Clinicopathological characterization of gliomas with *H3 K27M* mutation: a case series

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Background

31st European Congress of Pathology
Pathology is Nice
7 – 11 September 2019, Nice, France

WHO Classification of Tumours of the Central Nervous System

Background
**Diffuse midline glioma, H3 K27M-mutant**

**Background**

Diffuse astrocytic and oligodendrogial tumours
- 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
- Oligodendroglioma
- Anaplastic oligodendroglioma, IDH-mutated and/or 1p/19q-co-duplicated
- Anaplastic oligodendroglioma, IDH-wildtype
- Anaplastic oligodendroglioma, NOS
- Oligoastrocytoma, WHO Grade II / III

**Other astrocytic tumours**
- Pilocytic astrocytoma
- Pilocytic astrocytoma, NOS
- Subependymal giant cell astrocytoma
- Hemangioblastoma
- Anaplastic pleomorphic xanthoastrocytoma

**Ependymal tumours**
- Subependymoma
- Desmoplastic ependymoma
- Ganglioglioma
- Gliomatous gangliocytoma
- Desmoplastic infantile ganglioglioma
- Dendroglioma
- Dural ependymoma

**Other gliomas**
- Chordoid glioma of the third ventricle
- Arachnoid cyst
- Chordoid plexus tumours
- Chordoid plexus papilloma
- Chordoid plexus carcinoma

**Neoplastic meningiomas**
- Meningothelial meningioma
- Meningeal atypical meningioma
- Malignant meningioma

**Leptomeningeal spread of tumour**
- Extracranial spread of tumour
- Metastatic disease

**Metastatic tumours**
- Brain metastasis
- Primary/malignant brain tumours

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**WHO Classification of Tumours of the Central Nervous System**

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Background

Histone 3 – variants:
H3.3 - \(H3F3A\) gene
H3.1 - \(HIST1H3B/C\) gene

Lysine residues
(K4, K9, K27, K36)

Histone Tails
Nucleosome core particle (NCP)

K27M
\(H3F3A\) gene (3x)

Gliomagenesis
Background

• Diffuse midline glioma, *H3 K27M*-mutant
  
  **Median patient age**: 5-11 years old  
  (adults)
  
  No sex predilection

  **Location**: pons (children), thalamus and spinal cord (adults)  
  cerebellum (occasionally)

  **Histology**  
  High grade glioma with a predominant astrocytic differentiation

  10% - lack mitotic figures, microvascular proliferation and necrosis
Background

• Diffuse midline glioma, \textit{H3 K27M}-mutant

Median patient age: 5-11 years old (adults)

No sex predilection

Location: pons (children), thalamus and spinal cord (adults)
cerebellum (occasionally)

Histology

High grade glioma with a predominant astrocytic differentiation

WHO grade IV

2-year survival rate <10%

10% - lack mitotic figures, microvascular proliferation and necrosis
Background

• Diffuse midline glioma, \textit{H3 K27M}-mutant

- HIT-HGG protocol
- STUPP protocol

>70 years-old
Low performance status

Methylation of the \textit{MGMT} gene promoter

- Temozolomide
- Hypofractionated radiotherapy
Material and methods

Gliomas with \textit{H3 K27M} mutation
Portuguese tertiary centre
2016 – 2018

n=5

Clinicopathological features
Results

<table>
<thead>
<tr>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% n=2</td>
<td>60% n=3</td>
</tr>
</tbody>
</table>

**Age at time of diagnosis (years old)**

<table>
<thead>
<tr>
<th>Age</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>45</td>
<td>45</td>
</tr>
</tbody>
</table>

**Mean age (years old)**

33.2
Results

- **80% (n=4)**
  - Corpus callosum
  - Basal ganglia
  - Thalamus
  - Amygdala

- **20% (n=1)**
  - Cerebellum
  - Brainstem
Results

MRI

T1 - Transversal

Iso/Hipointense (n=5)
Results

MRI

T2 - Transversal

Hyperintense (n=5)
Results

Infiltrative (n=2)

