

PROBLEM – SOLVING ARTICLE

Tumefactive Multiple Sclerosis Mimicking Neoplasm

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Summary. Acute demyelination may present as a rapidly expanding space-occupying or tumefactive lesion (TDL). Tumefactive demyelinating lesions are misdiagnosed quite frequently and can result in unnecessary and potentially harmful surgical resection, radiation or toxic chemotherapeutic interventions therapy. Systematic literature review from available articles and abstracts in PubMed database was summarized in purpose to describe typical presentation and diagnostically challenging features of TDL. One clinical case report presenting tumor-like lesion of the brain, when the diagnosis of TDL was established, is added as an illustrative material.

Key words: multiple sclerosis, neoplasm, tumefactive, demyelination, lesion.

Abbreviations: ADEM– acute demyelinating encephalomyelitis, CNS– central nervous system, CT– computer tomography, FLAIR– fluid attenuated inversion recovery, MELAS– mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes, MRI–magnetic resonance imaging, MS–multiple sclerosis, PML– progressive multifocal leukoencephalopathy, TDL–tumefactive demyelinating lesion.

INTRODUCTION

Demyelinating diseases, such as multiple sclerosis (MS) and acute demyelinating encephalomyelitis (ADEM) as well, can simulate brain tumor. Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system. It is characterized by multifocal demyelinating lesions in the central nervous system (CNS). The diagnosis is often based on clinical picture and confirmed by specific MRI white matter changes disseminated in space and time.

Clinical Picture of MS. MS is the commonest of the demyelinating diseases, caused by the interaction of multiple genetic and environmental factors. It usually affects young adults and onset of the first clinical episode is between 15 and 50 although cases of developing initial symptoms in child or elderly have been reported. Twice as many women as men suffer of MS. Typically clinical course is relapsing remitting in approximately 85% with usually sub acute, evolving over hours to days, onset and various inter-attack intervals. Patients develop spectrum of symptoms ranging from visual impairment, motor weakness, sensory disturbances, incoordination, cognitive problems, to fatigue and sphincter dysfunction, leading gradually to significant neurological disability. Visual symptoms are among the most common manifestations of demyelinating disease in adults as the initial symptom. An isolated long tract dysfunction as an initial symptom in MS patients is described in 46%, optic neuritis 21%, brainstem dysfunction 9%, combination of symptoms in 24% with complete recovery from the first episode in 83% (4). An epilepsy, aphasia, visual fields defects, sudden cognitive deficit were described rarely (4,11,14).

Radiological Picture of MS. The classic radiological appearance of multiple sclerosis is multiple sharply demarcated plaques found in the white matter, typically in the periventricular areas, septocallosal interface, and

also in the juxtacortical and infratentorial locations, spinal cord during examination by magnetic resonance (MRI). Contrast enhancement occurs in acute rather than chronic lesions (5,14).

The MRI lesions of ADEM are variable, and range from small to large size, with solid or ring enhancement, and predominantly affecting white but also grey matter. In the majority, the lesions are multifocal and asymmetric in distribution (21).

Histological Picture of MS. MS is the chronic inflammatory demyelinating disease of the central nervous system manifested morphologically by inflammation, demyelination, axonal loss and gliosis. The inflammatory lesions are characterized by massive infiltration by a heterogeneous population of components of the immune system, including T cells, B cells, macrophages and microglia, as well as a broad range of cytokines, chemokines, antibodies, complement and other toxic substances. The appearance of such lesions is associated with clinical relapses. Recent detailed immunopathological studies of early, acute lesions revealed profound heterogeneity in the patterns of demyelination and the factors of the immune system involved. During remission, resolution of inflammation is the main factor which leads to clinical improvement of patients (2,13).

Tumefactive Picture of MS. The signs and symptoms related to MS are diverse and white matter abnormalities on MRI are not specific. In a small number of patients with MS brain MRI may be normal and in others it may show diffuse, large or atypical lesions, so as clinical picture is not always classical. A subset of patients with demyelinating disease present with large solitary lesions with prominent edema and mass effect that masquerade as intracranial neoplasm, called demyelinating tumefactive or tumor-like lesion (TDL).

The occurrence of TDL is rare; being estimated at

1–2/1000 cases of multiple sclerosis, but can cause diagnostic difficulties and also implies further management (8).

Definition of TDL. The tumefactive demyelinating lesions are solitary large (greater than 2 cm) lesions with mass-like features and typically showing perilesional edema and/or incomplete ring enhancement in post-gadolinium MR imaging which clinically and radiologically may mimic primary and secondary brain tumor, brain abscess, tuberculous abscess, or other inflammatory disorders(5,10,16).

