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## Case 33-2004: A 34-Year-Old Man with a Seizure and a Frontal-Lobe Brain Lesion

Emad N. Eskandar, M.D., Jay S. Loeffler, M.D., Alison M. O'Neill, M.D.,  
George J. Hunter, M.D., and David N. Louis, M.D.

### PRESENTATION OF CASE

A 34-year-old man was admitted to the hospital because of a seizure and a lesion in the frontal lobe of the brain.

The patient had a history of obstructive sleep apnea for which he used a continuous-positive-airway-pressure (CPAP) machine at night. On the morning of admission, a friend found him unresponsive on the floor with his CPAP mask in place. When the mask was removed, he was frothing at the mouth and had jerking movements of the arms and legs. Emergency services personnel were called, and en route to the hospital he was seen to have an additional generalized seizure.

The patient had had deep venous thrombosis of the left leg two and a half years earlier, which had been treated by thrombectomy. This condition had been followed by chronic venous insufficiency. The patient worked as a consultant, and his job required frequent air travel. He had smoked one pack of cigarettes per week for several years and reported moderate alcohol intake on weekends. The patient's father had a diagnosis of Parkinson's disease, but there was no other family history of neurologic disease or cancer; his mother and siblings were well.

The initial neurologic evaluation in the emergency department showed that the patient was obtunded, could be roused by voice, and was oriented to his name, but he was able to follow commands only intermittently. Funduscopic examination was limited but suggested papilledema in the right eye. The pupils were round and equal; they constricted from 5 mm to 2 mm on exposure to light. Eye movements were full with oculoccephalic maneuvers. Corneal reflexes were suppressed bilaterally. There was no facial asymmetry. The patient moved his arms and legs vigorously and symmetrically and withdrew them appropriately in response to noxious stimuli. Deep-tendon reflexes were graded 1+ and the responses were symmetric throughout; there was bilateral extensor plantar response (Babinski's reflex was present).

Phenytoin was administered, and the patient's mental status returned to normal over the next several hours. Computed tomographic (CT) scanning of the head disclosed an ill-defined area of low attenuation in the right frontal lobe with local mass effect. The patient was admitted to the hospital. A magnetic resonance imaging (MRI) scan was obtained later in the day, which further characterized the imaging abnor-

From the Neurosurgical Service (E.N.E.), and the Departments of Radiation Oncology (J.S.L.), Neurology (A.M.O.), Radiology (G.J.H.), and Pathology (D.N.L.), Massachusetts General Hospital and Harvard Medical School.

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mality as an infiltrative, nonenhancing, heterogeneous lesion; it appeared hypointense on T<sub>1</sub>-weighted sequences and hyperintense on T<sub>2</sub>-weighted sequences.

A diagnostic procedure was performed on the third hospital day.

#### DIFFERENTIAL DIAGNOSIS

*Dr. George J. Hunter:* CT scans of the head obtained when the patient was in the emergency department showed a heterogeneous region of low attenuation in the right frontal lobe, without evidence of enhancement after administration of contrast material. There was mass effect on the adjacent structures with no evidence of calcification in relation to the lesion, suggesting that this was a tumor rather than a territorial infarction. MRI of the brain was performed. T<sub>1</sub>-weighted sequences were obtained in multiple planes before and after the administration of contrast material; images were obtained in the axial plane before the administration of contrast material with T<sub>2</sub>-weighted and fluid-attenuated inversion recovery (FLAIR) sequences; and magnetic resonance spectroscopy was performed over both frontal lobes.

There is a heterogeneous, infiltrative mass in the right frontal lobe involving both gray and white matter (Fig. 1A and 1B). The bulk of the lesion has signal characteristics of solid tissue — namely, bright on the T<sub>2</sub>-weighted and FLAIR sequences and isointense to slightly hypointense to the gray matter on the T<sub>1</sub>-weighted sequences. There is a small region just behind and lateral to the center of the lesion that is bright on the T<sub>2</sub>-weighted sequences and dark on the FLAIR and T<sub>1</sub>-weighted sequences; this represents a cystic component (Fig. 1A, arrow). There is no appreciable enhancement. There is mass effect on the adjacent ventricle and minimal midline shift. Some subtle abnormal T<sub>2</sub> signal is visible along the genu of the corpus callosum, suggesting infiltration in this area. At this stage, the differential diagnosis included a low-grade astrocytic tumor and a low-grade oligodendroglioma.

