

Neuroimaging of tumefactive multiple sclerosis with atypical features

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Tumefactive demyelinating lesions or tumefactive multiple sclerosis (TMS) constitute a unique presentation of demyelinating disease that frequently mimics intracranial neoplasm, infection or other, non-demyelinating intracranial pathology. Consequently, these lesions, which are larger than typical multiple sclerosis plaques and are generally characterized by certain MRI features including edema and incomplete ring enhancement, pose a serious diagnostic challenge that frequently prompts biopsy in initial evaluation. Biopsy can be averted when imaging features for TMS are seen on MRI. We present a biopsy-proven case of TMS with atypical imaging features, evaluated using MRI and diffusion-tensor imaging.

Case report

A 45-year-old man with recent adult-onset seizure disorder presented to the emergency department with altered mental status after a witnessed, generalized, tonic-clonic seizure. For one month, he had a history of waxing and waning aphasia, word-finding difficulty, and right-lower-extremity paresis. Six years before, he had experienced his first and only previous seizure. Following the cardinal seizure, his outpatient neurologist started him on levetiracetam for seizure prophylaxis and had imaging studies obtained (Fig 1).

Magnetic resonance imaging (MRI) on admission revealed diffuse disease, worse within the left cerebral hemisphere, predominantly superiorly in both frontal lobes and in the left temporal lobe, with associated edema with a left-

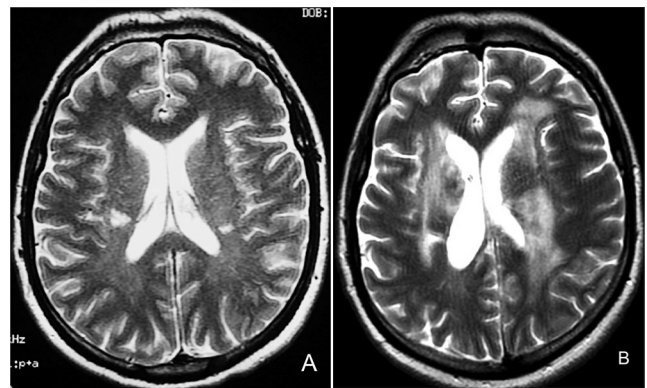


Figure 1. 45-year-old male with TMS. Initial imaging of patient, performed at first with new-onset seizure, demonstrates a small periventricular hyperintense lesion (A), with marked worsening of periventricular lesions on imaging performed 6 years later (B) on conventional T2-weighted MRI images.

to-right midline shift of approximately 7 mm, all appearing since an MRI scan six years earlier (Figs 1, 2). A right periventricular lesion likely represented a worsening of a similar lesion that was present on prior imaging (Fig. 1). There were also multiple intra-axial, heterogeneously enhancing lesions in the bilateral cerebral hemispheres with surrounding vasogenic edema (Fig. 2). The largest lesion in

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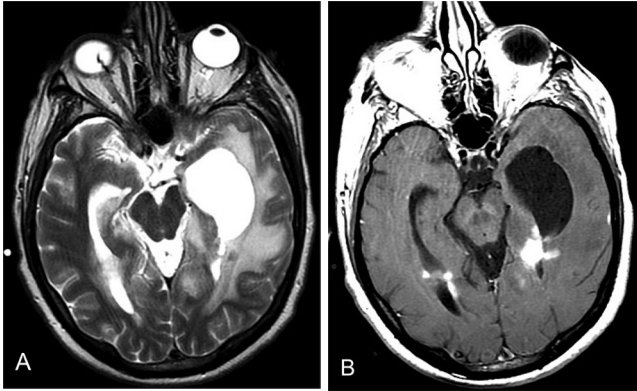


Figure 2. 45-year-old male with TMS. MRI scans performed on this hospital admission of patient demonstrate a large area of periventricular edema and a trapped left lateral ventricle on conventional T2-weighted MRI (A), with periventricular enhancement on gadolinium-enhanced T1-weighted imaging (B).

the left temporal lobe had a large fluid component corresponding to an enlarged trapped left temporal horn, a very rare and atypical feature in TMS.

In addition to conventional brain MRI, diffusion tensor imaging (DTI) was also performed. DTI maps as well as conventional MRI scans demonstrated destruction, displacement, and invasion of adjacent cerebral parenchyma, white-matter tracts, and juxtacortical U-fibers, imaging features suggestive of a demyelinating process (Figs. 3, 4).

