Patient Management Problem

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The following Patient Management Problem was chosen to reinforce the subject matter presented in the issue. It emphasizes decisions facing the practicing physician. As you read through the case you will be asked to complete 12 questions regarding history, examination, diagnostic evaluation, therapy, and management. For each item, select the single best response.

In order to obtain CME credits for this activity, subscribers must complete this Patient Management Problem online at www.aan.com/continuum/cme. A tally sheet is provided with this issue to allow the option of marking answers before entering them online. A faxable scorecard is available only upon request to subscribers who do not have computer access or to nonsubscribers who have purchased single back issues (send an email to ContinuumCME@aan.com).

Upon completion of the Patient Management Problem, participants may earn up to 2 hours of AMA PRA Category 1 Credits™. Participants have up to 3 years from the date of publication to earn CME credits. No CME will be awarded for this issue after April 30, 2018.

Learning Objectives
Upon completion of this activity, the participant will be able to:

- Discuss the optimal medical and neurologic management of patients with high-grade gliomas
- Recognize the most frequent adverse events related to treatments in patients with high-grade gliomas
- Choose the best treatment for patients with high-grade gliomas
- Recognize the pitfalls and advantages of neuroimaging studies in high-grade gliomas

Case
A 62-year-old right-handed man with a history of hypertension and type 2 diabetes mellitus presents to the emergency department after 3 days of progressive right arm weakness accompanied by speech problems and mild headaches. His wife reports he has also had problems with attention and memory over the previous 8 weeks. On examination, he has 4/5 weakness involving the right arm and 2/5 weakness of the right hand, as well as a mild motor aphasia. No sensory deficits are detected. The patient has no fever, cough, weight loss, hemoptysis, or gastrointestinal bleeding. There is no history of foreign travel, alcohol or drug addiction, or high-risk sexual behavior. Complete blood count, routine blood chemistry, and chest x-ray are normal. However, a CT scan of the head shows a single contrast-enhancing left frontoparietal lesion surrounded by low-density signal compatible with vasogenic edema.
1. Which of the following is the most appropriate and efficient approach to achieve a diagnosis with minimum delay?

A. assess results of blood cultures, sputum cytology and CSF analysis if the patient does not have significant midline shift
B. obtain a brain MRI with and without contrast complemented with other sequences (spectroscopy, diffusion-weighted sequences, apparent diffusion coefficient maps, and perfusion parameters such as relative cerebral blood volume)
C. obtain a chest, abdomen, and pelvis CT scan and upper and lower gastrointestinal endoscopy
D. obtain a repeat CT of the brain with contrast in 4 weeks to assess for change in the size of the lesion
E. obtain brain and whole-body positron emission tomography (PET) scans

Brain MRI shows an isolated ring-enhancing lesion in the left frontoparietal lobe, surrounded by increased fluid-attenuated inversion recovery (FLAIR) signal, sparing the cortex, and involving the pyramidal pathways and opercular area. There is no midline shift; moreover, the enhancing and nonenhancing lesion shows an increased relative cerebral blood volume (rCBV) and hypointense signal in diffusion-weighted imaging (DWI) sequences with increased apparent diffusion coefficient (ADC) maps, together with detection of lactate and lipid peaks and an increased choline-to-creatine ratio and decreased N-acetyl aspartate (NAA) on magnetic resonance spectroscopy, suggesting that a high-grade glioma is the most likely diagnosis.

2. Which is the best initial medical treatment for this patient at this time?

A. 4 mg to 8 mg dexamethasone daily, given in one or two daily doses
B. 4 mg to 8 mg dexamethasone daily, given in three to four daily doses
C. 12 mg to 16 mg dexamethasone daily, given in one or two daily doses
D. 12 mg to 16 mg dexamethasone daily, given in three to four daily doses
E. 500 mg acetaminophen every 8 hours, avoiding steroids

The patient shows marked clinical improvement after 3 days of corticosteroid treatment at a total dose of 8 mg daily in two divided doses. His headaches have resolved, and there is partial recovery of speech and strength in his arm, although he still has some cognitive complaints and 3/5 weakness of his right hand.