The metabolic structure of this lesion was investigated with magnetic resonance spectroscopy, with a focus on three key metabolites: N-acetyl aspartate, choline, and creatine. In a nuclear resonance magnetic spectrum from a normal brain, the N-acetyl aspartate peak is dominant, and the ratio of the choline peak to the creatine peak is less than

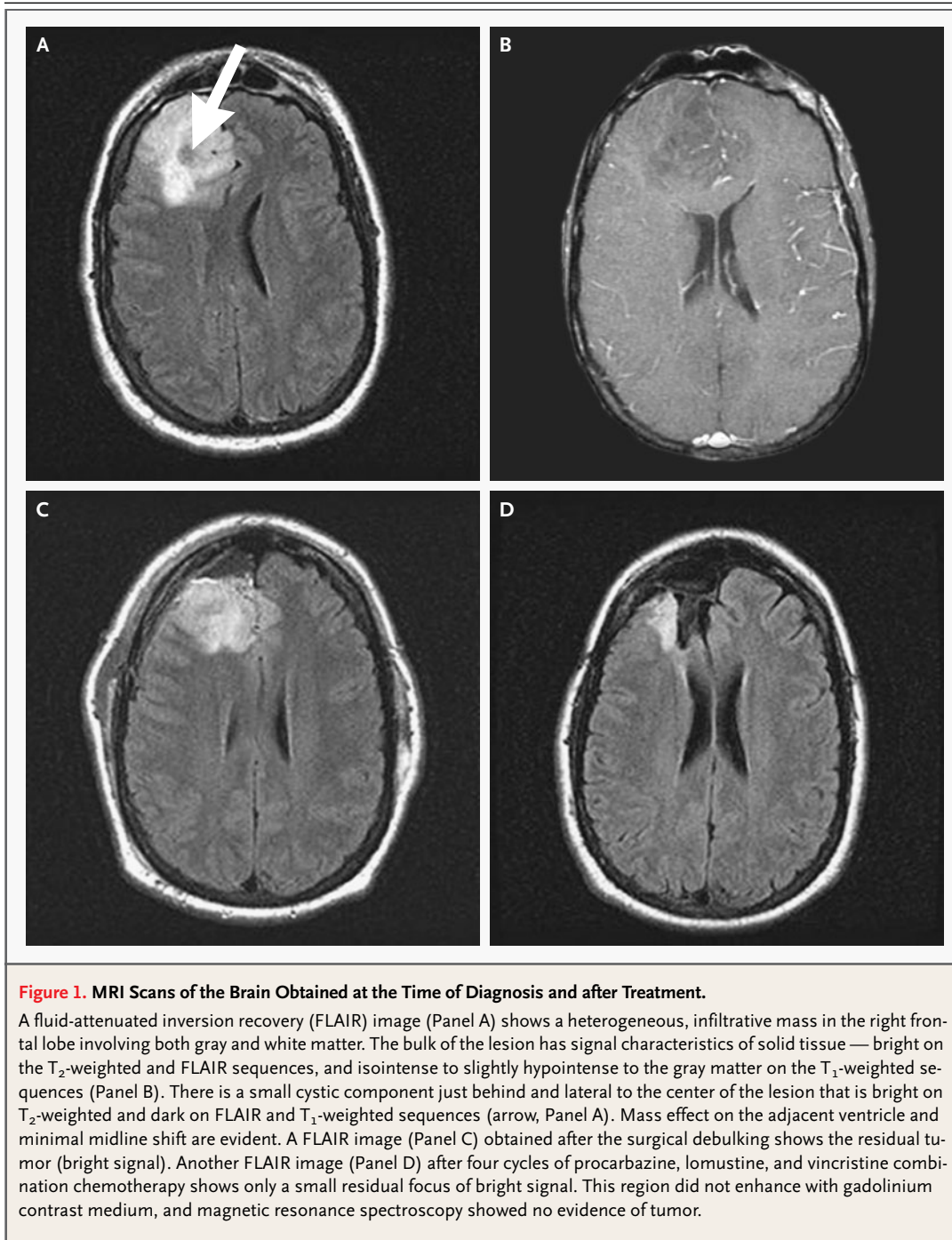
2:1. In tumors, the level of N-acetyl aspartate is depressed, as there is little or no neuronal tissue, and the ratio of choline to creatine increases. The causes of increased choline are incompletely understood but include proliferation of cell membranes and breakdown of phosphatidylcholine, which releases choline that is visible with magnetic resonance spectroscopy.