Well-defined (n=3)
Results

<table>
<thead>
<tr>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 - Transversal</td>
</tr>
</tbody>
</table>

Cystic/necrotic component (n=4)
Results

<table>
<thead>
<tr>
<th>MRI</th>
<th>T1 - Transversal with contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhancement (n=4)</td>
<td></td>
</tr>
</tbody>
</table>
Results

High grade (n=4)

Low grade (n=1)
Results

80% (n=4)

20% (n=1)

Partial ressection
Stereotaxic biopsy

Partial ressection
Results

Histology

HE, 200x

High cellularity (n=4)

Moderate cellularity (n=1)
Results

<table>
<thead>
<tr>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic activity (400x)</td>
</tr>
<tr>
<td>Microvascular proliferation (200x)</td>
</tr>
<tr>
<td>Necrosis (200x)</td>
</tr>
</tbody>
</table>

- [0, 24] mitosis per 10 HPF
- 80% (n=4)
- 40% (n=2)
Results

Radiology

Histology

High grade (n=4)

Low grade (n=1)

High grade (n=4)

Low grade (n=1)
100% (n=5) - Astrocytic phenotype
20% (n=1) - Oligodendroglioma-like features
20% (n=1) - Pilomyxoid features
20% (n=1) - Rosette-like structures
## Results

<table>
<thead>
<tr>
<th>Immunohistochemistry</th>
<th>GFAP</th>
<th>+ (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLIG-2</td>
<td>+ (n=5)</td>
<td></td>
</tr>
<tr>
<td>ATRX</td>
<td>Preserved (n=3)</td>
<td>Loss (n=1)</td>
</tr>
<tr>
<td><em>IDH1 (R132H)</em></td>
<td>Absent (n=5)</td>
<td></td>
</tr>
<tr>
<td>p53</td>
<td>Wild-type (n=4)</td>
<td>Overexpression (n=1)</td>
</tr>
<tr>
<td>Ki-67</td>
<td>Variable [1, 80]%</td>
<td></td>
</tr>
<tr>
<td><em>H3 K27M</em></td>
<td>+ (n=5)</td>
<td></td>
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</tbody>
</table>

NA: Not available
Results

- Molecular studies
  - Cerebellum

Results

• Treatment

<table>
<thead>
<tr>
<th>Age at diagnosis (years old)</th>
<th>HIT-HGG protocol</th>
<th>STUPP protocol</th>
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Hypofractionated radiotherapy
Results

• Follow-up

60% (n=3): Radiological progression → Death of disease

Mean survival: 12.3 months
Results

• Follow-up

7 months

STUPP protocol

Clinical and radiologically stable
Results

• Follow-up

17 months

STUPP protocol

Slight radiological progression

11th month - Stereotaxic surgery

Clinical and radiologically stable
Conclusions

• Diffuse midline glioma, *H3 K27M*-mutant
  
  • Heterogeneous tumour

• Not exclusively of paediatric population

• Importance of the diagnosis
  • WHO grade IV
  • Potential target therapy (e.g. Histone deacetylase inhibitors)
Conclusions

- Diffuse midline glioma, $H3\ K27M$-mutant
  - Diffuse midline glioma, IDH-1 wild-type
    - Can be low grade
    - Immunohistochemistry

- Effective tool
  - Nuclear staining
  - Internal negative control: endothelial cells

- Pitfalls
  - Nonspecific cytoplasmic staining (macrophages/microglia)
  - $HIST1H3B/C$ gene mutation
Conclusions

Other tumours with H3 K27M-mutant
- Ependymomas
- Pilocytic astrocytomas
- Pediatric diffuse astrocytomas
- Gangliogliomas

Immunohistochemistry
Molecular
Diffuse
Midline
Glioma
References

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