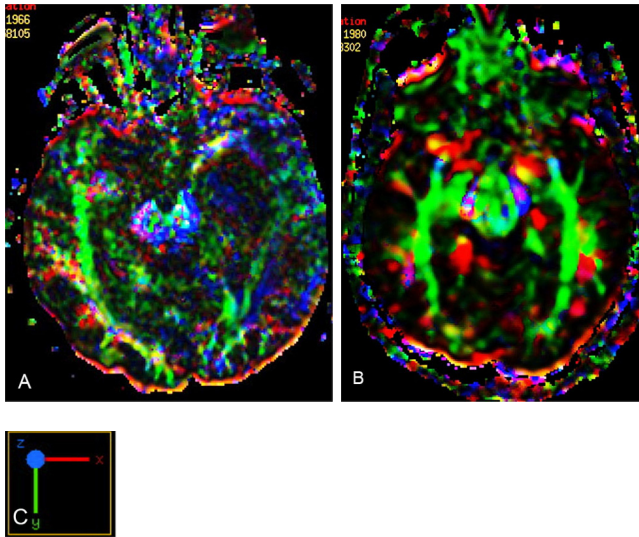


Figure 3. 45-year-old male with TMS. Diffusion tensor imaging (DTI) shows affected periventricular pathways and optic radiations in this case of TMS (A) as compared with a normal control (B) with a loss of color due to decreased neuronal integrity in (A). The fractional anisotropy color legend (C) depicts fiber tract directions.

Measures to reduce intracranial pressure, including high-dose corticosteroids, were at once initiated on hospital admission. During the course of his hospital stay, the patient required intubation for central respiratory failure. A temporary right external ventricular drain and a left ventricu-

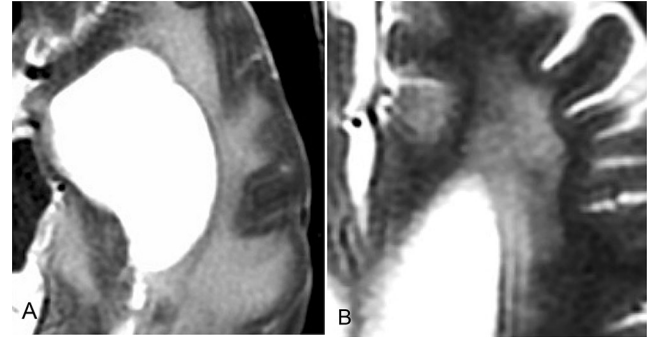


Figure 4. 45-year-old male with TMS. U-fibers are involved by demyelination in this case of TMS (A) but spared in a comparison case of ischemic small vessel disease (B) as seen on conventional T2-weighted MRI images.

loperitoneal shunt were placed for correction of hydrocephalus, with brain biopsy obtained on neurosurgical intervention. Histopathology of the tissue revealed foam-cell macrophages and T-lymphocytes with reactive astrocytes, loss of myelin, and preservation of axons—findings consistent with active demyelination (Fig. 5). The differential diagnosis by pathology at this point was acute demyelinating encephalomyelitis (ADEM), post-infectious demyelination, and multiple sclerosis (MS) of the tumefactive subtype.

Extensive cerebrospinal fluid analysis following lumbar puncture provided no evidence of infectious etiology. It revealed an elevated IgG index without intrathecal IgG synthesis, and no oligoclonal bands. Further corroborative history later revealed that the patient had four years earlier been informed that he might have MS. High-dose steroids for presumed TMS were continued at this time.

Following treatment with steroids, the patient demonstrated improving mentation and right hemiparesis, and restoration of normal speech. The ventriculoperitoneal shunt was kept in place, and the patient was given the diagnosis of TMS with atypical imaging features.

Discussion

MS is an immune-mediated demyelinating disease resulting in neurologic deficits. Unlike the typical clinical presentation of MS, which is generally more insidious, TMS first presents with focal neurological deficits, seizure, or aphasia and may even be attributed to an acute ischemic stroke in some cases (see summary table) (1). TMS is itself an unusual presentation of MS, some suggesting that the incidence of tumefactive brain lesions is only 2.8% in MS patients (2). Our case is biopsy-proven tumefactive MS with atypical features even for TMS, a rare imaging presentation. As in all MS, inflammation with loss of myelination

