Case Study: Ms. S is a 52-year-old woman who was diagnosed with infiltrating ductal breast carcinoma two years prior. She was treated with mastectomy followed by focal radiation and FAC (5-fluorouracil, adriamycin, and cyclophosphamide). One year ago, she began experiencing headaches. A magnetic resonance imaging scan with gadolinium revealed a 2 cm enhancing mass in the left temporal lobe, and she received whole-brain irradiation.

Ms. S presents to the clinic and reports that she has been experiencing brief episodes of confusion. At the onset of each episode, she smells an unusual “electrical” odor, followed by several seconds of being awake and aware of her surroundings but unable to respond. She first experienced one of the episodes a week ago; since then, she has had at least one similar episode per day. Following each episode, she has trouble thinking of the words she wants to say for about one hour. She denies any headache, weakness, or sensory changes.

Any new neurologic symptoms in patients with cancer warrant investigation. Ms. S. already is known to have a brain metastasis, which occurs in as many as 170,000 people each year in the United States (Chidel, Suh, & Barnett, 2000; Wen, Black, & Loeffler, 2005). The most common neurologic symptoms associated with brain metastases are headache, cognitive dysfunction, motor weakness, and seizures (Armstrong & Gilbert, 2000; Taillibert & Delattre, 2005). The most common neurologic symptoms associated with brain metastases are headache, cognitive dysfunction, motor weakness, and seizures (Armstrong & Gilbert, 2000; Taillibert & Delattre, 2005).

The types of symptoms experienced by patients and the time courses in which they occur often are helpful in determining etiology. Symptoms that are fixed or gradually progressing may indicate structural abnormality (e.g., growing metastases, hemorrhage, infection) or metabolic disturbance (e.g., encephalopathy associated with hypoxia or hyponatremia). The most likely diagnosis in patients presenting with brief, self-limiting episodes of neurologic dysfunction is seizure activity.

Pathophysiology

Seizures are defined as sudden changes in behavior caused by the abnormal firing of nerve cells in the brain and characterized by changes in sensory perception or motor activity (Armstrong, Kanusky, & Gilbert, 2003). The term is used synonymously with epilepsy, which is defined as a condition caused by recurrent seizures.

The exact cellular mechanism associated with seizures is unknown. Seizures are believed to start from an area of hyperactive neuronal activity (the epileptic focus) or from alterations in the brain microenvironment. Seizures can start from a nidus of activity (termed simple partial or complex partial seizures) or can occur as consequences of generalized neuronal dysfunction (termed generalized seizures). Partial seizures are characterized by focal neurologic activity (such as tonic-clonic movement in the arm or leg) with consciousness maintained. Generalized seizures involve loss of consciousness and may be accompanied by bilateral tonic-clonic movements and incontinence. Most tumor-related seizures initially are focal in origin, occurring as consequences of a lesion in the brain. However, they can progress quickly to generalized seizures; the focal phase may go unrecognized (Sperling & Ko, 2006).

Risk Factors

In patients with cancer, spread of disease to the central nervous system (CNS) is the factor most commonly associated with seizures (Sperling & Ko, 2006). This includes parenchymal lesions and leptomeningeal disease. Seizures are among the most common symptoms associated with CNS tumors, whether primary or metastatic (Posner, 1995). The incidence of seizures is highest in patients with primary low-grade brain tumors; seizures are less common in those with higher-grade tumors and metastatic disease (Beaumont & Whittle, 2000; Hildebrand, Lecaille, Perennes, &
Delattre, 2005; Posner; Sperling & Ko). Epilepsy has been reported in more than 80% of patients diagnosed with low-grade gliomas, 30%–60% of patients with high-grade gliomas, 40% of patients with meningiomas, and approximately 20% of patients with primary CNS lymphomas (Hildebrand et al.). Pancytopenia, with the development of intracranial infection or hemorrhage, also can lead to seizures (Gilbert, Armstrong, & Tremont-Lucas, 2002). Other risk factors include CNS ischemia, cerebral hemorrhage associated with a rapidly growing lesion, medication toxicity, and metabolic imbalances such as hyponatremia or hypomagnesemia (Armstrong et al., 2003).

