Case Report

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The diagnostic challenge of differentiating tumefactive multiple sclerosis (TMS) from other brain lesions: a case report and literature review on a rare subtype of MS

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Introduction and importance: This case report is a clinical diagnosis walk through of a rare subtype of multiple sclerosis (MS). It gives an overview of how tumefactive multiple sclerosis (TMS) is systematically narrowed down as the definitive diagnosis.
Case presentation: This 29-year-old male patient presented to the emergency department. He collapsed after experiencing pain over his right frontotemporal region followed by a seizure witnessed by his family. Magnetic Resonance Imaging of the brain displayed diffuse enlargement and abnormal T2 weighted and FLAIR hyperintense signals in the diagnostic impressions described by the radiologist of the right temporoparietal region.
Clinical discussion: Liquefactive multiple sclerosis, also known as tumefactive multiple sclerosis or Marburg-type multiple sclerosis, is a rare subtype of the neurological disorder that can be difficult to diagnose. Unlike the traditional form of MS, TMS can present as a brain tumor and must be diagnosed with a biopsy rather than via MRI and clinical findings alone. Patients can typically present with headache, cognitive abnormalities, mental confusion, aphasia, apraxia, seizures, and weakness. Here, the authors discuss the presentation, disease diagnosis process and patient management.
Conclusion: The patient was stabilized and discharged with a referral to the neurosurgery and neurology departments for outpatient consultation for future clinical management and treatment of their condition.

Keywords: case report, confirmatory temporal lobe biopsy, diagnostic approach, tumefactive multiple sclerosis

Introduction

Liquefactive multiple sclerosis, also sometimes referred to as tumefactive multiple sclerosis (TMS) or Marburg-type multiple sclerosis (a type of TMS but sometimes used synonymously), is a rare subtype of the neurological disorder that can be difficult to diagnose. It affects 1–2 cases per 1000 MS cases, or 3 cases per 1 million overall[1]. The etiology is heterogeneous, and proposed causes include neuromyelitis optica spectrum disorder (NMOSD)[2], interferon beta treatment in NMOSD[3], human immunodeficiency virus infection[4], and paraneoplastic syndromes[5]. Typically, patients have a suspicious lesion greater than 2 cm in size on brain MRI, which can represent a possible brain tumor or, less likely, an infectious process[1]. Symptoms can range based on the size of the lesion and location, but a patient may present with complaints such as a headache, cognitive abnormalities, mental confusion, aphasia, apraxia, seizures, and weakness[1]. The definitive diagnosis comes from a biopsy of the lesion. On histopathology, TMS shows characteristic findings of an acute inflammatory lesion, with hypercellularity, myelin-containing foamy macrophages, multinucleated reactive astrocytes called Creuztfelt–Peters cells, and lack of angiogenesis or perivascular inflammation, which

HIGHLIGHTS

- Tumefactive multiple sclerosis can mimic a brain tumor or abscess on radiological imaging.
- Here, we stress on timely clinical investigations to differentiate it from other such brain tumors and initiate treatment.
- A prompt confirmatory biopsy prior to the onset of progressively irreversible neurological sequelae is the gold standard.

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helps differentiate it from neoplastic lesions[6]. Even then, the biopsy may be mistaken for a cancerous lesion and thus careful diagnosis that is based on clinical findings, patient history, symptoms, and biopsy findings must be combined to yield the most accurate treatment plan. This case report discusses a 29-year-old male patient who presented with extreme lethargy after a witnessed seizure. The patient had several possible differential diagnoses and a thorough work-up was required, which highlights the approach needed to diagnose TMS. This case report has been reported in line with the SCARE Criteria[7]. Written informed consent was obtained from the patient for the publication of this case information and the accompanying investigations.

