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STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Oncology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in oncology. Each manual reviews a topic essential to the current practice of oncology.

NOTE FROM THE PUBLISHER:
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Primary Brain Tumors

Series Editor:
Arthur T. Skarin, MD, FACP, FCCP
Distinguished Physician, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Contributors:
Jai Grewal, MD
Long Island Brain Tumor Center at NSPC, Great Neck, NY

Harpreet Kaur Grewal, MD
University of Texas Health Sciences Center at Houston, Houston, TX

Santosh Kesari, MD, PhD
Director, Neuro-Oncology Program, Translational Neuro-Oncology Laboratories, Neurotoxicity Treatment Center, Moores Cancer Center, University of California San Diego Health System, La Jolla, CA

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Primary Brain Tumors

Jai Grewal, MD, Harpreet Kaur Grewal, MD, and Santosh Kesari, MD, PhD

INTRODUCTION

Primary central nervous system tumors are relatively rare, but they can cause significant morbidity. They are also among the most lethal of all neoplasms. Brain tumors are the second most common cause of death due to intracranial disease, second only to stroke. The estimated annual incidence of primary brain tumors is approximately 21 per 100,000 individuals in the United States.[1] The incidence of brain tumors varies by gender, age, race, ethnicity, and geography and has increased over time.[2] Gliomas and germ cell tumors are more common in men, whereas meningiomas are twice as common in women. The only validated environmental risk factor for primary brain tumors is exposure to ionizing radiation. Other etiologies include inherited cancer syndromes and primary central nervous system lymphoma associated with AIDS.[3] Approximately 5% to 10% of gliomas are associated with a family history.[4] Inherited cancer syndromes involving brain tumors are listed in **Table 1**.

Primary brain tumors are classified according to the World Health Organization 2007 classification,[5] as shown in **Table 2**. The TNM staging system is not used for primary brain tumors. Primary brain tumors are rarely metastatic outside the central nervous system, with some exceptions (embryonal tumors, malignant meningiomas). Tumors are graded from I to IV based on histological grading and prognosis, with grade IV being the most aggressive. Notable features of selected nervous system tumors are shown in **Table 3**. Gliomas account for 78% of all primary malignant central nervous system tumors,[1] and glioblastoma (WHO grade IV) is the most common malignant primary brain tumor in adults. Despite advances in the field of oncology, the prognosis of these aggressive tumors remains poor.

This review focuses on the evaluation and management of primary brain tumors, in particular glioblastoma (the most common malignant brain tumor in adults), and highlights new advances in treatment options. Management of common complications associated with brain tumors will also be discussed.

CASE PRESENTATION

A 40-year-old right-handed nonsmoking man presents to the emergency department (ED) with the sudden onset of right-sided weakness. His family reports that he has had

Table 1. Genetic Syndromes Associated with Nervous System Tumors

Syndrome	Nervous System	Skin	Other	Locus	Gene	Protein	Function
Neurofibromatosis type 1	Neurofibroma, MPNST, optic nerve glioma, astrocytoma	Café-au-lait, axillary freckling	Iris hamartomas, osseous lesions, pheochromocytoma, leukemia	17q11	NF1	Neurofibromin	Tumor suppressor gene, ras GTPase-activating protein regulates cell proliferation and differentiation
Neurofibromatosis type 2	Bilateral vestibular schwannomas, peripheral schwannomas, meningiomas, meningioangiomatosis, spinal ependymoma, astrocytoma, glial hamartins, cerebral calcifications	None	Posterior lens opacities, retinal hamartoma	22q12	NF2	Merlin or schwannomin	Tumor suppressor gene, binds to actin, regulating membrane cytoskeleton
Tuberous sclerosis	Subependymal giant cell astrocytoma, cortical glioneuronal hamartomas (tubers), ependymal hamartomas (candle gutterings)	Angiofibroma (adenoma sebaceum), subungual fibromas	Cardiac rhabdomyoma, renal angiomyolipoma, pulmonary lymphangiomatosis	9q34 (TSC1), 16p13 (TSC2) 60% sporadic	TSC1, TSC2	Hamartin (TSC 1), tuberin (TSC2)	Tumor suppressor genes, tuberin-harmartin complex suppresses activation of the mTOR pathway (which increases proliferation and cell growth)
von Hippel-Lindau	Cerebrellar and spinal cord hemangioblastoma	None	Renal cell carcinoma, pheochromocytoma, renal angiomatosis, cysts of kidney and pancreas, cyst adenoma of epididymis	3p25	VHL	pVHL	Tumor suppressor gene, role in protein degradation and angiogenesis
Li-Fraumeni	Diffuse astrocytoma, medulloblastoma, supratentorial PNET	None	Bone and soft tissue sarcoma, breast cancer	17p13	TP53	p53	Tumor suppressor gene, promotes apoptosis in cells with DNA damage

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progressive difficulty speaking over the last 3 to 4 weeks. He has had particular trouble with finding the right word. One hour prior to presentation to the ED, he had been preparing lunch when he noticed that his right arm was shaking. After about 30 seconds, the shaking stopped but he could not hold anything in his right hand. Examination reveals an alert man with expressive aphasia, who is otherwise cognitively intact and follows commands. He is noted to make frequent paraphasic errors. Nam-

Table 1. Genetic Syndromes Associated with Nervous System Tumors *(continued)*

Syndrome	Nervous System	Skin	Other	Locus	Gene	Protein	Function
Cowden	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos)	Multiple trichilemmoma, fibroma	Oral mucosa fibroma, hamartomatous colon polyps, thyroid tumors, breast cancer	10q23	PTEN	PTEN	Tumor suppressor gene, expression causes cell cycle arrest and apoptosis, regulates PI3K/Akt pathway
Turcot	Medulloblastoma, glioblastoma	Café-au-lait	Colorectal polyps or carcinoma	5q21, 3p21, 7p22w	APC, hMLH1, hPMS2	APC, hMLH1, hPMS2	APC-tumor suppressor gene regulating β-catenin, hMLH1, hPMS2-mismatch repair proteins
Gorlin	Medulloblastoma (desmoplastic)	Nevoid basal cell carcinomas, palmar and plantar pits	Jaw keratocysts, ovarian fibroma	9q22	PTCH1	Ptc1	Tumor suppressor, suppresses smoothened-mediated cell proliferation

APC = adenomatous polyposis coli; hMLH1 = human MutL homolog; hPMS2 = human postmeiotic segregation increased 2; MPNST = malignant peripheral nerve sheath tumor; mTOR = mammalian target of rapamycin; PI3K = phosphoinositide-3-kinase, PTCH = Drosophila patched homolog 1; PTEN = phosphatase and tensin homolog.

ing and repetition are impaired. Motor examination reveals significant weakness in his right hand. Deep tendon reflexes are more brisk on the entire right side. The right plantar response is upgoing. Coordination testing on the right side is hampered by weakness, but is intact on the left side. The remainder of the examination is unremarkable.