A choline-to-creatine ratio greater than 2:1 is considered abnormal, and a ratio greater than 3:1 is suggestive of a malignant lesion. Low-grade astrocytic or oligodendroglial tumors usually have a choline-to-creatine ratio of less than 3:1, whereas higher-grade tumors have a ratio greater than 3:1. Figure 2A shows a color map of the choline-to-creatine ratio over a T<sub>1</sub>-weighted image, in which a single focus where the choline-to-creatine ratio is more than 4:1 can be seen just lateral to the cystic area (arrow). The spectrum from this region is shown at the top in Figure 2B, and compared with the spectrum from a region of a normal brain (bottom). The finding of a region of higher metabolic activity within a predominantly low-grade tumor suggests either an astrocytic tumor, grade 2 to 3, or a low-grade oligodendroglioma with anaplastic components.

*Dr. Emad N. Eskandar:* This is a relatively young, previously healthy patient with a new onset of seizures. The MRI revealed a nonenhancing right frontal-lobe lesion with some mass effect. The clinical presentation and overall appearance of this lesion were consistent with features of a primary brain tumor. The most likely candidates were an astrocytoma and an oligodendroglioma, although other less common tumors were also possible. Other causes, such as infection, an infarct, trauma, or a congenital abnormality, were less likely.

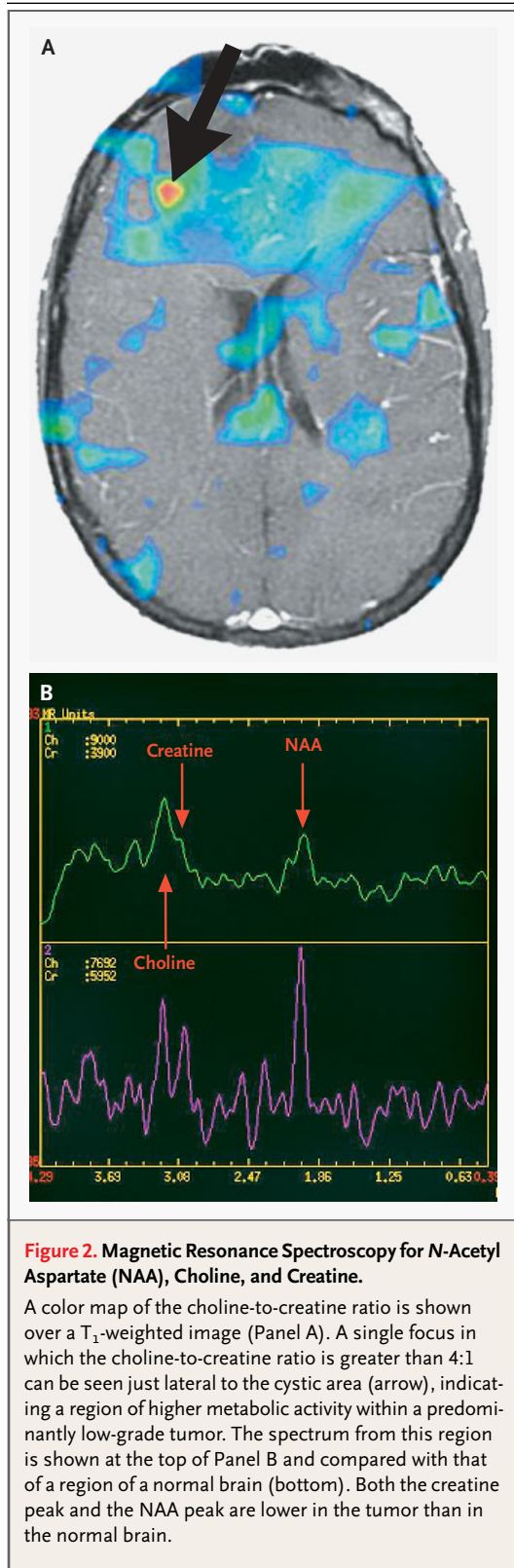
Given the clinical and radiologic information, the first decision was whether to perform a stereotactic biopsy or a craniotomy and resection of the lesion. A stereotactic biopsy is usually performed with the patient awake and involves placing the patient in a stereotactic frame, obtaining an MRI or CT scan, computing the coordinates of the lesion, and then obtaining several small tissue samples through a burr hole for diagnostic purposes. A craniotomy is usually performed under general anesthesia and allows the physicians to obtain a specimen for diagnostic purposes as well as to resect the tumor, thereby gaining some therapeutic benefit.

