Glioblastoma multiforme (GBM) is the most lethal and aggressive primary brain tumor. Several other abnormalities (neoplastic, infectious, or vascular) can mimic symptoms seen with GBM. This article reviews GBM and presents a case study that demonstrates the rationale for biopsy and pathologic diagnosis prior to the initiation of treatment for malignant brain tumors.

At a Glance
- Many conditions present as clinical mimics of glioblastoma multiforme.
- Surgical intervention allows for biopsy, which permits accurate clinical diagnosis and possible debulking of tumor mass.
- Pathologic diagnosis enables safe and effective treatment decisions and planning.

Glioblastoma multiforme (GBM) is the most common, aggressive, and difficult to treat primary brain tumor in adults. It accounts for about 50% of all primary malignant brain tumors. More than 23,000 cases are diagnosed annually in the United States (Ohagaki & Kleihues, 2005) with a mean survival of 12–24 months and little improvement in survival times despite treatment (Kumar, Abbas, & Fausto, 2004). Treatment issues include the relative inability of chemotherapy to cross the blood-brain barrier (BBB), avoidance of damage to non-regenerating neurons while causing damage to malignant regenerating astrocytes, and the likelihood of several different molecular signatures within the broad class of GBM (Chamberlain, Glantz, Chalmers, Van Horn, & Sloan, 2006; Dall’oglio et al., 2008; Mason, Mirimanoff, & Stupp, 2006).

Diagnostic biopsy and maximal safe resection are recommended prior to treatment planning (National Comprehensive Cancer Network, 2015). Some community clinical practices start treatment based on radiographic data without pathologic confirmation. Avoiding surgery and biopsy has been seen as beneficial if the presumption is that surgery will be debilitating, futile, or result in prolonged convalescence. Some clinicians have suggested that surgery is not indicated with a presumed terminal diagnosis because the treatment would not change. This case study presents compelling evidence for biopsy to confirm the diagnosis prior to initiating treatment for brain tumors.

Case Study
C.C. is a 71-year-old right-handed retired man who was in good health until four weeks prior to evaluation. He had noted difficulty reading and an inability to see letters on the left side of the page. An ophthalmologic examination revealed a left homonymous hemianopsia, a visual defect involving visual loss on the same side of both eyes. Magnetic resonance imaging (MRI) revealed a contrast enhancing right occipital lesion with significant vasogenic edema. C.C. was started on dexamethasone 4 mg orally three times a day and referred to a neurosurgeon. His prior medical history was negative. A review of systems was negative with the exception of visual changes. C.C. is retired and widowed, and he is living with a female partner. He did not have a history of smoking or of drug use or abuse. He reported no recent foreign travel. On physical examination, he had left homonymous hemianopsia on gross confrontation. The differential diagnosis included primary brain tumor, metastatic brain tumor, and intracranial abscesses.

A computed tomography scan of C.C.’s chest, abdomen, and pelvis revealed no radiographic evidence of primary cancer. Based on his age, presentation, MRI characteristics, and absence of obvious systemic neoplasm, primary brain tumor was the most likely diagnosis. The plan was to perform biopsy immediately, followed by maximal safe tumor resection, if indicated, during the initial surgery.

Epidemiology
The incidence of gliomas, like many cancers, is associated with aging; this diagnosis occurs more often in older
adults. Low-grade gliomas typically occur in adults aged younger than 45 years. GBM commonly appears in the late fifth, sixth, and seventh decades and shows a slight preference for men (1.3:1) (Kumar et al., 2004; Ohagaki & Kleihues, 2005), with increased occurrence in Caucasians and Asians. In the United States, about 356,000 individuals are living with gliomas, and the annual incidence is estimated at 25,000 cases (Ohagaki & Kleihues, 2005). Less than 5% of GBMs are hereditary and may be associated with other hereditary disorders, such as neurofibromatosis, Li-Fraumeni syndrome, hereditary nonpolyposis colon cancer, von Hippel-Lindau syndrome, and tuberous sclerosis (Yarbro, Wujcik, & Gobel, 2011).