3. Which of the following represents the next appropriate diagnostic and treatment step?

A. administer chemotherapy or radiation therapy without histologic confirmation
B. maintain the steroid schedule and refer the patient to the palliative care service because of the poor prognosis of his disease
C. perform gross total resection despite the possibility of producing neurologic deficits following a radical removal
D. perform maximal safe surgical resection assisted by preoperative functional MRI (fMRI) and, if necessary, intraoperative language and motor mapping techniques
E. perform stereotactic biopsy because the tumor probably infiltrates eloquent areas
The patient undergoes fMRI, which shows that the tumor is adjacent to the language area, leading to surgery with intraoperative neurophysiologic monitoring with language and motor mapping. The immediate postsurgical MRI shows a 95% tumor removal from its initial volume, and he has no new neurologic symptoms postoperatively. After the postoperative recovery, the patient has a Karnofsky Performance Status Scale score of 70. The pathology report indicates that the tumor is a glioblastoma (World Health Organization [WHO] grade IV). Following surgery, the patient’s corticosteroid dose is tapered to 4 mg dexamethasone daily. He is referred to the neuro-oncology clinic for additional treatment options.

4. Which of the following is the most appropriate next step in medical management of this patient?

A. progressive tapering of corticosteroids until the patient is off them completely if no worsening of neurologic symptoms occurs
B. prophylactic use of lacosamide to reduce the risk of seizures and progressive tapering of corticosteroids until the patient is off them completely if no worsening of neurologic symptoms occurs
C. prophylactic use of levetiracetam to reduce the risk of seizures and progressive tapering of corticosteroids until the patient is off them completely if no worsening of neurologic symptoms occurs
D. prophylactic use of phenytoin to reduce the risk of seizures and progressive tapering of corticosteroids until the patient is off them completely if no worsening of neurologic symptoms occurs
E. prophylactic use of valproic acid to reduce the risk of seizures and progressive tapering of corticosteroids until the patient is off them completely if no worsening of neurologic symptoms occurs

The patient is decreased to 4 mg of dexamethasone after the first postoperative week. On his postoperative evaluation, the patient is doing well with the same Karnofsky Performance Status Scale score and neurologic function as the immediate presurgical evaluation. In addition to a histologic diagnosis of glioblastoma, additional molecular analysis of the tumor shows the promoter of the O-6-methylguanine-DNA methyltransferase (MGMT) gene is methylated, the isocitrate dehydrogenase 1 (IDH1) gene is not mutated, the epidermal growth factor receptor (EGFR) is amplified, and Ki-67 index (a cellular proliferation marker) is 38%.

5. What is the most appropriate oncologic treatment for this patient?

A. a clinical trial that includes radiation therapy plus concurrent and adjuvant temozolomide as well as assessment of an investigational drug
B. radiation therapy
C. radiation therapy with concurrent temozolomide, followed by temozolomide
D. radiation therapy with concurrent temozolomide plus bevacizumab, followed by temozolomide and bevacizumab
E. surgery only
The patient receives 6 weeks of radiation therapy and concurrent temozolomide (no clinical trials of first-line treatments with investigational drugs are available for this patient at this time). During the last days of radiation therapy and the 4-week break between radiation therapy and the beginning of adjuvant chemotherapy with temozolomide, the patient becomes more fatigued and experiences a slight worsening of cognitive function. The neurologic examination does not show other changes.

**6. What is the most appropriate next step in this patient’s management?**

A. obtain brain MRI before starting adjuvant treatment, then go on with the planned treatment irrespective of the status of the irradiated lesion  
B. obtain brain MRI before starting adjuvant treatment, then go on with the planned treatment unless a new lesion is clearly visible outside the radiation field  
C. obtain brain MRI to assess the response, and if the residual tumor is larger than on the postsurgical MRI, assume that it is due to early progression of the disease and change the treatment  
D. obtain brain MRI to assess the response, and if the residual tumor is larger than on the postsurgical MRI, obtain a new biopsy  
E. proceed with the adjuvant temozolomide, and obtain brain MRI to assess the response after two or three temozolomide cycles

A brain MRI obtained 4 weeks after completion of radiation therapy and before starting adjuvant chemotherapy shows mildly increased fluid-attenuated inversion recovery (FLAIR) signal intensity and contrast enhancement but no new lesions outside of the radiation field. These changes are felt to be consistent with pseudoprogression related to radiation effects. The patient proceeds with his planned chemotherapy treatment with temozolomide at 150 mg/m$^2$/d for 5 days for the first 28-day cycle, maintaining the same steroid dose. The worsening of symptoms that appeared during radiation therapy resolves over the next month. A repeat brain MRI after the first cycle of adjuvant temozolomide shows a mild decrease in enhancement compared to his postradiation therapy MRI, suggesting that the changes on the first MRI were due to pseudoprogression. The patient tolerates the chemotherapy without hematologic toxicity. His temozolomide is increased in the second cycle to the full dose of 200 mg/m$^2$/d for 5 days. However, during the third cycle of temozolomide, he develops a partial motor seizure with secondary generalization.

