Tumor Location and Growth Pattern Correlate with Genetic Signature in Oligodendrogliomas

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Abstract

Molecular genetic subsets of anaplastic oligodendroglioma behave in biologically distinct ways, in both their rates of growth and their responses to standard therapies. In a series of 64 cases, we evaluated whether allelic loss of chromosomal arms 1p and 19q, an early molecular event in the genesis of chemo-sensitive oligodendrogliomas, is related to tumor location and extent of tumor spread in the brain. We observed that tumor genotype was closely associated with tumor location (P < 0.001). Anaplastic oligodendrogliomas located in the frontal, parietal, and occipital lobes were significantly more likely to harbor allelic loss of chromosomal arms 1p and 19q than histologically indistinguishable tumors arising in the temporal lobe, insula, and diencephalon (P < 0.001). In addition, loss of heterozygosity for 1p and 19q was significantly associated with a bilateral pattern of growth (P = 0.037); all seven bilaterally distributed anaplastic oligodendrogliomas had 1p and 19q allelic loss. We conclude, therefore, that molecular subtypes of oligodendrogliomas may arise preferentially in certain lobes of the brain and have differential patterns of growth, with tumors having allelic loss of chromosomes 1p and 19q occurring most frequently in the frontal lobes and having a tendency for widespread growth across the midline. These findings encourage inquiries into the biological basis of such marked differences and already have implications for the current management of these neoplasms.

Introduction

Oligodendrogliomas were the first of the common malignant gliomas shown to be responsive to chemotherapy (1, 2) and the first shown to have specific molecular genetic predictors of chemotherapeutic response and survival (3, 4). In anaplastic oligodendrogliomas, response to chemotherapy, duration of response to chemotherapy, progression-free survival after radiotherapy, and overall survival time are highly associated with allelic loss of chromosomal arms 1p and 19q (3, 5, 6). This genetic signature is also the earliest known molecular derangement in 50–70% of oligodendrogliargical neoplasms. Today, effective therapies are available for a substantial percentage of patients with oligodendrogliargical neoplasms; genetic testing guides their use (5). Moreover, such testing permits treatment-resistant oligodendrogliomas to be identified in advance of the administration of ineffective, toxic, and costly treatments. The study of oligodendrogliomas has therefore provided a paradigm for developing rational treatment strategies for tumors of the central nervous system and promises to afford researchers with unique insights into the biology and treatment of glial tumors.

In the course of treating patients with newly diagnosed anaplastic oligodendrogliomas with chemotherapy, we noticed that tumors located in the temporal lobe, insula, and diencephalon responded to chemotherapy less frequently. We also noticed that oligodendrogliomas in these locations often tended to be well circumscribed on magnetic resonance images and to grow in an expansile, as opposed to infiltrative, fashion. These observations led us to inquire whether anaplastic oligodendrogliomas growing in different regions of the brain or growing in different ways might vary in their molecular makeup. The following analysis was designed to address these issues.

Materials and Methods

Case Selection. Cases for this study were culled from a database of patients with newly diagnosed anaplastic oligodendrogliomas who had received chemotherapy as their principal initial treatment. Information on tumor location and the status of chromosomal regions 1p and 19q (i.e., both regions) were the sole additional eligibility requirements for this analysis.

Tumor Location. Tumor location was considered to be the lobe or region of the brain within which the bulk of the oligodendroglioma resided. Tumors that extended into neighboring lobes or regions were considered multilobar in distribution, those that appeared to arise in several distinct locations were deemed multifocal, and those that traversed the corpus callosum to involve the opposite cerebral hemisphere were judged to be bilateral. These assignments were based on an evaluation of patient records, imaging studies, or both.

Genetic Studies. We assessed allelic chromosomal loss by loss of heterozygosity assays in constitutional DNA/tumor DNA pairs, using microsatellite markers on 1p36 (D15S2734, D1S199, and D15S508) and 19q13 (D19S219, D19S112, D19S412, and D19S596; Ref. 5). Tumor DNA was extracted from microdissected, formalin-fixed, paraffin-embedded sections; constitutional DNA was extracted from blood leukocytes or paraffin sections of adjacent, uninvolved brain or other tissues (7).

Statistical Considerations. Fisher’s exact test was used to assess the significance of associations between 1p and 19q allelic loss versus tumor location and growth pattern.

