Classification of Diffuse Gliomas: Progress, Pearls and Pitfalls

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Objectives

• Explain why the designation ‘high grade glioma’ is preferable to ‘GBM’ for intraoperative diagnosis.

• State the diagnostic pathologic requirements for the diagnosis of oligodendroglial glioma.

• Recognize that retained ATRX immunostaining suggests 1p/19q codeletion in IDH-mut glioma.
Illustrative Case 1

- 34 yo woman
- Severe headaches
- Left frontal mass resected
- Received chemotherapy (PCV)
- Recurred 13 years later
- Re-resection specimen sent to Moffitt for review
GFAP

ATRX

Mutant IDH1 R132H

Ki-67 5%
Diagnosis

• POSITIVE for 1p/19q codeletion
• Oligodendroglioma WHO grade 2
  – IDH mutated
  – ATRX retained
  – Does not meet criteria for anaplastic oligo
Glial neoplasms

- Resemble astrocytes, oligodendrocytes or ependyma
  - Precursor cells unknown in most cases
- Diffuse vs circumscribed
- Incidence depends on age, location
  - Childhood
    - Cerebrum – diffuse or pilocytic astrocytoma
    - Brainstem - diffuse or exophytic astrocytoma, ependymoma
    - Cerebellum – pilocytic astrocytoma, ependymoma
    - Spinal cord – diffuse or pilocytic astrocytoma, ependymoma
  - Adults
    - Cerebrum – astrocytoma, oligodendroglioma, ependymoma
    - Others similar to childhood but relatively less frequent
- WHO Grades 1-4, depends on histologic subtype
Diffuse Gliomas

- **IDH-mutated**
  - Astrocytoma (including grade 4 => glioblastoma-IDH-mut)
  - Oligodendroglioma (including grade 3 => anaplastic)

- **IDH-wildtype**
  - Glioblastoma (including ‘pre-GbM’ or undersampled)
  - Epithelioid GbM
  - Diffuse midline glioma, histone H3 K27M-mutant
  - Hemispheric GbM, histone H3F3A G34R/V mutation

- **IDH-unknown**
  - ‘NOS’ => incomplete work-up
Oligodendroglioma

- Neoplastic cells resemble oligos: small, round
  - Morphology no longer a criterion for classification
- WHO grades 2 or 3, never grade 4
- Requires IDH-mutation and 1p/19q codeletion
  - TERT promoter mutation in > 90%
- Other characteristics
  - CIC (>50%)
  - FUBP1 (25%)
  - Notch1
  - PIK3CA
Diagnosis of Diffuse Glioma

• STEP ONE:
  – Nuclear atypia required to label as ‘neoplasm’
  – Hypercellularity, satellitosis, aggregation helpful

• IDH Status is now STEP TWO
  – Most common IDH mutation is IDH1 R132H, but
    • About 10% of IDH-mut are not IDH1 R132H
    • IDH2 mutations rare, usually R172H
    • Fundamental to pathobiology, diagnosis, progression, treatment response, outcome

• IDH R132H immunopositivity is **diagnostic** even without nuclear atypia or hypercellularity (peripheral margin)
IDH-Mutation is Carcinogenic

- Mutant IDH generates 2-hydroxyglutarate (2-HG)
  - Disrupts chromatin structure
  - Global hypermethylation/ g-CIMP
- Likely early (?initiating) event
  - Not documented before mid-teens
  - Subsequent genetic and epigenetic events determine phenotype and grade
IDH-mutation status is clinically relevant

Survival of glioblastoma patients treated with surgery plus radiotherapy.

Mutated IDH1
(median, 24.0 months, n=17)

Wild-type IDH1
(median, 9.9 months, n=186)


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IDH1 (C2) or IDH2 (C15) mutations

Astrocytoma WHO grade 2 or 3 (80%)
  Negative for 1p/19q codeletion (by definition)

Oligodendroglioma grade 2 or 3 (by definition)
  Positive for 1p/19q codeletion (by definition)

Glioblastoma: fewer than 10% have IDH-mutation
Telomeres in Diffuse Gliomas

- **Telomerase** – RNA/protein complex: hTERT subunit
  - TERT promoter mutations common in gliomas
- **Alpha thalassemia/mental retardation syndrome X-linked (ATRX)**
  - Linked to epigenetic stability/chromatin remodelling
  - ATRX(-) tumors exhibit alternate lengthening of telomeres
  - Mutated/lost in a variety of neoplasms including gliomas
ATRX loss of expression in tumor cells

If 1p/19q is codeleted: ATRX is retained
   hTERT promoter mutations in >90%
   No quick test for HTERT promoter mutation (yet)

If 1p/19q is not codeleted: ATRX is usually lost
   Some astrocytomas do not show ATRX loss (?significance)

Preliminary Classification of IDH-mutated Gliomas
   In practice, ATRX loss is highly predictive of astrocytoma
   Retained ATRX is highly suggestive of oligodendroglioma
Illustrative Case 2

- 74 yo woman
- Gradually progressive personality change
Diagnosis:
Glioblastoma- IDH-mutated, WHO grade 4
ATRX lost, TP53 mutated

NEGATIVE for 1p/19q codeletion
Clinical course

2 year follow-up imaging: no recurrence
Illustrative Case 3

• 54 yo woman
• Generalized seizure
• Left frontoparietal mass previously resected
• Aphasia prompted rescanning
Diagnosis

• Anaplastic oligodendroglioma WHO grade 3
  – Positive for IDH R132H mutation
  – Retained ATRX
  – Positive for 1p/19q codeletion
  – Positive for KRAS, EGFR and PIK3CA mutations

Contrast enhanced, 2 years after recurrence & Chemoradiotherapy
Grading of Diffuse Gliomas

• Features predicting progression (i.e. grade)
  – Mitotic figures (any, in A, >5/10 hpf for OGD)
  – Vascular proliferation (glomeruloid)
  – Necrosis (with or without palisading)
  – None of these features is helpful for diagnosis, since they may occur in non-neoplastic conditions

• Astrocytoma can be grade 2, 3 or 4 (=GbM)
  – Add one grade per met criterion

• Oligo can be 2 or 3 (= anaplastic OGD)
Mutations vs Age in HGG

[courtesy Dr Cynthia Hawkins]
Survival data of molecular subtypes

Conclusions

• IDH mutational status is essential for glioma diagnosis
  – IDH-mut gliomas are either:
    • astrocytoma (ATRX lost) WHO grades 2, 3 or 4 (GbM);
    or
    • oligodendroglioma (1p/19q codel) WHO grades 2 or 3
• IDH-wildtype GBM is a mixed bag
  – Adult IDH-wt gliomas are underdiagnosed GBMs
• Intraoperative diagnosis of GBM is hazardous
  – If IDH-mut and 1p/19q codeleted, AO grade 3
  – More accurate to use ‘high grade glioma’
Questions?