- **What are the common presenting features of a brain tumor?**

CLINICAL FEATURES OF BRAIN TUMORS

Symptoms from a brain tumor can be focal or generalized. The most common presenting symptoms in patients with brain tumor include headaches, seizures, cognitive impairment, personality changes, and focal neurological deficits. Focal signs and symptoms reflect the location of the tumor within the central nervous system.

Headache is a presenting symptom in approximately 48% of newly diagnosed brain tumors.[6] It is often dull, non-throbbing, and intermittent. Supratentorial masses can result in frontal headache. Posterior fossa masses cause headache in occipital and cervical areas. Early morning headache is considered a classic presentation because of increased intracranial pressure (ICP) in the recumbent position. However, this classic presentation occurs in a minority of patients.[6]

Seizures are the presenting feature of brain tumors in approximately one-third of cases. They occur due to irritation of the brain parenchyma. There is evidence that blood–brain-barrier failure may be an etiological factor contributing to the development of seizures.[7]

Low-grade tumors, particularly oligodendrogliomas, have a relatively greater tendency to present with seizures (over 70% in some series).[8,9] Even if seizures do not occur at presentation, they may

Table 2. Abbreviated 2007 World Health Organization Classification of Brain Tumors

Tumors of neuroepithelial tissue
Astrocytic tumors
Pilocytic astrocytoma
Subependymal giant cell astrocytoma
Pleomorphic xanthoastrocytoma
Diffuse astrocytoma
Anaplastic astrocytoma
Glioblastoma
Gliomatosis cerebri
Oligodendroglial tumors
Oligodendroglioma
Anaplastic oligodendroglioma
Oligoastrocytic (mixed) tumors
Oligoastrocytoma
Anaplastic oligoastrocytoma
Ependymal tumors
Subependymoma
Myxopapillary ependymoma
Ependymoma
Anaplastic ependymoma
Choroid plexus tumors
Choroid plexus papilloma
Choroid plexus carcinoma
Neuronal and mixed neuronal-glial tumors
Dysplastic gangliocytoma of cerebellum
Dysembryoplastic neuroepithelial tumor
Gangliocytoma
Ganglioglioma
Anaplastic ganglioglioma
Central neurocytoma
Paraganglioma
Tumors of the pineal region
Pineocytoma
Pineal parenchymal tumor of intermediate differentiation
Pineoblastoma
Embryonal tumors
Medulloblastoma
CNS primitive neuroectodermal tumor
CNS neuroblastoma
Atypical teratoid/rhabdoid tumor
Tumors of cranial and paraspinal nerves
Schwannoma
Neurofibroma
Malignant peripheral nerve sheath tumor
Tumors of the meninges
Meningioma (15 variants)
Hemangioblastoma
Hemangiopericytoma
Primary CNS lymphoma
Germ cell tumors
Germinoma
Embryonal carcinoma
Yolk-sac tumor
Choriocarcinoma
Teratoma
Mixed germ cell tumor
Tumors of the sellar region
Craniopharyngioma
Granular cell tumor of the neurohypophysis
Metastatic tumors

CNS = central nervous system.

Adapted from Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, eds. WHO classification of tumours of the central nervous system. Lyon, France: IARC; 2007.

occur later in 40% to 60% of patients with brain tumors. Seizures tend to be partial with possible secondary generalization; seizure semiology will correlate with the tumor location within the brain. Seizure frequency varies among patients. In patients who have experienced an extensive surgical resection, there may be a marked improvement in seizure frequency (or even complete seizure resolution) if the active seizure focus has been removed. Conversely, worsening of seizure type or seizure frequency (or even status epilepticus) may herald radiologic tumor progression.[10]

Table 3. Notable Features of Selected Central and Peripheral Nervous System Tumors

Tumor	Clinical	Radiologic	Pathologic
Central Nervous System			
Oligodendroglioma	Often present with seizures	Calcifications	"Fried egg" appearance 1p and 19q chromosomal deletions
Diffuse low-grade astrocytoma	May present with seizures or subtle symptoms	Nonenhancing diffuse area of T2 signal Gyral expansion	Low mitotic activity Positive for p53, associated with IDH1/2 mutations
Ependymoma	Peak age 15 yr May present as obstructive hydrocephalus	Majority are in fourth ventricle or spinal cord Enhancing May spread via CSF pathways	Perivascular pseudorosettes
Meningioma	Most common primary CNS tumor (40%) More common in women Pregnancy may promote growth	Diffuse contrast enhancement Dural tail sign Locations: convexity, parasagittal, sphenoid wing, spinal, cavernous sinus	EMA-positive Desmosomes Progesterone receptors Many variants
Primary CNS lymphoma	May shrink or disappear (transiently) with corticosteroids May be associated with HIV	Diffuse contrast enhancement Periventricular lesions Restricted diffusion on DWI	Most B-cell Perivascular cuffing CD20+ (B-cell type)
Glioblastoma	Most common adult malignant primary tumor Peak age 55, median survival 14.6 mo Chemotherapy shown to prolong survival in RCT	Ring-enhancing, irregular, necrotic-appearing mass(es)	Vascular proliferation Necrosis Pseudopalisadating arrangement of tumor cells
Medulloblastoma	Peaks in first and third decades of life May present with obstructive hydrocephalus or cerebellar signs	Posterior fossa enhancing mass May seed via CSF pathways ("drop metastases")	Small, round blue cells (on H&E stain) Homer-Wright rosettes (characteristic of all PNETs)
Ependymoblastoma	First 5 years of life Prognosis poor	Supratentorial enhancing mass with possible CSF seeding	True rosettes
Gangliocytoma/ganglioglioma	First 2 decades of life Intractable complex-partial seizures	Temporal lobe mass	Gangliocytoma: only neoplastic neuronal cells Ganglioglioma: mixed neoplastic neuronal and glial cells; eosinophilic granular bodies
Dysembryoplastic neuroepithelial Tumor	Second and third decades of life Rarely regrows after surgical resection	Medial temporal lobe	Neuronal and glial elements
Choroid plexus papilloma	In adults tumor of choroid plexus more likely to be metastatic	Children: lateral ventricle Adults: fourth ventricle	