A number of factors come into play in deciding whether to proceed first with a stereotactic biopsy or to perform a craniotomy (Table 1). Indications



for the stereotactic biopsy as the first procedure include the following: deep-seated tumors that are not amenable to resection; lesions in which the radiologic and clinical findings are ambiguous; diffuse lesions; multiple lesions; an appearance that suggests a lymphoma, which would not require re-

section; a change in the appearance of a previously diagnosed or treated tumor; and a wish to assess tumors after treatment (e.g., to distinguish between radiation necrosis and tumor recurrence). The choice may also be dictated by the patient's overall condition; for instance, the patient may be too



**Figure 2. Magnetic Resonance Spectroscopy for N-Acetyl Aspartate (NAA), Choline, and Creatine.**

A color map of the choline-to-creatine ratio is shown over a T<sub>1</sub>-weighted image (Panel A). A single focus in which the choline-to-creatine ratio is greater than 4:1 can be seen just lateral to the cystic area (arrow), indicating a region of higher metabolic activity within a predominantly low-grade tumor. The spectrum from this region is shown at the top of Panel B and compared with that of a region of a normal brain (bottom). Both the creatine peak and the NAA peak are lower in the tumor than in the normal brain.

**Table 1. Relative Indications for Stereotactic Biopsy as Compared with Craniotomy as a First Procedure.**

Stereotactic Biopsy	Craniotomy
Deep-seated tumor	Superficial tumor
Unresectable tumor	Resectable tumor
Multiple lesions	Single lesion
Unclear appearance in radiologic images	Clear appearance in radiologic images
Change in appearance	New diagnosis
No mass effect	Mass effect
Normal intracranial pressure	Raised intracranial pressure
Patient with systemic disease	Healthy patient
Diagnostic potential	Diagnostic and therapeutic potential

ill to tolerate a craniotomy. In addition to providing the opportunity to obtain diagnostic tissue, a stereotactic operation may in some cases make it possible to deliver radiotherapy or other antitumor agents to the lesion, although these approaches are still experimental.

A craniotomy provides the opportunity for diagnosis and treatment in one operation. Indications for craniotomy include lesions that appear to be surgically resectable and that are in accessible and relatively “silent” areas of the brain or in areas of the brain in which a mild postoperative neurologic deficit is considered acceptable to the patient and the clinicians, an appearance consistent with tumor on the MRI, and large tumors exerting mass effect. Resecting the bulk of the tumor reduces the overall tumor burden, reduces intracranial pressure along with mass effect, and possibly potentiates the effects of adjuvant therapies such as chemotherapy and radiation. Finally, brain tumors are not uniform and can have areas of higher grade mixed in with areas of lower grade. Since the overall behavior of the tumor is determined by its most malignant areas, resection makes possible a more complete sampling of the lesion.

The goal of surgery is to resect safely as much of the tumor as possible, with a complete resection of all gross tumor being the ideal outcome. Intraoperative delineation of tumor boundaries is often difficult because gliomas are by nature infiltrative and clear boundaries may not exist. There are a number of approaches to help guide intraoperative tumor



resection, including frameless stereotaxy, intraoperative imaging, and other experimental techniques that capitalize on the biologic differences between tumor tissue and brain tissue. There are advantages and disadvantages associated with each of these techniques (Table 2).

This patient had a tumor in the right frontal lobe that was readily accessible and had a radiologic appearance that was consistent with a primary brain tumor. There was mass effect that had led to seizures, so the decision was made to perform a craniotomy. An intraoperative, frameless stereotactic system was used to guide the tumor resection. The patient underwent a right frontal craniotomy and resection of the right frontal pole along with the tumor. The tumor had a slightly gray color and a somewhat firm texture, which were only subtly different from the surrounding brain tissue. The resection was carried inferiorly to the floor of the anterior cranial fossa and medially to the falx cerebri. The result of analysis of an intraoperative frozen section was consistent with low-grade glioma. At the completion of surgery we believed that we had achieved our goals, which were to obtain tissue for diagnosis and to debulk the tumor safely.