Clinical presentation

A 29-year-old male with no past medical history presented to the emergency department due to extreme lethargy and a seizure witnessed by the patient's family. Per the patient, he had woken up with a severe headache over the right frontotemporal region and collapsed soon after getting up out of bed. He had been experiencing some left-sided weakness, lethargy, and impulsivity for the last few weeks; additionally, he had lost 30–45 pounds in the previous six months. When he presented to the emergency department, he was not able to provide a history; midazolam was given in the field and naloxone and intravenous (IV) fluids in the hospital due to uncertain history. The patient's family informed us that they had relatives with Behcet's disease, so the rheumatology department was consulted. Given the lack of other classic findings, they deemed that Behcet's would be a diagnosis of exclusion and felt that malignancy was more likely the etiology of his symptoms. One of the differentials added to the list was acute disseminated encephalomyelitis (ADEM) due to a recent upper respiratory tract infection, for which the patient had undergone a course of ceftriaxone. The ophthalmology department also examined the patient and no evidence of uveitis was observed at that time. Laboratory blood tests showed an elevated white blood cell count of 17.1×10^9/l (normal: $4.5–11\times10^9$/l) with a left neutrophil shift, borderline-low serum sodium of 135 mEq/l (normal: 136–145 mEq/l), slightly hemolyzed, elevated serum potassium at 5.3 mEq/l (normal: 3.5–5.0 mEq/l), low chloride at 95 mEq/l (normal: 98–106 mEq/l), and a serum creatinine of 1.26 mg/dl (normal: 0.70–1.30 mg/dl). He was admitted to the inpatient department for a more detailed work-up the following day. The formal diagnosis at that time was encephalopathy of unknown etiology, Behcet's disease related encephalopathy, ADEM, hyperkalemia, acute kidney injury, and a seizure of a yet undetermined etiology.

A full diagnostic work-up was initiated. The patient was more alert and interactive the second day, with a normal neurological examination including intact cranial nerves 2–12, normal reflexes in the bilateral upper and lower extremities, no pronator drift, and intact memory and cognition. CT head without contrast showed decreased attenuation in the right parietal deep white matter and the deep white matter in the right temporal lobe. A brain MRI without contrast was performed because the patient could not tolerate contrast at the time. Imaging showed expansile T2 hyperintense signal in the midbrain, pons, middle cerebellar peduncles right greater than left, right pontomedullary junction, right anterior cerebellar hemisphere, as well as extending into the splenium of corpus callosum, right side of the thalamus, and the posterior basal ganglia. There was edema in the supratentorial brain involving the right frontal parietal temporal lobes as well as posterior basal ganglia and right thalamus with a shine-through effect on diffusion-weighted sequences without definite restricted diffusion and likely related to the edema (Fig. 1). The finding was suspicious of an underlying mass or primary brain neoplasm. A brain MRI with and without IV contrast redemonstrated the diffuse enlargement and abnormal T2 and FLAIR hyperintense signals in various cerebral regions (Fig. 2). At this time, a video electroencephalogram (vEEG) was ordered to take place for the next 3 days and he was given Keppra 1g BID and Decadron 4 mg q6h. The vEEG demonstrated 1.502 Hz delta waves with occasional sharp spikes in the right hemisphere, which was deemed abnormal. Neurosurgery and neuro-oncology departments were consulted for assistance in patient management as well. CRP, ESR, HIV, and HSV labs were ordered at this time. CRP was found to be 7.63, ESR was 48, HIV antigen/antibody 4th generation was non-reactive, and HSV 1 and 2 via PCR was negative. A lumbar puncture was also performed, which showed mild pleocytosis, elevated protein, and positive major basic protein. It was negative for any infectious work-up. Other laboratory testing that was ordered included a paraneoplastic panel, West Nile Virus, Human polyomavirus 2 (JC Virus), a meningitis panel, venereal disease research laboratory test (VDRL), antinuclear antibody (ANA), and Anti-N-methyl-d-aspartate (NMDA); all of which were negative or non-reactive. These test results greatly helped in narrowing down our differential diagnosis.