(continued on page 7)

Table 3. Notable Features of Selected Central and Peripheral Nervous System Tumors *(continued)*

Tumor	Clinical	Radiologic	Pathologic
Peripheral Nervous System			
Neuroblastoma	First decade of life May present with "dancing eyes" (opsoclonus-myoclonus)	Sympathetic chain in chest or abdomen	Similar to medulloblastomas May form "flourettes"
Neurofibromas	Associated with NF1	Dorsal spinal nerve roots	Hyperplasia of Schwann cells
Schwannomas	Tinnitis, hearing loss Bilateral schwannomas May be associated with NF2	Cerebropontine angle mass	Antoni A and B Verocay bodies

CNS = central nervous system; CSF = cerebrospinal fluid; DWI = diffusion-weighted imaging; EMA = epithelial membrane antigen; H&E = hematoxylin and eosin; RCT = randomized controlled trial; NF1 = neurofibromatosis 1; NF2 = neurofibromatosis 2; PNET = primitive neuroectodermal tumor.

Altered mental status is a presenting feature in 15% to 20% of cases.[11] Tumors associated with elevated ICP, gliomatosis cerebri, and those located in the frontal lobes are more likely to be associated with altered mental status at presentation. The severity can range from mild inattention to deep coma.

Focal neurological deficits such as aphasia, hemiparesis, sensory loss, and visual field loss may also occur at presentation and correlate with tumor location. Aphasia is associated with involvement of the dominant hemisphere (usually the left), while sensorimotor and visual deficits can occur if the tumor affects the corresponding pathways within the central nervous system.

The time course of symptoms often correlates with the growth rate of the neoplasm. Symptoms may gradually progress over time. In the case presented, the patient comes to medical attention after an acute event. Careful history taking revealed that neurological symptoms had been apparent for several weeks before this. Patients with slow-growing tumors may have less pronounced symptoms than patients with fast growing masses of similar size and location.

CASE CONTINUED

Computed tomography (CT) of the brain shows a left frontal hypodensity with surrounding mass effect. This is followed by magnetic resonance imaging (MRI) of the brain, which reveals a heterogeneous mass in the left frontal lobe. The lesion is hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging with extensive surrounding edema. There is associated mass effect. Post-gadolinium T1-weighted imaging reveals an irregularly shaped ring-enhancing mass with necrosis (*see* **Figure 1** for imaging findings from a similar case). Due to the patient's recent seizure and evidence of mass effect, intravenous levetiracetam and dexamethasone are initiated.

- **What is the work-up of a patient with a possible brain tumor?**

NARROWING THE DIFFERENTIAL DIAGNOSIS

A patient suspected of possibly having a brain tumor should undergo a thorough general and neurological evaluation. Often, a noncontrast head CT is the initial imaging study. It is favored due to its wide availability and short imaging time. It is helpful in the rapid diagnosis of intracranial