Little is known about GBM causative factors, and most cases are sporadic with no known genetic predisposition. No demonstrated association has been found between GBM and smoking, diet, cell phone use, or electromagnetic field exposure (National Cancer Institute, n.d.). Smaller studies have suggested possible associations between GBM and viruses (e.g., polymavirus simian virus 40, cytomegalovirus), ionizing radiation exposure, and occupational exposures to polyvinyl chloride and lead (Marchesi et al., 2007; Vlčchez, Kozinetz, Arrington, Madden, & Butel, 2003). The World Health Organization has reported elevated brain tumor rates in individuals with malaria, suggesting that the anopheline mosquito may serve as a vector for a possible viral entity (Lehrer, 2010).

Pathophysiology and Clinical Presentation

Gliomas are found most frequently in white matter (myelinated axon tracts) and the gray–white junction (Kumar et al., 2004). GBMs arise from uncontrolled, rapid growth of astrocytes, the glial cells that surround and support neurons and maintain the blood supply in close proximity to the tissue. Neurons are essentially nonmitotic cells and do not exhibit malignancy but are damaged by compression from the rapidly enlarging astrocytic mass and disruption of collateral circulation and redistribution of blood flow to feed the rapid astrocytic growth. These tumors are characterized by necrotic areas surrounded by anaplastic cells, giving rise to the term pseudopalisading necrosis, which describes waves of tumor cells migrating away from areas of hypoxia (Chamberlain et al., 2006). Gliomas have varying clinical presentations as a result of the brain function associated with the location of the tumor. The brain itself has no pain nerve endings; therefore, headache usually occurs when the lesion and/or edema volume stretches and puts tension on the surrounding dura, which is rich in pain nerve endings (Kumar et al., 2004).

Seizures can occur because edema and necrosis act as an irritant in the conduction of electrical impulses. Seizures are more common in eloquent brain areas with increased electrical activity. Motor, sensory, or speech symptoms occur with lesions in the frontal, parietal, and/or temporal lobes, and visual ability and visual field deficits are common with tumors in the occipital lobes or the visual tracts (Carpenter & Reddi, 2012).

Treatment

Traditional treatment for GBM focuses on maximal safe resection to decrease the tumor burden, relieve pressure, and lessen the total volume of malignant cells, based on the theory that any treatment will be more effective with fewer target cells. Following resection, external beam radiation therapy is given to damage the cellular DNA, leaving the astrocyte unable to replicate but allowing the neuron sufficient off-treatment time and low enough exposure to prevent cell death and maintain function. Temozolomide (Temodar®), an oral agent believed to be a radiation sensitizer that crosses the BBB, is now used in conjunction with radiation (D’All’oglio et al., 2008; Neyns, Tosoni, Hwu, & Reardon, 2010).

Following radiation treatment, treatment with temozolomide alone may continue for 21-30 days per month for 6-12 months in an attempt to further damage cellular DNA and prevent cell replication (Mutter & Stupp, 2006). The side effects of temozolomide (stomatitis, mucositis, bone marrow suppression) are caused by the destruction of rapidly reproducing cells; temozolomide rarely causes hair loss, diarrhea, and anorexia (Villano, Seery, & Bressler, 2009).

Bevacizumab (Avastin®), a recombinant humanized monoclonal antibody, is a recent addition to GBM treatment. It binds to and neutralizes the activity of vascular endothelial growth factor (VEGF) by inhibiting the binding of VEGF to its receptors and hindering angiogenesis (production of new blood vessels). Side effects may include hypertension (often able to be controlled medically) and intestinal perforation because of the lack of new collateral blood supply to the gastrointestinal tract (Genentech, Inc., 2015).

Diagnosis and Follow-Up

C.C. underwent maximal safe resection of the lesion, using intraoperative monitoring and diffusion tractography imaging. These procedures allowed direct approach to the lesion without the need for surgical retraction or mannitol, as well as minimal disruption of the normal surrounding brain tissue.