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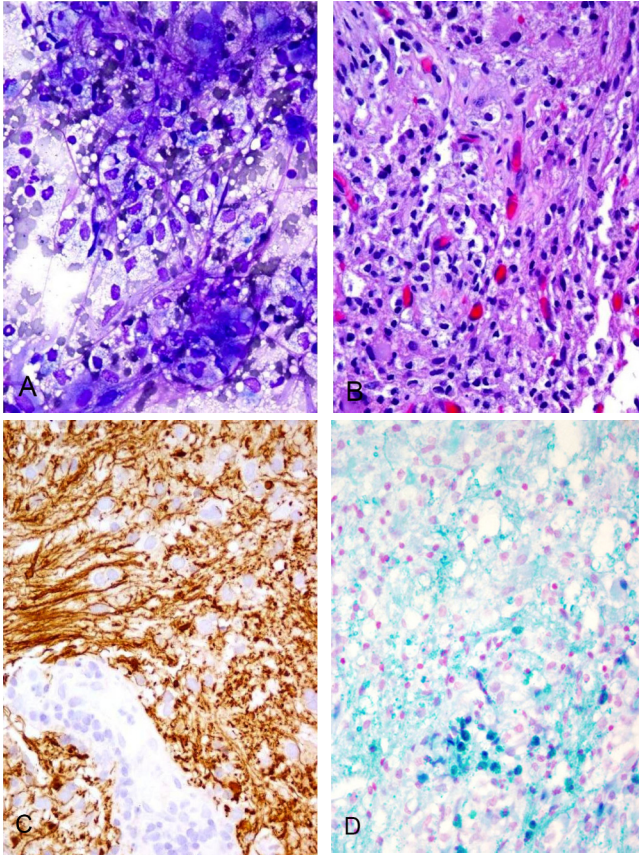


Figure 5. 45-year-old male with TMS. Histochemical and immunohistochemical stains of this patient's periventricular lesion (magnified 400x). (A) Romanovsky smear preparation showing predominance of foam cell macrophages; (B) Hematoxylin and eosin (H&E) stain shows a hypercellular macrophage-rich lesion; (C) Neurofilament protein stain shows persistence of axons (brown); (D) Luxol Fast Blue demonstrates myelin loss (LFB stains myelin blue).

seen on histological examination is a key diagnostic feature. MRI is the most sensitive noninvasive means of detecting MS lesions and can characterize lesions suspicious for TMS as well, in many cases avoiding the need for biopsy.

Classic MRI findings of MS include bright, regular-appearing, ovoid periventricular or subcortical white matter lesions on T2-weighted and FLAIR with or without contrast enhancement, reflective of active demyelination. Also seen are "dark lesions" on T1-weighted imaging that portend a worse prognosis and reflect neuronal cell death. Ex-vacuo ventriculomegaly and diffuse white matter atrophy may also occur in this condition (3).

TMS, as opposed to typical MS, poses multiple diagnostic challenges aside from imaging studies. Histochemical analysis for possible oligoclonal-band positivity in cerebrospinal fluid may not be present in tumefactive disease, as was the case in our patient (2). Unlike MS, which presents on imaging with multiple focal periventricular white-matter

lesions, TMS often presents as large enhancing lesions, mimicking neoplasm, abscess, or stroke; clinical presentations parallel these conditions, thereby obfuscating the differential diagnosis. The existence of mass effect and edema surrounding a lesion greater than 2 cm does not help in excluding neoplasm or infection versus tumefactive demyelinating lesions. Radiological-pathological correlations do, however, suggest that certain peculiar imaging appearances on MRI such as "open" or "broken" ring gadolinium enhancement (Fig. 6) suggest lesions with atypical demyelination (that is, TMS) rather than neoplasm or infection (4-6). Some other studies suggest that dilatation of cerebral veins either in or around these tumefactive lesions may suggest this alternative diagnosis as well (5, 7). In cases where these hallmark imaging features (see summary table) are not present and where clinical diagnosis is uncertain, brain biopsy may be used to narrow the differential diagnosis. Where brain biopsy is declined or not indicated, some authors have found that followup imaging may be used as a diagnostic aid to confirm the diagnosis, with interval improvement of these lesions following steroid therapy (8). Moreover, many cases of TMS will go on to develop definite MS (70%), and most will have multiple lesions on followup imaging studies (83%), suggesting that looking for the characteristic time-space phenomenon of MS lesions may help avert brain biopsy (9).

