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A 54-year-old man was admitted to this hospital because of visual-field loss and a mass in the brain.

The patient had been well until 3 weeks before admission, when loss of vision in the right eye, associated with diplopia, developed while he was jogging; it resolved spontaneously after several minutes. Four days before admission, the symptoms recurred transiently, and he bumped into a tree while running. On the morning of admission, dizziness and loss of vision in the right lower visual field in both eyes developed, which did not resolve and resulted in difficulty driving. He went to the emergency department at another hospital. On examination, nystagmus was present in both eyes on left and right gaze. The vital signs and the remainder of the examination were normal, as were the results of laboratory tests, including a complete blood count; blood levels of electrolytes, calcium, and glucose; and tests of coagulation and renal and hepatic function. Magnetic resonance imaging (MRI) of the brain, after the administration of gadolinium, revealed two adjacent masses (2 cm by 2 cm and 1 cm by 1.5 cm) in the left occipital and posterior parietal regions. Mass effect on the left occipital horn was associated with abnormal $T_2$-weighted and fluid-attenuated inversion recovery (FLAIR) signal hyperintensity extending through the splenium of the corpus callosum. The patient was admitted to the hospital, and acetylsalicylic acid, dexamethasone, and phenytoin were administered. Later that day, he was transferred to this hospital.

The patient reported difficulty seeing objects in the right lower visual field and dizziness. He reported no headache, nausea, vomiting, numbness, weakness, bowel or bladder dysfunction, or seizures. He had a history of gastroesophageal reflux disease and *Helicobacter pylori* infection and had recently had hematuria. A computed tomographic (CT) scan of the abdomen obtained 3 months before admission showed prostatic enlargement and was otherwise normal. He had had inguinal herniorrhaphies in the past. He took esomeprazole and had no known allergies. He was divorced, had children, and was physically active, running daily and competing in multiple marathons. He drank alcohol in moderation, had never smoked, and had...
no recent exposure to ill persons, tuberculosis, or asbestos. An uncle had had an inoperable primary brain tumor; the patient’s siblings and children were healthy.

On examination, there was bilateral right inferior quadrantanopia; the vital signs, oxygen saturation, and remainder of the general and neurologic examination were normal. The administration of dexamethasone was continued, and omeprazole was added. The blood glucose level was 199 mg per deciliter (11.0 mmol per liter) (reference range, 70 to 110 mg per deciliter [3.9 to 6.1 mmol per liter]), and the lactate dehydrogenase level 217 U per liter (reference range, 110 to 210). The complete blood count and blood levels of electrolytes, protein, albumin, globulin, calcium, phosphorus, magnesium, carcinoembryonic antigen, prostate-specific antigen, CA 19-9, and nonmaternal alpha-fetoprotein were normal, as were tests of coagulation and renal function and a urinalysis. A chest radiograph was normal. On the second day, an MRI scan of the brain, obtained after the administration of gadolinium, showed two heterogeneous-ly enhancing, well-circumscribed lesions in the left occipital lobe (2.2 cm by 1.8 cm and 1.1 cm by 1.4 cm). Within the enhancing portions of the lesions, there was restricted diffusion. Extensive signal abnormality on T₂-weighted and FLAIR images was seen in the surrounding white matter of the left occipital lobe, extending into the posterior left temporal lobe and the splenium of the corpus callosum. Mass effect was present on the surrounding sulci and occipital horn and trigone of the left lateral ventricle, with no evidence of midline shift or hydrocephalus.

The next day, an MRI scan of the abdomen and pelvis after the administration of gadolinium, a CT scan of the chest, and a bone scan showed no evidence of cancer. The patient was discharged on the fourth hospital day, taking omeprazole and dexamethasone.

Three days later, the patient was readmitted, and a diagnostic procedure was performed.

**Differential Diagnosis**

Dr. Tracy T. Batchelor: May we see the imaging studies?

Dr. A. Gregory Sorensen: MRI examination reveals two masses in the left occipital lobe that are enhanced on images obtained after the administration of gadolinium (Fig. 1A). There is abnormal T₂-weighted signal in the left occipital lobe surrounding the foci of enhancement and extending across the splenium of the corpus callosum (Fig. 1B), a feature consistent with edema. Additional imaging studies showed no evidence of highly restrictive diffusion that would be typical for an infarct; instead they showed increased diffusion of water, a finding consistent with edema. Susceptibility-weighted MRI scans showed that the masses had small regions of very short T₂-weighted signal that were consistent with micro-hemorrhages or calcifications (Fig. 1C).

