Tumefactive demyelinating lesions in multiple sclerosis
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Introduction

This article includes discussion of tumefactive multiple sclerosis, tumor-like multiple sclerosis, pseudotumoral multiple sclerosis, and tumefactive demyelinating lesions. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Multiple sclerosis presenting with clinical and radiographic features similar to a brain tumor is referred to as tumefactive multiple sclerosis. This often poses a diagnostic challenge for the neurologist, neurosurgeon, radiologist, and pathologist. In this article, Drs. Meredith Frederick and Michelle Cameron of the Oregon Health and Science University Department of Neurology discuss the spectrum of central nervous system inflammatory demyelinating disease that can have a tumefactive clinical or radiographic presentation, including the Marburg variant of multiple sclerosis and Balo concentric sclerosis. Acute disseminated encephalomyelitis, acute hemorrhage leukoencephalitis, and neuromyelitis optica can also have tumefactive presentations, but are beyond the scope of this article.

Key points

- Tumefactive demyelinating lesions can be caused by a number of diseases, including multiple sclerosis. It is important to recognize that use of the terms tumefactive demyelinating lesions and tumefactive multiple sclerosis in the literature is not standardized and can cause confusion.
- A spectrum of disorders causes inflammatory demyelination of the central nervous system; the disorders are collectively referred to as CNS idiopathic inflammatory demyelinating diseases.
- Any type of CNS idiopathic inflammatory demyelinating disease may present clinically and radiographically as a tumefactive lesion.
- Multiple sclerosis is the most common CNS idiopathic inflammatory demyelinating disease.
- Pathological features of multiple sclerosis lesions include focal demyelination, variable inflammation, gliosis, and relative axonal preservation.
- Two thirds of patients who present with tumefactive demyelinating lesions subsequently develop multiple sclerosis, with a relapsing-remitting disease course.
- MRI features associated with tumefactive demyelination include multifocal lesions with at least a single dominant lesion larger than 2.0 cm, variable presence of mass effect or edema, and ring enhancement.
- High-dose intravenous corticosteroids are the first line management for tumefactive relapses.
- Aggressive supportive management in the acute phase is crucial because the predicted long-term outcome of many patients is good.

Historical note and terminology

Multiple sclerosis is a chronic CNS idiopathic inflammatory demyelinating disease characterized by multiple lesions disseminated in time and space. Multiple sclerosis is the most common CNS idiopathic inflammatory demyelinating disease across all age groups. Typical multiple sclerosis lesions involve the white matter, with a predilection for the periventricular areas, cerebellum, brainstem, spinal cord, and optic nerves. Lesions typically range in size from a few millimeters to a centimeter in diameter (Paty et al 1988). Multiple sclerosis is diagnosed on the basis of demonstrating multiple lesions disseminated in time and space clinically or radiographically (McDonald et al 2001; Polman et al 2010). Occasionally, patients are found to have large CNS demyelinating lesions that appear tumor-like. These are known as tumefactive demyelinating lesions.
The terms tumefactive demyelinating lesions and tumefactive multiple sclerosis are often used interchangeably, although these terms are not synonymous. A tumefactive demyelinating lesion is any CNS demyelinating lesion that appears tumor-like. Tumefactive demyelinating lesions can be caused by a variety of disorders, including, but not limited to, multiple sclerosis. The term tumefactive multiple sclerosis usually refers to multiple sclerosis with tumor-like lesions, but this term is sometimes used to refer to both typical multiple sclerosis and the rare multiple sclerosis variants that can cause tumefactive lesions, including Marburg acute multiple sclerosis, Balo concentric sclerosis, and Schilder disease. This article focuses on tumefactive multiple sclerosis and the variants of multiple sclerosis that present with tumefactive lesions:

- Tumefactive multiple sclerosis
- Marburg acute multiple sclerosis
- Balo concentric sclerosis
- Schilder disease

Acute disseminated encephalomyelitis (ADEM), acute hemorrhagic leukoencephalomyelitis, and neuromyelitis optica can also have tumefactive presentations but are beyond the scope of this article.

**Tumefactive multiple sclerosis.** Although this term is not used uniformly and consistently in the literature, it typically refers to demyelinating brain lesions 2 cm or larger in size, often with features of edema and mass effect. Radiographic features may include a solitary large lesion or multiple lesions with variable contrast enhancement. These lesions may occur in prototypic multiple sclerosis, as part of a monophasic illness, or in the acute fulminant variants of CNS idiopathic inflammatory demyelinating diseases described below. In the largest study of patients with biopsy-proven tumefactive demyelinating lesions that included 168 patients (Lucchinetti et al 2008), the majority had multiple sclerosis. When tumefactive lesions occur in prototypic multiple sclerosis, it is most often at initial presentation, although there are increasing reports of tumefactive lesions in the setting of use or withdrawal of some of the newer disease-modifying therapies for multiple sclerosis, most notably fingolimod (Hardy and Chataway 2013; Pilz et al 2013).