Results and Discussion

Sixty-four patients (34 men and 30 women), ages 17 to 82 years (mean age, 45 years), with a median Karnofsky Performance Score of 80 received chemotherapy as the principal initial postoperative treatment for a newly diagnosed anaplastic oligodendroglioma. Thirty-four tumors were located predominantly in the frontal lobe, 15 in the temporal lobe, 7 in the parietal lobe, 1 in the occipital lobe, 5 in the insula, and 2 in the diencephalon. Forty tumors were confined to a single lobe or region of the brain, and 24 were multilobar. Sixty-three tumors were unifocal, and only 1 anaplastic oligodendroglioma was judged to be multifocal in origin. Fifty-seven tumors were unifocal, and only 1 anaplastic oligodendroglioma was judged to be multifocal in origin. Fifty-seven tumors were unifocal, and only 1 anaplastic oligodendroglioma was judged to be multifocal in origin. Fifty-seven tumors were unifocal, and only 1 anaplastic oligodendroglioma was judged to be multifocal in origin. Fifty-seven tumors were unifocal, and only 1 anaplastic oligodendroglioma was judged to be multifocal in origin.
copies of chromosome 1p were intact in 25 tumors. The clinical, radiological, and genetic data are summarized in Table 1.

In this series of newly diagnosed anaplastic oligodendrogliomas, we observed a statistically significant association between genetic signature (i.e., 1p and 19q allelic loss versus 1p intact) and tumor location ($P < 0.001$). Moreover, our specific hypothesis that anaplastic oligodendrogliomas located in the temporal lobe, insula, and diencephalon are biologically distinct from histologically similar tumors in other locations is supported by these data. Tumors in the temporal lobe, insula, and diencephalon were significantly less likely to harbor allelic loss of chromosomes 1p and 19q ($P < 0.001$). Moreover, the 1p and 19q molecular signature was significantly associated with a bilateral versus unilateral pattern of growth ($P = 0.037$); all seven bilaterally distributed anaplastic oligodendrogliomas harbored 1p and 19q allelic loss. There was no significant association between genetic signature and unilobar versus multilobar distribution, and data were insufficient to analyze the association between genetic signature and multifocality.

The relationship between tumor location and contrast enhancement was also explored. We detected a statistically significant association between tumor location and contrast enhancement (grouped as no enhancement, enhancement, and ring enhancement; $P < 0.001$). Those anaplastic oligodendrogliomas that were located in the frontal, parietal, and occipital lobes were significantly more likely to enhance with contrast ($P = 0.002$), whereas those tumors located in the temporal lobe, insula, and diencephalon that were enhanced with contrast were significantly more likely to display a ring enhancing pattern ($P = 0.01$). There was no statistically significant relationship between tumor location, as grouped above, and patient survival after adjusting for genetic signature ($P = 0.139$).

It has become clear over the past few years that molecular subsets of oligodendroglioma behave in biologically distinct ways, in both their growth rates and their responses to standard therapies (3, 5, 7). This report extends those observations to show that molecular variants of oligodendroglioma have a predilection for certain lobes of the brain and vary in their extent of spread throughout the brain. Indeed, all seven cases of bilateral frontal oligodendrogliomas had 1p and 19q loss. To some extent, these findings mirror what has been observed in colonic carcinomas, in which right-sided and left-sided colon tumors exhibit different spectra of genetic alterations and may have different behaviors (8).

The association of oligodendroglioma genotype with location and extent of spread raises a number of interesting possibilities and questions. One potential explanation for such an association posits that different types of oligodendrogliomas arise from different precursor cells that are relatively region-specific in the brain or appear at different stages of brain development. In this scenario, the cells of origin would determine the eventual behavior or location of the neoplasm. Hence, tumors arising from migratory precursor cells would themselves be migratory and grow as locally invasive cancers both radiologically and pathologically. Likewise, transformational events at distinct developmental stages would yield tumors that are differentially located in the brain. Indeed, different regions of the mammalian forebrain are known to contain glial progenitor cells that are preferentially committed to specific fates and destinations (9). Furthermore, recent animal modeling has suggested that targeting oncogenic hits to particular progenitors cells can result in distinct phenotypes of oligodendrogial neoplasms (10, 11).

