A 54-year-old woman presented to the emergency department with complaints of slurred speech and right foot heaviness. She first noticed the symptoms 3 weeks earlier, and associated it with fatigue. However, the symptoms progressed, and she eventually also noticed difficulty thinking of the “right words to say.” She stated that she sometimes forgot words, as if she had trouble “getting them out.” By the time of presentation her right foot was very “heavy”; if she did not lift her leg high enough she would stumble. She had no headaches, nausea, vomiting, fevers, night sweats, visual, or sensory complaints.

She had a past medical history of depression, but no hypertension, hyperlipidemia, or diabetes. She was married, and had smoked 1/2 packs of cigarettes per day for the past 5 years. She drank a glass of wine per day and did not use any illicit substances. In the 3-years she had been out of the country two times – to Guatemala and Belize. Her family history was remarkable for a mother with an atrial myxoma, father with renal cell cancer and spinal malignancies, and a brother with a spindle cell tumor of the left arm. There was no family history of cardiovascular disease. Review of systems was unremarkable.

Blood pressure and other vital signs were normal. General physical examination was unremarkable. Neurologic examination was remarkable for slurred impaired fluency and repetition, with preserved comprehension, reading, and writing. She had a right lower facial droop, right pronator drift, and mild right hemiparesis. Muscle stretch reflexes were brisk and symmetric. Plantar responses were flexor. She had decreased dexterity on the right and an unsteady gait, with slight circumduction of her right leg.

Laboratory testing showed normal blood indices (normal white blood cell differential), and a normal metabolic profile. Chest radiograph was unremarkable. Cranial computerized tomography (CT) showed a low density mass with peripheral high attenuation rim within the left frontal lobe with adjacent vasogenic edema and trace midline shift (Figure 1).

Magnetic resonance imaging (MRI) of her brain showed a 3.1-cm × 2.3-cm × 1.9-cm rim-enhancing left posterior frontal intra-axial mass that mildly restricted diffusion in the periphery and did not have a hemorrhagic component (Figure 2). Differential diagnosis of the lesion based on history, exam, and imaging included subacute/chronic infectious, neoplastic (primary brain vs. metastatic), and demyelinating processes. Empiric antibiotics and dexamethasone were started for initial concern of abscess and mild mass effect. Stereotactic brain biopsy of the lesion in the left frontal lobe was obtained.
FIGURE 2 | Coronal post-gadolinium T1-weighted MRI shows a mass in the subcortical left frontoparietal region abutting into the left lateral ventricle with associated peripheral ring-like enhancement.

FIGURE 3 | H and E staining shows brain parenchyma with focal lymphocytic infiltrates, numerous macrophages and reactive gliosis (A) and perivascular lymphocytic infiltrates (B,C).

FIGURE 4 | H and E staining remarkable for astrocytes with fragmented nuclear inclusions (Creutzfeldt-Peters cells) and numerous lipid-laden macrophages.

FIGURE 5 | Glial fibrillary acidic protein staining shows relative a reactive gliosis pattern.

PATHOLOGY
DISCUSSION
Histology sections revealed brain parenchyma with evidence of demyelination, perivascular lymphocytic infiltrates, macrophages, reactive gliosis, and relative preservation of axons; consistent with a demyelinating process. There were no cells to suggest neoplastic atypia. Gram, Grocott methenamine silver (GMS), AFB, and SV40 stains were negative for microorganisms. A diagnosis of tumefactive multiple sclerosis (MS) was made based on her clinical history and imaging with the pathologic diagnosis (Figures 3–6).

Tumefactive MS is a rare variant of MS characterized by the presence of large demyelinating plaques (>2 cm) on MRI (Pittock et al., 2005). Other atypical imaging features include mass effect, edema, and/or post-gadolinium enhancement (Lucchinetti et al., 2008). Potential gadolinium-enhancing patterns of tumefactive MS include ring (closed-ring most common), heterogeneous (punctuate and nodular), patchy and diffuse, cotton-ball, and homogeneous (Lucchinetti et al., 2008). Patients may present with a variety of clinical manifestations depending on the size and location of the lesion. Acute aphasia may be a common presentation, as in our patient, and is not necessarily indicative of a poor prognosis (Lacour et al., 2004).
Radiologically, the lesions may mimic neoplasms, and are typically supratentorial (Hu and Lucchinetti, 2009). Pathology reveals hypercellular confluent demyelinating lesions with inflammatory infiltrates, dominated by myelin-laden macrophages. There is relative axonal preservation. Creutzfeldt-Peters cells (Figure 4), astrocytes with fragmented nuclear inclusions, are present and may be confused with mitotic cells seen in glioblastoma (Hu and Lucchinetti, 2009). Most patients with initial presentation of tumefactive MS go on to develop a relapsing-remitting type MS. There are, however, rare reports of relapsing-remitting MS of the tumefactive type (Selkirk and Shi, 2005). Tumefactive lesions can also be associated with spontaneous intracranial hemorrhage. Magnetic resonance spectroscopy (mRS) generally shows decreased N-acetylaspartate (NAA)/creatinine (Cr) ratio, an increased choline (Cho)/Cr ratio, and presence of glutamate/glutamine or lactate peaks. These findings, however, are observed in various disease conditions (including neoplasia) and thus are not helpful in differentiating large tumefactive lesions from neoplasms (Kiriyama et al., 2010). Moreover, the imaging characteristics on mRS are not seen in all tumefactive demyelinating lesions, and thus biopsy is sometimes essential to diagnose patients presenting with tumefactive
demyelination and no history of demyelinating disease (Kiriyama et al., 2010).

Acute exacerbations of tumefactive MS are treated with high-dose intravenous steroids and plasma exchange (Nilsson et al., 2009). In cases of malignant cerebral edema, hemorhagic transtentorial herniation with mass effect, stroke or mass effect, hyperventilation and the presence of increased intracranial pressure, craniectomy is indicated (Gormley and Zajicek, 2006; Nilsson et al., 2009). Immunomodulating agents may be necessary with a relapsing-remitting course or with progressive tumefactive demyelination despite above measures. In addition to traditional medications used to treat relapsing-remitting MS, case studies have shown favorable outcomes using Rituximab (Leussink et al., 2008), Mitoxantrone (Jeffery et al., 2004), Alemtuzumab (Gormley and Zajicek, 2006), and stem cell transplantation (Kimiskidis et al., 2007) in treating tumefactive demyelinating lesions.

Our patient was started on methylprednisolone with marked improvement of her weakness and language difficulty.

Several months later she complained of increased fatigue, right arm and thigh swelling, and worsening dexterity of her right hand. Repeat imaging was remarkable for a discrete, contiguous enhancing hyperintense lesion just posterior to the previous one (Figure 7).

She was readmitted for plasmapheresis and discharged on oral prednisone and Rituximab for relapsing-remitting tumefactive MS. On recent follow-up, approximately 1 year after initial presentation, she was noted to have a residual mild motor aphasia and spastic right hemiparesis. She has had no further clinical relapses to date.

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