**7. In addition to repeating the brain MRI, which of the following drugs is most appropriate for the initial management of this patient’s seizure?**

A. lacosamide  
B. lamotrigine  
C. levetiracetam  
D. oxcarbazepine  
E. phenytoin

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**CONTINUUM Patient Management Problem**

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Levetiracetam is started. A repeat brain MRI does not show tumor-related complications or tumor progression. The patient continues with his chemotherapy treatment as planned. At the end of the sixth adjuvant temozolomide cycle, a new MRI shows significant reduction of the T1 gadolinium-enhancing lesion. However, clinically the patient has deteriorated. While hand strength and language are slightly improved, he has serious difficulties getting up from a chair, walking, and climbing stairs, as well as new-onset bilateral tremor in both hands. He is irritable and has insomnia and blurred vision.

8. How should this patient’s new neurologic problems be managed?

A. give benzodiazepines
B. increase dexamethasone dose to 8 mg daily
C. obtain nerve conduction studies
D. obtain spinal cord MRI to exclude drop metastases or leptomeningeal dissemination
E. withdraw dexamethasone progressively and completely

The patient receives physical therapy, and after the steroids are tapered off he gradually regains strength in his legs and his gait becomes steadier. However, during the next month, his cognitive complaints remain. His wife notices increasing problems with his short-term memory, decreased concentration, and lack of initiative, despite the fact that his MRI shows stable disease.

9. Which of the following next steps in management or diagnosis is most appropriate at this time?

A. administration of an antidepressant
B. administration of donepezil 10 mg/d
C. administration of memantine 20 mg/d
D. administration of methylphenidate 20 mg/d
E. neuropsychological testing, including assessment for depression, and cognitive rehabilitation

Formal neuropsychological testing shows no evidence of depression. Cognitive rehabilitation is started. Over the following months, the patient’s MRIs show stable disease. However, he remains tired throughout the day and has no energy for many of his daily activities.

10. Which of the following is the most appropriate intervention to improve this patient’s fatigue?

A. administration of erythropoietin 30,000 units weekly
B. administration of low doses of steroids
C. administration of methylphenidate 10 mg/d or modafinil 200 mg/d
D. administration of paroxetine 20 mg/d
E. switch from levetiracetam to gabapentin
Blood tests, including assessment of endocrine function, are unrevealing. The patient’s fatigue improves slightly with administration of modafinil, and he remains clinically stable for the next 7 months. However, the patient then develops increased right arm weakness. An MRI shows a new enhancing lesion adjacent to the surgical cavity, which is not felt to be amendable to gross total resection.

11. Which of the following tumor treatments is the best option for this patient?

A. bevacizumab plus irinotecan  
B. CCNU (lomustine) plus bevacizumab  
C. dose-dense temozolomide schedule (75 mg/m² to 100 mg/m² for 21 consecutive days of a 28-day cycle)  
D. enrollment in a clinical trial  
E. temozolomide rechallenge  

The patient does not have access to a clinical trial near his home, so he proceeds with treatment with CCNU and bevacizumab. He is stable neurologically, but his fatigue worsens. The third cycle of CCNU is delayed because of hematologic toxicity. MRI performed prior to initiation of the third cycle shows a significant reduction of the T1-weighted contrast-enhancing areas with increase in the extent of FLAIR signal.

12. What is the most accurate assessment, given this MRI result?

A. the patient had a partial response because the T1-weighted contrast-enhancing lesion has decreased in size  
B. the patient has progressive disease because the FLAIR signal has increased  
C. the patient has stable disease because he has not changed clinically  
D. the patient has stable disease because the T1-enhancing lesion has decreased in size but the FLAIR signal has increased  
E. this is a pseudoprogression phenomenon due to the nitrosourea treatment  

Soon afterward, the patient’s clinical condition begins to decline. After an extensive discussion of the goals of care, he decides to stop active therapy and focus on comfort measures.