Lesion location is the most important factor in determining susceptibility to seizures and seizure presentation (Sperling & Ko, 2006). Lesions located infratentorially (basal ganglia, cerebellum, and brainstem) are not associated with seizure activity. Lesions involving the cerebral hemispheres, especially those located on the brain surface or associated with hemorrhage or edema, are more likely to result in seizure activity (Sperling & Ko). In frontal lobe tumors, focal tonic-clonic movement may involve one extremity, whereas seizures originating in the occipital lobe may cause visual disturbances. Temporal lobe lesions are associated with complex partial seizures during which patients may have gustatory or olfactory symptoms, difficulty speaking, or personality changes associated with altered consciousness. Such seizures often are associated with an aura, an unusual odor or sensation, prior to their occurrence. The symptoms Ms. S described in the case study are a classic description of complex partial seizures.

**History**

Factors precipitating seizure occurrence often can be uncovered by history and used to guide further assessment. History may be provided by patients for focal seizure activity or by individuals who have witnessed the events for generalized seizure activity. Components of the history should include type of cancer and tumor node metastases (TNM) staging, cancer treatment and current medications (including prescribed and over the counter), personal history of neurologic

**Evaluation**

Seizures often are a diagnosis of exclusion, based on history of self-limiting, brief episodes of altered neurologic function. However, following the first report of seizure activity in patients with known cancer diagnoses, systematic evaluation should be performed to uncover precipitating factors. Awareness of potential etiologies and associated symptoms may assist in immediate diagnosis and prompt treatment (Sirven & Waterhouse, 2003), which may aid in preventing prolonged seizures as well as future seizures. The steps for the evaluation and management of patients suspected of having seizures are outlined in Figure 1.

**Figure 1. Algorithm for Seizure Management**

illness or family history of seizures, alcohol and illicit drug use, and any concurrent illness (Armstrong, Baumgartner, & Min, 2006). Medications associated with seizures include high doses of narcotics and phenothiazine antiemetics (Gregory, Grossman, & Sheidler, 1992; Szeto et al., 1977). Several chemotherapeutic agents also have been associated with seizures; however, chemotherapy-related seizures are uncommon and typically a diagnosis of exclusion (Armstrong et al., 2003).

Healthcare professionals should obtain a history of precipitating signs and symptoms, whether onset was focal or generalized, the duration of the episode, and any postictal state. Symptoms may be precipitated acutely by an aura, which may include an unusual odor, taste change, nausea, or altered consciousness. Neurologic symptoms such as focal weakness or trouble finding words may pinpoint the location of a brain lesion precipitating seizure activity.

Missed medication is the most common cause of seizures in patients who have an underlying diagnosis of epilepsy or are undergoing medical management for seizures associated with cancer (Cramer, Glassman, & Rienzi, 2002). Therefore, obtaining a careful history of precipitating events and current medications is critical to evaluate compliance.

Physical Examination

Physical examination should include evaluation of general health in addition to focused neurologic examination. General examination should include a search for precipitating illnesses (e.g., infection, illnesses associated with hypoxia or arrhythmias, signs of drug abuse). In addition, injury or illness resulting from the seizure should be assessed. This may include oral, head, or extremity trauma; lung consolidation associated with aspiration; hypoxia; and hypotension. Focused neurologic examination is required to evaluate level of consciousness, orientation, and any focal deficits. Included in this examination is assessment of mental status (including confusion, speech fluency or aphasia, and short-term memory deficits); cranial nerve dysfunction (such as eye-movement abnormalities, dysarthria, and difficulty swallowing); asymmetric weakness of the face, arms, or legs; numbness or tingling in the extremities; and ability to walk (ACEP Clinical Policies Committee, Clinical Policies Subcommittee on Seizures, 2004; Armstrong et al., 2006).

Diagnostic Studies

Laboratory assessment should include complete blood count, urinalysis, serum chemistries, and liver enzymes (Gilbert & Armstrong, 1995). Electrolyte imbalance, including hypokalemia, hypernatremia, hypocalcemia, hyperkalemia, and hypomagnesemia, can cause or be contributing factors to seizure activity.

Additional laboratory evaluation may include pregnancy test for women of childbearing age, which is necessary prior to initiating anticonvulsant therapy. Drug levels should be assessed in patients who are taking prescribed antiepileptics to obtain drug serum levels that have a known therapeutic range. Blood alcohol level and drug screen to evaluate for illicit drug use (e.g., cocaine, crack, heroin) also may be indicated (Armstrong et al., 2006).

