64-Year-Old Woman With Aphasia and Troponin Elevation

Bryce Kalei Chang, MD; Jana Wieland, MD; and Christopher J. Klein, MD

A 64-year-old right-handed woman presented to the emergency department with aphasia of 20 hours' duration, for which a stroke code was activated. She was unable to state her name; her speech was effortful, with many paraphasic errors, but some intact automatic phrases (sorry, yes, no). The family stated that her last known well was 20 hours ago. Additional history suggested several months of decline consisting of punctuated episodes of mild memory, attention, concentration, and language difficulty. Also, she complained of periodically smelling something burning that others could not smell (phantosmia). Per family, she had not had weakness, loss of feeling, dysarthria, headaches, change in vision, fever, recent infectious illness, trauma, alcohol, or illicit drug use. Her history was significant for granulomatosis with polyangiitis (GPA), primarily affecting her kidneys last treated with rituximab 1 year before. She was thought to be in remission, currently off all other immunosuppressants, and taking no medications. There was no history of neurologic or cardiac disease.

Emergency department vital signs were unremarkable, with a blood pressure of 135/88 mm Hg, pulse of 91 beats per minute, and temperature 36.8 °C. She appeared alert and comfortable but was frustrated when trying to communicate. No skin lesions were noted. There was no cervical, submandibular, or supraclavicular lymphadenopathy or neck stiffness. She did not have an arrhythmia on heart monitor and was without murmurs, jugular venous distension, or peripheral edema on cardiac examination. Respirations were nonlabored, with clear and equal bilateral breath sounds. Her abdomen was soft, nontender, and nondistended. On neurologic examination, her National Institutes of Health Stroke Scale (NIHSS) score was 7—with inability to answer questions and follow verbal commands—and aphasia. She alerted spontaneously and without fluctuation but could not orient even when presented with the proper choices. She was able to reproduce simple nonverbal mimed commands (thumbs up, 2 fingers) but unable to follow complex, cross body, or any verbal commands. Her language was impaired in fluency, comprehension, repetition, reading, and writing. Naming impairment (anomia) is a universal finding in aphasias. Broca’s area lesions in the dominant left frontal lobe result in expressive aphasia in which fluency, repetition, and writing are impaired, with preserved comprehension. In contrast, a lesion of Wernicke area in the dominant left temporal lobe causes a fluent aphasia with impairments in 1. Which one of the following is the most likely localization of this patient’s aphasia?
   a) Left frontal lobe
   b) Left temporal lobe
   c) Right frontal lobe
   d) Right temporal lobe
   e) Left perisylvian region

Localization of aphasic lesions is assisted by considering the specific impairments in language including fluency, comprehension, repetition, reading, and writing. Naming impairment (anomia) is a universal finding in aphasias. Broca’s area lesions in the dominant left frontal lobe result in expressive aphasia in which fluency, repetition, and writing are impaired, with preserved comprehension. In contrast, a lesion of Wernicke area in the dominant left temporal lobe causes a fluent aphasia with impairments in
comprehension, repetition, reading, and writing. Lesions to the corresponding nondominant hemispheres would cause dysprosodies or deficits in propositional language affecting initiation and suppression of speech utterance (right frontal) or emotional comprehension, inflection, in language emphasis (right temporal). Therefore, affected patients can have either muted speech or loss of inhibition in talking, often with a monotone quality. This patient had global impairment in language function, with relative preservation of drawing, consistent with localization within the broad left perisylvian region, which includes and integrates both Broca and Wernicke areas. Importantly, she did not have right upper or lower extremity weakness, which assisted in consideration of the causal etiology of her problem.

2. Which one of the following is the most likely etiology for this patient’s aphasia?

a) Infection
b) Vasculitis
c) Seizure
d) Neurodegeneration
e) Ischemia

This patient’s history of immunosuppression, although remote, raised initial concern for brain infection secondary to immune compromise; however, she had been off immunosuppressants for 1 year without recent illness, fever, or meningeal signs, making this unlikely. Conversely, because she was off immunotherapy and had a history of perinuclear antineutrophil cytoplasmic antibody (P-ANCA)-associated GPA, concern was raised of possible central nervous system vasculitic process. However, her temporal course with several months of punctuated episodes of language and memory decline, spells of phantosmia (olfactory hallucination), and the global aphasia was most concerning for a left temporal mass lesion possibly causing a seizure, postictal state, or nonconvulsive status; however, good alertness would argue against dominant-hemisphere foci status epilepticus. Long-term language difficulties could be seen in frontotemporal dementia; however, her episodic nature made insidious neurodegenerative disease less likely. Although this patient had appreciated cognitive declines, language difficulties were more prominent than disturbances in other behavioral and cognitive domains of frontotemporal dementia. Finally, the absence of right-extremity weakness with global aphasia and good alertness would argue against a large left-middle cerebral artery infarction; however, a smaller focal infarct was still plausible.