At the time of surgery, the pathologist noted that, rather than the typical cellular morphology seen with gliomas (pseudopalisading necrosis, hypercellularity, increased mitotic activity), the frozen section indicated a classical presentation of toxoplasmosis (Coppens et al., 2006), and permanent pathologic sections confirmed the diagnosis. C.C. was referred to infectious disease specialists for appropriate management. C.C. denied having any contact with cats or litter boxes but did admit to being a prolific gourmet cook who enjoyed eating raw meat while cooking. Of additional concern and interest was the immunologic event that allowed the parasite to become clinically active. He denied use of steroids or immune modulators, as well as recent illness.

Toxoplasmosis

Toxoplasma gondii is a protozoan parasite capable of infecting most warm-blooded animals, including humans, and it causes the disease toxoplasmosis. The protozoa are believed to be carried by more than 22% of the U.S. population aged older than 12 years—or 60 million individuals. Elsewhere in the world, as much as 95% of certain populations may be infected with Toxoplasma gondii. Prevalence is often highest in areas with hot, humid climates and those at lower altitudes (Robert-Gangneux & Dardé, 2012). Individuals with intact immune systems are able to keep the parasite in a subclinical state where it does not cause illness. The symptoms of toxoplasmosis infection are flu-like (e.g., lymphadenopathy, headache,
fever, fatigue, muscle aches, muscle and joint pain), and symptoms can last for several days to weeks. Toxoplasmosis is not passed from person to person, except in instances of congenital transmission, blood transfusion, or organ transplantation. Individuals typically become infected by foodborne or zoonotic transmission (Robert-Gangneux & Dardé, 2012). In the human host, the parasites form tissue cysts, commonly in skeletal muscle, myocardium, the brain, and eyes. Diagnosis is made by positive serology or visualization of the cyst in stained biopsy specimens (Ryan & Ray, 2004).

Most healthy people recover from toxoplasmosis without treatment. If treatment is required, a combination of drugs—such as pyrimethamine (Daraprim®), sulfadiazine (Microsulfon®), and folinic acid—are usually recommended. Treatment for those with compromised immune systems is recommended until improvement occurs in immune deficiency. For patients with AIDS, continuation of medication for the remainder of their lives may be required, or for as long as they are immunosuppressed (Ryan & Ray, 2004).

Conclusion

C.C. was referred to the infectious disease service to determine the existence of a contributing immune system event and decide on a treatment plan. He had no prior history of immunodeficiency, no contact with cats or cat litter, no exposure to unpasteurized milk, and no apparent HIV risk factors, but he tested positive for HIV. White blood cell count was 3,300 k/mcl, absolute lymphocyte count was 450 k/mcl, and HIV viral load was greater than 500,000 copies with a CD4 of 7. HIV genotype was negative for any important mutations, with only minor mutations to protease inhibitors. To treat his HIV, C.C. was started on tenofovir disoproxil/emtricitabine (Truvada®) and raltegravir (Sentriense®) as antiretroviral treatment in addition to atovaquone (Malarone®), pyrimethamine, and folinic acid for toxoplasmosis treatment (Gazzinelli, Xu, Hieny, Cheever, & Sher, 1992).

C.C. continues to do well with his treatment regimen and has remained active, with a Karnofsky Performance Status score of 90 (able to carry on normal activity with only minor signs or symptoms of disease) on a scale of 0–100. His only neurologic findings are a persistent left visual field defect and occasional seizure activity, believed to be related to the irritation of lesions actively responding to treatment. He is seizure-free on levetiracetam (Keppra®), 1,000 mg three times per day and able to return to volunteer work, travel, and other normal activities. His partner remains HIV negative and continues to be his major caregiver and support system.

This case study offers evidence that, at a minimum, biopsy and pathological determination needs to be accomplished prior to initiation of treatment for presumed brain tumors. Without the appropriate clinical information obtained at biopsy, C.C. would have likely been offered radiation therapy and temozolomide with potentially disastrous results. In addition, his immunocompromised state would have gone undetected, and HIV treatment likely would not have been initiated.

References