The patient had a smooth recovery. However, the postoperative MRI showed a small amount of residual disease. At that point, the options were a second operation for further resection or treatment with radiation and chemotherapy. Although the extent of resection is correlated with improved survival in higher-grade tumors, there is no evidence that a second operation imparts further benefit in this situation.<sup>1-4</sup> Since there is evidence that certain subtypes of oligodendroglioma respond particularly well to chemotherapy, we elected to wait for the results of the pathological examination and genetic testing before deciding on the next step.<sup>5-7</sup>

#### PATHOLOGICAL DISCUSSION

*Dr. David N. Louis:* This tumor is a diffusely infiltrating glioma with the classic features of oligodendroglioma, which include a monomorphic population of cells with rounded nuclei and perinuclear halos as well as a delicate branching vasculature (Fig. 3A). In some regions, the tumor has markedly increased cell density, high mitotic activity, microvascular proliferation, nuclear pleomorphism, and numerous apoptotic cells (Fig. 3B). An immunohistochemical evaluation using MIB-1 antibody technology, which labels dividing cells, demonstrat-

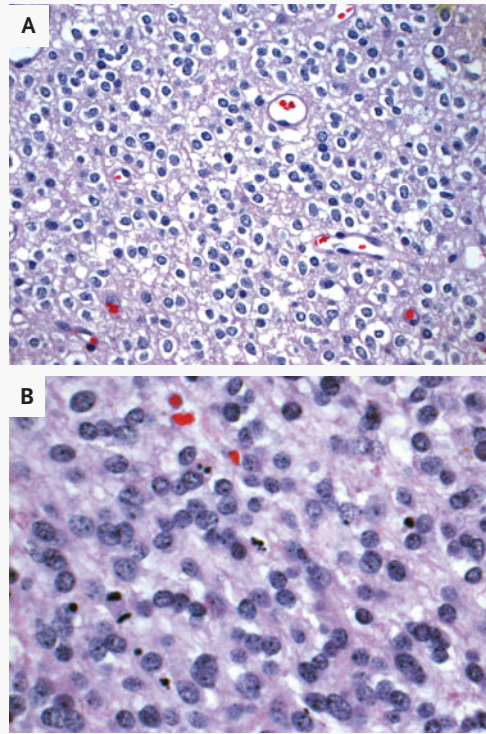
**Table 2. Comparison of Intraoperative Guidance Techniques.**

Technique	Advantages	Disadvantages
Frame-based stereotaxy	Excellent resolution	Cumbersomeness
	Excellent accuracy	Difficulty in assessing boundaries
	Established technology	Brain shift during operation
Frameless stereotaxy	Good resolution	Brain shift during operation
Intraoperative CT	Ease of use	Cumbersomeness
	Real-time imaging	Less anatomical detail than MRI
Intraoperative MRI	Geometric accuracy	High cost
	Real-time imaging	Specialized equipment needed
	Good anatomical detail	

ed a proliferation index of 11 percent. All these histologic features are diagnostic of an anaplastic oligodendroglioma, categorized according to the system of the World Health Organization (WHO) as WHO grade III.

DNA was extracted from the formalin-fixed, paraffin-embedded tumor tissue, as well as from peripheral-blood leukocytes. The constitutional and blood DNA was amplified with a polymerase-chain-reaction assay and compared at three polymorphic markers on the short arm of chromosome 1 (1p) and at three polymorphic markers on the long arm of chromosome 19 (19q). These assays demonstrated allelic loss ("loss of heterozygosity") for both 1p and 19q (Fig. 4).

For anaplastic oligodendrogliomas, the therapeutic relevance of molecular subtyping has been demonstrated.<sup>5-7</sup> No clinical or pathological feature predicts response reliably, whereas allelic loss of chromosome 1p is a powerful predictor of a response to combination chemotherapy with procarbazine, lomustine, and vincristine, and the combined loss of 1p and 19q is a strong predictor of longer survival.<sup>5-7</sup> We have divided anaplastic oligodendrogliomas into four therapeutically and prognostically relevant subgroups.<sup>6</sup> Patients whose tumors have combined but isolated losses of 1p and 19q tend to have marked and durable responses associated with long survival, with or (in some cases) without postoperative radiation therapy. Other tumors with chromosome 1p alterations also respond to chemotherapy, but with a shorter dura-

