Diagnosis and Predictors of Treatment Outcomes in Meningiomas with Atypical or Anaplastic Histology

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ABSTRACT

Atypical and anaplastic meningiomas (WHO grade II and III) are uncommon tumors with poorer prognosis than benign meningiomas. They represent a small and heterogeneous subgroup of meningiomas that has more aggressive biological nature and higher frequency of recurrence. Treatment of these tumors remains challenging and recurrence is common even after gross total resection. We report five year experience of an experienced neurosurgical center (INC) reviewing treatment options and predictor of treatment outcomes for malignant meningiomas.

Key words: Anaplastic meningioma; Atypical meningioma; Prognostic factor

INTRODUCTION

Up to 26% of all intracranial tumors are meningiomas that are classically divided into three general subtypes, according to World Health Organization: grade I (benign), grade II (atypical), grade III (anaplastic). Atypical meningiomas are uncommon (4.7-20% of all meningiomas) while anaplastic meningiomas account for only 1-2.8% of all meningiomas. Their symptoms depend on the intracranial location as well as the surgical challenge does.

Historically the treatment involves radical resection (according to Simpson Score) followed by radio and chemotherapy for malignant (grade II and III) subtypes. The evolution of malignant meningiomas remains unsatisfactory with high rates of recurrence and progression despite the treatment offered to those patients. After the development of genetic/molecular medicine besides high precision radiotherapy/radiosurgery, the paradigm for treatment of these tumors has changed. We reviewed current prevailing treatment of meningiomas focusing on the new discovers in genetic/molecular and radiotherapy field.

Materials and Methods

In our database, we reviewed all meningiomas operated on 2012 to 2017 in our institution to describe the epidemiologic characteristics of atypical and anaplastic subtypes, as well as a case report with focus on the treatment option and results in long-term follow-up. Also, literature was reviewed with WHO 2016 classification for diagnoses and treatment option guided through genetic/molecular analyses.
RESULTS

A total of 170 new diagnosed patients harboring intracranial meningiomas underwent microsurgical resection at the Neurological Institute of Curitiba (INC) between January 2012 – June 2017. Ninety-four (55%) tumors were classified as skull base tumors, 58 (34%) convexity tumors, 10 (5.8%) parasagittal tumors and 8 (4.7%) falce meningiomas.

In our series 76.4% (130) of patients were female. Only 6 (3.5%) patients had atypical/anaplastic tumors with mean age of 53 years. Simpson Grade I resection was achieved in all patients with malignant histology and radiotherapy was reserved for progression. Only one patient with atypical meningioma received up-front radiotherapy because of high Ki-67 index. Any case of skull base meningioma exhibited progression to malignant subtypes in this series.

Table 1. Malignant meningioma at INC (2012-2017).

<table>
<thead>
<tr>
<th>Gender</th>
<th>Topography</th>
<th>Histology at 2nd reaction (WHO)</th>
<th>Histology at 1st reaction (Simpson)</th>
<th>Time to evolution</th>
<th>Radiotherapy modality after anaplastic diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Grade I</td>
<td>Grade I</td>
<td></td>
<td>EBT</td>
</tr>
<tr>
<td>Patient 1</td>
<td>F</td>
<td>Parasagittal</td>
<td>Convexity</td>
<td>7m</td>
<td>EBRT</td>
</tr>
<tr>
<td>Patient 2</td>
<td>M</td>
<td>Parasagittal</td>
<td>Convexity</td>
<td>26m</td>
<td>EBRT</td>
</tr>
<tr>
<td>Patient 3</td>
<td>M</td>
<td>Parasagittal</td>
<td>Convexity</td>
<td>9m</td>
<td>EBRT</td>
</tr>
<tr>
<td>Patient 4</td>
<td>F</td>
<td>Convexity</td>
<td>Convexity</td>
<td>-</td>
<td>EBRT</td>
</tr>
<tr>
<td>Patient 5</td>
<td>F</td>
<td>Convexity</td>
<td>Convexity</td>
<td>-</td>
<td>EBRT</td>
</tr>
<tr>
<td>Patient 6</td>
<td>F</td>
<td>Convexity</td>
<td>Grade I</td>
<td>16 yrs</td>
<td>EBRT</td>
</tr>
</tbody>
</table>