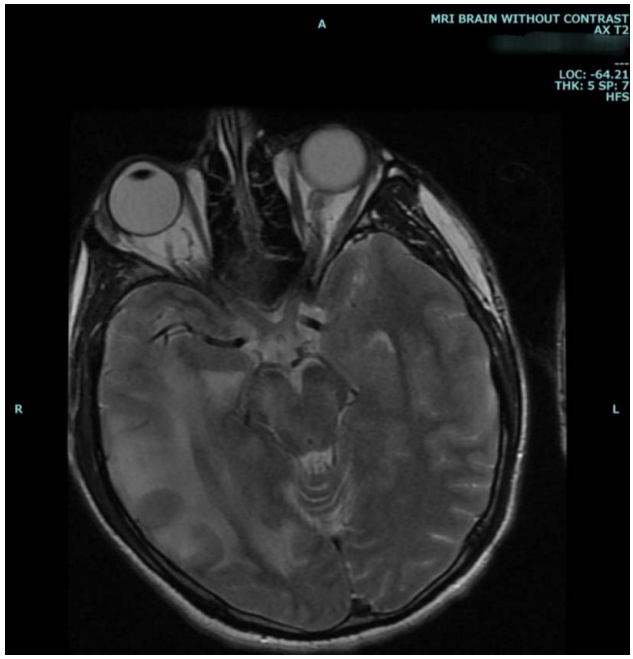

Figure 1. MRI brain without contrast. Shows an expansile T2 hyperintense signal in the midbrain, pons, middle cerebellar peduncles, right pontomedullary junction, right anterior cerebellar hemisphere, extending into the splenium of corpus callosum, right side of the thalamus, and the posterior basal ganglia; edema in the supratentorial brain involving the right frontal parietal temporal lobes, posterior basal ganglia, and right thalamus with a shine-through effect on diffusion-weighted sequences without definite restricted diffusion.

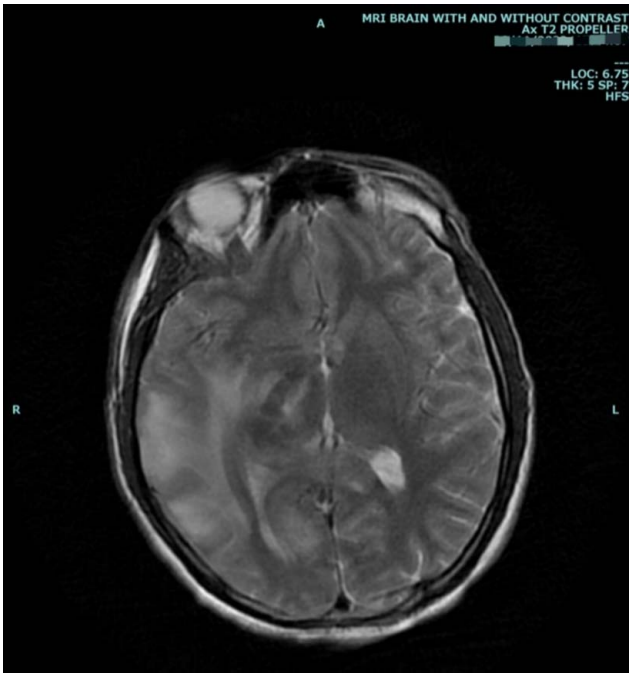

Figure 2. MRI brain with and without contrast. Shows diffuse enlargement and abnormal T2 and FLAIR hyperintense signals in various cerebral regions.

The following few days, the patient underwent a magnetic resonance angiogram (MRA), which did not show any evidence to support a diagnosis of vasculitis. Ten days after presenting to the emergency department, the patient underwent a right temporal biopsy. On gross examination, the biopsy specimen appeared tan white, glistening and slightly congested brain tissue. Biopsy results showed mild gliosis and predominantly focal vacuolizations involving predominantly in the white matter as compared to the cortex. No evidence of a glioma, lymphoma, vasculitis, or viral infection was observed. Immunohistochemistry showed IDH1 R132H (negative for the mutant protein), CD68 (highlighting macrophages and macroglia), CD3 (showing few T cells), CD20 (indicating very rare B cells present) and GFAP (highlighting gliosis). The biopsy confirmed a definitive diagnosis of Tumefactive Multiple Sclerosis (TMS). The patient was discharged the following day in stable condition from the inpatient department with no complications noted. He was instructed for an outpatient follow-up with neurosurgery and neurology departments for appropriate management and medication regimen. Subsequently, the patient was lost to follow-up.