An electroencephalogram should be performed if healthcare professionals are concerned that a patient is experiencing ongoing seizure activity or subclinical status. Subclinical status is a condition of ongoing seizure activity, manifesting as reduced level of consciousness and sometimes associated with eye fluttering or periods of lucency. An electroencephalogram is diagnostic only if a patient experiences a seizure during the test period; the test also may help to uncover an anatomic nidus from which a seizure can be generated.

Other diagnostic tests that should be considered include skull x-ray if trauma is suspected and computed tomography scan of the brain to evaluate for masses, blood clots, abnormal vessels or abscesses, and increased intracranial pressure. Lumbar puncture should be performed when infection is suspected or to evaluate malignancy (Yamamoto, Olaes, & Lopez, 2004).

Various disorders result in abnormal movement, sensations, and loss of awareness that are seizure imitators but not associated with abnormal electrical discharge in the brain. Examples include syncope (cardiac arrhythmia, vasovagal, and dysautonomia), hypoxia, transient ischemic attack, migraine, hypoglycemia, paroxysmal vertigo, narcolepsy, psychogenic spells (e.g., panic attacks, hyperventilation), and drug reactions (Yamamoto et al., 2004). The distinction between those disorders and seizure activity is based on thorough history, neurologic examination, and laboratory assessment.

Management

Seizure management is dependent on the type and duration of seizure activity. For patients presenting with generalized seizures or evidence of status epilepticus (seizures lasting longer than five minutes or one seizure after another without recovery), emergency management with antiepileptic drugs is recommended (Armstrong et al., 2003). Patients with uncontrolled seizures may become metabolically unstable because of conditions such as respiratory/metabolic acidosis and anoxemia, persistent hyperkalemia that may result in cardiac arrhythmias, and rhabdomyolysis that may lead to renal failure (Leppik, 2000). In addition, persistent seizure activity can cause elevations in intracranial pressure. Herniation also is possible if a large brain tumor is present or is associated with a mass effect (Posner, 1995; Sperling & Ko, 2006).

The treatment goal for patients with generalized seizures or status epilepticus is to control seizures with the fewest side effects and interactions with other pharmacologic agents. Although no standardized treatment exists for status epilepticus, studies have reported early seizure termination with the use of lorazepam or diazepam (Leppik, 2000; Leppik et al., 1983). Lorazepam is preferred because of its prolonged efficacy (Leppik et al.). The recommended protocols for the treatment of status epilepticus are presented in Figure 2.

**Protocol A:** lorazepam 4 mg via IV followed by fosphenytoin 20 mg/kg

**Protocol B:** fosphenytoin 20 mg/kg with small doses of lorazepam or diazepam as needed

**Alternate:** phenobarbital 20 mg/kg

*Note.* Status epilepticus may be associated with respiratory depression, requiring intubation and ventilatory support prior to administration of loading dose.

**Figure 2. Recommended Protocols for Management of Status Epilepticus**

*Note.* Based on information from Leppik, 2000.
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Anticonvulsant therapy with antiepileptic drugs is the accepted medical treatment for long-term seizure management (Sperling & Ko, 2006). However, tumor-related seizures often are difficult to control. Monotherapy commonly is used, but combined regimens may be necessary in cases of tumor progression or increased cerebral edema (Oberndorfer et al., 2005). The clinical picture can be complicated further by frequent interactions between antiepileptic drugs and other medications (Maschio, Dinapoli, Zarabia, & Jandolo, 2006). Antiepileptic drugs are classified as either enzyme inducing or non–enzyme inducing (see Figure 3). Enzyme-inducing antiepileptic drugs enhance the metabolism of other concurrent medications, including steroids, warfarin, and some of the antipsychotic, antidepressant, and antineoplastic medications. Interactions of enzyme-inducing antiepileptic drugs with the CYP 450 system may result in alterations in the metabolism of the antiepileptic drugs and concurrent antineoplastic agents (Armstrong et al., 2003; Chang et al., 2001; Mathijsen, Sparreboom, Dumez, van Oosterom, & de Bruijn, 2002). These interactions may cause insufficient seizure control, increased hemotoxicity, and various other side effects.