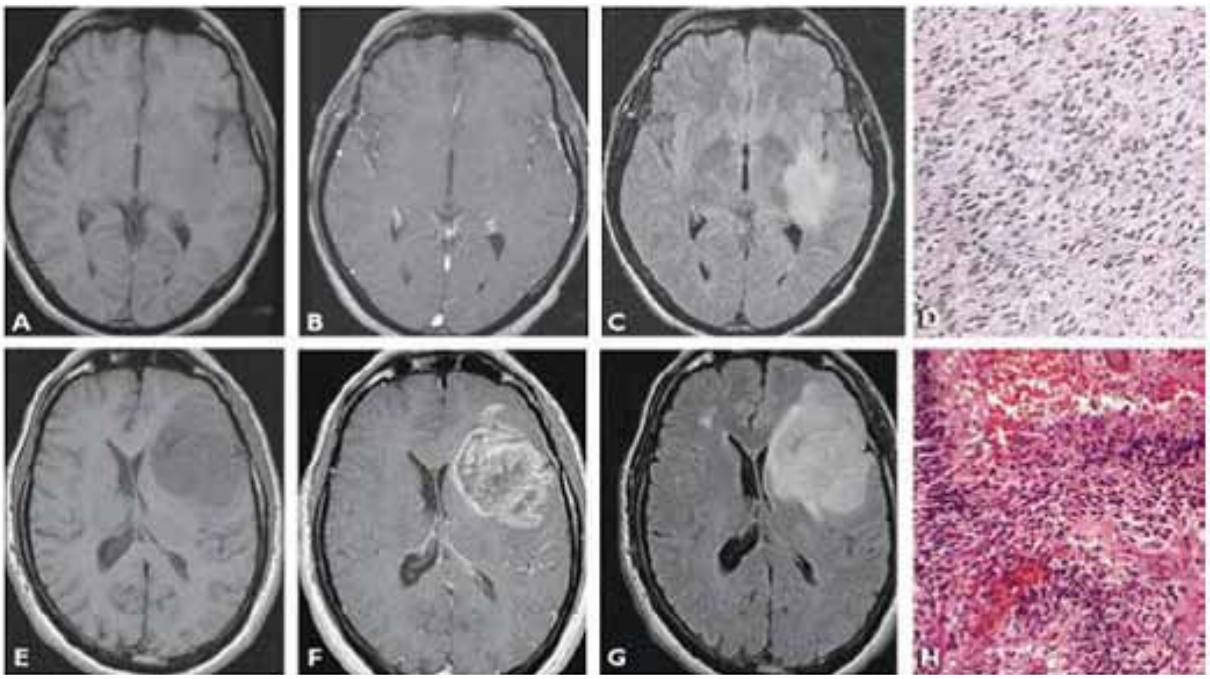

Figure 1. Magnetic resonance imaging (MRI) and pathologic features of an anaplastic glioma (A–D) and glioblastoma (E–H). Axial T1-weighted images (A, E) show no definite abnormality in the case of low-grade glioma and marked hypodensity in the case of glioblastoma; axial T1-weighted post-gadolinium images (B, F) show no enhancement in the case of low-grade glioma and marked heterogeneous enhancement in the case of glioblastoma; axial fluid-attenuated inversion recovery MRI images (C, G) show T2 hyperintensity within and surrounding the tumor, more so in glioblastoma; and pathologic specimens from low-grade glioma (D) and glioblastoma (H) show characteristic features. Low-grade tumors are moderately hypercellular and composed of well-differentiated astrocytes that infiltrate into normal brain. Modest nuclear atypia is present, but mitoses, necrosis, and vascular proliferation are absent. Glioblastoma shows very high cellularity, marked nuclear atypia, vascular proliferation, many mitoses, and geographic necrosis with pseudopalisading. (Adapted with permission from Norden AD, Kesari S. Cancer neurology: Primary and metastatic brain tumors. Hospital Physician Neurology Board Review Manual. Wayne [PA]: Turner White Communications; 2006:10[Pt 3]:1–16).

hemorrhage, in identifying mass effect, and for visualization of calcifications and bony destruction. Patients with contraindication to MRI may benefit from a subsequent contrast-enhanced head CT evaluation.

An MRI of the brain with gadolinium contrast is usually the test of choice, and often follows a head CT scan. An MRI provides greater anatomic and pathologic detail than a CT scan. On MRI, tumors generally appear as a hypointense area on T1-weighted imaging with corresponding hyperintensity on T2-weighted imaging (Figure 1). The presence of enhancement on administration of gadolinium indicates the breakdown of the blood-brain barrier and suggests a high-grade neoplasm. Low- and high-grade gliomas usually show poorly defined margins, heterogeneous areas of hemorrhage and necrosis, and significant surrounding vasogenic edema. These findings are usually less prominent in low-grade lesions. Calcifications within the mass (better seen on CT) are generally suggestive of a more indolent (lower grade) neoplasm, such as an oligodendroglioma and craniopharyngioma.

With certain tumors (eg, medulloblastoma), imaging of the spine is required to exclude drop metastases. Leptomeningeal metastasis may be evident on MRI as abnormal meningeal enhancement or tumor nodules within the cerebrospinal fluid (CSF) flow pathways. CSF cytology is considered the gold standard for this diagnosis; however, lumbar puncture may be contraindicated if there is significant mass effect on imaging. A systemic evaluation should be considered to exclude metastatic cancer presenting as brain metastasis. This includes testicular, breast, and prostate exams, and imaging of the chest, abdomen and pelvis. Of these, CT of the chest has the highest yield.[12] A lesion that is more accessible to biopsy than the CNS mass may become evident. Additional diagnostic studies, such as bone marrow biopsy, positron emission tomography (PET), or tumor markers, may be useful if brain metastasis or lymphoma is suspected. An abscess or demyelinating lesion might be distinguished based on clinical and imaging features. For most primary central nervous system neoplasms, tissue diagnosis with biopsy or resection is necessary. Occasionally, such as in the case of diffuse intrinsic brainstem gliomas, a presumptive diagnosis is made based on imaging and clinical findings, as biopsy in this area carries significant risk.

Newer imaging techniques provide additional information about a suspicious mass. Magnetic resonance spectroscopy (MRS) may demonstrate an elevated ratio of choline to creatine in tumors due to increased cell membrane turnover (**Figure 2**). Neuronal loss due to infiltration of tumor results in decreased levels of N-acetylaspartate (NAA). Multivoxel technique can evaluate different regions of the tumor to determine where high-grade features are more likely to be found on biopsy; this can be helpful in surgical planning.[13] Other MR techniques with potential utility include tractography (diffusion tensor imaging), in which illustration of the white matter tracts associated with a tumor may be helpful in surgical planning. Also, MR perfusion is an evolving technique which may help differentiate between tumor recurrence and treatment effects (eg, radiation necrosis).

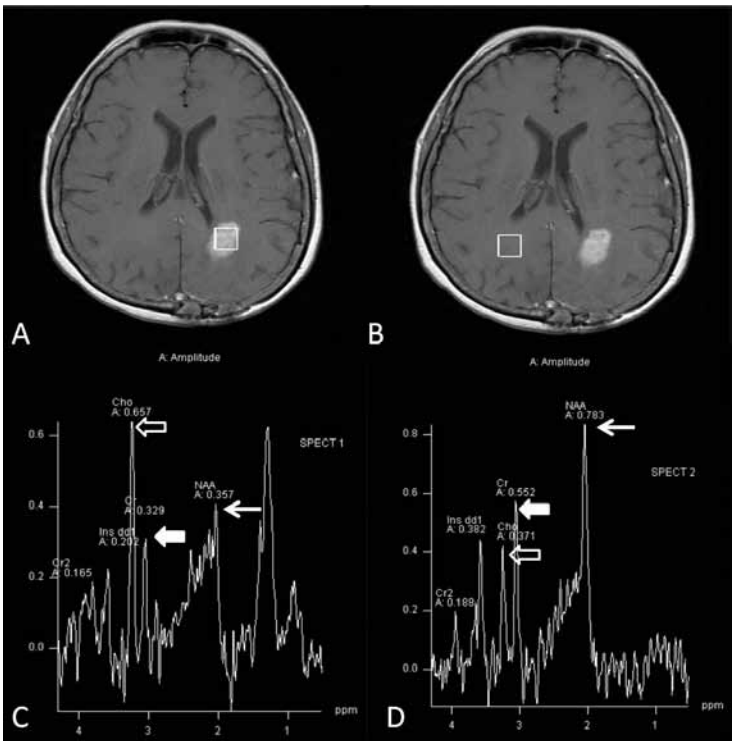

Figure 2. Magnetic resonance spectroscopy in a patient with glioblastoma from (**A**) the area of abnormal enhancement and (**B**) normal brain. Voxel placement is shown. The spectrum corresponding to the area of tumor (**C**) reveals an increased ratio of choline (*thick hollow arrows*) to creatine (*thick solid arrows*) and decreased N-acetylaspartate (*thin arrows*) when compared with the contralateral, unaffected brain (**D**). This is suggestive of increased cell membrane turnover and neuronal destruction, respectively.