**Multiple sclerosis disease-modifying therapy-associated tumefactive demyelination.** There are growing numbers of reports of tumefactive demyelination in association with fingolimod and a single report in association with natalizumab. At least 20 cases of tumefactive demyelination associated with fingolimod have been reported (Centonze et al 2012; Jander et al 2012; Hardy and Chataway 2013; Pilz et al 2013; Hellmann et al 2014; Totaro et al 2016). These events have occurred directly after drug initiation, 13 months into treatment, and shortly after discontinuation of fingolimod (Totaro et al 2016). Although a causal link has not been proven, the association is striking. A few of these cases occurred as patients were transitioned from natalizumab to fingolimod (Centonze et al 2012; Jander et al 2012). One published case with biopsy of the tumefactive lesion showed typical pathologic changes associated with demyelination in multiple sclerosis (Hellmann et al 2014). The authors of this article are in agreement with the authors of these studies that this likely represents a unique phenomenon and is not simply emergence of underlying highly active multiple sclerosis (Hellmann et al 2014). Because tumefactive demyelination occurs more commonly as the first demyelinating event and tumefactive lesions have not been reported in association with interferons or glatiramer acetate, it is reasonable to hypothesize that there is an immunologic phenomenon occurring as a result of fingolimod treatment that triggers these tumefactive lesions (Hellmann et al 2014). It is possible that immune cells that have been educated in the lymph nodes are released into the circulation after fingolimod is withdrawn.

A single reported case of tumefactive demyelination occurred soon after natalizumab was restarted after prior discontinuation of the medication (Beume et al 2015). This patient discontinued natalizumab, then had a relapse of multiple sclerosis without tumefactive lesions, which prompted the providers to restart natalizumab. After restarting, she had a severe inflammatory relapse with tumefactive lesions. This case is notable because of the severity of the tumefactive disease activity, leading to stupor and quadriplegia. Biopsy of one of the tumefactive lesions showed demyelination and inflammation dominated by B cells. There are other reports of high-rebound disease activity without tumefactive lesions with discontinuation of natalizumab, but this may reflect more active disease in patients selected for treatment with natalizumab. The case presented by Beume and colleagues suggests the possibility of modification of the immune response by restarting natalizumab, leading to malignant disease activity.

**Marburg acute multiple sclerosis.** This is an acute, fulminant, monophasic CNS idiopathic inflammatory demyelinating disease characterized by large hemispheric cerebral lesions and rapid progression to death within months to 1 year from onset. Marburg acute multiple sclerosis was first described by Otto Marburg in 1906. He described a 30-year-old woman presenting with confusion, headache, vomiting, ataxia, and left hemiparesis, rapidly progressing to death.
within 1 month. Autopsy revealed widespread destructive inflammatory demyelination. The clinical diagnosis of Marburg acute multiple sclerosis is often made in retrospect because it is difficult to predict the course and outcome at the onset of symptoms. Cases described in the literature typically show little or no response to treatment, including with high-dose corticosteroids, intravenous immunoglobulins, plasma exchange, azathioprine, cyclophosphamide, and mitoxantrone (Turatti et al 2010; Talab and Kundrata 2011; Suzuki et al 2013). There is one case report with a favorable response to high-dose cyclophosphamide (Nozaki and Abou-Fayssal 2010). An additional patient eventually reached long-term disease stability, although with significant disability, after treatment with corticosteroids, cyclophosphamide, plasma exchange, and interferon-beta (Turatti et al 2010).

**Balo concentric sclerosis.** This acute CNS idiopathic inflammatory demyelinating disease is pathologically and radiographically characterized by a unique pattern of concentric demyelination. Josef Balo from Hungary first characterized the pathology of this disease in 1928 (Balo 1928). Balo described a 23-year-old gentleman presenting with progressive right hemiparesis and numbness. Patients with Balo concentric sclerosis have traditionally been thought to have an acute fulminant presentation with rapid progression to death within 1 year, similar to Marburg acute multiple sclerosis; however, some people with Balo-like lesions detected on MRI have favorable outcomes (Karaarslan et al 2001; Hardy and Miller 2014). MRI is characterized by lesions with alternating concentric hyperintense and hypointense rings that may enhance with gadolinium (Ng et al 1999). Lesions range in size from 1 centimeter to large sections of a cerebral hemisphere. Their distinctive appearance allows them to be distinguished from lesions in other CNS tumefactive disorders. The diagnosis of Balo concentric sclerosis is typically made based on MRI or autopsy findings demonstrating the pathologic hallmark of concentric demyelination.