Laboratory studies revealed the following (reference ranges shown parenthetically): She had elevated, changing troponin T of 592 ng/L with 2-hour delta of −126 ng/L and 6-hour delta of −153 ng/L, and elevated N-terminal pro B-type natriuretic peptide (NT-Pro BNP) of 3435 pg/mL (≤185 pg/mL). Electrocardiogram (ECG) showed normal sinus rhythm with slight ST-elevation in anteroseptal leads. She had mild leukocytosis, 14.3×10⁹/L (3.4 to 9.6×10⁹/L); microcytic anemia with hemoglobin, 10.0 g/dL (13.2 to 16.6 g/dL); mean corpuscular volume, 74.5 fl (78.2 to 97.9 fl); international normalized ratio (INR), 1.1 (0.9 to 1.1U); sodium, 141 mmol/L (133 to 144 mmol/L); potassium, 3.5 mmol/L (3.4 to 5.3 mmol/L); bicarbonate, 23 mmol/L (22 to 29 mmol/L); creatinine, 0.73 mg/dL (0.74 to 1.35 mg/dL); glucose, 120 mg/dL (70 to 99 mg/dL); erythrocyte sedimentation rate (ESR), 13 mm per hour (2 to 22 mm per hour); total calcium, 9.5 mg/dL (8.8 to 10.2 mg/dL); alanine aminotransferase, 11 U/L (7 to 45 U/L); alkaline phosphatase, 67 U/L (8 to 43 U/L); total bilirubin, 0.3 mg/dL (≤1.2 mg/dL); thyroid stimulating hormone, 1.1 mIU/L (0.3 to 4.2 mIU/L); and creatine kinase, 178 U/L (26 to 192 U/L).

Stat computed tomography (CT) head with contrast-enhanced angiogram and venogram showed a 4.5-cm maximal diameter heterogeneous-enhancing hypodense lesion in the left temporal lobe, with surrounding edema extending into the posterior left frontal lobe. No acute infarcts, significant arterial stenosis, or venous thrombosis were seen.
Brain magnetic resonance imaging (MRI), without and with gadolinium enhancement, redemonstrated the 4.7-cm large left temporal mass. On T1-weighted imaging, the mass was hypointense with central necrosis and irregularly contoured with heterogeneous and predominately peripheral enhancement projecting into the left lateral fissure. There was effacement of ventricles and sulci and early uncal herniation. On T2-weighted imaging, the mass was hyperintense, nonenhancing, infiltrating, with extensive vasogenic edema. On diffusion-weighted images (DWI), the enhancing components of the mass were relatively isodense to gray matter. On perfusion MRI, the mass enhancements had elevated relative cerebral blood volume (rCVB).

3. Which one of the following is the most likely etiology of the brain MRI findings in this patient?
   a) Metastases
   b) Abscess
   c) Glioma
   d) Demyelination
   e) Infarct

Multiple peripherally located cortical or subcortical round, discrete, enhancing lesions in vascular border zones at the gray and white matter junction with vasogenic edema would be more consistent with brain metastases, the most common intracranial tumor in adults; however, one-half of patients with metastatic disease initially present with solitary brain lesions. A brain abscess would be bright on DWI and have a hyperintense core with surrounding hypointense edema on T1 and a hypointense cavity with surrounding hyperintense edema on T2 imaging. This patient’s large heterogeneously enhancing mass with central necrosis displacing adjacent structures causing early herniation was most concerning for glioblastoma multiforme (GBM). Similar lesions without enhancement could be a lower-grade glioma. Similar lesions with conglomerate calcifications could be suggestive of oligodendroglioma. In contrast to neoplastic disease, inflammatory demyelination usually would not cause mass effect, and, if it did, low perfusion correlated with a low rCVB may differentiate tumefactive demyelination from neoplasmin. An acute ischemic infarct would be more likely with an acute neurologic deficit, corresponding to a wedge-shaped cortical lesion involving both gray and white matter, and appear on MRI as hyperintense on both T2 and DWI. Given suspicion of GBM with clear vasogenic edema, mass effect, and this patient’s aphasia, dexamethasone 4 mg every 6 hours was started.