- **What is the initial management of a patient found to have a mass lesion?**

INITIAL MANAGEMENT

Seizures

The patient's symptoms of shaking of the right arm followed by hand weakness are suggestive

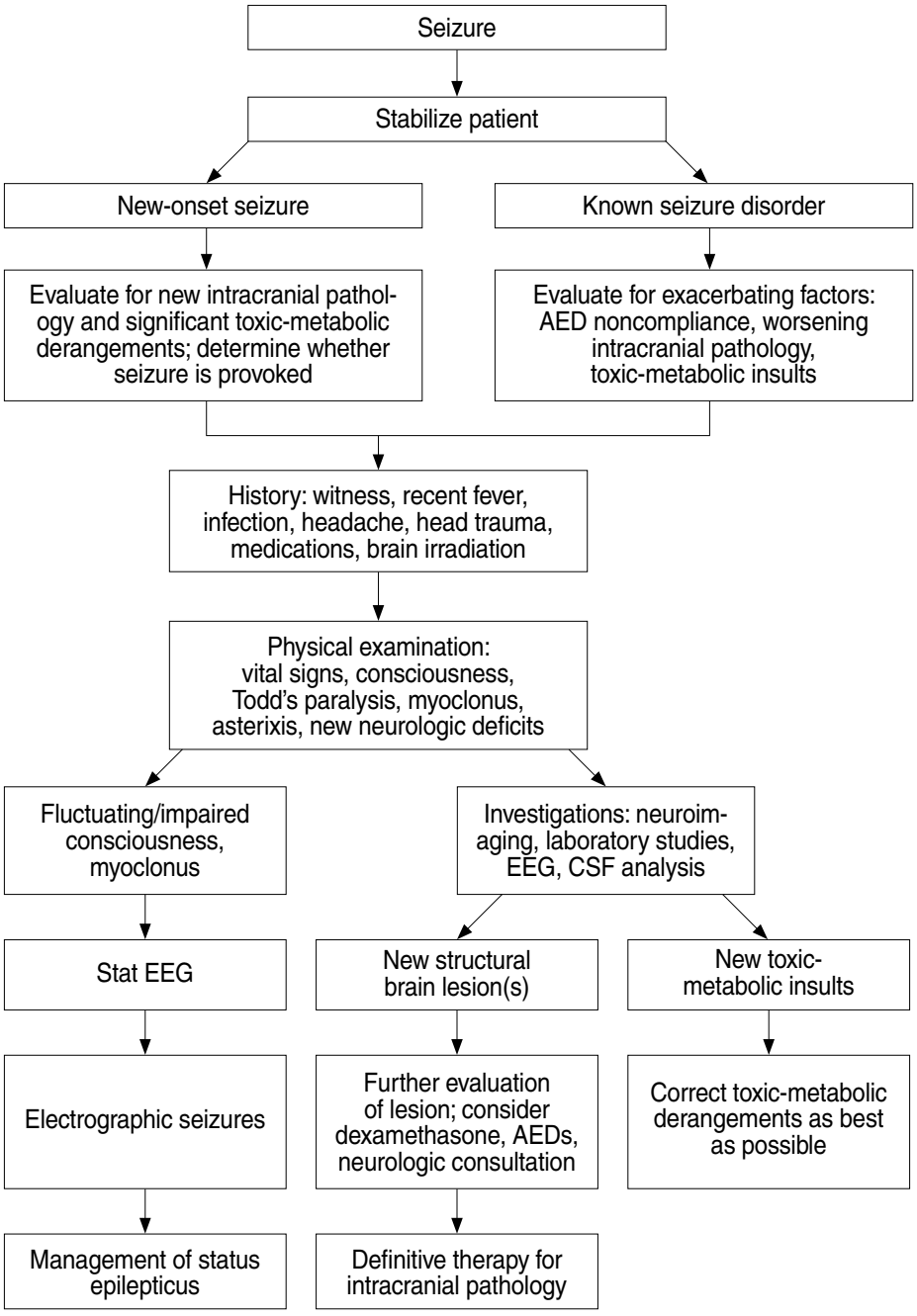

Figure 3. An approach to seizures in patients with brain tumors. AEDs = antiepileptic drugs; CSF = cerebrospinal fluid; EEG = electroencephalography. (Adapted with permission from Grewal J, Grewal HK, Forman AD. Seizures and epilepsy in cancer: etiologies, evaluation, and management. Curr Onc Rep 2008;10:64–72.)

of a seizure and Todd's paralysis. An approach to management of the patient with seizures is outlined in **Figure 3**. Because the patient experienced a seizure, initiation of an antiepileptic drug (AED) for secondary prophylaxis of seizures is warranted. Although AEDs may not completely prevent all

seizures, data show that they can reduce seizure generalization.[14] Traditionally, anticonvulsants such as phenytoin, phenobarbital, and valproic acid have been used as first-line agents, particularly in the acute setting. A major drawback of using these older AEDs is the relative frequency of interactions with chemotherapeutic agents that are used in the treatment of brain tumors.[15,16] Enzyme-inducing AEDs such as phenytoin, phenobarbital, and carbamazepine may increase the clearance and reduce the clinical efficacy of corticosteroids and antineoplastic agents that are metabolized by the cytochrome P450 system.

Newer AEDs such as levetiracetam, lacosamide, and pregabalin have fewer adverse effects and do not have significant interactions with chemotherapeutic agents. Therefore, they are preferred over older AEDs in the brain tumor (and systemic cancer) population. Intravenous formulations of levetiracetam and lacosamide are available. In the setting of refractory seizures or status epilepticus, acute treatment with classical AEDs should be strongly considered.

