression on recurrence is not uncommon, although it is thought to be less frequent than in diffuse astrocytoma. The WHO grading system recognizes two malignancy grades for these neoplasms: WHO grade II for well differentiated and WHO grade III for anaplastic oligodendroglioma.

Histopathological diagnosis

The histopathological diagnosis of oligodendroglial tumors is highly subjective because there are no immunohistochemical markers available for their specific recognition and there are no reliable histological criteria by which well-differentiated oligodendroglioma can be separated from anaplastic examples. Most studies have supported a combination of histological parameters that may be associated with worse prognosis. These include cellular density, nuclear atypia, high mitotic activity, microvascular proliferation and necrosis. Nevertheless, application of these criteria to individual cases often reveals a lack of consistency and reproducibility in classifying oligodendroglial tumor among different observers.

Molecular genetics

Molecular genetic studies have shown that oligodendroglial tumors display distinctive genetic parameters that could provide an objective and reproducible framework for classifying these neoplasms. The oligodendroglial genetic profile consists of loss of the entire 1p (40%-90%) and 19q (50%-80%) chromosomal arms. Virtually all oligodendrogliomas with LOH on 1p have also lost alleles on 19q, a finding that suggests a synergistic effect of both alterations. In contrast to astrocytic tumors LOH on 17p is rare (<10%), as well as the mutations in the p53 gene (10-15%). Besides this, well-differentiated oligodendroglioma has the EGFR and PDGF/PDGF overexpression. Anaplastic oligodendroglioma shows LOH on several others chromosomes, most frequently 9p and 10q (less commonly) and homoygotic deletion of C6KN2 gene. EGFR or CDK4 amplification is restricted to small subsets (<10%) of these neoplasms (12).

Association between clinical and histopathological parameters and survival

Factors associated with more favorable prognosis of oligodendroglialoma include younger age, frontal lobe location, complete surgical removal and better histological differentiation. Recent studies have shown that high proliferative activity (Ki-67 labeling indices of higher than 3%) is indicative of a worse prognosis.

Association between molecular parameters and survival

Molecular findings are of great value for prognostic and therapeutic evaluation of oligodendroglialomas. Recent studies have indicated markedly improved prognosis of that oligodendroglioma with allelic losses on chromosomal arms 1p and 19q. These losses also may predict favorable response to chemotheraphy of anaplastic oligodendroglioma (14).

CONCLUSION

Histopathological evaluation should remain the chief support of brain tumor classification. Nevertheless, molecular genetic studies can play an important part in standardizing tumor categorization and resolving difficult diagnostic problems. These studies can be used to subdivide GBM into biologically distinct subsets and are currently being used to predict therapeutic response and survival in patients with anaplastic oligodendroglioma.

REFERENCES