Dr. Batchelor: I cared for this patient and am aware of the diagnosis. This 54-year-old man presented with episodic, reversible neurologic deficits, followed by persistent bilateral right inferior quadrantanopia. Cranial MRI showed contrast-enhancing masses in the left occipital lobe, and additional imaging showed no evidence of lesions outside the brain. A tumor was the leading diagnostic possibility, and a primary brain tumor was more likely than a metastatic tumor.

Other neurologic diseases were in the differential diagnosis. On cranial MRI, a cerebral abscess may have an appearance similar to that of a tumor; however, this patient had no systemic symptoms, no fever, and no recent craniofacial infections or procedures that might have conferred the risk of an abscess. Acute disseminated encephalomyelitis may present as a contrast-enhancing mass lesion; however, the absence of more severe neurologic deficits would be somewhat atypical. His transient neurologic symptoms raised the possibility of transient ischemic attacks, with a subsequent infarct. Although infarcts may be contrast enhancing, the appearance of two discrete, contrast-enhancing mass lesions is more typical of tumor than of cerebral infarcts. Moreover, there was no restricted diffusion on the initial cranial MRI scan to suggest acute infarction.

The leading diagnosis in this case was therefore a primary malignant tumor of the brain parenchyma. The appearance on imaging and the patient’s age make glioblastoma the most likely diagnosis.

Resection of a suspected malignant brain tumor confers several benefits. A resection specimen provides representative tumor tissue for pathological diagnosis, including molecular genetic tests. A debulking resection may also reduce mass effect and intracranial pressure, leading to clinical improvement and decreasing the need for...
Figure 1. Initial Imaging Studies and Biopsy Specimen.

An axial T₁-weighted MRI scan obtained after the administration of gadolinium (Panel A) shows two areas of abnormal enhancement in the left occipital lobe. Panel B shows abnormal T₂-weighted signal surrounding the foci of enhancement and extending across the splenium of the corpus callosum. Within the enhancing masses are small areas of very short T₂-weighted signal, which appear as dark areas on this susceptibility-weighted image (Panel C). Histologic examination (Panel D, hematoxylin and eosin) of a specimen of the tumor in the left occipital lobe shows a densely cellular, pleomorphic glial tumor with vascular proliferation (arrow) and necrosis (arrowhead).
medications such as glucocorticoids to reduce intracerebral edema. A prospective, randomized trial showed that, in a subset of patients with glioblastoma, gross total resection conferred a survival benefit as compared with subtotal resection.\(^4\) Therefore, craniotomy for both diagnosis and resection of the mass was recommended and performed.

**Dr. Tracy T. Batchelor’s Diagnosis**

Malignant primary brain tumor, most likely glioblastoma.

**Pathological Discussion**

*Dr. David N. Louis:* Examination of the specimen of the tumor in the left occipital lobe showed a densely cellular glial tumor with mitoses, microvascular (so-called endothelial) proliferation, and necrosis (Fig. 1D), features diagnostic of glioblastoma (World Health Organization [WHO] grade IV of IV). Methylation-specific polymerase chain reaction (PCR) to evaluate the methylation status of the 0\(^\text{th}\)-methylguanine–DNA methyltransferase (MGMT) gene promoter, performed on DNA extracted from the formalin-fixed, paraffin-embedded block of tumor, showed methylated alleles. MGMT is a DNA-repair protein; the methylation status of the MGMT promoter has prognostic and potentially predictive significance. In glioblastoma, Methylation of the MGMT promoter has been associated with longer overall survival in patients with glioblastoma, regardless of the methylation status of MGMT. However, in patients with glioblastoma who are treated with this regimen, the methylation status of the MGMT promoter has prognostic implications. In one study, patients with glioblastoma whose tumors were positive for MGMT methylation, as this patient's was, had a median survival of 21.7 months and 2-year survival of 46\%, as compared with patients whose tumors were negative for MGMT methylation, who had a median survival of 12.7 months and 2-year survival of 13.8\%.

Since drugs that target the vascular endothelial growth factor (VEGF) signal-transduction pathway and consequently inhibit angiogenesis have shown some benefit in patients with recurrent glioblastoma, this patient was enrolled in a phase 1 clinical trial in which vatalanib, an oral, pan-VEGF tyrosine kinase inhibitor, was added to concurrent radiation and temozolomide.\(^4\)

The patient received this regimen with no adverse effects. Four weeks after completion of the 6-week course, a routine follow-up cranial MRI was performed, at which time, the patient was asymptomatic, physically active, and managing all his activities of daily living.