Another possibility is that the oncogenic events that allow oligodendrogliomas to develop (e.g., inactivation of putative tumor suppressors on 1p and 19q) are only tumorigenic in certain cells of origin or certain regions of the brain. Thus, 1p and 19q loss would facilitate tumorigenesis only in a particular cell type, which might be restricted to a certain region of the brain. Such susceptibility to neoplasia may be related to the expression pattern of a given cell type. For example, it is known that glia from different regions of the brain express varying growth factor repertoires (12). If oncogenesis involving the putative 1p/19q pathways occurred only in cells overexpressing a specific growth factor, such tumors might arise only in particular regions of the brain. Alternatively, tumorigenesis in concert with 1p and 19q loss might be related to the extracellular environment. For example, secreted growth factors or other molecules characteristic of a particular brain region might facilitate the growth of only certain neoplastic cells, such as those with inactivation of the putative 1p/19q pathways. Such tumors might preferentially invade along tracts such as the corpus callosum and so result in bilateral tumors, as we have observed in the present report. Certainly, these data encourage further investigations into the relationship between tumor genotype and tumor site.

Regardless of the biological basis for this association, the observation already holds potential clinical relevance. At present, diagnostic testing of oligodendrogial tumors for 1p and 19q loss offers important therapeutic information for clinical patient management (3–5). Unfortunately, such testing is not yet widely available, nor is such testing widely reimbursed by insurance companies. In addition, there are disadvantages to each of the commonly used approaches (loss of heterozygosity studies and fluorescence in situ hybridization), with no consensus on optimal methodology for clinical use. There is therefore an existing need for alternative methods of predicting oligodendroglioma behavior. We have previously noted that tumors displaying ring enhancement on neuroimaging seldom respond in a meaningful way to chemotherapy, especially PCV.3 Thus, patients with such tumors should probably be spared the then unnecessary toxicity of the PCV regimen (3, 5).

The present observation that bilateral frontal oligodendrogliomas have 1p and 19q loss confirms our impression that frontal lobe oligodendrogliomas often respond to PCV therapy because, in our experience, essentially 100% of tumors with 1p and 19q loss respond to PCV (3, 5). In the setting of a biopsy-based diagnosis of an oligodendrogloma, the appearance of a bilateral frontal tumor on neuroimaging might therefore encourage aggressive chemotherapy in such patients, including in centers where molecular testing for 1p and 19q loss is not available at present. PCV or similar chemotherapy might be an especially attractive alternative in these cases because bilateral irradiation of the frontal lobes, the only other proven effective therapy, may be accompanied by significant neurotoxicity years after successful treatment of the tumor.

Table 1: Clinical, radiological, and genetic features

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range) age at diagnosis, years</td>
<td>45 (17–82)</td>
</tr>
<tr>
<td>M/F (n)</td>
<td>34/30</td>
</tr>
<tr>
<td>Median KPS*</td>
<td>80</td>
</tr>
<tr>
<td>Contrast enhancement present, n (%)</td>
<td>48/64 (75%)</td>
</tr>
<tr>
<td>Ring enhancement present, n (%)</td>
<td>8/48 (17%)</td>
</tr>
<tr>
<td>Tumor location, n (%)</td>
<td></td>
</tr>
<tr>
<td>Frontal lobe location</td>
<td>34/64 (53%)</td>
</tr>
<tr>
<td>Temporal lobe location</td>
<td>15/64 (23%)</td>
</tr>
<tr>
<td>Parietal lobe location</td>
<td>7/64 (11%)</td>
</tr>
<tr>
<td>Occipital lobe location</td>
<td>1/64 (2%)</td>
</tr>
<tr>
<td>Insular location</td>
<td>5/64 (8%)</td>
</tr>
<tr>
<td>Diencephalon</td>
<td>2/64 (3%)</td>
</tr>
<tr>
<td>Unilobar/Multilobar (n)</td>
<td>40/24</td>
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<tr>
<td>Unifocal/Multifocal (n)</td>
<td>63/1</td>
</tr>
<tr>
<td>Bilateral/Bilateral (n)</td>
<td>57/7</td>
</tr>
<tr>
<td>1p and 19q LOH* present, n (%)</td>
<td>39/64 (61%)</td>
</tr>
<tr>
<td>1p alleles intact, n (%)</td>
<td>25/64 (39%)</td>
</tr>
</tbody>
</table>

* KPS, Karnofsky Performance Score; LOH, loss of heterozygosity.

3 The abbreviation used is: PCV, procarbazine, lomustine, and vincristine.
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References

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