What’s New from the WHO in Brain Tumor Classification: Preview of 2016 through Illustrative Cases
CSP Video Tutorial
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Cases for discussion

1. Frontal lobe mass in a 33 year old male
2. Frontal lobe mass in a 24 year old female
3. Ring enhancing parietal mass in a 26 year old male
4. Enhancing posterior fossa mass in a 5 year old male
5. 42 year old female with posterior fossa mass with hydrocephalus
6. 17 year old male with well-circumscribed enhancing temporoparietal tumor
**Oligodendrogliaoma in the WHO 2016**

Oligodendrogliaoma, IDH mutant and 1p/19q codeleted
Oligodendrogliaoma, NOS

Anaplastic oligodendrogliaoma, IDH mutant and 1p/19q codeleted
Anaplastic oligodendrogliaoma, NOS

- “NOS”: A diffusely infiltrating WHO grade II glioma with classic oligodendrogial histology for which molecular testing for combined IDH mutation and 1p/19q codeletion could not be fully performed or remained inconclusive.

- An astrocytic tumor morphology is compatible with the diagnosis of oligodendrogliaoma when molecular testing reveals the entity-defining combination of IDH mutation and 1p/19q codeletion.”

- Rare tumors may demonstrate classic oligodendrogial histology but lack IDH mutation and 1p/19q codeletion upon molecular testing, a situation most frequently encountered in pediatric oligodendrogliomas. These tumors should not be classified as oligodendrogliaoma, NOS, but need to be further evaluated to exclude histological mimics like dysembryoplastic neuroepithelial tumor, clear cell ependymoma, neurocytoma, pilocytic astrocytoma and others. Once these histological mimics are excluded, such tumors may be tentatively classified as “oligodendrogliaoma lacking IDH mutation and 1p/19q codeletion” (“pediatric oligodendrogliaoma”).

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**Oligoastrocytoma. WHO 2016: Possible in principle, but a bad diagnosis**

Oligoastrocytoma, NOS
Anaplastic oligoastrocytoma, NOS

- A diffusely infiltrating, slowly growing glioma that is (i) composed of a conspicuous mixture of two distinct neoplastic cell types morphologically resembling tumor cells with either oligodendroglial or astrocytic features and (ii) for which molecular testing could not have been performed or remained inconclusive.

- Oligoastrocytoma, NOS, is an exceptional diagnosis, as most diffuse gliomas with mixed or ambiguous histology can be assigned to either diffuse astrocytoma, IDH mutant, or oligodendroglioma, IDH mutant and 1p/19q codeleted, based on molecular testing.

- “The new WHO classification discourages the diagnosis of oligoastrocytoma or mixed glioma.”
Diffuse astrocytoma. WHO 2016

- Diffuse astrocytoma, IDH wild-type, is rare, since most gliomas with a histological appearance resembling diffuse astrocytoma but without IDH gene mutation can be reclassified as other tumors with additional genetic analyses. Tumors that fit into this diagnosis most likely constitute a variety of entities and therefore may follow a broader range of clinical courses.

Changes from initial WHO to integrated diagnosis in 160 patients with IDH wt astrocytoma. Width of bars indicates relative proportions of the initial tumor groups.
- A II: diffuse astrocytoma WHO grade II
- AA III: anaplastic astrocytoma WHO grade III
- GBM: glioblastoma
- GBM-H3: glioblastoma H3F3A mutated
- MID-HGG: midline high grade glioma


Astrocytoma and oligodendroglioma are now genetically defined

Definitions from WHO 2016:
- Diffuse astrocytoma, IDH mutated: “The presence of an oligodendroglioma morphology is compatible with this diagnosis in the absence of 1p/19q codeletion”
- Oligodendroglioma, IDH mutated and 1p/19q-co-deleted: “An astrocytic tumor morphology is compatible with the diagnosis of oligodendroglioma when molecular testing reveals the entity-defining combination of IDH mutation and 1p/19q codeletion.”

