The Biology Behind

Imaging Molecular Signatures in Oligodendroglioma

Commentary on Walker et al., pages 7182–7191

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In this issue of Clinical Cancer Research, Walker et al. (1) report a comprehensive analysis of metabolic rate, tumor grade, contrast enhancement, and molecular genetic alterations in oligodendrogliomas and oligoastrocytomas. Brain tumor metabolism was assessed by single-photon emission computed tomography (SPECT) using two radiolabeled tracers, $^{201}$Thallium ($^{201}$TI) and $^{18}$Fluorodeoxyglucose (FDG). $^{201}$TI crosses a disrupted blood–brain barrier, where it is pumped into viable and proliferating cells. $^{18}$FDG, a glucose analog, enters the brain by facilitated diffuse and is trapped in proliferating cells low in glucose-6-phosphate. Each oligodendrogliarial tumor was typed and graded using World Health Organization criteria, and the presence or absence of contrast enhancement was determined by reexamination of clinical magnetic resonance imaging (MRI) and computed tomography (CT) scans, done proximate to the SPECT studies. Allelic imbalance was assessed by loss of heterozygosity assays in tumor-DNA/normal-DNA pairs using microsatellite markers on 1p, 10p, 10q, 17p, and 19q. As anticipated, there was a positive correlation between $^{201}$TI and $^{18}$FDG uptake. There was also a positive correlation between metabolic rate and both histologic grade and contrast enhancement, notably for $^{201}$TI SPECT. These intuitive associations were seen before in analyses of astrocytic tumor metabolism using SPECT and positron emission tomography. However, two remarkable findings emerged: first, high metabolic rates were detected in many low-grade oligodendrogliomas, which were usually nonenhancing; and second, coincident loss of chromosomal arms 1p and 19q was associated with a hypermetabolic state, especially in low-grade oligodendrogliomas. No such associations were detected for oligoastrocytomas. High metabolic activity has been observed previously in oligodendrogliomas (2), although it has not been associated with their genotype until now, and oligodendrogliomas are sometimes better “visualized” by $^{11}$C)methionine than $^{18}$FDG positron emission tomography (3). But why might Walker et al. (1) have chosen to study metabolic activity in oligodendrogliomas?

Oligodendrogliomas have long been a brain tumor of interest to clinicians with neurologic specialization. Neurologists have found them interesting because they often cause seizures in young adults that become increasingly refractory to drug therapy as the tumor slowly infiltrates the cerebral cortex. Seizures and side effects secondary to multiple anticonvulsant medications pose very challenging problems for patients with oligodendrogliomas. Neurosurgeons have found oligodendrogliomas interesting because they often grow in the frontal lobes of the brain, where they are more amenable to radical resection than are many other types of infiltrating glioma. Many oligodendrogliomas grow slowly; consequently, multiple surgical resections, which can relieve seizures and other symptoms, often constitute the mainstay of treatment for this type of brain tumor for many years. Furthermore, advances in surgical techniques, including intraoperative functional mapping and brain imaging, have enabled oligodendrogliomas to be more extensively resected with greater safety, thus enhancing the therapeutic role of surgical intervention. Neuroradiologists have long found them interesting because, unlike most types of glioma, oligodendrogliomas are often heavily calcified, making it possible to surmise the histologic diagnosis on the basis of the appearance of the tumor on a CT scan of the brain. There are relatively few mass lesions in the brain that are frequently associated with irregular, bulky calcification. Indeed, macroscopic calcification was the original imaging signature of the oligodendroglioma, a fact that has been forgotten in recent years because tumor-associated calcification is less conspicuous on magnetic resonance images of the brain than on CT. This clinical caveat is much less helpful now because MRI has replaced CT as the imaging modality of choice in the assessment of patients with seizures or other neurologic symptoms.

Oligodendrogliomas have also been tumors of interest to neuropathologists, who have long been intrigued by the handsome microscopic appearance of oligodendrogliomas with small, round, regular nuclei, reminiscent of oligodendrocytes; distinctive perinuclear halos; and branching vascular pattern (Fig. 1). In addition, oligodendrogliomas may contain microscopic areas of mineralization said to be calcification and frequently contain numerous neoplastic astrocytes, which then elicits from the neuropathologist a diagnosis of oligoastrocytoma. For decades, strict histologic criteria were used to diagnose oligodendroglioma; consequently, both low- and high-grade versions of the tumor were considered relatively uncommon. In recent years, however, the criteria for diagnosis of an oligodendroglioma have been liberalized, and now up to 25% of newly diagnosed infiltrating glial tumors in adults are called oligodendrogliomas. This tendency for liberal diagnosis has extended to the oligoastrocytoma, a tumor of uncertain
parentage. Although the wisdom of relaxed diagnostic criteria has been called into question, it is clear that the high rate of diagnosis of oligodendroglioma and oligoastrocytoma is here to stay. Neuropathologists have also led the way in cataloging the molecular changes that occur in oligodendrogliomas, describing loss of chromosomes 1p and 19q in up to 70% of cases (4). Coincident allelic loss of 1p and 19q is the earliest known genetic change in oligodendrogliomas; it typically accompanies classic histopathology and is regarded as the “genetic signature” of this tumor.