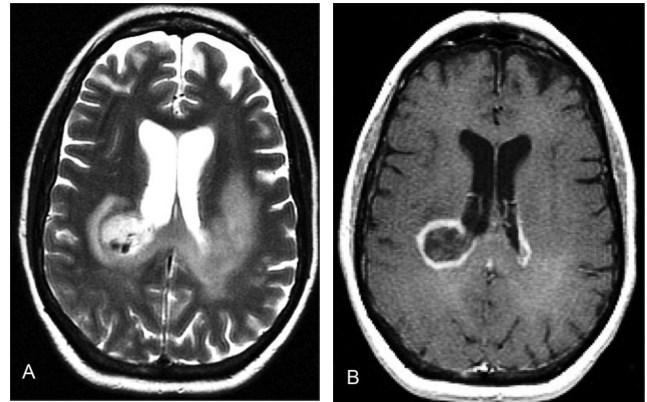


Figure 6. 45-year-old male with TMS. MRI of this separate comparison case of TMS in an adult male patient is characterized by more classic features, including a periventricular lesion on conventional T2-weighted MRI with edema and minimal midline shift (A), with an incomplete ring of enhancement on gadolinium-enhanced T1-weighted images (B).

On magnetic resonance spectroscopy, decreased N-acetylaspartate (NAA) levels and other patterns proposed by some authors may aid in differentiation of tumefactive demyelination from neoplasm, though there is much controversy on this subject (see differential diagnosis table) (5, 10, 11). However, demonstrating abnormal levels of choline, N-acetyl aspartate, glutamate-glutamine, and lactate by MR spectroscopy has been suggested to help differenti-

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ate tumefactive lesions of MS (10). An elevated choline/creatine ratio, increased lactate, and normal N-acetylaspartate/creatine ratio may be regarded as suggestive of inflammation or demyelination (1). However, the role of MRS in helping to clarify the diagnosis of TMS is not yet definitely established.

In conclusion, we reviewed the imaging findings of a biopsy-proven case of TMS with atypical features. This case had the unusual feature of an enlarged temporal horn that was likely due to ependymal adhesions. Multiple enhancing lesions in this setting suggest neoplasm, infection, or ischemia (12). However, in this case there was evidence of periventricular disease, hinting at the diagnosis of TMS despite the presence and configuration of the atypical features, which was confirmed with biopsy and verified by followup imaging demonstrating rapid resolution with steroid therapy.

A diagnosis of TMS relies on the correlation of clinical examination and history with the potential imaging findings of a tumefactive lesion on MRI, such as an incomplete ring of enhancement (Fig. 6). This case highlights the variable imaging presentation and atypical nature of TMS that continues to challenge clinicians evaluating patients with atypical intracranial lesions and unusual clinical presentations.

Differential table

| Diagnosis | MRI |
|-----------|---|
| TMS | Acute lesions larger than 2 cm often associated with edema and open or "broken ring" enhancement. Mass effect and a resulting shift across midline may also be present. |
| Neoplasm | Similar to TMS, but with complete ring enhancement; mass effect is generally greater. |
| Abscess | Similar to TMS, but with complete ring enhancement. Extensive edema compared to lesion size is often characteristic. |
| Stroke | Similar to TMS, but without incomplete ring enhancement. |

Summary table

| Features | Description |
|---------------------|--|
| Etiology | The cause of MS is unknown, but it is considered an autoimmune disease. Inflammation and demyelination are hallmark features of its pathogenesis. TMS is an uncommon presentation of MS. |
| Incidence | 0.1-2.8% of multiple sclerosis patients. |
| Gender ratio | 1.2:1 female to male predominance |
| Age predilection | 10% before age of 20 years, 70% between 20 and 40, and 20% after age 40. Median age of onset is 37 years. |
| Treatment | Glucocorticoids |
| Prognosis | Relapsing, remitting MS is characterized by periods of neurological disability followed by periods of recovery. 85% of MS cases present with relapsing remitting MS; 50% of these will develop secondary progressive MS within 10 years, and 90% will within 25 years. Secondary progressive MS involves increasing, permanent neurological damage. 10% present with primary progressive MS, which involves a steady and permanent decline in neurological function from the onset. 5% present with progressive relapsing MS, in which there is permanent neurological decline, as well as acute MS attacks. |
| Findings on imaging | TMS is characterized by atypical features of MS such as lesions greater than 2 cm in diameter, mass effect (71%), edema (100%), and ring enhancement with Gadolinium-enhanced MRI (38-50%), usually open-ring (31%). Venous dilatations may be seen in or around these lesions. |

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