Table 5. Example of integrated diagnoses for WHO grade II adult diffuse gliomas

<table>
<thead>
<tr>
<th>Molecular information</th>
<th>Diffuse astrocytoma</th>
<th>Oligodendroglioma</th>
<th>“Oligoastrocytoma” or ambiguous histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH-mut, 1p/19q-mendel, ATRX loss</td>
<td>Diffuse astrocytoma, ATRX loss of expression</td>
<td>Diffuse glioma* oligodendroglioma phenotype, 1p/19q non-deleted, ATRX loss of expression</td>
<td>Diffuse astrocytoma, ATRX loss of expression</td>
</tr>
<tr>
<td>IDH-mut, 1p/19q-code, ATRX intact</td>
<td>Diffuse glioma (astrocytoma phenotype, 1p/19q-codeleted)</td>
<td>Oligodendroglioma, 1p/19q-codeleted</td>
<td>Oligodendroglioma, 1p/19q-codeleted</td>
</tr>
<tr>
<td>IDH wild type</td>
<td>Diffuse astrocytoma, IDH wild type*</td>
<td>Diffuse glioma* oligodendroglioma phenotype, IDH wild type*</td>
<td>Diffuse astrocytoma, IDH wild type*</td>
</tr>
<tr>
<td>Testing not performed</td>
<td>Diffuse astrocytoma, NOS</td>
<td>Oligodendroglioma, NOS</td>
<td>“Diffuse glioma, NOS”</td>
</tr>
</tbody>
</table>
Glioblastoma. WHO 2016

Glioblastoma, IDH wild-type
Giant cell glioblastoma
Gliosarcoma
Epithelioid glioblastoma
Glioblastoma, IDH mutant
Glioblastoma, NOS

Definition: A high-grade glioma with predominantly astrocytic differentiation; featuring nuclear atypia, cellular pleomorphism in most cases, mitotic activity and typically a diffuse growth pattern, as well as microvascular proliferation and/or necrosis.

The designation "IDH wild-type" should ideally be used if 1) mutant R132H IDH1 immunohistochemistry and 2) subsequent IDH1/2 sequencing both reveal wildtype sequences for IDH1 codon 132 and IDH2 codon 172. However, there are situations in which it may, for practical purposes, be sufficient to rely on negative R132H IDH1 immunohistochemistry alone, most notably in an older patient with a histologically classical glioblastoma that is not occurring in a midline location (unless an H3 K27M mutation has also been excluded) and without prior history of a pre-existing lower grade glioma. An exact age cut-off is not possible, but one algorithm has suggested that, in the setting of negative R132H IDH1 immunohistochemistry in a glioblastoma from a patient without prior lower-grade glioma, the likelihood of an alternative IDH mutation is less than 6% in a 50-year-old patient and falls to less than 1% in patients older than 54 years. The designation "IDH wild-type" can therefore safely be applied in this setting even in the absence of IDH sequencing.

Glioblastoma in WHO 2016

Glioblastoma, IDH wild-type
Giant cell glioblastoma
Gliosarcoma
Epithelioid glioblastoma
Glioblastoma, IDH mutant
Glioblastoma, NOS

In younger patients, certain findings should even more strongly suggest the need for IDH sequencing prior to designating a tumor "IDH wild-type": a history of a lower-grade glioma or absence of nuclear ATRX expression (particularly if p53 immunohistochemistry shows strong and diffuse nuclear positivity and in the absence of H3F3A K27M staining). In such a setting, if IDH sequencing cannot be performed, a diagnosis of Glioblastoma, NOS should be rendered along with a note stating that R132H immunohistochemistry was negative.
Glioblastoma. WHO 2016

- Glioblastoma, IDH wild-type
- Giant cell glioblastoma
- Gliosarcoma
- Epithelioid glioblastoma
- Glioblastoma, IDH mutant
- Glioblastoma, NOS

Epithelioid glioblastoma

- Differential diagnosis: melanoma
- Often in young patients
- Can be cytokeratin positive
- Can be associated with PXA
- 50% BRAF V600E mutation:
- Treatment with BRAF inhibitor?

Pilocytic astrocytoma. WHO 2016

- Pilocytic astrocytoma
  - Pilomyxoid astrocytoma

**Definition:**
An astrocytoma classically characterized by a biphasic pattern with varying proportions of compacted bipolar cells with Rosenthal fibers and loose textured multipolar cells with microcysts and occasional granular bodies. Genetically, pilocytic astrocytomas are characterized by the presence of mutations of genes coding for proteins involved in the Mitogen Activated Protein Kinase (MAPK) pathway.