Only recently has the oligodendroglioma emerged as a cancer of interest. Interest among radiation oncologists surfaced in the context of analyses of cognitive and neuroendocrine dysfunction in long-term survivors of radiation for low-grade glioma. Dementia and panhypopituitarism were often the consequences of successful treatment when high doses of radiation and large treatment fields were used. Moderate doses of radiation to small, conformal fields, often delayed for many years, have been important changes in the treatment of patients with oligodendrogliomas who require nonsurgical therapy (5). However, it was the serendipitous discovery that many aggressive oligodendrogliomas are sensitive to alkylating agent chemotherapy that catapulted this type of brain tumor to the forefront of research in neuro-oncology (6, 7). Investigators at many centers across North America and Europe have reported that a high proportion of patients with both anaplastic tumors and symptomatic, enlarging, nonenhancing, low-grade oligodendrogliomas are sensitive to procarbazine, lomustine, vincristine (PCV), a nitrosourea-based chemotherapy regimen, or temozolomide (TMZ), a new orally administered DNA methylating agent with few side effects (8, 9). Anaplastic oligodendrogliomas respond quickly and sometimes completely to PCV or TMZ, whereas low-grade oligodendrogliomas also tend to respond but shrink slowly or not at all. These differences in the kinetics and degree of radiographic response are intriguing and have raised questions about the optimal dose, scheduling, and duration of chemotherapy, especially for low-grade lesions. Questions about the most appropriate definition of response to treatment and the pros and cons of MRI versus other brain imaging methods to detect response have also arisen. Moreover, the role of chemotherapy in the overall management of patients with oligodendrogliomas is under study. Clinical trials that examine the merits of TMZ versus radiation as initial treatment for low-grade oligodendrogliomas are being planned, whereas data on high-grade oligodendrogliomas suggest that the addition of PCV chemotherapy to radiation does not prolong survival compared with sequential therapy with radiation initially and cytotoxic agents at recurrence (10).

Interest in oligodendrogliomas escalated further when genetic subtypes with different natural histories and responses to treatment were identified. In oligodendrogliomas, coincident allelic loss of chromosomal arms 1p and 19q is associated with radiographic response to chemotherapy in both low- and high-grade tumors (9, 11). Moreover, the duration of tumor control after chemotherapy or radiotherapy (12) and long survival times (13) have been associated with 1p and 19q loss, with isolated combined allelic loss being the most favorable genetic signature identified to date (14). This molecular genetic marker introduces an important new consideration into the design and interpretation of clinical trials for oligodendrogliomas (15) and is beginning to influence treatment strategies for individual patients stricken with this tumor. These elements, added to the perennial challenge of accurate microscopic diagnosis, explain why testing for allelic loss of 1p and 19q by fluorescence in situ hybridization or polymerase chain reaction-based methods is now widely available (16).

The exploration of oligodendrogliomas recently took another interesting turn, further expanding the horizon of possi-
bilities for discovery in neuro-oncology. Possible insights into the origins of oligodendrogliomas have come from correlative studies that have examined the relationship between specific imaging features of oligodendrogliomas and their genetic signatures. Two groups have shown a correlation between tumor location and genetic signature. In one study, oligodendrogliomas harboring allelic loss of 1p and 19q were significantly more likely to be located in the frontal lobes or bilaterally than tumors with intact alleles, which predominated in the temporal lobes and diencephalon, “older” and deeper regions of the brain (17). A second study confirmed that oligodendrogliomas with 1p and 19q loss were less likely to be located in the temporal lobes (18). These results can be interpreted in different ways, but they suggest a link between the origins of oligodendrogliomas and the molecular regulation of brain development. Visions of precursor cells migrating in waves to different regions of the brain, with each wave susceptible to transformation by different genetic events, are evoked by these data.

The finding that location and genotype might be related led to a study inquiring whether allelic loss of 1p and 19q could be “detected” noninvasively. A study in the July issue of Clinical Cancer Research supports the feasibility of molecular diagnosis of oligodendroglioma by MRI (19). Using clinical-grade MRI, an association between imaging features and tumor genotype was noted. Oligodendrogliomas with 1p and 19q loss were significantly more likely to have an indistinct border on T1 images, whereas a sharp border on T1 was more characteristic of tumors with intact alleles. An association was also noted between tumor genotype and paramagnetic susceptibility effects. Oligodendrogliomas harboring 1p and 19q loss were more likely to display paramagnetic changes, whereas the absence of paramagnetic susceptibility was associated with intact 1p and 19q alleles. An association between intratumoral calcification and paramagnetic effects and between calcification and 1p and 19q allelic loss were also observed. This study raised the further possibility that clues to the function of the genes on 1p and 19q that “cause” oligodendrogliomas might be gleaned through image analysis, which brings us full circle. Using a functional imaging modality, as distinct from a structural one, such as MRI, Walker et al. (1) have identified metabolic imaging features that correlate with 1p and 19q loss in oligodendrogliomas. Indeed, the list of brain imaging characteristics possibly associated with allelic loss of 1p and 19q in oligodendrogliomas is growing quickly and now includes calcification on CT, diffuse tumor border, bilateral spread and paramagnetic susceptibility on MRI, and high 201Tl and [18F]FDG uptake on SPECT.

Through the study of oligodendrogliomas and other uncommon brain tumors, the field of neuro-oncology has come of age. The introduction of rigorous, imaging-based response criteria for clinical trials, molecular testing to refine diagnosis and individualize therapy, and the commitment to large intergroup randomized studies for brain tumor can be traced, in part, to a series of cases in the neurologic literature in which the remarkable chemosensitivity of oligodendrogliomas was first reported. However, the best is yet to come. The next few years will see the molecular basis of oligodendroglial tumors precisely delineated and the relationship between 1p and 19q loss and their relatively favorable natural history and sensitivity to chemotherapy thoroughly understood. Moreover, imaging-based molecular diagnosis of oligodendrogliomas should be possible within a decade.

REFERENCES

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