*Dr. Sorensen:* An MRI scan obtained 3 months after surgery showed irregular feathery enhancement around the surgical cavity, as well as mass effect as evidenced by compression of the left lateral ventricle (Fig. 2A); both findings were new in comparison with immediate postoperative images. Extensive edema was evident on the T\(_2\)-weighted FLAIR image (Fig. 2B). Diffusion-weighted images showed increased water mobility (i.e., increased diffusion of water), a feature consistent with edema, and perfusion-weighted images showed no evidence of elevated cerebral
Figure 2. Follow-up Imaging Studies and Biopsy Specimen.

Three months after surgery, an axial T₁-weighted image obtained after the administration of gadolinium (Panel A) shows irregular enhancement around the surgical cavity, as well as mass effect. A T₂-weighted fluid-attenuated inversion recovery (FLAIR) image (Panel B) shows extensive edema around the surgical site. A biopsy specimen of the left occipital lobe (Panel C, hematoxylin and eosin) shows necrosis with microcalcifications, which is characteristic of treatment-related necrosis. An axial T₁-weighted image of the brain obtained after the administration of gadolinium (Panel D) shows much less enhancement in the left occipital lobe 18 months after surgery.
blood volume or hypervascularity in the region. Positron-emission tomography after the administration of $^{18}$F-fluorodeoxyglucose revealed no evidence of hypermetabolism in the region. These imaging-based physiological and functional assays indicated that there was no active tumor, despite the presence of a clear mass effect.

**Dr. Batchelor:** The changes observed on the first postradiation cranial MRI could represent either tumor progression or tumor pseudoprogression, which is a reaction of the tumor and tumor microenvironment to the radiation and chemotherapy. Tumor pseudoprogression usually occurs within 3 months after completion of radiation and chemotherapy. Since no imaging studies are specific for distinguishing pseudoprogression from actual tumor progression, we were concerned that the changes could represent tumor progression in this patient. Therefore, we performed a stereotactic biopsy of the enhancing abnormalities in the left occipital lobe.

**Dr. Louis:** Three biopsy specimens of the left occipital lobe contained extensive necrotic debris with microcalcifications (Fig. 2C). The specimens also contained viable brain tissue with some atypical glial cells and marked hyalinization of small blood vessels that had plump endothelial cells with prominent nuclei. These features are characteristic effects of radiation and other therapies. No areas of solid, mitotically active tumor were present. The pathological findings were consistent with pseudoprogression.

**Dr. Batchelor:** Pseudoprogression, as observed in this patient, occurs in approximately 20 to 40% of patients with glioblastoma after chemoradiation. Patients with tumors that have methylation of the MGMT promoter may be at a higher risk for this complication — in one series, pseudoprogression was observed in 21 of 23 patients with MGMT-methylated glioblastomas that were treated with chemoradiation. Interestingly, in cases of glioblastoma, patients with tumors that showed pseudoprogression had improved survival relative to patients with tumors that did not develop pseudoprogression. Pseudoprogression may be associated with cerebral edema and increased intracranial pressure and can result in neurologic symptoms and signs, although it did not in this patient. In symptomatic patients, the administration of glucocorticoids may alleviate edema and neurologic symptoms. Small clinical studies have investigated the use of anti-VEGF therapy for radiation necrosis, but this treatment remains experimental. This patient was taking a VEGF inhibitor, vatalanib, which may have suppressed symptoms caused by pseudoprogression. Since he was asymptomatic at the time of the radiographic findings, we made no changes in his treatment. He continued taking temozolomide and vatalanib as part of the phase 1 trial for 12 monthly cycles, and then he entered a period of observation. He returned to work part-time and adapted well to his only neurologic deficit, bilateral right inferior quadrantanopia. Fourteen months after the diagnosis of pseudoprogression and 18 months after the initial diagnosis of glioblastoma, a routine follow-up MRI scan showed reduction in mass effect and markedly decreased enhancement as compared with the earlier scans. One month later, he had a generalized seizure. Repeat cranial MRI was performed.

**Dr. Sorensen:** An MRI scan of the brain obtained after the administration of gadolinium showed reduced enhancement in the left occipital lobe and no enhancement in the right temporal lobe 18 months after surgery (Fig. 2D), whereas an image obtained 1 month later showed a new enhancing mass in the right temporal lobe with midline shift, compression of the right temporal ventricular horn, and sulcal effacement (Fig. 3A). T$_2$-weighted FLAIR images showed marked edema surrounding the mass (Fig. 3B).

**Dr. Batchelor:** Because the imaging revealed a new mass in the contralateral hemisphere, a subtotal resection of the mass in the right temporal lobe was performed.

