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Cover Page Footnote

Special acknowledgement and heartfelt condolences to the patient's family.

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Differential Diagnostic Considerations in a Patient with New Onset Apathy: A Case Study on Frontal Lobe Glioblastoma Multiforme

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ABSTRACT

This case study involves a 50 year-old previously healthy female presenting with a two-week history of clinically significant apathy. The patient and her family assume her symptoms are due to a potential underlying psychiatric condition; however, neurologic and systemic disorders should also be considered when evaluating a patient with sudden personality change. After a thorough history and physical exam, further evaluation with neuroimaging is performed due to suspicion of neurological etiology. A sizable ring-enhancing lesion in the frontal lobe is noted on MRI, and a diagnosis of glioblastoma multiforme (GBM) is confirmed with biopsy. GBM, or grade 4 astrocytoma, is an aggressive primary brain tumor with a poor prognosis. Neurological deficits can develop quickly over days to weeks, and may vary depending on tumor location. Most GBMs are located supratentorial, with the majority in the frontal or temporal lobes. Sudden personality or mood changes are highly indicative of GBM located in the frontal lobe due to its role in managing executive functions, such as initiating and focusing on tasks, emotional control, and organization. After maximal surgical resection of the tumor, radiation, and chemotherapy, a patient with GBM may prolong their survival from 3-months to 15-months; therefore prompt diagnosis and early initiation of treatment is imperative. Working with a highly skilled multidisciplinary care team is also important in coordinating an individualized treatment plan for patients with GBM.

Keywords: personality change, apathy, glioblastoma multiforme, frontal lobe

INTRODUCTION

GBM, or grade 4 astrocytoma, is the most common malignant primary brain tumor in adults. GBM is a fast-growing tumor that accounts for approximately 20% of all intracranial tumors and 45% of primary malignant brain tumors (Thakkar et al., 2014). The median age at diagnosis is 64 years old, with a slight predilection for males (David, 2016). Patients rarely have a family history of GBM (Ellor et al., 2014). GBM can arise from neural stem cell precursors (primary) or transform from a low-grade or anaplastic astrocytoma (secondary) (Davis, 2016). "Multiforme" describes the tumor's variable pathophysiology and features. Similar to other malignant tumors, GBM is characterized histologically by atypical pleomorphic cells with mitotic figures and areas of pseudopalisading necrosis (Carlsson et al., 2014). Most GBMs are located in the supratentorial region, with the majority in the frontal or temporal lobes of the cerebral cortex (Davis, 2016). Risk factors for GBM

include ionizing radiation and certain genetic diseases such as neurofibromatosis type 1 and 2, Li-Fraumeni syndrome, and Turcot syndrome (Ellor et al., 2014).

CLINICAL PRESENTATION

Headaches are the most common early symptom seen with GBM. In a study evaluating common symptoms reported by patients with GBM, headaches presented in 57% of cases, followed by memory loss (39%), cognitive change (38%), motor deficit (approximately 36%), and personality change (27%) (Chang et al., 2005). Other symptoms include altered mental status, nausea and vomiting, seizure, sensory deficit, and visual problems. Neurological deficits can develop over days to weeks (McKinnon et al., 2021). Sudden personality or mood changes are highly indicative of GBM located in the frontal lobe due to its role in managing executive functions, such as initiating and focusing on tasks, emotional control, and organization (Hanif et al., 2017).

DIAGNOSIS

MR imaging with gadolinium contrast is the gold standard in evaluating patients with suspicion of brain tumor, followed by a biopsy (Nelson & Cha, 2003). A CT scan is an alternative option if an MRI is contraindicated or unavailable. On MRI, contrast-enhanced T1-weighted imaging will show a ring-enhancing lesion. The hypointense center reveals necrosis, and the hypointense surrounding area corresponds to edema. On T2-weighted or FLAIR, the lesion will appear as a hyperintense lesion with hyperintense surrounding edema. Due to its infiltrative characteristic, GBM will show irregular lesion margins on both imaging types. Tumors that cross the corpus callosum, or butterfly gliomas, are seen in 3 to 14% of patients with high grade malignant gliomas and are associated with a poorer prognosis (Boaro et al., 2019). The lesion and peritumoral edema can also contribute to a mass effect in the brain and is seen on imaging with midline shift, brain herniations, and/or lateral ventricle displacement (Steed et al., 2019).

