Tumefactive Demyelinating Lesions: A Case Series of 12 Patients

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ABSTRACT

Tumefactive demyelination, characterized by lesions >2cm, is a rare presentation of an inflammatory demyelinating disease in which radiographic features can mimic neoplasms (glioma or lymphoma) or infections (cerebral abscesses, parasitic cysts) on MRI. These overlapping characteristics make the diagnosis difficult in the very few patients presenting with these lesions. Our objective in this case series is to look at the clinical and radiological presentations of tumefactive demyelination. An analysis of 12 cases was conducted, looking at patient demographics, clinical presentation, diagnosis, MRI, treatment methods, and follow-up. Of the 12 patients examined, there was a biological-sex prevalence of 8 women to 4 men. Our mean age of onset was 32.8 years of age, and out of our 12 patients, 7 (58.3%) had a tumefactive onset and 5 (41.7%) had a previous history of demyelination. All 12 patients were given a subsequent diagnosis of multiple sclerosis. All patients were polysymptomatic, with motor symptoms being the most common, followed by sensory, cognitive, nonspecific, and visual symptoms. The most common enhancement pattern seen was ring enhancement, specifically an open-ring. The average lesion location was 4.21 cm and all, but one patient had additional white matter lesions of the examined MRI's. Tumefactive demyelinating lesions continue to present as a diagnostic issue for neurologists, however, certain clinical characteristics can be indicative of a tumefactive demyelinating lesion over differential diagnosis

INTRODUCTION

Tumefactive demyelination is a rare presentation of an inflammatory demyelinating disease (IDD) in the central nervous system (CNS) characterized by pseudo tumoral lesions, also known as tumefactive demyelinating lesions (TDL). These lesions are characterized as tumefactive when they are greater than 2cm in diameter [1,2,3]

The features of TDL's can mimic neoplasms or infections[5]. In these cases, it is the neurologist's job to deduce the cause of such lesions, creating a diagnostic challenge. In certain cases, a biopsy may be necessary in order to make a definitive diagnosis.

MS is the most common cause of TDLs[6]. For those with a TDL as their first presentation, about 2/3 will go on to follow a relapsing-remitting course of MS[6]. In literature, the term "tumefactive MS" will often be substituted when referring to tumefactive demyelination, however, not all TDLS are due to

MS[2,3]. For a TDL diagnosed as MS, the criteria of dissemination in time (DIS) and dissemination in space (DIS) still must be met. DIT is the presence and development of new lesions at least 30-days after the initial presentation, and DIS is the development of lesions in dissimilar areas of the CNS[7]. Without established DIT and DIS (or other specified McDonald Criteria such as oligoclonal bands in the cerebrospinal fluid), a single neurological episode of inflammation will be initially classified as a clinically isolated syndrome[7]. The frequency of TDL's in cases of MS is estimated to be around 2-3 per 1000 individuals[8]. This, however, is an unlikely estimate due to the number of unreported or misdiagnosed cases, so that actual prevalence could be much higher[9]. Despite this underestimation, TDLs are still an uncommon variant of an IDD.

MRI features presenting in patients are the most accurate biomarkers to indicate tumefactive MS[4]. TDL's will generally appear as hypointense on T1-weighted images and hyperintense of T2-weighted images. Imaging locations that best suggest demyelination, as opposed to neoplasms or infection, include hyperintensities in the corpus callosum, periventricular and deep white matter, juxta-cortical regions, the infratentorial compartment, and spinal cord[6]. Contrast enhancement with gadolinium occurs in 95-100 percent of cases[9], and almost any pattern of enhancement can be seen[1]. Most clinically proven TDL's have a closed ring enhancement[2] or open ring enhancement with its open portion towards the cortex[11]. Open-ring enhancement can be a highly specific diagnostic tool for identifying demyelination[11,12]. Generally, neoplasms and infections will not present with a pattern of open-ring enhancement on MRI. Depending on the location of the lesions, symptoms can include: headaches, cognitive impairment, aphasia, hemiplegia, apraxia, visual field defects, and seizures[2]. In general, these symptoms are atypical for presentations MS. Depending on the size of the lesions, some symptoms may present more severely[3].

STATEMENT OF PURPOSE

This retrospective case analysis hopes to further contribute to the growing body of research dedicated to TDLs, to take steps towards reducing misdiagnosis and use of unnecessary, invasive diagnostic tests, as well as improving treatment management for patients affected by this rare demyelinating disorder.