As a consequence of potential interactions, newer agents such as lamotrigine, levetiracetam, gabapentin, and topiramate often are used for long-term seizure management in patients who also are receiving chemotherapy (Siomin, Angelov, Li, & Vogelbaum, 2005; Sperling & Ko, 2006). Levetiracetam is a new antiepileptic drug with a different pharmacologic profile than that of traditional antiepileptic drugs, with no hepatic effects, no known interactions with other medications, and no need to assess therapeutic serum levels. Newton, Goldlust, and Pearl (2006) reported that levetiracetam was effective and well tolerated in patients with brain tumors who either had persistent seizures or were intolerant to other antiepileptic drugs. Levetiracetam also was found to be a good choice for add-on or monotherapy in primary and metastatic brain tumors.

Typical side effects of antiepileptic drugs may be experienced more frequently in patients with brain tumors in comparison to other groups with seizures, even when levels are within therapeutic ranges (Spering & Ko, 2006). Common side effects of antiepileptic drugs in patients with brain tumors are changes in cognition, behavioral changes, elevated liver enzymes, myelosuppression, ataxia, and rash.

**Issues in Management**

Lifestyle modifications and education are integral parts of care of patients with cancer who have experienced seizures. Depending on state of residence, driving may be restricted for three months to a year from the last seizure (Krauss, Ampaw, & Krumholz, 2001). Currently, six states have mandatory reporting requirements, meaning that healthcare professionals are required by law to report seizures to the state’s department of motor vehicles.

After mandatory driving restrictions have passed, if fixed neurologic deficits exist, returning to driving may not be in patients’ best interest. Driving ability can be formally evaluated through a brain-injury rehabilitation program. Additionally, activities that are associated with risk of injury should be modified. For example, tub baths when alone in the home, swimming alone, and operating heavy machinery should be avoided (Hadjikoutsis & Smith, 2005).

No standard has been established for monitoring patients with cancer on antiepileptic therapy. A general standard for patients taking antiepileptic drugs with recognized therapeutic serum levels is to measure concentrations 10–14 days after drug initiation, anytime breakthrough seizures occur, or if a question arises about compliance (Leppik, 2000). Levels may be monitored more frequently for patients receiving chemotherapy as a consequence of the potential impact on concentrations, as noted earlier. Patients should be monitored regarding compliance and signs of individual drug toxicity during each clinical assessment.

How long antiepileptic drugs should be continued is not known (Gilbert et al., 2002). If the precipitating factor, such as a medication or metabolic imbalance, can be identified and corrected, the risk for further seizures may be minimal, and antiepileptic drugs can be discontinued. However, even then, antiepileptic drugs should be tapered slowly over weeks to months (Specchio, Tramacere, La Neve, & Beghi, 2002). Most clinicians recommend continuation of antiepileptic drugs for at least two years from initial seizure before consideration of withdrawal.

**Case Study Follow-Up**

Ms. S was diagnosed with complex partial seizure activity. Repeat brain imaging revealed a small hemorrhage in the body of her known brain metastasis; however, the lesion was stable in size and imaging was otherwise negative. The bleeding was thought to have precipitated the seizure activity.

Several antiepileptic drugs are used clinically for the treatment of complex partial seizures. Although many of the newer antiepileptic drugs are approved by the U.S. Food and Drug Administration only as adjunctive therapy for patients with partial-onset seizures, data from European comparative monotherapy trials and recent small retrospective trials have shown similar efficacy with fewer side effects (Gilbert et al., 2002; Labate et al., 2006; Newton et al., 2006; Sperling & Ko, 2006).

Ms. S started levetiracetam 500 mg twice daily for two days followed by

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**Enzyme-Inducing Antiepileptic Drugs**

- Carbamazepine
- Felbamate
- Oxcarbazepine
- Phenytoin
- Primidone

**Non–Enzyme-Inducing Antiepileptic Drugs**

- Gabapentin
- Lamotrigine
- Levetiracetam
- Tiagabine
- Topiramate
- Zonisamide

**Figure 3. Classification of Antiepileptic Drugs by Interaction With the CYP 450 System**
1,000 mg twice daily. She was instructed not to drive for a period of six months from her last episode. Initially, she complained of somnolence and dizziness after starting the medication, but the symptoms subsided after three weeks. She has not had any repeated episodes.

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**References**


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**Spot on state driving laws and epilepsy . . .**

Every state regulates whether people with certain medical conditions are eligible for driver’s licenses. To check your state’s laws, and to learn whether healthcare professionals in your state must report seizures in patients, visit www.epilepsyfoundation.org/answerplace/Social/driving/statedrivinglaws.cfm.