Primary prophylaxis of seizures is not recommended by the American Academy of Neurology guidelines for brain tumor patients who have never had a seizure.[17] Clinical trials to determine the efficacy of prophylactic anticonvulsants in this situation have not yet demonstrated a benefit that outweighs the risks.[18,19] Therefore, anticonvulsants should be reserved for brain tumor patients who have demonstrated a tendency to have seizures. It should be mentioned that many of these newer anticonvulsants are not FDA-approved for use as monotherapy or treatment of status epilepticus.

Cerebral Edema

Cerebral edema in the setting of brain tumors is vasogenic, and vasogenic edema increases the ICP. Corticosteroids are the mainstay for management of cerebral edema. The most commonly used corticosteroid is dexamethasone. It has high potency, a long half-life, and minimal mineralocorticoid effect. A typical regimen consists of an initial dose of 10 mg intravenously followed by 4 mg every 6 hours; however, a lower dose may produce similar benefit.[20] Once definitive therapy has been delivered and clinical improvement is seen, the dose is gradually tapered to avoid serious long-term side effects such as gastric ulcers, cataracts, osteoporosis, hyperglycemia, adrenal suppression, muscle wasting, weight gain, and Cushing's syndrome.

CASE CONTINUED

The patient undergoes a CT scan of the chest, abdomen, and pelvis, which does not reveal a systemic malignancy. A neurosurgical consultation is obtained and the patient receives a subtotal resection. The pathology is consistent with glioblastoma, exhibiting a pseudopalisading pattern, microvascular proliferation, and necrosis (Figure 1). The patient is counseled regarding his diagnosis and treatment options. A plan is made to administer outpatient external-beam radiation therapy (EBRT) with concurrent chemotherapy. The radiation therapy consists of a total dose of 59.4 Gy delivered in 33 fractions of 1.8 Gy each. Oral concurrent temozolomide (TMZ) is administered daily at 75 mg/m^2 for 42 consecutive doses (over 6 weeks).

- **What treatment options are recommended for a patient with newly diagnosed glioblastoma?**

TREATMENT OF GLIOBLASTOMA

Based on the results of a phase III randomized, controlled trial,[21] the standard of care for a patient

Table 4. Tumors Treated by Surgical Resection

Pilocytic astrocytoma
Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma
Subependymoma
Myxopapillary ependymoma
Paraganglioma of the filum terminale
Dysplastic gangliocytoma of the cerebellum
Dysembryoplastic neuroepithelial tumor
Ganglioglioma
Central neurocytoma
Meningioma
Hemangioblastoma

with newly diagnosed glioblastoma involves maximal safe surgical resection followed by the combination of EBRT and concurrent chemotherapy with daily TMZ. The patient is then assessed clinically and by MRI approximately 3 to 4 weeks following the completion of this treatment. If the tumor does not progress, chemoradiation is followed by at least 6 cycles of adjuvant TMZ on days 1 through 5 of a 28-day cycle.

Surgery

The extent of tumor removal by surgery depends on tumor location (especially proximity to eloquent brain), general health of the patient, and the presence of mass effect. While a biopsy poses minimal risk to the patient and is well tolerated, it allows for pathological evaluation of only a small portion of the tumor. The pathological grade may change nearly half the time if resection is performed after biopsy.[22] Class I data do not exist regarding the issue of whether extensive surgical debulking provides a survival benefit. One small randomized study[23] did find a small but statistically significant benefit of craniotomy and resection over biopsy alone. A number of larger retrospective studies do suggest a survival benefit for initial,[24–26] recurrent,[27] and multiple[28] resections for glioblastoma. At the time of initial resection, the data suggest a possible survival benefit for patients with an extent of resection of 78% or greater.[26] In one study, the morbidity from gross total resection was not significantly increased over biopsy or subtotal resection, and the risk at the time of initial surgery did not differ from the risk at reoperation.[29] Carmustine (BCNU)-impregnated wafers can be placed into a tumor resection cavity at the time of operation. They are FDA-approved for newly diagnosed malignant glioma, although in the associated clinical trial, statistical significance was not achieved in the glioblastoma subgroup.[30]

A prospective, randomized, phase III clinical trial utilizing 5-aminolevulinic acid for intraoperative visualization of tumor under fluoroscopic light was completed.[31] Improved progression-free survival was seen in the group in which this technique was utilized. Preoperative imaging (such as functional MRI), intraoperative MRI, and other techniques (such as awake surgery) may help safely increase the extent of resection.[32,33] A list of primary brain tumors potentially curable by surgical resection is outlined in **Table 4**.

Radiation Therapy

EBRT is the most important type of radiation therapy used in treating infiltrating tumors such as glioblastoma.[34] While whole brain radiation therapy (WBRT) has been used in the past, data show that a more focused approach spares some of the toxicity of WBRT without a loss of efficacy.[35,36] A typical dose would be approximately 60 Gy to the tumor evident on imaging with a 2-cm margin. Clear survival advantages have been demonstrated in several studies at 50 to 60 Gy, but above 60 Gy there is a marked increase in toxicity.[37,38] It is unknown whether the benefit observed with TMZ

in glioblastoma is predominantly due to a radiosensitization effect, from the use of an effective alkylating agent, or both.[39]

Chemotherapy

Temozolomide is a member of the class of drugs known as imidotetrazines. It was developed as a less toxic alternative to precursor compounds and exhibited excellent penetration into the central nervous system.[40,41] In 1999, it was first approved in the United States for recurrent anaplastic astrocytoma.[42] Following the positive results of an international phase III trial for glioblastoma,[21] concurrent TMZ and radiation therapy has become the standard of care for patients with newly diagnosed glioblastoma. This multicenter, randomized, controlled trial compared the efficacy and safety of TMZ administered concurrently and following radiation therapy (RT) with RT alone in patients with newly diagnosed glioblastoma. TMZ combined with RT was more effective than RT alone, and the combined treatment was well tolerated. Median overall survival time (OS) was 14.6 months in the TMZ plus RT group as compared to 12.1 months in the RT alone group. Based on the results of this study, the FDA approved TMZ in 2005 for the treatment of adult patients with newly diagnosed glioblastoma. TMZ has 100% oral bioavailability and readily crosses the blood-brain barrier. It acts by methylating the O^6 position of guanine in DNA. Mispairing of thymidine with the O^6-methylguanine results in DNA strand breakage and cell death.