Discussion

TMS is a rare subset of multiple sclerosis affecting less than three cases per 1 million cases overall[1]. Patients with MS typically present in the second or third decade of their life, although this disease can affect anyone outside of the "typical" age of diagnosis[8]. One study conducted in Minnesota under Mayo Clinic found that TMS was 1.9% of the total MS population studied with men and women nearly equally affected; a tumefactive lesion being the first episode of their MS was found in 50% of the population[9]. Much like traditional cases of MS, the exact underlying pathophysiological causes are largely unknown. There are different types of disease spectrums that carry tumefactive lesions, with some of these being Marburg-acute MS, Schilder's Disease, and Balo's concentric sclerosis[10]. Tumefactive lesions are unique in that they are usually poly-symptomatic and are much more likely to have cortical dysfunction such as aphasia, apraxia, memory dysfunction, or Gerstmann Syndrome as compared to patients who do not have tumefactive demyelinating lesions[10].

The first step to diagnosis, after clinical presentation, is to do further imaging studies; most times, this is a brain MRI. Tumefactive lesions are defined as demyelinating tumor-like lesions greater than 2 cm and usually have some mass effect or localized edema involved. These lesions are typically found in the white matter and have a predilection for the frontal and parietal lobes, though these lesions can be found in the gray matter and other parts of the CNS as well. While these findings are typically non-specific for a tumefactive demyelinating lesion, other findings can help yield a more accurate diagnosis. The presence of a T2-hypointense ring and other demyelinating, typical MS lesions can help favor tumefactive disease over a neoplastic one[9,10]. Moreover, most tumefactive lesions will enhance with gadolinium in numerous ways. Other imaging studies have been employed with varied data. Positron emission tomography (PET) may be useful if trying to distinguish whether a lesion in question is neoplastic or not; while glucose metabolism is increased in tumefactive lesions, it is much less so in comparison to a tumorous process and thereby may carry some merit in helping to rule out a neoplastic process[10]. Cerebrospinal fluid studies are limited in TMS. Findings may be normal or stereotypical findings of increased protein and/or oligoclonal bands may be present, but more research needs to be conducted to determine the efficacy in utilizing this finding and relating it to TMS.

Definitive diagnosis is performed via biopsy of the lesion in question. Biopsy findings can show atypical reactive astrocytes, called Creutzfeldt-Peter cells, and myelin loss, reactive gliosis, and lymphocytic infiltration[1]. However, misdiagnosis is still relatively high after a biopsy with one study citing as high as 31% misdiagnosis rate. This is because tumefactive lesions greatly mimic other differential diagnoses, with the most common being a CNS lymphoma, which may also have demyelination as its only defining feature[10]. In addition, gliomas appear differently in patients with MS than the population with this demyelinating disease, hence why new suspicious lesions on imaging cannot be assumed to be a demyelinating process[10]. Other differentials that are commonly misdiagnosed include a low-grade astrocytoma or an infarct[10].

Currently, there are no trials that provide clinicians with a definitive treatment approach to demyelinating conditions. The mainstay treatment remains high-dose intravenous steroids during a period of acute functional decline. 80% of patients have an excellent response to this treatment; once study recommends IV methylprednisolone 1g a day for 3–5 days followed by an oral taper[10]. Other proposed treatment plans include plasma exchange, rituximab, or cyclophosphamide for an acute episode of symptoms due to TMS. Long-term management with disease-modifying therapies and/or other immunosuppressant agents should actually be avoided in TMS unless the patient meets the criteria for MS or another CNS idiopathic inflammatory demyelinating condition that will be known to cause relapses. If such criteria is met, it may be prudent to avoid fingolimod as several case studies have suggested that tumefactive lesions

appear even with the use of this medication; natalizumab case reports have also found similar results[11].