Concentric CNS lesions can also rarely occur in other demyelinating disorders. Two case reports of patients with Balo-like brainstem lesions have been described. One patient had neuromyelitis optica (Graber et al 2009), and the other had multiple sclerosis (Kishimoto et al 2008). Balo-like lesions have also been described in patients with progressive multifocal leukoencephalopathy (Markiewicz et al 1977), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (Chitnis and Hollmann 2012), and a patient with active hepatitis C and CSF positive for human herpes virus 6 (Ferreira et al 2011).

**Schilder disease (myelinoclastic diffuse sclerosis).** This very rare CNS idiopathic inflammatory demyelinating disease was initially described by Paul Schilder in 1912. It is a progressive, degenerative, demyelinating disorder of the CNS that usually begins in childhood or young adulthood (mostly males between the ages of 7 and 12). A number of patients initially diagnosed with Schilder disease were subsequently found to have other CNS disorders, including metabolic and hereditary leukodystrophies (eg, adrenoleukodystrophy = Addison-Schilder disease). Schilder disease typically causes bilateral, large hemispheric demyelinating lesions with progressively larger lesions that interfere with motor function, speech, personality, hearing, and vision and, ultimately, autonomic functions. In 1986, Poser and colleagues proposed criteria for this diagnosis (Poser et al 1986). It is difficult to distinguish Schilder disease from acute or subacute fulminant multiple sclerosis.

**Clinical manifestations**

**Presentation and course**

Tumefactive multiple sclerosis lesions can cause atypical neurologic symptoms because of their size, location, and potential for associated mass effect and edema. Among the largest cohort of biopsy-proven tumefactive multiple sclerosis cases analyzed to date (n=168), common presenting symptoms in decreasing frequency included motor, cognitive, cerebellar, and brainstem dysfunction (Lucchinetti et al 2008). Additional symptoms included headache, seizures, aphasia, cortical sensory loss, or psychosis. Unlike typical CNS demyelinating lesions, tumefactive lesions are more likely to cause cortical signs, such as altered mental status and visual field deficits. The tumefactive episode represented the initial event in 61% of cases; however, 29% of patients had a prior history of relapsing neurologic symptoms, and 5% carried an established diagnosis of multiple sclerosis.

Two thirds of patients with tumefactive multiple sclerosis lesions subsequently develop a relapsing-remitting disease course with more typical multiple sclerosis lesions, although a small subset of these patients will have tumefactive lesions at relapse (Lucchinetti et al 2008; Altintas et al 2012). Their median time to the second relapse was 4.8 years, an interval longer than reported for prototypic multiple sclerosis. The remaining one third of patients had a monophasic illness at last follow-up. These findings contrast with an earlier study suggesting that patients with biopsy-proven tumefactive demyelinating lesions uniformly have a monophasic disease course (Kepes 1993). However, Kepes'
duration of follow-up was less than 5 years for most of the patients. Another study, also with less than 5 years of follow-up for most patients, found that two thirds of patients had a monophasic course in contrast to Lucchinetti's two thirds with a relapsing course. However, the proportion with a relapsing course increased to 50% when the initial lesion was ring-enhancing, though Lucchinetti did not find a similar association. The presence of concomitant typical multiple sclerosis-appearing lesions increased the frequency of relapse (41.3% vs 9.6%, p<0.005) no matter what the imaging characteristics of the initial tumefactive lesions were (Wallner-Blazek et al 2013). Longer follow up is clearly needed based on Lucchinetti's finding that the average time to relapse is 4.8 years.

The results from a newer cohort of patients with tumefactive demyelinating lesions differed markedly from Lucchinetti's (Nagappa et al 2013). In this cohort of 39 patients with tumefactive demyelinating lesions, the median time to relapse was 4 months, with the majority of patients having tumefactive lesions at relapse (Nagappa et al 2013). Importantly, this was an Indian cohort where the incidence of multiple sclerosis is significantly lower and the cohort included children, who have a higher incidence of ADEM. The discrepancies between findings in these various studies highlight the challenges of studying tumefactive demyelinating lesions, which are rare, may require longer follow up to record relapses, and are caused by a heterogeneous group of diseases.

