Disclosure of Relevant Financial Relationships

Dr. Fausto J. Rodriguez declares his affiliation with Johns Hopkins Pathology and may receive royalties from the Surgical Neuropathology App illustrated in Selected Slides

Clinical History

- 65 year-old male developed word-finding difficulties and increased forgetfulness for 1 week

Clinical History

- Left sided craniotomy with resection of the mass was performed.
Diagnosis
Glioblastoma, IDH-wildtype
( WHO 2016)

Layered Diagnosis
• Integrated: Glioblastoma, IDH-wildtype, WHO grade IV
• Histological Classification: Infiltrating astrocytoma
• WHO grade: IV
• Molecular Information:
  • PIK3CA mutation, TP53 mutation, MGMT gene methylation, partial 1p/19q deletions
  • IDH1, IDH2, BRAF, ATRX wildtype

Gliomas
WHO Classification 2007
• I-Astrocytic Tumors
  • Pilocytic Astrocytoma (WHO grade I)
  • Pleomorphic Xanthoastrocytoma (WHO grade II)
  • Diffuse Astrocytoma (WHO grade II)
  • Anaplastic Astrocytoma (WHO grade III)
  • Glioblastoma (WHO grade IV)
• II-Oligodendroglial tumors
  • Oligodendroglioma and oligoastrocytoma (WHO grade II)
  • Anaplastic Oligodendroglioma and OA (WHO grade III)
• III-Ependymal Tumors
Gliomas
WHO Classification 2016
- Diffuse astrocytoma, IDH-mutant
- Diffuse astrocytoma, IDH-wildtype
- Diffuse astrocytoma, NOS
- Anaplastic astrocytoma, IDH-mutant
- Anaplastic astrocytoma, IDH-wildtype
- Anaplastic astrocytoma, NOS
- Glioblastoma, IDH-wildtype
- Glioblastoma, IDH mutant
- Glioblastoma, NOS

Gliomas
WHO Classification 2016
- Diffuse midline glioma, H3 K27M-mutant
- Oligodendroglioma, IDH-mutant and 1p/19q codeleted
- Oligodendroglioma, NOS
- Anaplastic oligodendroglioma, IDH-mutant and 1p/19q codeleted
- Anaplastic oligodendroglioma NOS
- Oligoastrocytoma, NOS
- Anaplastic oligoastrocytoma, NOS

Oligodendroglial Neoplasms
Pathology
- Includes oligodendrogliomas (WHO grade II-III)
- Grading based on brisk mitotic activity/endothelial changes/necrosis (grade III)
- Improved prognosis and treatment sensitivity compared to infiltrating astrocytomas

Oligodendroglial Neoplasms
Low grade (II)

Oligodendroglial Neoplasms
Anaplastic (WHO grade III)
Oligodendrogial Neoplasms

1p19q codeletion
- Present in the majority of oligodendrogliomas (up to 90% of grade II, 60% of grade III)
- Strongly associated with “classic” oligodendrogliarial histology
- Associated with improved prognosis and responsiveness to treatment

1p19q in Oligodendrogial Neoplasms

Testing methods
- Fluorescence in situ hybridization (FISH)
- Microsatellite Analysis
- Copy number array analysis
  - Comparative genomic hybridization (CGH)
  - Single nucleotide polymorphism (SNP)

Problems in current assays (FISH, STR)
- The probes or primers interrogate only small portions of the chromosomes.
  - Small deletions can be missed or misinterpreted as involving the whole arm.
- STR loci are not always informative; i.e. some of them could be germline homozygous.
  - STR analysis of normal tissue of the same patient helps to resolve the problem, but not always available.
- FISH can detect only deletions but not copy neutral-LOH
- STR cannot distinguish CN-LOH from deletions

Mechanism

Copy Number Determination
- B allele frequency (BAF) / Allele Ratio
  - Discrimination between the A and B alleles performed by a single nucleotide extension step using two dye chemistry
- Copy Number
- Log R Ratio (LRR)
  - The sum of the measured intensities compared to normal controls

HumanCytoSNP12v1 BeadChip microarray
- B allele frequency
- Copy Number
- Log R Ratio

~300,000 markers (~13,000 on 1p and ~6000 19q)
1p19q deletion

- STR: LOH
- SNP Array: del 1p12->pter, del 19q13.11->qter

1p19q in Oligodendrogial Neoplasms Diagnostic Usefulness

- Anaplastic oligodendroglioma vs. small cell astrocytoma
- Oligodendroglioma vs. morphologic mimics (DNET, clear cell ependymoma, central neurocytoma)
- Exception: extraventricular neurocytoma

Specific Genetic Predictors of Chemotherapeutic Response and Survival in Patients With Anaplastic Oligodendrogliomas


Kaplan-Meier estimates of overall survival by treatment for patients with 1p/19q codeleted anaplastic oligodendroglioma (AO)/anaplastic oligoastrocytoma (AOA).

Gregory Cairncross et al. JCO 2013;31:337-343
Overall survival in both treatment arms for (A) the patients with 1p/19q-codeleted tumors (n = 80) and (B) the patients with non-1p/19q-codeleted tumors (n = 236).

- Analysis of 491 glioblastomas
- 28 cases with 1p/19q codeletion by FISH or LOH studies
- 1/26 cases codeletion by both
- 1/28 cases with IDH1 pR132H
- No impact on survival
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