TMZ is given orally at a daily dose of 75 mg/m^2 for 6 weeks along with radiation therapy. Patients completing chemoradiation without disease progression may proceed to receive adjuvant TMZ at 150 to 200 mg/m^2 on days 1 through 5 of a 28-day cycle. Although the trial limited adjuvant TMZ to 6 cycles,[21] in clinical practice patients have been treated longer if there is no disease progression. Patients may receive *Pneumocystis carinii* prophylaxis during the concurrent phase of treatment. Adverse effects include myelosuppression, nausea, vomiting, anorexia, constipation, and fatigue. Hepatitis B reactivation has also been reported with the use of TMZ.[43,44]

Bevacizumab is a novel humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). This pathway is important for tumor angiogenesis. The use of bevacizumab for newly diagnosed disease is being evaluated in clinical trials and therefore is not considered standard of care at present.

- **What are the most important molecular markers in brain tumors?**

MOLECULAR MARKERS IN BRAIN TUMORS

Identifying subsets of patients who may be more likely to respond to a particular therapy is an important focus of brain tumor research. This is commonly done in the case of many other malignancies, such as testing for estrogen, progesterone, and HER2/neu receptors in breast cancer.

Anaplastic oligodendrogliomas have been reported to have a favorable response to chemotherapy (and radiation) if they are associated with 1p and 19q chromosomal co-deletions.[45] Two prospective, randomized, controlled trials evaluated the potential benefit of adding PCV chemotherapy (procarbazine, lomustine, vincristine) to radiation therapy alone as initial therapy.[46,47] The long-term analysis for both studies confirmed the importance of 1p and 19q co-deletions as favorable independent prognostic factors.[48,49]

Patients with glioblastoma associated with O^6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation experienced greater ben-

efit from TMZ.[50] The MGMT repair enzyme is one mechanism by which tumor cells repair DNA damage from alkylating agents such as TMZ. MGMT promoter methylation suggests decreased availability of this enzyme and alkylating chemotherapy may be more likely to lead to cell death.

Overexpression, amplification, or mutations of the epidermal growth factor receptor (EGFR) are common in glioblastoma.[51] Several EGFR inhibitors have been approved for other malignancies, but unfortunately clinical trials have failed to demonstrate a benefit in malignant glioma.[52] One interesting mutation results in a constitutively active receptor, the EGFRvIII. The co-expression of EGFRvIII and phosphatase and tensin homolog (PTEN) seems to predict sensitivity of recurrent GBM to EGFR inhibitors.[53] While found in other cancers, EFGRvIII is not found in normal human tissue. The unique protein structure is the target of a cancer vaccine in clinical trials for glioblastoma.[54] Other novel experimental therapies include small-molecule targeted agents, oncolytic viruses,[55,56] and dendritic-cell immunotherapies.[57]

Discovered in 2008, mutations of the isocitrate dehydrogenase glycolytic enzyme (IDH1 and IDH2) are commonly found in low-grade and secondary high-grade gliomas.[58] These mutations appear to occur early in the development of gliomas and change the function of IDH to produce 2-hydroxyglutarate, a potential oncometabolite. When compared with wild-type IDH, the presence of IDH1 and IDH2 mutations is associated with improved prognosis in glioma.

Significant work is being performed using microarray technology and sophisticated analysis to identify gene expression patterns that may have prognostic signficance.[59,60] One such analysis stratified tumors into 3 groups: proneural, mesenchymal, and proliferative,[59] with tumors exhibiting the proneural signature correlated with improved prognosis. It was noted that at recurrence, tumors tended to exhibit more of the mesenchymal pattern, which was correlated with a poorer prognosis.

CASE CONTINUED

Four weeks after the patient completed concurrent chemoradiation, an MRI of the brain was obtained. This revealed increased contrast enhancement and surrounding edema. The patient was clinically unchanged. Surgical re-operation was deemed risky. The patient was continued on adjuvant TMZ with a shorter interval of MRI tumor surveillance (4-week intervals). By the third scan following chemoradiation, there was marked reduction in the size of the contrast-enhancing lesion, measuring approximately 50% of the pre-radiation size. The early MRI changes were attributed to a transient post-treatment phenomenon known as pseudoprogression. MRI surveillance was changed to 8-week intervals (after every 2 cycles of TMZ).

- **What is the significance of transient radiologic worsening after concurrent radiation and chemotherapy?**

PSEUDOPROGRESSION

It is becoming increasingly evident that patients may experience transient radiological "progression" early after the completion of chemoradiation with TMZ. This phenomenon has been labeled *pseudoprogression*.[61–63] Patients may remain clinically stable in many of these cases. Up to half of all radiologic progression following chemoradiation may in fact fall under this category. The most significant consideration in a patient with possible pseudoprogression is whether to continue adjuvant TMZ, as a proportion of such patients have

been reported to experience an eventual response to therapy. Early radiation necrosis was found when these patients underwent re-operation.[61] Close imaging surveillance is warranted if a patient with suspected pseudoprogression is continued on adjuvant TMZ. Patients who do not exhibit an improvement on follow-up imaging may have true progression and should be switched to alternate therapy. Pseudoprogression appears to be more common in glioblastoma patients expressing MGMT promoter methylation.[64]

- **What are the neurologic complications of radiation therapy?**

Toxicity from RT can be divided into 3 types based on the amount of time that has elapsed since the completion of RT.[65] *Acute toxicity* manifests as encephalopathy within days to weeks of therapy. The risk increases with higher dose, larger volume of brain irradiated, and poorer baseline cognitive status. The pathogenesis may involve breakdown of the blood-brain barrier, leading to cerebral edema. Corticosteroids may be used to prevent and manage acute toxicity. *Early delayed toxicity* usually occurs within a few weeks of treatment and is usually reversible. It may present as somnolence and neurologic deterioration. It usually resolves spontaneously and may be managed with corticosteroids. *Late radiation injury* occurs months to years following therapy and is often irreversible. Radiation necrosis may be difficult to distinguish from tumor progression on imaging and can change similarly over time. If corticosteroids fail to control the necrotic process, surgical resection may be warranted. Bevacizumab has been reported to be beneficial for radiation necrosis in a prospective randomized clinical trial.[66] Cognitive impairment is one of the most frequent complications in long-term survivors (more problematic in patients with low-grade tumors due to longer survival), and can range in severity.[67] Deficits may involve attention, learning, memory, processing speed, ability to multitask, and word-finding. Psychostimulants (eg, methylphenidate) in conjunction with serial neuropsychological evaluations have been used to help patients remain functionally active.[68]

