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Molecular Diagnosis of Glial Neoplasms: A New Era

Gokden M*

Department of Pathology, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, USA

Editorial

Although genetic alterations involved in the development and progression of central nervous system (CNS) tumors and especially gliomas have long been recognized, identification of a number of molecular markers in these tumors has taken the center stage with the turn of this century due to the recognition of their role as diagnostic, prognostic and/or predictive markers. This not only allowed us to add molecular findings to our existing armamentarium, which largely consisted of morphology and special stains, but resulted in the recognition of specific entities characterized by specific molecular alterations, determination of the prognoses of some of these tumors based on the alterations they had, and development of specific therapies targeting certain tumors with particular molecular features. The impact of all these developments is reflected most recently in the revised 4th edition of World Health Organization (WHO) Classification of Tumours of the Central Nervous System [1]. This discussion is not meant to be an in-depth review of these discoveries, but rather, a reminder of the recent exciting changes in our approach to the biology, diagnosis and treatment of the tumors of the CNS.

One of the first of this group of genetic alterations that made its way into the diagnostic arena and had an impact in diagnostic neuropathology and neuro-oncology is codeletion of 1p and 19q in oligodendroglioma [2]. Although the diagnosis of typical oligodendroglial and astrocytic tumors by light microscopy had been straightforward, many of these tumors also had ambiguous cytohistomorphologic features that made accurate classification difficult, if not impossible, resulting in the diagnosis of oligoastrocytoma (the so-called intermingled histology), which admittedly, over time, turned into a wastebasket category for many cases. The histologic classification of these diffuse gliomas had a low diagnostic reproducibility among neuropathologists [3]. In spite of the recognition that codeletions of 1p and 19q were associated with oligodendrogliomas, much debate took place in the transition period over whether a subpopulation of oligoastrocytomas and astryctomas also could have this alteration, resulting in the realization that there are molecular subsets of these tumors [4], leading to the molecular classification of diffuse gliomas [5,6]. These and other studies now form the basis for the integrated diagnosis of CNS tumors emphasized in the current WHO classification [1].

Along similar lines, there has been a relatively recent explosion of additional markers, some of which also had an impact similar to and alongside 1p/19q codeletions. Isocitrate dehydrogenase 1 and 2 (IDH-1 and IDH-2, respectively) mutation analysis results have now been recognized as a must-have finding to report when a diagnosis of diffuse glioma is made, owing to their importance in the diagnosis and prognosis of these tumors [7]. IDH 1 and 2 mutations not only indicate a better prognosis, but they are useful to the neuropathologist for the dreaded differential diagnosis of neoplastic versus reactive glial proliferations and other well-circumscribed, low-grade glial or glioneuronal tumors such as pilocytic astrocytoma, ganglioglioma and dysempbroplastic neuroepithelial tumor in small tissue samples due to their presence exclusively in diffuse gliomas.

Loss of nuclear alpha thalassemia/mental retardation syndrome/X-linked (ATRX) expression by immunohistochemistry has been associated with astrocytic lineage in diffuse gliomas [8] and this parameter has been incorporated into the molecular classification of these tumors [6]. Testing for mutations in the BRAF gene brings to the table a useful tool to aid in the differential diagnosis of well-circumscribed gliomas from diffuse gliomas [9] due to its higher frequency in pleomorphic xanthoastrocytoma and ganglioglioma in contrast to diffuse astrocytomas. In addition, a smaller percentage of supratentorial pilocytic astrocytomas show the mutation in BRAF V600E, while cerebellar pilocytic astrocytomas have a higher frequency of BRAF/KIAA fusion. Immunohistochemistry is now available to identify BRAF V600E mutation on paraffin sections [10]. Additional recently-identified alterations applicable to glial neoplasms and their diagnosis are H3 K27M mutation, associated with the midline gliomas, leading to the specific diagnosis of "diffuse midline glioma, H3 K27M-mutant", imparting a grim prognosis [11]. This replaces the former designations of brain stem glioma and diffuse intrinsic pontine glioma. Although ependymal

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Correspondence:
Murat Gokden, Department of Pathology, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, 4301 West Markham Street, #517, Little Rock, Arkansas 72205, USA
Tel: 501-526-7746; Fax: 501-603-1479;
E-mail: mgokden@uams.edu

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neoplasms have been classified more definitively according to their location and age, along with their genetic alterations, "ependymoma, *RELA* fusion-positive" is currently the only well-established ependymoma in this group. *RELA* fusion is a supratentorial ependymoma, which can be WHO grade II or III (anaplastic) and has a worse prognosis [12].

Many advances have also been made and integrated into the diagnostic practice with subsequent prognostic and predictive implications in other tumor categories and will not be further discussed here. Most notable ones are the molecular classification of medulloblastomas by incorporating sonic hedgehog and WNT pathways. A new entity called embryonal tumor with multilayered rosettes, C19MC-altered, has taken its place in the new WHO Classification [1]. With these and other similar advances, the concept of "integrated diagnosis" of the tumors of the CNS has also emerged. The diagnostic line will now not only mention the usual histological appearance (such as diffuse astrocytoma), WHO grade (such as WHO grade II), but also the ancillary test results (such as IDH-mutant).