Data is relatively limited on TMS, but there are some definitive studies worth mentioning. A study published in 2021 looked at the long-term clinical, MRI, and cognitive follow-ups of biopsy-confirmed TMS. Their results found that, despite aggressive treatment, TMS typically has the same disease course as typical MS; cognitive impairment was most affected by index lesion severity and total lesion volume[12]. Another case series was published in 2021 and discussed the treatment protocols and implementations of patients diagnosed with TMS. Seven patients were discussed whose ages ranged from 19 to 62 years old with four of them being female and three of them being male; five were caucasian and two were hispanic[13]. Their study shows that biopsy has been necessary to yield a diagnosis on repeated occasions, and that their disease course greatly mirrors that of relapsing-remitting multiple sclerosis. In this case studies, patients often responded to Glatiramer acetate and dimethyl fumarate[13].

Additional studies have eluded that the differentiation between tumefactive lesions and high-grade gliomas is still rather difficult. In 2022, a study proposed certain parameters that may be able to lead clinicians to a more probable answer. This study suggested that tumefactive lesions are more likely in younger females with subacute or chronic symptoms; on MRI, a tumefactive lesion would appear smaller with an open rim enhancement, minimal edema and a T2-hypointense rim[14].

A case study published in 2022 outlined the case of a 36-year-old woman who had right-sided numbness with subsequent MRI showing a large brain mass in the frontal lobe[15]. Their patient did not undergo a brain biopsy as they may have had higher clinical suspicion; the patient outlined in their case study had previous episodes of weakness and blurry vision, and she improved on pulse steroids over the course of 3 days. She was prescribed fingolimod hcl 0.5mg and had not had another attack over the course of a year as described in the paper[15]. This was in contrast to the patient in our case study who had never had a previous episode to compare to. Another case study, published in 2020, discussed a patient who had presented to the E.D. for subacute onset of left-sided hemianesthesia associated with weakness and a bifrontal headache[16]. MRI showed a mass within the spinal cord at the C3 level with partial central enhancement. This patient was prescribed steroids and plasma exchange sessions, which also improved the patient's symptoms, allowing for her to be discharged and followed up with on an outpatient basis[16].

Conclusion

Liquefactive multiple sclerosis, also known as TMS or Marburg-type multiple sclerosis, is a rare subtype of the neurological disorder that can be difficult to diagnose. This is a rare case that helps lay a foundation for the possible presentation, hospital course, diagnostic work-up, and outcomes seen when investigating such a case. Future research should aim to identify the necessary tests which would exclude common differential diagnoses in most cases and reduce the cost on part of the patient. Clinicians should be mindful of the heterogeneous signs of TMS and consider it in the list of differential diagnoses in cases with unclear presentations.

Ethical approval

Ethical approval was not applicable as this was a case report. However, the written consent to publish the clinical data of the patient was given and is available on request.

Consent

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

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Author contribution

A.G.: conceptualization, project administration, supervision, visualization, writing—original draft. S.E.: writing—original draft; data curation, writing—review and editing. R.I.K.: writing—original draft; validation, writing—review and editing. Z.A.N.: conceptualization, writing—original draft, writing—review and editing. S.E.: conceptualization, methodology, writing—review and editing ; supervision. S.I.K.: writing—review and editing. M.A.: writing—review and editing. A.A.: writing—review and editing. A.A.: methodology; project administration; writing—review and editing.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable as we obtained written informed consent from the patient instead for the case report.

Guarantor

Aymar Akilimali.

Data availability statement

Upon reasonable request we agree to provide you with all patient data relevant to the case report in our possession.

Provenance and peer review

Not invited

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