ILLUSTRATIVE CASE

58 years-old male with sporadic new onset headache and MRI evidencing enhanced parasagittal homogeneous mass lesion with surrounding edema (Figure 1). Simpson grade I resection (Figure 2) was achieved at surgery and histopathology confirmed atypical meningioma.

Immunohistochemistry of first sample proved the trend toward malignization, with Ki-67 index of 70% in hot spots (Table 2). Only focal positiveness for progesterone receptor was seen. Because of high Ki-67 index, adjuvant external beam radiotherapy was added to the treatment.

After 1 year follow-up, recurrence at posterior border of previous surgical field was seen, and another gross total resection was necessary (Figure 3). Radiologically, the tumor expressed the same characteristic of first analysis, with homogeneous contrast enhancement and peritumoral edema. Histopathological analyses confirmed atypical histology. At this time chemotherapy with octreotide was introduced without response.

After 2 years from the first surgery, another recurrence was seen. At MRI, changes in previous pattern were seen with heterogeneous contrast enhancement and central necrosis (Figure 4). After complete tumor removal, progression to anaplastic meningioma was confirmed.

In comparative analyses, immunohistochemistry evidenced an increase in Ki-67 index from 70 to 90 % of the cells. The epithelial membrane antigen (EMA), focal positive at first analysis, now expressed diffuse negativeness. Reduction in progesterone receptor expression was also documented (Table 3).

DISCUSSION

Ninety percent of meningiomas are benign tumors. Atypical meningiomas are uncommon (4.7-20 % of all meningiomas) while anaplastic meningiomas account for only 1-2.8 % of all meningiomas1-4.

The WHO 2016 classification included brain invasion to the previous histological characteristic (4-19 mitotic figure and 3 of 5 histologic features: increased cellularity, small cells (tumor clusters with high nuclear/cytoplasmatic ratio), prominent nucleoli, sheeting (loss of whorling or fascicular architecture) and spontaneous necrosis) in the diagnosis of atypical meningiomas.

Anaplastic menigiomas are diagnosed with 20 or more mitotic figure, presence of frank sarcomatous or carcinomatous histology3.

Despite of diagnostics criteria, the exact mechanism through how benign meningiomas progress to malignant subtypes remain unclear. Several molecular and genetic hypothesis have been postulated but the real significance of these alterations are still speculative4.

Evidence-based literature suggests that the extent of surgical resection, accordingly to Simpson grade system, is the most important prognostic factor for good outcome among those...
patients harboring malignant meningioma. In our series those cases with atypical or anaplastic subtypes at primary surgery, demonstrated better response to Simpson grade I resection and adjuvant radiotherapy than those cases that progressed from grade I subtype. Some genetic alteration related to progression, as previously reported in literature, can probably explain different evolution among tumors expressing the same histology like in these series.

Among those with atypical and anaplastic histology, tumor size and female gender have been related to poor outcome and presence of radiological features as heterogeneous enhancement, peritumoral edema, cyst formation and absence of calcification have been implicated with lower median recurrence free survival.

In our illustration case, the tumor progression was followed by changes in radiological characteristics and immunohistochemical pattern. Possibly, in this case, the first immunohistochemistry analysis evidenced some characteristics of aggressiveness. In this scenario, Czonka et al. have previously published the utility of p53 gene expression and Ki-67 index in predicting meningioma progression.

Radiotherapy is a special topic in the treatment of malignant meningiomas. Increase from 15 to 80% in 5 year-progression free survival was reported when EBRT was added to surgical resection for anaplastic meningioma. In this topic, no consensus exists for atypical meningiomas and EBRT has mostly been reserved for recurrence and progression.