CASE CONTINUED

The patient remains clinically stable after 5 cycles of TMZ. Prior to completing his sixth adjuvant cycle, he experiences the sudden onset of shortness of breath, tachycardia, and chest pain. Examination reveals a swollen and tender right calf. The patient is given 100% oxygen by mask and receives an emergent spiral CT arteriogram of the chest, which confirms extensive bilateral pulmonary embolism. A lower extremity Doppler ultrasound reveals deep vein thrombosis. The patient is admitted to the hospital and is initiated on low-molecular-weight heparin (LMWH). An inferior vena cava filter is not placed. Over the next 4 days, his symptoms improve and he is discharged home on the same anticoagulant. His wife is trained to subcutaneously administer the LMWH daily at home.

- **What is the incidence and management of venous thromboembolism (VTE) in patients with brain tumors?**

Thromboembolic complications are very common, occurring in 30% to 60% of malignant glioma patients.[69–71] VTE is a frequent complication following craniotomy for brain tumors. This increased risk is shared with other cancers, in particular, multiple myeloma. However, the pathogenesis of VTE in glioblastoma is not completely understood. In

addition to typical risk factors such as immobility, it is possible that circulating factors produced by the tumor may be contributory, as these patients have altered hematologic profiles.[72,73]

Surveillance of thromboembolic complications is important. Intermittent pneumatic compression of the calf reduces the incidence of VTE during the perioperative period. A randomized, prospective, double-blind clinical trial showed that a multimodality approach with enoxaparin or unfractionated heparin in combination with graduated compression stockings, intermittent pneumatic compression, and surveillance venous ultrasonography of the legs was safe and effective in the primary prevention of VTE.[74] Patients should be counseled regarding the risk of VTE and the importance of notifying their physician of appropriate symptoms.

LMWH may be the therapy of choice for secondary prevention of VTE. A randomized, controlled trial of LMWH versus warfarin reported a survival advantage for LMWH in patients with cancer.[75] Inferior vena cava interruption by a filter is indicated when oral anticoagulation is contraindicated or ineffective. Although filters are convenient for patients at a high risk for bleeding, thrombosis may occur at or above the filter site and lead to pulmonary embolism or complete obstruction of venous return below the placement site.

CASE CONTINUED

The patient obtains a brain MRI after his sixth cycle of adjuvant TMZ and is found to have tumor progression. On examination, his aphasia appears to be worse. He is still ambulatory and is able to perform his own activities of daily living. He is offered participation in a clinical trial for recurrent glioblastoma and receives an experimental therapy along with bevacizumab. He continues to have neurologic deterioration and has radiologic progression. He does not wish to pursue additional therapy and is referred to hospice. He dies shortly thereafter, 10 months after his diagnosis.

- **What is the management of tumor recurrence?**

The majority of glioblastoma recurrences occur within 2 cm of the primary tumor site. Treatment options for recurrent glioblastoma include re-operation, additional radiation, and additional chemotherapy. Referral for a clinical trial should also be a consideration in patients with adequate functional status. Surgical re-resection offers the opportunity to remove a significant tumor burden in selected patients. Carmustine (BCNU)-impregnated wafers may be placed into the surgical cavity and have shown benefit in recurrent high-grade glioma.[76]

Additional radiation may be delivered in several ways. Additional EBRT may be delivered but may cause significant toxicity from overlapping fields unless several years have elapsed from the initial radiation.[77] Stereotactic radiosurgery (SRS) may be considered as a salvage option for a subgroup of patients with smaller lesions of recurrent glioblastoma, and is well tolerated.[78] Other radiotherapy options include brachytherapy with an implanted (GliaSite) balloon system.[79]

Standard recurrent high-grade glioma chemotherapy options include nitrosoureas (carmustine, lomustine), irinotecan, carboplatin, cisplatin, and etoposide, often in combination. Bevacizumab is a humanized monoclonal antibody targeting VEGF. When compared with other agents, significant response rates have been reported both as monotherapy and in combination with other cytotoxic agents.[80] Based on this data, bevacizumab has received FDA approval as monotherapy for recurrent glioblastoma. However, the use of beva-

cizumab and its effect upon neuroimaging has led to the development of new imaging criteria to assess response to treatment, particularly in the setting of anti-angiogenic agents.[81] Recently, a device utilizing alternating electrical fields (NovoTTF, Novocure, Portsmouth, NH) worn on the head was approved by the FDA as monotherapy for recurrent glioblastoma.[82]

- **What is the prognosis of glioblastoma?**

The likelihood of a patient becoming a 2-year survivor increased from 10% with RT alone to 26% with the combination of radiation and TMZ.[21] In subsequent long-term analysis, the likelihood of becoming a 5-year survivor after initial treatment with radiation and concurrent TMZ was 9.8% versus 1.9% with radiation alone.[83] Validated prognostic factors which influence survival in glioblastoma include age, performance status, extent of resection, and neurologic function.[84] Other factors which might affect prognosis include mental status and tumor size.[85] The role of molecular markers beyond MGMT and IDH1 in stratifying patients into prognostic categories is an important subject of research.

CONCLUSION

Glioblastoma represents one of the most aggressive central nervous system neoplasms in adults. Unfortunately, it is also the most common malignant primary central nervous system tumor. The advent of TMZ has increased survival and solidified the role of chemotherapy in treating this neoplasm. However, even with current standards of care, more research is needed to stratify patients into prognostic categories and guide therapy. Novel therapies are on the horizon for this and other cancers; patients and their caregivers should remain hopeful that research will lead to more effective and less toxic therapies in the near future.

BOARD REVIEW QUESTIONS

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