**Dr. Louis:** Specimens obtained from the right temporal lobe consisted of densely cellular, viable, and mitotically active tumor, as well as tumor diffusely infiltrating the adjacent white matter, findings diagnostic of recurrent glioblastoma (Fig. 3C). There were also foci of necrosis, findings consistent with treatment effects. Methylation-specific PCR confirmed the continued presence of methylation of the MGMT promoter in the recurrent tumor. Studies of the methylation status of the MGMT promoter in primary and recurrent glioblastomas have shown that recurrent tumors may change their methylation status, particularly if the primary tumor had a methylated MGMT promoter; however, methylation status of the MGMT promoter...
promoter at recurrence does not appear to be predictive of subsequent outcome.7

Dr. Batchelor: This patient now has recurrent glioblastoma, 19 months after surgical excision, remote from the original site and outside the original radiation field. In patients treated with radiation alone, CT-based investigations of the patterns of glioblastoma recurrence revealed that 90% of patients had tumor progression within 2 cm of the original tumor site and within the region of the brain that had received radiation.8 However, more recent studies involving patients receiving temozolomide plus radiation have shown a higher proportion of patients with the development of tumor progression outside the radiation field, as well as a longer interval to recurrence and improved survival.9 This patient had a relapse at 19 months, outside the radiation field; the timing and location are characteristic of MGMT-methylated tumors that have been treated with temozolomide and radiation.

Treatment options for this patient with recurrent glioblastoma are limited. Bevacizumab, a monoclonal antibody that binds the circulating VEGF ligand, is approved by the Food and Drug Administration for recurrent glioblastoma. In a randomized, noncomparative trial of bevacizumab with and without irinotecan (an inhibitor of topoisomerase II), radiographic responses were observed in 28% and 37% of patients, respectively.10 These rates are higher than those observed in historical control patients not treated with bevacizumab. Carboplatin alone has limited activity in cases of recurrent glioblastoma, but it is not known whether treatment with a combination of carboplatin and bevacizumab will confer an improved result. After subtotal resection of the recurrent tumor, this patient received a repeated 6-week course of temozolomide plus radiation. He was then begun on treatment with bevacizumab and carboplatin.

Dr. Sorensen: Images obtained before the initiation of bevacizumab therapy show areas of enhancement in the right temporal lobe (Fig. 4A) that are surrounded by extensive edema (Fig. 4B), confirmed on maps of the apparent diffusion coefficient (Fig. 4C). The effects of surgery in the right temporal lobe are evident: the enhancing region has been removed (Fig. 4D), and the edema has been reduced (Fig. 4E). Of note, however, is a focus of markedly restricted diffusion (Fig. 4F), consistent with more cellular tissue and suggestive of active tumor.

Dr. Batchelor: Despite radiographic improvement, the patient had progressive neurologic decline while on treatment. It is possible that the reduction in contrast enhancement represented pseudoresponse (i.e., reduction of vessel permeability) and that the expanding regions of restricted diffusion were representative of progressive glioblastoma. In view of his neurologic decline, we elected, in consultation with the patient and his family, to
stop therapy, and the patient was transferred to hospice care. He died 8 months after the recurrence and 28 months after the initial diagnosis of glioblastoma. Unfortunately, this survival is typical of the best that can be achieved with current therapy for glioblastoma.

Dr. Louis: Are there any questions?

Dr. Jay Loeffler (Radiation Oncology): The imaging at the time of the recurrence, in the right temporal lobe, did not reveal disease connecting that site to the originally affected left occipital lobe. Would you comment on that?

Dr. Louis: In studies involving large sections of brains obtained at autopsy from patients with glioma, infiltrating tumor cells can be found between foci of cerebral glioma in the majority of the cases, confirming the microscopical contiguity of most malignant cerebral gliomas. An autopsy was not performed in this patient to examine this question at a histologic or molecular level.

Dr. Andrew S. Chi (Neurology): Were there any histologic differences between the primary and the recurrent tumor?

Dr. Louis: Many recurrent glioblastomas look histologically similar to the primary tumors, although recurrences within the treated field typically show changes characteristic of previous treatment, including necrosis with punctate mineralization or hyalinized blood vessels with activated-appearing endothelial cells. In this patient,
there were no notable differences between the histologic appearances of the two tumors.

Michelle R. Pisapia (Nurse Practitioner, Neurology): Are there any restrictions in the way the protocols are written for these new study drugs regarding whether the diagnosis is pseudoprogression and whether a patient can stay on the drugs?

Dr. Batchelor: Yes, clinical trials for recurrent glioblastoma are designed such that patients in whom radiographic progression develops in the radiation treatment field within 3 months after the completion of chemoradiation are excluded unless there is a pathological diagnosis of recurrent tumor.

ANATOMICAL DIAGNOSIS

Glioblastoma, WHO grade IV of IV, with methylation of the MGMT promoter.

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REFERENCES


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