Due to the possibility of margin inclusion in irradiation field with EBRT, radiosurgery is no longer indicated for malignant meningiomas. However, Lubgan et al. have reported excellent results with stereotactic radiotherapy when used as adjuvant after gross-total resection or as definitive treatment regime.

In our case, the lower progesterone receptor expression and higher Ki-67 index could probably predict the chance of progression and help in earlier adjuvant decision.

Several chemotherapy agents have been used for atypical and anaplastic meningiomas refractory to surgery and radiotherapy. In the largest revision, Kaley et al. found 47 publications using different chemotherapy agents (hydroxyurea, temozolamide, irinotecan, interferon-alpha, mifepristone, octreotide analogues, megestrol acetate, bevacizumab, imatinib, erlotinib and gefitinib) with an average six-month progression-free survival of 26%, concluding that the available chemotherapy agents provide poor outcomes for refractory malignant meningiomas.

Conclusion

Malignant meningiomas remain a challenge pathology and no effective treatment is current available. Against literature evidence, we presume that the biological signature of this specific tumor is more important for evolution than previous reported prognostic factor. In this scenario, new studies aiming objective analyses of immunohistochemistry patterns and genetic profile of meningiomas are probably the next step for comprehension of such complex neurosurgical pathology.
Figure 2. Postoperative MRI with Post-gadolinium-DTPA axial T1-weighted gradient echo (FSPGR) sequence exhibiting complete resection of parasagittal meningioma.

Figure 4. Axial Post-gadolinium-DTPA. A. T1-weighted gradient echo (FSPGR) showing irregular contrast enhancement and tumoral necrosis. B. Axial FLAIR magnetic resonance evidencing extensive peritumoral edema with changes in radiological aspect from original lesion.

Table 2. Markers and Results.

<table>
<thead>
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<th>Antibody</th>
<th>Clone</th>
<th>Result</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-100 Protein</td>
<td>Polyclonal</td>
<td>Focal positive for the minority of cells</td>
<td></td>
</tr>
<tr>
<td>Epithelial Membrane Antigen (EMA)</td>
<td>E-29</td>
<td>Focal positive; wide negative areas</td>
<td></td>
</tr>
<tr>
<td>Progesterone receptor (PR)</td>
<td>PgR636</td>
<td>Focal positive; wide negative areas</td>
<td></td>
</tr>
<tr>
<td>Cytokeratins of 40, 48, 50 and 50,8 KDa</td>
<td>AE1/AE3</td>
<td>Sparse cellular foci Positive</td>
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</tr>
<tr>
<td>Chromogranin A</td>
<td>DAK-A3</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Cell proliferation antigen</td>
<td>MIB1</td>
<td>Positive</td>
<td>70 for hotspots</td>
</tr>
<tr>
<td>Ki-67</td>
<td></td>
<td></td>
<td></td>
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</table>

Table 3. Markers and Results.

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<tr>
<th>Antibody</th>
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<th>Result</th>
<th>%</th>
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<tbody>
<tr>
<td>S-100 Protein</td>
<td>Polyclonal</td>
<td>Sparse positive cells</td>
<td></td>
</tr>
<tr>
<td>Epithelial Membrane Antigen (EMA)</td>
<td>E-29</td>
<td>Diffuse negative</td>
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<tr>
<td>Progesterone receptor (PR)</td>
<td>PgR636</td>
<td>Negative for the majority of cells</td>
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<tr>
<td>Cytokeratins of 40, 48, 50 and 50,8 KDa</td>
<td>AE1/AE3</td>
<td>Negative</td>
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<tr>
<td>Cell proliferation antigen</td>
<td>MIB1</td>
<td>Positive</td>
<td>80-90</td>
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Study conducted at the Neurological Institute of Curitiba (INC)