PROGNOSIS AND MANAGEMENT

GBM has a poor prognosis due to its aggressive nature and high recurrence rate. Without treatment, patients with GBM have an average survival of three months (Mirimanoff et al., 2006). Treatment with surgical resection, radiation, and chemotherapy increases the survival rate to 14-15 months (Hanif et al., 2017). The Recursive Partitioning Analysis (RPA) classification, which includes factors such as the patient's age at diagnosis and the Karnofsky Performance Status (KPS), can be used to predict survival probability (Gittleman et al., 2017). RPA classes III and IV are associated with a slightly more favorable survival of 15-17 months, and a 2-year survival rate of 20-43% for patients receiving treatment (Thakkar et al., 2014). Location of GBM also affects prognosis, with butterfly GBM having a survival of 6 months and optic pathway GBM having a survival of 8 months (Chojak et al., 2021; Reithmeier et al., 2010).

Maximal surgical tumor resection preceding radiation and chemotherapy is the current standard of care for GBM management (Carlsson et al., 2014). Patients who are able to undergo total versus subtotal resection have better survival rates; however, the completeness of tumor removal vastly depends on the extent of the lesion's growth and involvement of sensitive brain structures and vasculature (Carlsson et al., 2014). In efforts to optimize maximal tumor resection results, ongoing clinical trials are studying tumor-targeted fluorescent staining during surgery, as well as early biomarker detection and various mutations involved in the evolution of lower grade gliomas into GBM (Carlsson et al., 2014). Following surgery, oral chemotherapy (such as temozolomide) and radiation is typically initiated for six weeks (Cabrera et al., 2016). After radiation, the maintenance phase for temozolomide is administered for 5 days every 28 days for six cycles (Abrey et al., 2001). Blood counts should be monitored for toxicity when temozolomide is used concurrently with radiation therapy.

Supportive care should also be implemented to manage symptoms of GBM. Levetiracetam is preferred for seizures because it has low-toxicity and no drug interactions with temozolomide (Omuro & DeAngelis, 2013). Treatment can be tapered after six months if the patient remains seizure free. Dexamethasone can help reduce neurological symptoms caused by increased intracranial pressure (Omuro & DeAngelis, 2013). Due to its low mineralocorticoid activity, dexamethasone is associated with less adverse effects of corticosteroids such as immunosuppression (Omuro & DeAngelis, 2013). The medication is tapered after the neurological symptoms are managed at early stages of treatment. Working with a highly skilled multidisciplinary care

team is also imperative to coordinate an individualized treatment plan for patients with GBM; particularly with the goals of preventing tumor growth, maintaining cognitive and physical functioning, minimizing disease complications or adverse effects of treatment medication, and providing support to caregivers.

DIFFERENTIAL DIAGNOSIS

Psychiatric, neurologic, and other medical disorders should be considered when evaluating a patient with sudden onset personality change. Conducting a thorough history and physical and maintaining a broad differential are crucial in diagnosing and promptly treating these patients. Identifying a specific mood change can help focus the differential diagnosis list. For this patient, the main presenting mood complaint is acute lack of motivation or apathy. Disorders that can result in pathologic apathy include type II schizophrenia, depression, Parkinson's, Alzheimer's or other causes of dementia, Huntington's disease, frontoparietal stroke or other frontal lobe injury, withdrawal from cocaine or amphetamines, progressive supranuclear palsy, apathetic thyrotoxicosis, or certain infectious or inflammatory conditions such as granulomatous disease, syphilis, or HIV (Ishizaki, & Mimura, 2011; Mann, 2019). Patients with an abnormal neurological exam and high clinical suspicion of neurologic etiology, such as in this patient, may warrant further evaluation such as neuroimaging, neuropsychological testing, EEG, or lumbar puncture (Mann, 2019).

CASE PRESENTATION

History. A previously healthy 50-year-old female is brought to her Primary Care office by her husband because he states she has been uncharacteristically apathetic for the past two weeks. The patient herself does not share her husband's concern, thus only came to the appointment to oblige him. The husband explains that she is neglecting household and work responsibilities and becoming forgetful. Her boss, a longtime family friend, has also taken note of the patient's abrupt personality change, stating she is reporting late to work, missing deadlines, and making simple mistakes which is unusual for her typically meticulous work ethic. The husband cannot help but wonder if his wife's symptoms are the result of a "psychotic break" subconsciously triggered by stress from the recent COVID pandemic.

She has no complaints, except a "seasonal sinus headache" for the past month which is outside of her usual allergy season. She denies fever, fatigue, weight change, night sweats, chills, nausea, vomiting, altered mental status, focal neurologic deficit, gait abnormality or imbalance, vision changes, seizures, manic episodes, depression, anxiety, suicidal or homicidal ideations, hallucinations, and bowel or bladder incontinence. She denies head trauma, heavy alcohol use, illicit drug use, foreign travel, recent or recurrent illness, or having prior episodes of these "mood changes." She states she is happily married and feels safe at home.