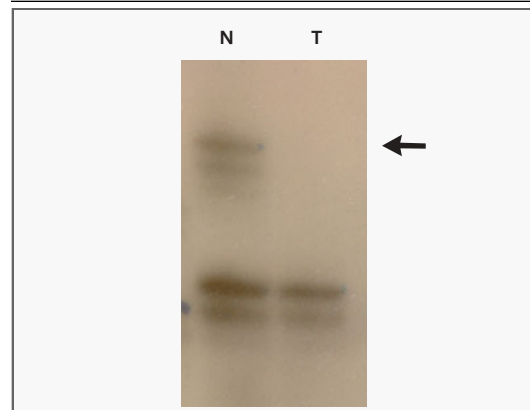


**Figure 3. Brain-Biopsy Specimen (Hematoxylin and Eosin).**

The specimen from the patient had the classic appearance of an oligodendroglioma, which features infiltrating glioma cells with rounded nuclei and perinuclear halos (Panel A). Some regions had marked hypercellularity, anaplastic nuclei, mitotic figures, and apoptotic cells (Panel B); together, these features are diagnostic of anaplastic oligodendroglioma.

tion of response and shorter survival. Tumors lacking loss of 1p can be divided into two subgroups: those with a *TP53* mutation, which often respond to chemotherapy but recur quickly; and those without a *TP53* mutation, which are poorly responsive, aggressive tumors. These results suggest that genetic analysis can be used to tailor therapy at the time of diagnosis.

For glioblastomas, genetic subgroups have also been defined on the basis of mutually exclusive gene alterations: for example, one subgroup features frank amplification of the epidermal growth factor–receptor (*EGFR*) gene, as compared with a subgroup that has a *TP53* mutation and allelic loss of chromosome 17p.<sup>8–10</sup> The glioma pathway that includes *TP53* inactivation is characteristic of (but not restricted to) glioblastomas that have arisen in younger adults through malignant progression



**Figure 4. Loss of Heterozygosity.**

An autoradiograph shows allelic loss at a polymorphic locus on the short arm of chromosome 1 (D1S199) when tumor (T) and blood (N) DNA are compared. Note the loss of the upper allele (arrow) in the tumor DNA.

from a lower-grade astrocytoma<sup>9,10</sup> and of giant-cell glioblastomas.<sup>11</sup> Glioblastomas with *EGFR* amplification, in contrast, most often occur in older patients with a short clinical history and no definite prior lower-grade astrocytoma<sup>9,12</sup> and in those with a small-cell phenotype.<sup>13</sup> Although the relationships between the glioblastoma genotype and clinical features are complex,<sup>14</sup> the ability of molecular techniques to detect biologic heterogeneity in glioblastomas raises the possibility that new approaches to overall classification and therapy of gliomas could be based on objective biologic variables.

As a result of these studies, clinical testing for loss of chromosome 1p and 19q can be recommended for patients with anaplastic oligodendrogliomas, for patients with small-cell malignant tumors in which the differential diagnosis includes anaplastic oligodendroglioma rather than small-cell glioblastoma, as well as for selected patients with grade II oligodendrogliomas for whom decisions about therapy might be influenced by additional knowledge about the probable behavior of the tumor.

#### DISCUSSION OF MANAGEMENT

*Dr. Alison M. O'Neill:* The management of anaplastic oligodendrogliomas is a multidisciplinary clinical field. The area in which the most change has occurred in the past several years has been in the role of chemotherapy in the treatment of these tumors

and, in particular, the identification of subgroups of patients who will respond well to chemotherapy.

In the late 1980s, Cairncross and Macdonald reported that some patients with malignant oligodendroglial tumors responded much more briskly to chemotherapy, in particular combination chemotherapy with procarbazine, lomustine, and vincristine, than patients with other types of malignant glial tumors.<sup>15</sup> In a later series of patients with residual or recurrent anaplastic oligodendrogliomas who were treated with a dose-intense regimen of procarbazine, lomustine, and vincristine, the investigators found a 75 percent response rate to chemotherapy using rigorous imaging criteria.<sup>16</sup> As Dr. Louis has described, the emergence of molecular diagnostic techniques has allowed the identification of patterns of chromosomal alterations in anaplastic oligodendrogliomas that correlate with chemosensitivity and prolonged survival.<sup>5-7</sup> Thus, we can now predict which patients with a particular subgroup of malignant glioma are likely to respond well to chemotherapy on the basis of chromosomal analysis of the tumor tissue. This observation raises the question whether chemotherapy alone may be used in the initial treatment of patients with chemosensitive tumors; in addition, the usefulness of other chemotherapeutic regimens in this disease and the implications of these findings for the management of other types of glial tumors remain to be explored.