METHODS AND MATERIALS

We performed a retrospective chart review of patients with identified TDLs using patient charts from the NYU Multiple Sclerosis Care Center. A list of subjects was identified from an existing list of patients over the past 15 years who presented with TDL's. Study population included

people ages 18-60 with radiologically or biopsy-proven TDLs who met the following inclusion criteria: A minimum of one MRI taken within one year of initial presentation available for review. Cases of neoplasm, infection, or other non-demyelinating diseases that may be similar to tumefactive demyelination were excluded. 12 patients were identified who met the inclusion criteria. Radiographic and clinical data were collected. Current and previous medical status have been established by neurologists at NYU Langone Health.

Patient demographics (age of TDL onset, biological sex), presence demyelinating disease prior to TDL onset, lesions (location, size, pattern of enhancement, edema and mass effect, clinical presentation (symptoms), biopsy and cerebrospinal fluid analysis, final diagnosis, choice of treatment, and long-term follow-up (when available) were analyzed.

Lesion enhancement patterns were categorized into subtypes (megacystic, infiltrative, ring-like, balo-like, and non-specific) based on the MAGNIMS recommended classifications for atypical demyelinating lesions[13] as well as other classifications as punctate and homogenous.

RESULTS

Demographics

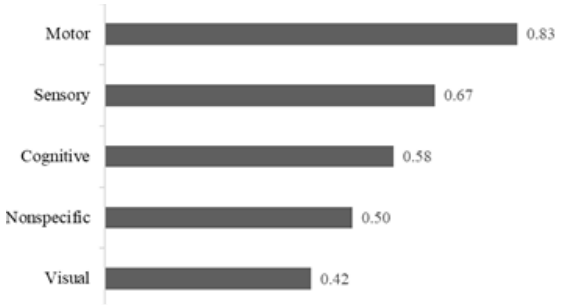
66.7% of our patients were female (n=8) and 33.3% were male (n=4). The average age of first TDL presentation was 32.75 years (min: 19, max: 49). Mean follow up was 49.3 months (min: 6 months, max: 100).

Clinical Features

Out of 12 patients, 58.3% of patients had a tumefactive onset (n=7), while 41.7% had a previous history of a demyelinating episode (n=5). 33.3% had a previous diagnosis of MS (n=4). The mean age of onset for those with a tumefactive onset was 34.3 years of age (min: 25, max: 49), while those with a previous history of demyelination had an average age of 30.6 (min: 19, max: 39) years.

Clinical presentations of patients all presented as polysymptomatic, Symptoms were categorized into 5 subtypes: cognitive, motor, visual, sensory and nonspecific.

Figure 1. Symptom Type Prevalence



Clinical Course

25% of patients went on to have no additional attacks. 58.3% of patients had a single additional attack, two of those being

tumefactive relapses, while 8.3% went on to have two additional attacks, and 8.3% had 3 or more additional attacks, one of those also being a tumefactive relapse.

Radiological Characteristics

Due to the fact that two patients that were identified as having tumefactive relapses and one patient presented with 3 TDL's on a single MRI, the radiological characteristics of 16 distinct TDL's were examined.

The most common enhancement pattern was ring-like (50%). Open-ring was the most prevalent ring-like enhancement. Balo-like, homogenous, punctate, megacystic, and nonspecific lesion types were also seen.

The average lesion size was 4.21 cm (min: 2.00 cm, max: 6.70 cm). Most TDL's seen had a predilection towards the frontal lobe. Polyregional lesions were also seen, generally suspending across the parieto-occipital lobes or the temporal-occipital lobes. Isolate lesions were also seen in the temporal lobe.

Edema and mass effect was categorized as none, mild, significant. A lack of mass effect was seen in the majority of patients (66.7%), however, patients did present with mild (16.7%) and significant (16.7%) edema.

Every patient examined in this study showed a T2hyperintense rim on MRI. 91.7% (n=11) patients had additional multiple sclerosis lesions present on the examined MRI's.