Prognosis and complications

The prognosis for patients with tumefactive demyelinating lesions is impacted primarily by the underlying CNS idiopathic inflammatory demyelinating disease, the location and size of the tumefactive lesions, the extent of mass effect, and the response to initial treatment. Patients with tumefactive multiple sclerosis lesions typically develop a classic relapsing-remitting course. A small subset of patients presenting with tumefactive multiple sclerosis may relapse in a strictly tumefactive fashion. The presence of ring enhancement on MRI and other typical multiple sclerosis-appearing lesions at presentation are associated with a higher incidence of relapse (Wallner-Blazek et al 2013). Most studies agree that tumefactive multiple sclerosis does not typically evolve into a more active subtype of multiple sclerosis and recovery from tumefactive lesions is, in general, favorable (Lucchinetti et al 2008; Altintas et al 2012; Wallner-Blazek et al 2013). Long-term disability associated with tumefactive multiple sclerosis is similar to a population-based multiple sclerosis cohort matched for disease duration (Pittock et al 2006; Lucchinetti et al 2008). Index lesion size, location, and presence of mass effect or edema are not predictive of conversion to multiple sclerosis (Lucchinetti et al 2008).

Clinical vignette

A 23-year-old woman initially presented at 12 years of age with new-onset progressive left hemiparesis. The symptoms started in the left hand, then progressed to involve the left face and left lower extremity over a period of 1 week. Brain MRI revealed a large open-ring, gadolinium-enhancing lesion involving the right frontal lobe. She was treated with intravenous steroids and had a rapid beneficial response. At the age of 23 years, she had ascending sensory loss to the umbilicus associated with urinary urgency. She was treated with intravenous steroids and completely recovered 11 days later. She was started on multiple sclerosis disease modifying therapy with interferon beta1a weekly intramuscular injections for relapsing-remitting multiple sclerosis. Her EDSS score was 1.0 at last follow-up, 13 years after disease onset.

Biological basis

Etiology and pathogenesis

Pathology and pathogenesis differs depending on the type of CNS idiopathic inflammatory demyelinating disease.

Tumefactive multiple sclerosis.

Pathology. Tumefactive lesions in multiple sclerosis have the same histological features as classic multiple sclerosis lesions. Pathological features of multiple sclerosis lesions include focal demyelination, variable inflammation, gliosis, and relative axonal preservation.

Up to 31% of diagnostic biopsies from patients with demyelinating lesions are misinterpreted. The most common misdiagnoses include glioma and infarction. Pathological features that cause difficulty in interpretation include hypercellularity, presence of necrosis and cystic changes, and the presence of reactive astrocytes with bizarre appearance and mitotic figures, referred to as Creutzfeldt cells (Zagzag et al 1993; Annesley-Williams et al 2000; Di
Patre et al 2003). Zagzag and colleagues noted that the presence of foamy macrophages is an important feature suggestive of a demyelinating etiology. Once this is suspected, staining for myelin and axons can confirm the diagnosis (Zagzag et al 1993). Sampling is also a factor that may contribute to misinterpretation of demyelinating biopsies. Samples from the lesion edge may be misinterpreted as glioma; whereas samples obtained from the lesion center may resemble infarcts (Annesley-Williams et al 2000).

Pathogenesis. The immunopathogenesis of tumefactive demyelinating lesions remains uncertain. Early case reports suggested an association between tumefactive demyelinating lesions and vaccinations, leading to the hypothesis that these lesions represent an intermediate phenotype between multiple sclerosis and acute disseminated encephalomyelitis. However, this association was not found in subsequent studies (Kepes 1993; Lucchinetti et al 2008; Altintas et al 2013; Hardy and Chataway 2013). Additionally, the occurrence of these lesions among patients who typically go on to develop classic multiple sclerosis argues that these lesions are part of the heterogenous spectrum of multiple sclerosis and not a transitional phenotype between acute disseminated encephalomyelitis and multiple sclerosis (Kepes 1993), recurrent acute disseminated encephalomyelitis (Brinar 2004), or a tumefactive multiple sclerosis variant (Poser et al 1992).