This patient was treated with procarbazine, lomustine, and vincristine chemotherapy for a total of nine cycles over the course of the following year. He had no significant adverse side effects from the chemotherapy, but he was admitted to the hospital 10 months after beginning the chemotherapy with a pulmonary embolus. During the initial preoperative evaluation at the time of his presentation with the brain tumor, he was found to have the factor V Leiden mutation, which predisposes a patient to thrombotic events. He has been maintained on warfarin since the discovery of the pulmonary embolus and has had no further problems. After the completion of his chemotherapy, he had no neurologic abnormalities on examination, but he did have some impairment of short-term memory. He was referred to Dr. Loeffler for radiation therapy.

*Dr. Hunter:* Further imaging was performed after surgery (Fig. 1C) and again seven months later while the patient was receiving the chemotherapy regimen (Fig. 1D). On the final study, there remains some dorsolateral infiltrative signal, but the

initial high-grade component is no longer present. The residual area of T<sub>2</sub> hyperintensity did not enhance with gadolinium contrast medium and did not have characteristics of malignancy on images obtained with magnetic resonance spectroscopy.

*Dr. Jay S. Loeffler:* The role of radiation therapy in the postoperative management of an anaplastic oligodendroglioma in a patient such as this is undergoing reevaluation. In the past, patients with this type of tumor were treated in a very similar fashion to patients with anaplastic astrocytoma, with surgery and radiation being the predominant forms of therapy. The recently identified sensitivity to chemotherapy of anaplastic oligodendrogliomas with allelic loss of chromosome 1p has led some investigators to consider chemotherapy to be the primary postoperative method, with radiation reserved for patients with tumor progression.

Does the allelic loss of 1p predict the response to radiation therapy, as it appears to predict the response to chemotherapy? Bauman et al.<sup>17</sup> reviewed progression-free survival in 36 patients treated with radiation and whose 1p status was known. The median progression-free survival for the 19 patients with 1p loss was 49.8 months, as compared with 5.7 months for those retaining 1p. However, since many of the patients had received procarbazine, lomustine, and vincristine chemotherapy before radiation therapy was initiated, it is not clear if the difference in progression-free survival could be completely explained by differences in the response to radiation therapy alone. Several clinical protocols are under way to delineate better the role and sequencing of radiation therapy and chemotherapy for patients with anaplastic oligodendroglioma. This patient was treated with conformal external-beam therapy at the completion of his regimen of procarbazine, lomustine, and vincristine. CT and MRI image correlation with image fusion was performed as part of his treatment planning.<sup>18</sup> Radiation therapy consisted of 59.4 Gy delivered in 33 fractions to the area of the abnormalities revealed by the T<sub>2</sub>-weighted MRI scan, plus a margin. The patient tolerated the treatment without significant difficulty. Given the relatively modest treatment volume and the location of the tumor, the probability of clinically significant late neurocognitive or neuroendocrine effects is anticipated to be low.

*A Physician:* Do you believe that the development of venous thrombosis and sleep apnea in the patient were related to his brain tumor?

*Dr. O'Neill:* I do not believe that the sleep apnea

was related to his brain tumor, but there is a markedly elevated risk of deep venous thrombosis in patients with brain tumors, in addition to the risk associated with the factor V Leiden mutation.

*Dr. Tracy Batchelor (Neuro-oncology):* Now that it is four months after the completion of radiation therapy and almost two years after his initial seizure, the patient has no evidence of recurrence of his tumor, and he hopes to be able to return to work soon. He is socially and physically active, and in

fact, his greatest concern is that because of the necessity for long-term anticoagulant medication, he is unable to participate in physical activities that he enjoys, such as mountain biking and aggressive skiing.

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#### ANATOMICAL DIAGNOSIS

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Anaplastic oligodendroglioma with allelic loss of chromosomes 1p and 19q.

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