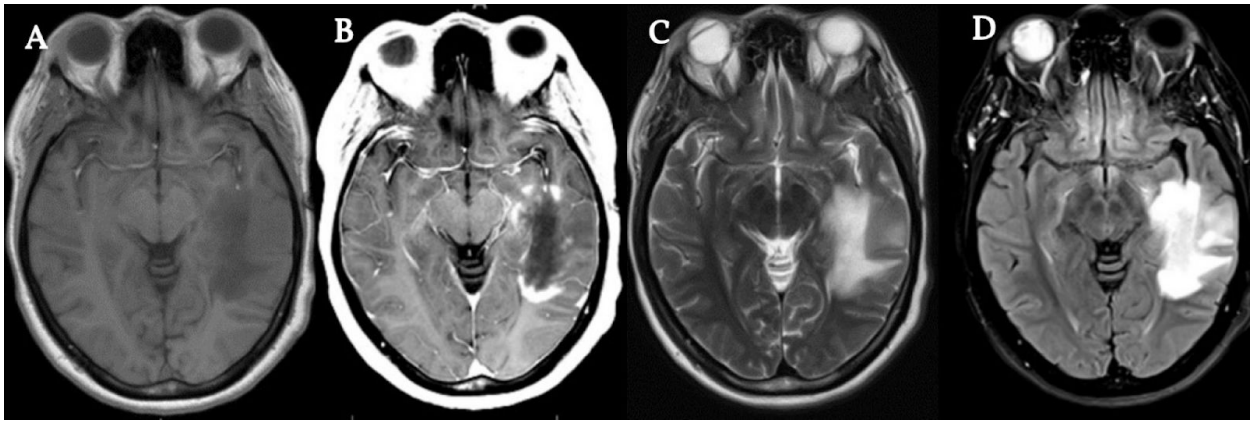


Figure 2. Patient 1 MRI Imaging (A) T1 Pre Contrast (B) T1 Post Contrast (C) Axial T2 (D) Axial Flair. Imaging shows a large ovoid lesion in the left temporal lobe. Open-ring enhcanement is seen with no mass effect present. Several additional smaller lesions are present within the right superior frontal gyrus, left pons, and left ventral medulla.

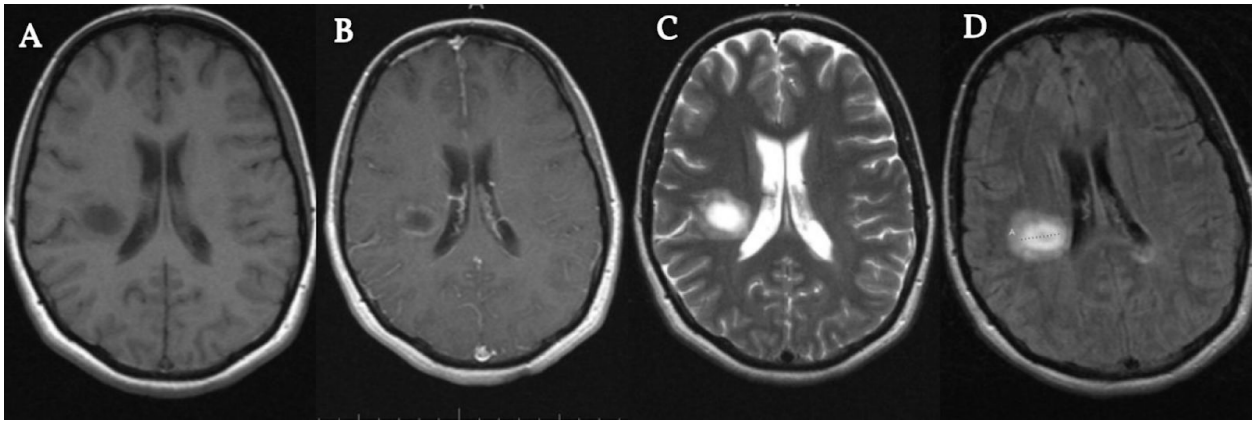


Figure 3. Patient 3 MRI Imaging. (A) T1 Pre Contrast (B) T1 Post Contrast (C) Axial T2 (D) Axial Flair. There is a 2 cm oval lesion within the right posterior frontal lobe. An open-ring enhancement pattern is seen. It demonstrates a central region of intense T2/flair hyperintensity more moderate at the periphery. Centrally it is T1 hypointense.