It is also important to recognize that multiple sclerosis patients may develop neoplasms. A review of gliomas in multiple sclerosis reported 30% of gliomas associated with multiple sclerosis are multicentric or diffusely infiltrative as compared to a frequency in 2.5% to 5% of gliomas not associated with multiple sclerosis, suggesting a causal relationship to the multifocal disease of multiple sclerosis (Sega et al 2006). Case reports vary as to whether the neoplastic process is adjacent to or infiltrates the multiple sclerosis lesions. Shuangshoti and colleagues hypothesize that neoplastic cells may originate from reactive astrocytes in inflammatory lesions (Shuangshoti et al 2003). In cases with multiple sclerosis and oligodendrogliomas, a causal relationship can be hypothesized with damage to oligodendrocytes causing oligodendrocyte proliferation in an effort to remyelinate axons, thus, making the oligodendrocytes susceptible to malignant transformation (Sega et al 2006). Based on the existing data, it is difficult to draw conclusions on whether a true association exists between these two conditions; however, this potential concurrence should raise suspicion of an alternative diagnosis in a multiple sclerosis patient developing a new atypical mass lesion. There should be careful clinical and radiographic follow up of patients presenting with new mass lesions.

Marburg acute multiple sclerosis.

Pathology. Lesions may be disseminated throughout the brain and spinal cord, ranging in size from small to large confluent plaques. In some cases, there is diffuse demyelination throughout the brain and spinal cord. Microscopically, lesions are more destructive than typical multiple sclerosis lesions and characterized by significant macrophage infiltration, acute axonal injury, necrosis, and cavitation. Despite the degree of tissue destruction, variable remyelination is also evident.

Pathogenesis. The etiology of Marburg variant of multiple sclerosis is unclear. Myelin basic protein in patients with Marburg variant of multiple sclerosis was found to have 18 citrullinyl residues compared with 6 in patients with chronic multiple sclerosis. The number of citrullinyl residues is thought to result in structural instability of myelin, causing severe demyelination as is seen in these patients (Beniac et al 1999). In a case report of a serial biopsy from a patient with Marburg variant, the initial biopsy (done on day 33) showed marked inflammation in the absence of demyelination, which became evident by the subsequent biopsy (day 109 of disease) (Bitsch et al 1999). These findings are consistent with inflammation preceding demyelination.

Balo concentric sclerosis.

Pathology. Patients with Balo concentric sclerosis may have 1 or more lesions in the cerebral white matter, often sparing the cortical U fibers. Other reported sites are less common but include the basal ganglia, pons, cerebellum, and, rarely, the spinal cord and optic nerves. The pathological hallmark consists of concentric demyelination and oligodendrocyte loss characterized by alternating bands of demyelination with normal myelination or partial demyelination giving the appearance of onion bulbs.

Pathogenesis. This pathological pattern of demyelination and tissue injury resembles a pattern seen in tissue ischemia. Similar to acute ischemia, a preferential loss of myelin-associated glycoprotein and oligodendrocyte apoptosis is seen in a subset of multiple sclerosis lesions. Because myelin-associated glycoprotein is localized at the distal inner glial loop, its early loss is interpreted as evidence of a dying-back gliopathy where the oligodendrocyte is unable to support
the distal axon.

Different cellular responses to injury are found in the different rings of Balo concentric sclerosis lesions and display similarities to cellular mechanisms observed in hypoxia. In active areas of demyelination, macrophages and microglia express nitric oxide synthase, indicating an attempt, although unsuccessful, to mitigate damage. In areas with rings of preserved myelin, oligodendrocytes express protective proteins involved in tissue preconditioning (e.g., hypoxia-inducible factor 1alpha and heat shock protein 70). Astrocytes and macrophages in the same location also express these proteins, though to a lesser extent. This cellular rim is more resistant to further damage and forms the layer of preserved myelin in the lesion. This overexpression of tissue preconditioning molecules near the layer of active demyelination supports a role for histotoxic hypoxia in mediating the concentric pathology of demyelination (Stadelmann et al. 2005). Studies have also found decreased levels of aquaporin 4 and connexins, highlighting the role of astrocyte dysfunction in Balo concentric sclerosis (Linnoila and Chitnis 2014).

Epidemiology

The incidence of tumefactive multiple sclerosis lesions is low, and precise estimates vary. Masdeu and colleagues estimated the incidence to be 0.3 per 100,000 per year, based on a review of 2 hospital-based studies of 11 and 40 patients extrapolated from total number of people within the catchment area and average number of patients with prototypic multiple sclerosis (Masdeu et al. 2000). Poser estimated the prevalence at 1 to 2 per 1000 cases of multiple sclerosis (Poser et al. 1992).