- BRAF fusions are present in nearly 70% of all PAs, compared to about 15% of all other low-grade gliomas in the differential
- BRAF fusions are seen in approximately 75 to 80% of cerebellar PAs and 55% of noncerebellar (mostly supratentorial) PAs
- BRAF alteration with the constitutively active V600E point mutation in 10% of PAs (but only 2% of cerebellar tumors).
**Medulloblastoma. WHO 2016**

- **Medulloblastoma, genetically defined**
  - Medulloblastoma, WNT activated
  - Medulloblastoma, SHH activated, TP53 mutated
  - Medulloblastoma, SHH activated, TP53 wild-type
  - Medulloblastoma, non-WNT/non-SHH
  - **Medulloblastoma, group 3**
  - **Medulloblastoma, group 4**

- **Medulloblastoma, histologically defined**
  - Medulloblastoma, classic
  - Medulloblastoma, desmoplastic/nodular
  - Medulloblastoma with extensive nodularity
  - Medulloblastoma, large cell/anaplastic
  - **Medulloblastoma, NOS**

- "A histopathological classification is retained because of its clinical utility when molecular analysis is limited or not feasible."
- "Group 3 / 4 tumors are listed as provisional variants, because they are less well separated than WNT and SHH medulloblastomas in molecular clustering analyses and by most current clinical laboratory assays."

**Medulloblastoma. WHO 2016**

**Molecular Subgroups of Medulloblastoma**

<table>
<thead>
<tr>
<th>CONSENSUS</th>
<th>WNT</th>
<th>SHH</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chio (2010)</td>
<td>A</td>
<td>B</td>
<td>C/D</td>
<td>C/D</td>
</tr>
</tbody>
</table>

**DEMOGRAPHICS**

- **Gender:**
  - Male
  - Female

**CLINICAL FEATURES**

- **Histology:**
  - Classic
  - SHH

- **Metastasis:**
  - Common
  - Rare

- **Prognosis:**
  - Excellent
  - Intermediate

**GENETICS**

- **CTNNB1 mutation:**
  - Yes
  - No

- **WNT signaling:**
  - Activated
  - Inactivated

- **SHH signaling:**
  - Activated
  - Inactivated

- **Other mutations:**
  - APC
  - TP53
  - NOTCH1

**GENE EXPRESSION**

- **Neural/Neuroglial:**
  - High
  - Low

**10% 30% 20% 40%**

*Acta neuropathologica, April 2012*
Ependymoma. WHO 2016

Subependymoma
Myxopapillary ependymoma
Ependymoma
Papillary ependymoma
Clear cell ependymoma
Tanyctytic ependymoma
Ependymoma, RELA fusion-positive
Anaplastic ependymoma

RELA fusion-positive
- 70% of childhood supratentorial ependymomas
- Rare in adults
- Unfavorable prognosis

Example of WHO 2016 at a transitional stage

Molecular Subgrouping of Ependymal Tumors is Superior to Histopathological Grading for Risk Stratification

New word for the day! Chromothripsis

- WHO 2016 features a new, separate ependymoma subtype: RELA fusion-positive ependymoma

- RELA fusion refers to the juxtaposition of the RELA gene (the principle effector of NF-κB signaling which controls DNA transcription and cell survival) to the poorly characterized C11orf95 gene.

- Fusion of these two genes is brought about by chromothripsis, a term first coined in 2011 that literally means "chromosome shattering".

- Chromothripsis occurs when chromosomal segments first fragment into many pieces and then get stitched back together in random order by DNA repair processes.

- Seen in the setting of some malignancies, chromothripsis in a particular segment of chromosome 11 can result in C11orf95-RELA fusion, which in turn drives oncogenic NF-κB signaling in ependymoma.

- Although chromothripsis is a novel model for oncogenesis, it does not necessarily contradict more established models of progressive cancer development as there is no definitive proof that chromothripsis has to occur as a single catastrophic event. Nevertheless, this is a fascinating area of research which will undoubtedly yield more insights into the progression of at least a subset of cancers.

Neuropathology blog, posted October 1, 2015
http://neuropathologyblog.blogspot.com/

Final diagnoses

1. Frontal lobe mass in a 33 year old male: Oligodendroglioma WHO Grade II

2. Frontal lobe mass in a 24 year old female: Anaplastic astrocytoma WHO Grade III

3. Ring enhancing parietal mass in a 26 year old male. Epithelioid GBM WHO Grade IV

4. Enhancing posterior fossa mass in a 5 year old male. Pilocytic astrocytoma WHO Grade I

5. 42 year old female with posterior fossa mass with hydrocephalus. Medulloblastoma WHO Grade IV

6. 17 year old male with well-circumscribed enhancing temporoparietal tumor. Anaplastic RELA fusion-positive ependymoma WHO Grade III