

Tumefactive demyelinating lesions: Characteristics of individual lesions, individual patients, or a unique disease entity?

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Abstract: Whether or not recurrent tumefactive demyelinating lesions are a unique form of CNS demyelinating disease or part of the continuum of multiple sclerosis is a question raised by the case report on which this commentary is based. Detailed review and immunopathologic study of biopsy material may not only confirm or refute a diagnosis of demyelinating disease, but potentially uncover unique features that may assist in understanding pathophysiology and nosology of rare cases with recurrent tumefactive demyelination.

Keywords: Tumefactive, demyelinating disease, multiple sclerosis, brain biopsy

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Inflammatory demyelinating disease of the central nervous system (CNS) is legendary for its heterogeneity. Lesions may present in almost every part of the CNS from the cortex¹ to the conus. They can result in pleotropic manifestations ranging from positive (e.g. irritative symptoms such as paroxysmal dystonia, seizures, neuralgia) to negative (e.g. paralytic or anesthetic) symptoms. Attacks or new lesion frequencies are highly variable and skewed in distribution as consistently demonstrated in clinical trials. Lesions can be well circumscribed or diffuse,² large or small; they can remain solitary over long periods of time³ or may be innumerable. Although most patients have combinations of brain, optic nerve and cord lesions, some, for reasons not understood, have a remarkable predilection to one or two of these regions almost to the exclusion of other regions. Because of this heterogeneity between patients and even within a single patient, there has been an understandable reluctance to accept any subset of characteristics as indicative of a unique disease as long as there is no clear evidence of an underlying systemic disease and no unique pathology suggesting that a patient has other than an idiopathic inflammatory demyelinating disease. Neuromyelitis optica (NMO) was somewhat of a game changer. This subtype of CNS inflammatory disease had typical manifestations of multiple sclerosis (MS) (optic neuritis and myelitis), but was distinguished initially based on a composite of clinical features including its tendency preferentially to target the brain and spinal cord, somewhat unique radiological features and prognosis, and subsequently by careful immunopathological studies, a specific biomarker, and demonstration that the

target antigen of the disease is selectively absent in acute lesions. Does the quest for defining unique and specific diseases end with NMO, or are there other entities within the spectrum of the inflammatory demyelinating diseases of the CNS that we will ultimately characterize as distinct diseases? Recurrent tumefactive demyelination would be a possible candidate.

Miante et al. report the case of a 37-year-old woman with recurrent attacks over seven years of lesions with radiological characteristics suggestive of demyelination, including relatively modest mass effect, resolution and recurrence in a different location.⁴ The symptoms are non-specific, but that is the case with most patients with tumefactive MS, which most commonly targets the supratentorial white matter. The cerebrospinal fluid showed absence of IgG markers of intrathecal IgG synthesis, but these markers are not required for a diagnosis of MS. The biopsy showed perivascular inflammation, foamy macrophages and reactive astrocytes and the absence of malignant cells. These characteristics are consistent with demyelinating disease, although it is the arrangement and intimate admixture of macrophages with reactive astrocytes throughout the lesion that adds significantly to the certainty of the diagnosis of MS; these characteristics are not described in detail in the report. The biopsy rules out lymphoma, although it is worthwhile pointing out that demyelinating disease, confirmed at biopsy, has occasionally been followed by recurrent tumefactive lesions that prove to be lymphoma.⁵ The time course makes this unlikely for this case; however, this entity is something of which

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clinicians should be mindful in this situation. Tumefactive lesions and diffuse ‘acute disseminated encephalomyelitis-like’ lesions may be seen in patients with neuromyelitis optica;⁶ in this context, immunostaining for aquaporin-4 may discriminate these lesions from MS.⁷ This patient had negative results of serological testing for aquaporin-4-specific antibodies, but did not have immunostaining of the brain biopsy. Balo’s concentric sclerosis is a condition that is usually monophasic; its relationship to other demyelinating diseases of the CNS is unclear. Without an adequate biopsy to define rings of alternating demyelination and remyelination, it might not be discriminated from other tumefactive lesions. Occasionally, the characteristics of Balo’s are not apparent until lesions become quite large. The images in this case are not suggestive of Balo’s.

Lucchinetti *et al.* have reported a large series of patients with demyelinating disease >2.0 cm.⁸ While the authors emphasized that the majority of patients developed these lesions in the context of other non-tumefactive demyelinating lesions and that the prognosis was not heavily influenced by the fact that they had developed a tumefactive lesion, they comment:

We did identify a small subset of patients who demonstrated a tendency to develop relapsing demyelinating episodes associated with radiographic evidence of recurrent uni- or multi-focal lesions exceeding 2 cm. These patients had a slightly higher median EDSS [Expanded Disability Status Scale] at last follow-up (3.0 versus 2.5), but no other demographic, clinical or radiographic features that distinguished them from the remainder of the cohort. The reasons why some patients develop recurrent, large multiple sclerosis plaques are unknown.

Altintas *et al.* report that 16.7% of 54 patients with tumefactive demyelination developed recurrent tumefactive lesions over 38 months.⁹ The report by Mianze *et al.* highlights yet another patient with this syndrome.⁴ Perhaps it would be helpful to conduct a detailed examination of pathology and immunopathology of this and other cases to identify not only features that link this syndrome with MS (perivascular demyelination, macrophages admixed with reactive astrocytes), but also characteristics that might set it apart. Combined with a search for other biomarkers unique to this rare subgroup of recurrent tumefactive demyelinating disease might advance the understanding whether this patient is more than an outlier in the continuum of MS and whether she has a unique and thus far poorly characterized inflammatory demyelinating disease.

Conflict of interest

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