A number of authors have tried to estimate the prevalence of tumefactive multiple sclerosis based on reviews of brain biopsies. Sugita and colleagues reviewed brain biopsies from 1231 cases coded as brain tumor or "unclassified" and found demyelination in 3 patients (0.24%) (Sugita et al. 2001). Hunter and colleagues reported 5 of 1220 brain biopsies done over a 5-year period were consistent with inflammatory demyelinating disease (Hunter et al. 1987). Two of the 5 biopsies were from the same patient. Annesley-Williams reported 0.09% of 15,394 retrospectively-reviewed brain mass biopsy and autopsy specimens over a 22-year period demonstrated evidence of acute demyelination. Two of their patients had a prior history of multiple sclerosis (Annesley-Williams et al. 2000).

Tumefactive multiple sclerosis typically presents in the third decade (Lucchinetti et al. 2008; Altintas et al. 2012; Wallner-Blazek et al. 2013) although Schilder disease typically occurs in children. Tumefactive multiple sclerosis can also occur in childhood and old age. Case reports describe a 13-month-old child (Maeda et al. 1989) and an 87-year-old woman with pathologically confirmed tumefactive CNS demyelination (Takeuchi et al. 2008). In the biopsy cohort of Lucchinetti and colleagues, 4% of the cases were younger than 18 years and 4% older than 65 years. A predilection for women may be present, although findings from studies differ. The ratio of women to men in Lucchinetti’s cohort was 1.2:1, suggesting an equal ratio. However, selection bias may have played a role in Lucchinetti’s biopsy-based cohort if clinicians are less likely to suspect inflammatory demyelination in men and, therefore, more likely to biopsy. Two studies with patients enrolled based on radiographic findings of tumefactive demyelinating lesions found 62% to 68% of patients were women (Altintas et al. 2012; Wallner-Blazek et al. 2013).

Differential diagnosis

Making the diagnosis of tumefactive CNS idiopathic inflammatory demyelinating disease can be challenging. In addition to mimicking other diseases, such as brain tumors, tumefactive demyelinating lesions can be seen in other conditions (see Table 1). A detailed history and examination are essential to determine if there is evidence of previous demyelinating relapses. If CNS idiopathic inflammatory demyelinating disease is suspected, empiric therapy with intravenous steroids can be initiated. However, if CNS idiopathic inflammatory demyelinating disease is considered unlikely, steroids should be delayed to avoid obscuring the diagnosis, particularly of CNS lymphoma. Both tumefactive demyelinating disease and CNS lymphoma often demonstrate a radiographic response to steroids, making diagnosis in the absence of biopsy challenging. Additional important considerations are that tumefactive demyelination may be the only finding on biopsy in patients with CNS lymphoma not previously treated with steroids (Yamamoto et al. 2014) and that patients with known multiple sclerosis can develop brain tumors (Burgetova et al. 2008). Clinical and radiographic follow up are key, and repeat biopsy should be considered in cases where the diagnosis remains unclear. The differential diagnosis of tumefactive demyelinating lesions is wide and should be tailored to the clinical and radiological features. Table 1 summarizes the differential diagnosis of CNS idiopathic inflammatory demyelinating disease.
Table 1. Differential Diagnosis of CNS Idiopathic Inflammatory Demyelinating Disease

| Neoplastic                  | Primary: glioma, gliomatosis cerebri, primary CNS lymphoma, intravascular lymphoma.  
|                            | Secondary: metastatic |
| Paraneoplastic             | Brainstem encephalitis |
|                            | Limbic encephalitis, especially GABA(A) receptor encephalitis |
|                            | Progressive spasticity and dementia associated with anti-amphiphysin antibodies |
| Inflammatory               | Sarcoidosis |
|                            | Behçet disease |
|                            | Systemic lupus erythematosus |
|                            | Sjögren syndrome |
|                            | Hashimoto autoimmune encephalopathy |
| Infectious                 | Tuberculosis |
|                            | Progressive multifocal leukoencephalopathy |
|                            | Brain abscess |
|                            | HIV infection with primary or opportunistic infection |
|                            | Cysticercosis |
|                            | Slow virus infections (e.g., Subacute sclerosing panencephalitis) |
|                            | Hepatitis C and HHV-6 |
| Vascular                   | Neurosyphilis |
|                            | Thromboembolic stroke |
|                            | Susac syndrome |
|                            | Vasculitis: primary CNS vasculitis, systemic vasculitis with involvement of the CNS |
|                            | Venous infarction |
|                            | CADASIL |
| Toxic                      | Drugs: methotrexate, 5FU, tacrolimus, TNF-alpha inhibitors, fingolimod, natalizumab |
|                            | Solvents |
|                            | Carbon monoxide |
|                            | Lead |
| Metabolic                  | Mitochondrial cytopathy |
|                            | Vitamin B12 deficiency |
|                            | Central pontine myelinolysis |
|                            | Ketotic hyperglycinemia |
|                            | Adult onset leukodystrophies (e.g., adrenoleukodystrophy) |
| Radiation-induced          | Reversible posterior leukoencephalopathy |
| Other                      | |

Diagnostic workup

Diagnostic work-up should be focused to the specific clinical scenario, with careful attention to the symptoms, signs, and setting. In a patient known to have multiple sclerosis, the diagnosis is more obvious. Table 2 shows a list of possible diagnostic studies that can be considered in a patient suspected of having tumefactive demyelination.