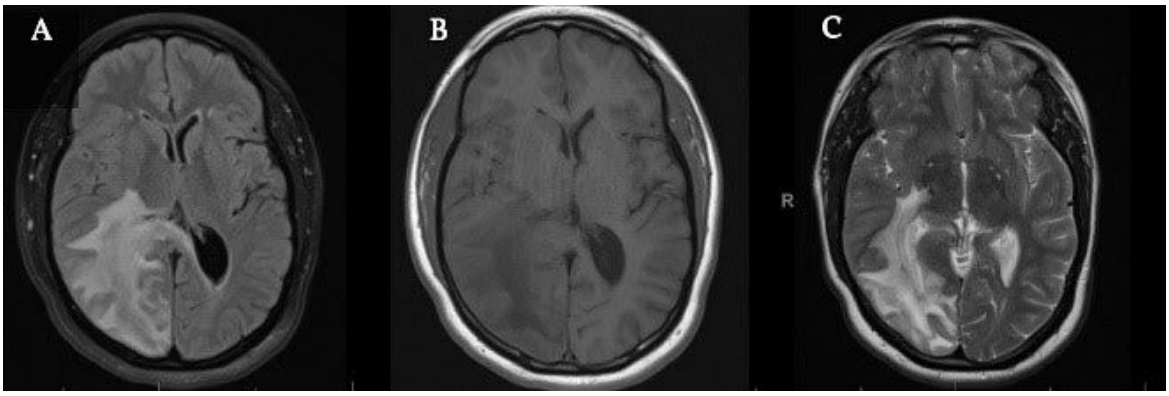


Figure 4. Patient 6 MRI Imaging. (A) Axial Flair (B) Axial T1 (C) Axial T2. MRI Imaging shows a 6.7 x 3.2 cm tumefactive demyelinating lesion of the left temporal-parietal lobe. Significant surrounding edema is seen in the posterior right cerebral hemisphere and splenium of the corpus callosum

Laboratory Data

8 patients underwent cerebrospinal fluid (CSF) analysis for the presence of oligoclonal bands (OCBs). 62.5% tested positive for OCBS. Additionally, 5 patients were tested for IgG synthesis rates, 80.0% had elevated IgG synthesis rates.

Final Diagnosis

100% of patients were ultimately given a diagnosis of MS. Differential diagnoses at patient presentation included neuromyelitis optica (NMO), acute disseminated encephalomyelitis, (ADEM), and progressive multifocal leukoencephalopathy (PML). Rare

variants of MS such as Marburg'svariant and Balo's concentric sclerosis were also considered.

Treatments

Most patients (83.3%) were given treatment during a suspected relapse. 4 were given intravenous methylprednisone (IVMP), 6 received a combination of both IVMP and plasma exchange (PLEX). No patient solely received PLEX as an attack treatment.

All patients received disease-modifying therapies (DMTs) and the treatment courses of most patients included the use of several DMTs, depending on the adverse reactions and symptoms of the DMTs. 10 DMTs were seen in total, the most popular being natalizumab (58.3%), rituximab (33.3%), dimethyl fumarate (33.3%), and fingolimod (33.3%).

Whilst being treated with DMTs, by the time the data collection window had closed, 33.3% of patients saw an improvement, 50% were stable, and 16.7% had worsened.

DISCUSSION

TDLs are a rare, but serious, presentation of an inflammatory demyelinating disorder. In this retrospective case analysis, we sought to further understand the clinical and radiological characteristics of TDLs. We examined demographic, radiographic, clinical, laboratory, and treatment data of 12 patients.

In our retrospective case analysis, MS was the most common cause of TDL's, coinciding with previous reports. In fact, MS was the only diagnosis seen in patients within this chart review, though non-MS cases of TDLs were purposefully excluded.

Demographic data also coincided with previous reports. Mean age of TDL onset in this case report 32.2 years, which is consistent with previous studies, reporting TDL's typically present in the third decade of life[4,13,14]. The mean age of onset for patients with a pre-existing MS diagnosis or demyelination was slightly lower than those with a tumefactive onset, being 30.6 and 34.3 years respectively, consistent with reports from Altintas 2012 of a lower mean age of TDL presentation for those with pre-existing demyelination, however the age difference was not statistically significant (p=.246).

Our ratio of females/males was 2, consistent with reports found in Sanchez 2017 and Altintas 2012 that TDLs predominantly effect females. The predominance of females in our sample could be attributed to the fact that MS was the only prognosis seen. Female to male prevalence in cases of MS generally presents with a parallel 2:1 ratio.

The most common diagnosis of patients in our case series was MS, which was the diagnosis for every single patient. 6 patients had a specified diagnosis of RRMS, while the other 6 were not given a specific course
of MS.

Looking at the difference between those with a TDL as their first presentation and those with a

previous history of demyelination was difficult due to the small number of patients observed with a prior history of demyelination and that the fact that all patients went on to receive a diagnosis of MS.

In terms of laboratory data, our findings were inconsistent with previous reports[3], only 1 out of 3 patients with a previous history of demyelination tested positive for OCBs, while 4 out of 5 of those tested with a tumefactive onset had OCBs present. Again, this could be due to the small sample size and the fact that all patients had a subsequent diagnosis of MS. Presence of OCBs is highly valuable for ruling out differential diagnoses of cerebral infections and neoplasms[7].

Whilst all 5 symptom types originally identified were seen across patients, motor symptoms were the most prevalent, consistent with previous findings.[2]

CONCLUSION

While TDL's still remain a diagnostic challenge for neurologists, clear work is being done to differentiate the clinical and radiological features that distinguish TDLs from other differential diagnoses.

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