4. Which one of the following is the next best step in management of this patient?
   a) Heparin, aspirin, and clopidogrel
   b) Transthoracic echocardiogram (TTE)
   c) CT of the chest, abdomen, and pelvis
   d) Pyrimethamine and sulfadiazine
   e) Stereotactic brain biopsy

This patient’s elevated and changing troponins with slight ST elevation in anteroseptal leads gave concern for acute myocardial infarction, but—given her brain mass suggestive of GBM and potential need for neurosurgical intervention—anticoagulation and dual antiplatelet therapy (DAPT) were held in favor of TTE. If TTE showed significant regional wall motion abnormalities (RWMA), necessitating catheterization, femoral access to coronary arteries could be achieved without heparin, aspirin, or clopidogrel; however, if angiography showed need for percutaneous coronary intervention, she would require DAPT. Her TTE showed mid-left ventricular (LV) hypokinesis with relative sparing of the apex and LV ejection fraction (EF) of 40%. A body CT scan would be useful for tumor staging and to look for primary or metastatic malignancy but took priority after her cardiac evaluation. If toxoplasmosis were suspected, empiric pyrimethamine and sulfadiazine would be started in the setting of AIDS or with CD4 count <200 cells/mm³ and multiple ring-enhancing brain lesions with positive toxoplasma serology. Brain biopsy would ultimately yield the neurologic diagnosis in
This patient’s TTE was consistent with the mid-ventricular variant of Takotsubo cardiomyopathy (TC), which explained her elevated troponin and ST elevations mimicking acute myocardial infarction as well as her elevated NT-Pro BNP. This is the second most common type of TC; apical ballooning is most common. Her TC was most likely secondary to her newly discovered left temporal mass, which may have led to stress-induced cardiomyopathy. As a postmenopausal woman with neurologic disease, this patient was at increased risk of TC; RWMA in a nonspecific coronary artery distribution made acute coronary syndrome (ACS) less likely. Cocaine-related ACS, myocarditis, and pheochromocytoma are also associated with ST-segment changes in absence of coronary artery disease; however, given this patient’s absent history of illicit drug use, recent illness, headache, or hypertension, these were also less likely. Given her low LVEF but absent signs of heart failure on examination, metoprolol 12.5 mg twice daily was started and uptitrated, as tolerated, to optimize her heart function. Subsequent CT scan of her chest, abdomen, and pelvis were negative for sources of brain malignancy.

5. Which one of the following is the next best step in the management of this patient?
   a) Surgical resection
   b) Chemotherapy
   c) Radiation
   d) Trimethoprim-sulfamethoxazole (TMP/SMX)
   e) Continuous electroencephalogram (EEG)