Table 2. Diagnostic Work-up For a Patient with Possible Tumefactive Demyelination

**Clinical or paraclinical evidence for demyelinating disease**

- Careful history and clinical examination for evidence of prior neurologic episodes
- MRI evidence of dissemination if disease: brain and spine
- CT without contrast
- Paraclinical tests supporting demyelinating disease: visual evoked potentials (VEP), brainstem auditory evoked potentials (BAEP), somatosensory evoked potentials (SSEP)
- CSF studies showing oligoclonal bands and elevated IgG index

**Exclusion of alternative diagnoses (selection of tests will depend on the clinical presentation)**

Laboratory studies (selected studies)
• ESR, ANCA
• ANA, ENA panel
• aquaporin-4 antibody
• ACE
• RPR
• Paraneoplastic antibodies
• Pyruvate, lactate
• Very long chain fatty acids
• Genetic studies

Additional CSF studies
• Pyruvate, lactate
• JC virus
• Cytology
• Flow cytometry
• Viral serologies and PCR
• Fungal and acid fast bacteria cultures

Additional studies
• Echocardiography
• Chest CT
• Abdominal and pelvic CT
• PPD skin test
• Brain biopsy

Brain biopsy

Magnetic resonance imaging (MRI). Tumefactive demyelinating lesions tend to be well circumscribed and typically involve the white matter; however, gray matter lesions may also occur. The majority of patients have multifocal lesions; however, typically there is a large dominant lesion (Comi 2004; Lucchinetti et al 2008). The large lesion is often supratentorial and usually involves the frontal or parietal lobes; however, periventricular, juxtacortical, subcortical, or corpus callosal lesions may also be observed. Lesions involving the corpus callosum may have a butterfly configuration. This was observed in 12% of lesions (Lucchinetti et al 2008). In addition, 45% of lesions are associated with mass effect and two thirds are associated with edema, though the degree of mass effect and edema tend to be less than is observed in tumors. Almost all lesions enhance with gadolinium with a variety of enhancement patterns. The most common patterns of enhancement are irregular rim and ring enhancement (either open- or closed-ring); however, other patterns are also observed (Kobayashi et al 2014; Lucchinetti et al 2008). Ring-like lesions are associated with a higher rate of relapse (Wallner-Blazek et al 2013). A pattern of open-ring enhancement with the ring open to the gray matter side can be an important clue to the presence of tumefactive demyelination (Masdeu et al 2000). A radiographic-pathologic correlation study found that MRI patterns of open-ring and irregular rim enhancement were associated with infiltration of macrophages and angiogenesis, whereas a pattern of inhomogeneous enhancement was associated with perivascular lymphocytic cuffing (Kobayashi et al 2014). Lesions with an inflammatory core can show increased intensity on diffusion-weighted sequences with correlated low signal of apparent diffusion coefficient sequences. Diffusion restriction may also be seen peripherally in the lesion. These correlations are similar to prior studies in multiple sclerosis without tumefactive demyelination.

Magnetic resonance spectroscopy. The role of magnetic resonance spectroscopy in the diagnosis of tumefactive demyelination is not clear. A serial study of a demyelinating lesion demonstrated an initial peak in lipid and lactate that normalized after 4 weeks. Reduction in NAA (neuronal marker) correlates with the degree of axonal damage in the lesion (Enzinger et al 2005). However, glioma and acute demyelinating plaques have a similar spectral pattern of increased Cho/Cr and reduction in NAA/Cr (Law et al 2002); therefore, in the absence of a prior history of neurologic symptoms, brain biopsy may be warranted to secure an accurate diagnosis.

Computed tomography. CT may serve as a helpful adjunct to MRI in distinguishing tumefactive demyelinating lesions from tumors. Areas of MRI enhancement are hypodense on unenhanced CT scan significantly more often with tumefactive demyelination (93%) than with tumors (4%), including CNS lymphoma (Kim et al 2009).