These improvements and their integration into the diagnosis and differential diagnosis of these tumors, leading to their refined classification, bring along potential drawbacks, most notably the issues of availability of these techniques in pathology laboratories and access to them by the practicing pathologists. Given the differences and many times large gaps among various institutions' technical capabilities and the availability of expertise in the performance and interpretation of these tests, as well as the availability of diagnostic neuropathology expertise, it can be argued that the consistency and reproducibility of the final diagnoses may be low. On the other hand, better defined and stricter diagnostic criteria, such as in the differentiation of gliomas of oligodendroglial and astrocytic lineage based on their molecular profiles, should more than compensate for these differences, especially with the availability of these molecular tests in many large medical centers and in commercial laboratories. As mentioned before, immunohistochemical staining techniques are also emerging as surrogate markers for these molecular alterations, rendering their identification more feasible, cost- and time-efficient. In more complicated situations, the time-honored practice of consultation should clarify many, if not all, of the remaining non-technical, expertise-related issues.

Overall, the accumulation of data in all aspects of neuro-oncology has necessitated this integration of molecular and genetic findings into what we already have known and practiced, leading us to this new era of molecular diagnostics and targeted therapies. All these, in a way, are reminiscent of the times when immunohistochemistry was emerging as the state of the art, sophisticated diagnostic tool about four decades ago. Likewise, we will soon become very well-familiar with all the intricacies of molecular test selection and relevance, as well as interpretation and incorporation of their results into patient care.

References

1. WHO Classification of Tumours of the Central Nervous System, revised 4th edition. Editors: Louis, DN, Ohgaki H, Wiestler OD, Cavenee WK. IARC: Lyon, 2016.
2. Reifenberger J, Reifenberger G, Liu L, James CD, Wechsler W, Collins VP. Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. Am J Pathol. 1994; 145: 1175-1190.
3. Coons SW, Johnson PC, Scheithauer BW, Yates AJ, Pearl DK. Improving diagnostic accuracy and interobserver concordance in the classification and grading of primary gliomas. Cancer. 1997; 79: 1381-1393.
4. Maintz D, Fiedler K, Koopmann J, Rollbrocker B, Nechev S, Lenartz D, et al. Molecular genetic evidence for subtypes of oligoastrocytomas. J Neuropathol Exper Neurol. 1997; 56: 1098-1104.
5. Mur P, Mollejo M, Hernandez-Iglesias T, Rodriguez de Lope A, Castresana JS, Garcia JF, et al. Molecular classification defines 4 prognostically distinct glioma groups irrespective of diagnosis and grade. J Neuropathol Exper Neurol. 2015; 74: 241-249.
6. Reuss DE, Sahm F, Schrimpf D, Wiestler B, Capper D, Koelsche C, et al. ATRX and IDH1-R132H immunohistochemistry with subsequent copy number analysis and IDH sequencing as a basis for an "integrated" diagnostic approach for adult astrocytoma, oligodendroglioma and glioblastoma. Acta Neuropathol. 2015; 129: 133-146.
7. Horbinski C. What do we know about IDH1/2 mutations so far, and how do we use it? Acta Neuropathol. 2013; 125: 621-636.
8. Abedalthagafi M, Phillips JJ, Kim GE, Mueller S, Haas-Kogen DA, Marshall RE, et al. The alternative lengthening of telomere phenotype is significantly associated with loss of ATRX expression in high-grade pediatric and adult astrocytomas: a multi-institutional study of 214 astrocytomas. Modern Pathol.2013; 26: 1425-1432.
9. Horbinski C. To BRAF or not to BRAF: Is that even a question anymore? J Neuropathol Exper Neurol. 2013; 72: 2-7.
10. Ida CM, Vrana JA, Rodriguez FJ, Jentoft ME, Caron AA, Jenkins SM, et al. Immunohistochemistry is highly sensitive and specific for detection of BRAF V600E mutation in pleomorphic xanthoastrocytoma. Acta Neuropathol Comm. 2013; 1: 20.
11. Hawkins C, Ellison DW, Sturm D. Diffuse midline glioma, H3 K27M-mutant, in: WHO Classification of Tumours of the Central Nervous System revised 4th edition. Editors: Louis, DN, Ohgaki H, Wiestler OD, Cavenee WK. IARC: Lyon, 2016; 57-59.
12. Ellison DW, Korshunov A, Witt H: Ependymoma, *RELA* fusion-positive, in: WHO Classification of Tumors of the Central Nervous System, revised 4th edition. Editors: Louis, DN, Ohgaki H, Wiestler OD, Cavenee WK. IARC: Lyon, 2016; 112.