Two months ago, she was seen for her annual physical, where no abnormalities were noted on examination or routine bloodwork. Her Primary Care Physician has always known the patient to present herself as an extremely pleasant, well-put together, and highly motivated individual.

Physical Exam. The patient's vital signs were normal. She was alert and oriented to person, place, time, and circumstance. She had a disheveled appearance, lying casually on the exam table in her pajamas with unkempt hair, and dirty mismatched socks without shoes. No significant findings were noted on a thorough physical exam except a subtle extensor plantar reflex on the left. Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder 7-item (GAD-7) Scores were zero.

Imaging. Given the patient's abrupt personality change, persisting headache, memory and cognitive impairment, and abnormal Babinski reflex, stat neuroimaging was ordered for high suspicion of an upper motor neuron lesion. MRI findings revealed a 6.0 cm peripherally enhancing, centrally necrotic intra-axial mass in the anterior right frontal lobe with a 17.0 mm leftward subfalcine herniation (Figure 1), and an additional area of masslike abnormal signal in the right parietal lobe on T2 imaging (Figure 2).

Figure 1: Axial T1 Post Contrast Multihance 10 mL

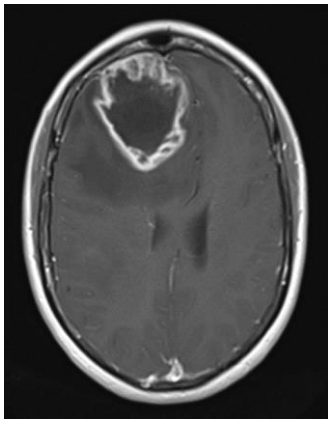
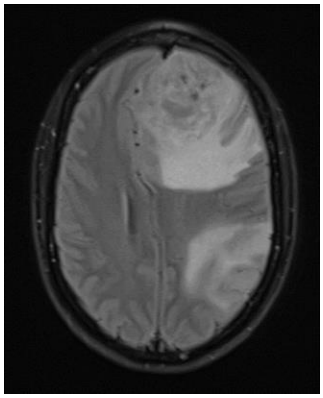


Figure 2: Axial T2* Relaxed Gradient Echo FLAIR



Initial Assessment and Plan. Radiographic images raised concern for multifocal glioma, with likely high-grade malignancy in the right frontal lobe. The patient was promptly referred to Neurosurgery and the frontal lobe mass was surgically resected. Biopsy confirmed a grade 4 glioblastoma multiforme (GBM).

Patient Outcome. Upon receipt of the abnormal MRI results, the primary care physician called the local neurosurgeon to discuss the case and review the imaging. The neurosurgeon met with the patient and her family the next day, and by the end of the week repeated the MRI and performed a successful near-total surgical resection of the brain lesion. The patient's headaches and apathy resolved almost immediately postoperatively. When pathology results confirmed GBM, the patient established care with a multidisciplinary team of specialists, including neurosurgery, hematology/oncology, and radiation oncology, at two renowned University-based hospitals in the patient's home state and neighboring state. An individualized care plan was initiated with the primary goal of preventing tumor regrowth. The patient began targeted radiation five days a week for a total of 30 treatments, oral chemotherapy with temozolomide, dexamethasone, and the use of Optune, which is a wearable FDA-approved medical device that creates electric fields to slow down GBM cell division. An Optune representative met with the patient to train her on device usage and was able to arrange coverage by her medical insurance. The patient was closely monitored for symptoms with cognitive and neurologic testing, and serial neuroimaging with MRI, CT, and PET scans.

Approximately six months after the initial diagnosis, neuroimaging revealed signs of tumor regrowth and the decision was made to add biweekly intravenous bevacizumab treatments in an attempt to postpone repeat surgery. Cognitive function remained intact, but the patient began to decline physically over the next three months. She developed progressive left-sided weakness, left hand spasticity, unstable gait, and became dependent on a caregiver to perform activities of daily living such as toileting, dressing, and transferring from a seated to standing position. She worked with occupational and physical therapy to maintain mobility. Eventually, the patient's appetite decreased, and she became excessively sleepy throughout the day, taking frequent naps, and began experiencing intermittent confusion. She developed thrombocytopenia and was left with large ecchymoses after her bevacizumab treatments. Repeat neuroimaging confirmed new tumor activity with increasing edema and significant midline shift. Approximately one year after her initial diagnosis, she was taken to the Emergency Room due to a seizure lasting ten minutes. Levetiracetam was restarted and the patient went home on hospice care. Psychosocial support was provided to address the emotional, financial, and physical burdens experienced by the patient and her family members. The patient died within two weeks of entering hospice.

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