Positron emission tomography. A small study of 5 patients using fluoro-deoxyglucose PET showed a marginal increase in metabolism in tumefactive lesions compared to the typical marked increase in metabolism seen in tumors, making PET potentially informative in distinguishing these lesions from neoplasms (Takenaka et al 2011).

CSF studies. No prior study has systematically analyzed CSF profiles in tumefactive demyelination. Furthermore, CSF
studies may be avoided in patients with large tumefactive lesions associated with mass effect due to concerns of raised intracranial pressure. In the study of Lucchinetti and colleagues, 62 of the patients had CSF studies prior to brain biopsy. In 33%, oligoclonal bands were present, and 35% had an elevated IgG synthesis rate (Lucchinetti et al 2008). This study was retrospective, and CSF analyses were done in different laboratories under different conditions; therefore, firm conclusions are difficult to draw. However, it is possible that patients with tumefactive demyelinating lesions have a lower frequency of oligoclonal bands and elevated IgG synthesis rate compared to prototypic multiple sclerosis. This may also be a result of selection bias in a biopsied cohort in that patients with positive oligoclonal bands were perhaps less likely to undergo brain biopsy.

**Brain biopsy.** Brain biopsy has an important role in diagnosis of tumefactive demyelination. It is indicated in situations when the diagnostic work-up is inconclusive and the patient is either severely ill or rapidly declining despite therapy and there is urgent need for a definitive diagnosis.

**Management**

There are no controlled trials of acute management of patients with tumefactive multiple sclerosis. High-dose intravenous corticosteroids (methylprednisolone 1 gram intravenous for 5 days) are typically the first-line management for tumefactive relapses. A subgroup of patients with fulminant attacks of CNS idiopathic inflammatory demyelinating disease refractory to steroid therapy may respond to plasma exchange (Jacquerye et al 1999; Weinshenker 1999; Mao-Draayer et al 2002). For patients who continue to worsen or have relapses of disabling tumefactive lesions, escalation to rituximab or cyclophosphamide, as described in case reports may be appropriate (Fan et al 2012; Sempere et al 2013; Siffrin et al 2014). Aggressive, supportive management in the acute phase, including measures to reduce raised intracranial pressure, is crucial because the anticipated long-term outcome of many of these patients is good. Decompressive surgery may be considered in patients with large demyelinating lesions causing impending herniation (Ragel et al 2006). For those patients diagnosed to have definite multiple sclerosis, treatment using currently approved multiple sclerosis immunomodulatory agents should be considered.

**References cited**


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References especially recommended by the author or editor for general reading.

ICD and OMIM codes

ICD codes

ICD-9:
Multiple sclerosis: 340.0
Neuromyelitis optica: 341.0
Schilder disease: 341.1
Demyelinating disease of the central nervous system unspecified: 341.9

ICD-10:
Multiple sclerosis: G35.
Neuromyelitis optica: G36.0
Schilder disease: G37.0
Balo concentric sclerosis: G37.5
Demyelinating disease of central nervous system, unspecified: G37.9

Profile

Age range of presentation

01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

**Sex preponderance**
female > male, >1:1

**Family history**
family history may be obtained

**Heredity**
heredity may be a factor

**Population groups selectively affected**
none selectively affected

**Occupation groups selectively affected**
none selectively affected

**Differential diagnosis list**
glioma
gliomatosis cerebri
primary CNS lymphoma
intravascular lymphoma
brainstem encephalitis
limbic encephalitis
progressive spasticity and dementia associated with anti-amphiphysin antibodies
sarcoidosis
Behçet disease
systemic lupus erythematosus
Sjögren syndrome
Hashimoto autoimmune encephalopathy
tuberculosis
progressive multifocal leukoencephalopathy
brain abscess
HIV infection with primary or opportunistic infection
cysticercosis
slow virus infections (eg, subacute sclerosing panencephalitis)
neurosyphilis
thromboembolic stroke
Susac syndrome
primary CNS vasculitis
systemic vasculitis with involvement of the CNS
venous infarction
CADASIL
mitochondrial cytopathy
vitamin B12 deficiency
central pontine myelinolysis
ketotic hyperglycinemia
reversible posterior leukoencephalopathy

**Associated disorders**
Balo concentric sclerosis
Fulminant multiple sclerosis
Marburg variant of multiple sclerosis
Multiple sclerosis
Schilder diffuse sclerosis

**Other topics to consider**

Acute disseminated encephalomyelitis
Acute necrotizing hemorrhagic leukoencephalitis
Balo concentric sclerosis
Interferon beta 1b
Multiple sclerosis
Neuromyelitis optica

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