Glioblastoma multiforme is typically managed with initial maximal gross surgical resection for histopathologic diagnosis, followed by adjuvant chemotherapy, based on molecular characterization and adjuvant postoperative radiation therapy. Given this patient’s healthy baseline Eastern Cooperative Oncology Group performance status of 0 and mild TC on beta blockade, she underwent subtotal tumor resection, as total resection was not feasible, given the location and significant language involvement. Her histopathology demonstrated a hypercellular infiltrating glioma with marked cytologic atypia, frequent mitoses, microvascular proliferation, and foci of palisading tumor necrosis, which confirmed the diagnosis of GBM. By immunohistochemistry, her tumor was isocitrate dehydrogenase (IDH) negative for IDH1-R132H mutation. The presence of IDH mutation suggests evolution of GBM from a lower grade glioma, which may have a better prognosis, although this is rare in patients >55 years old. By promotor methylation, her tumor was positive for epigenetic silencing of the gene for the DNA repair enzyme methylguanine methyltransferase (MGMT), a favorable prognostic factor, suggesting greater and more sustained response to the alkylating chemotherapy agent temozolomide. As such, she was then started on temozolomide 75 mg/m² daily, with concomitant 6 weeks of radiation therapy of 60 Gy, delivered in 30 daily fractions. At the same time, pneumocystis pneumonia prophylaxis was started with TMP/SMX. An EEG was indicated, given concern for postictal state or nonconvulsive status epilepticus; however, as she was clearly interactive and attempting to communicate, a continuous EEG was not necessary. The routine EEG did not show potentially epileptogenic activity; rather, features of slowed delta rhythm consistent with her sizable mass lesion. She was started on oral levetiracetam 1000 mg twice daily, given the potential for seizures in the setting of her tumor and the uncal herniation, which may have resulted in intermittent ictal olfactory hallucinosis. Her language improved to the point that she could name 3 of 4 objects and follow multiple-step commands, consistent with an earlier global language dysfunction originating from extensive edema surrounding the left temporal lobe GBM. The anti-inflammatory mechanism of steroid therapy would be expected to significantly improve deficits related to edema.
DISCUSSION
We report the case of a 64-year-old woman who presented with chronic episodes of cognitive decline, abnormal smell sensations, and global aphasia, who was found to have World Health Organization (WHO) grade IV glioma, IDH wildtype, MGMT-methylated left-temporal GBM. She was started on levetiracetam and dexamethasone, underwent surgical resection, and began temozolomide and radiation therapy. In addition, she was found to have—secondary to her GBM—stress-induced cardiomyopathy (TC) with initial troponin elevation and mild ST elevations, for which she was started on metoprolol.

As a postmenopausal woman with neurologic disease, this patient was at increased risk of TC. Indeed, the International Takotsubo Registry study found greater frequency of psychiatric or neurologic disorders, including brain tumors, in patients with TC (56%) than patients with ACS (26%). However, the pathogenesis of TC is unclear. It is hypothesized that the association with physical or emotional stress causes catecholamine-induced myocardial toxicity and coronary microvascular dysfunction, leading to myocardial stunning. Takotsubo cardiomyopathy is typically transient and treated with standard heart-failure medical therapy—including beta blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and diuretics, as needed for volume overload—until LV systolic function improves. However, the underlying physical stressor—that is, a brain tumor—inciting this patient’s TC may allow for a better prognosis, and follow-up echocardiogram is planned.

Glioblastoma multiforme is the most common malignant primary brain tumor in adults and, even with aggressive therapy, has a high rate of recurrence and poor median overall survival of 10 to 12 months. On T1-weighted MRI, GBM is typically large, irregular, hypointense with mass effect and heterogeneous peripheral ring enhancement with central clearing of necrosis; GBM, a WHO grade IV glioma, has 4 histopathologic criteria: nuclear pleomorphism, increased cellularity-mitoses, microvascular proliferation, and necrosis. Tumors classified as WHO grade II meet 2 criteria, grade III meet 3 criteria, and grade IV meet all histopathologic criteria. Favorable molecular prognostic factors include the presence of IDH mutation, suggesting evolution of GBM from a lower-grade glioma, which has an improved median survival of 27 months vs 1 year in IDH wildtype GBM, and MGMT methylation, which silences the DNA-repair enzyme responsible for mediating tumor resistance to alkylating chemotherapy and is associated with better response to alkylating agents, so the overall 2-year survival is 49% for patients with MGMT methylated tumors and 15% for those with unmethylated MGMT tumors. While on this alkylating agent, weekly complete blood counts are monitored for thrombocytopenia, lymphopenia, and neutropenia, and pneumocystis pneumonia prophylaxis is given during concomitant radiation.

This case highlights the localization of aphasia, preoperative management of TC, and GBM prognostication. First, aphasia localization is important, as surgeons may not maximally resect a language-centered tumor, and surgery is often performed while the patient is awake for language tests. Second, beta blockade is safe to start before surgery in cases of TC to optimize heart function. Finally, in patients presenting with new IDH wildtype, MGMT methylated GBM, temozolomide is favored for associated greater and more sustained response.

POTENTIAL COMPETING INTERESTS
The authors report no competing interests.

Correspondence: Address to Christopher J. Klein, MD, Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (klein.christopher@mayo.edu).

ORCID
Bryce Kalei Chang: https://orcid.org/0000-0002-6880-3462; Christopher J. Klein: https://orcid.org/0000-0002-4012-8856
REFERENCES


CORRECT ANSWERS: 1. e. 2. c. 3. c. 4. b. 5. a.