Clinical Picture of TDL. In the most clinical cases TDL produces clinical symptoms suggestive of a mass lesion. There are some clinical studies characterizing common clinical features of these single episodes in relation to natural course of demyelinating disease with large amount of cases. In most patients with TDLs only single acute clinical attacks have observed, and these generally do not progress to MS. Lucchinetti describes study with 168 patients where presentation of TDL prior to biopsy was a first neurological event in 61%, clinical course was relapsing remitting in 29% and progressive in 4%. The symptoms of clinical presentation are variable, dependant on lesion location and size, typically polysymptomatic, including headache, cognitive abnormalities, mental confusion, subacute progressive motor and/or sensory hemispheric, and cerebellar syndrome. Also aphasia, apraxia, seizures, visual field defects were observed in some cases. Although aphasia is reported in only 1% of multiple sclerosis patients Luchinetti reported that 17% of patients with TDL experienced language disturbances(9). Cognitive dysfunction was a frequent presenting symptom, and included memory dysfunction, mental confusion and disorders of attention in series with more cases analyzed. The seizures as an isolated feature have not been reported, mostly along with hemiparesis or hemianopia. Small number of patients have presented with pediatric or late onset disease (7,15,17).

MR Picture of TDL. Plaques of demyelination of varied size and shape can involve cerebral cortex and subcortical white and grey matter, cerebellar white matter, brain stem and spinal cord. Inflammation, demyelination, and axonal damage characterize MS lesions. Large (2 cm or more) TDL with mass-like features, although not classical, is a recognized finding in MS. The specificity and accuracy for the diagnosis of TDL were significantly increased by the combined modalities of MR imaging and unenhanced CT versus MR imaging alone with the use of at least one of the MR imaging criteria(6).

These lesions have been described to be generally well demarcated, hypodense on CT and of high T2 signal and relatively low signal on T1 signal on MRI. The lesions are notably found in the white matter. Contrast enhancement, mostly of the rim-enhancement type, is more common in the tumefactive variant than in the standard multiple sclerosis plaque. A helpful diagnostic feature is multiplicity of lesions, often with one of the lesions in a typical periventricular or infratentorial location. The relative lack of mass effect or vasogenic edema given the size of the lesions is also often a clue to the diagnosis. Several case reports and series show decreased perfusion with MR imaging (5,6,8,10).

Less typical radiological presentation of a solitary tumefactive demyelinating lesion mimics a neoplasm, and often necessitates a biopsy.

Pathology of TDL. The histopathological characteristics of demyelinating lesions are the preservation of axons by the presence of neurofilaments, the loss of myelin (negative luxol fast blue staining), presence of macrophages (presence of CD68) and an astrocytic proliferation (presence of glial fibrillary acidic protein) which is characteristic but not specific feature of TDL.

It is important to recognize the subtle differences in TDL before sending the material for histopathological investigation so as staining with Luxol fast blue used for confirmation of demyelination is not in routine tumors protocol.

The analysis of 66 patients regarding initial pathological interpretation shows that 19 (29%) were initially misdiagnosed by the referring institution (6 low grade astrocytoma, 2 high grade astrocytoma, 2 lymphoma, 1 vasculitis, 2 progressive multifocal leukoencephalopathy (PML), 1 infarction, 1 oligodendroglioma, 1 mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), and 3 non-diagnostic) (13).

Combination of MS and Tumor in CNS.

A number of cases have been reported when the coexistence of MS and tumor in the CNS was found, however the incidence of malignant neoplasms in the central nervous system of patients with MS was reported to be less frequent than among the general population (20).

Table 1. Case summary of literature review

	Author, Year	N of cases	Clinical picture	MRI/CT findings	Histhology	Other
1.	R.S.Bo-wer et al., 2010 ¹	1	58 M., 3/52 progressive apathy, irritability, confusion	MRI: contrastenhancing, bifrontal lesion crossing the corpus callosum, suggestive of high-grade glioma	Active demyelination. The large number of foamy macrophages and scattered reactive astrocytes in intraoperative smears and hematoxylin-eosin section. Luxol fast blue/periodic acid-Schiff stain demonstrates myelin loss while axons are preserved, as demonstrated by neurofilament stain	Complete recovery after corticosteroids
2.	H.M.Tan et al., 2004 ¹⁹		30 M., subacute onset of right-sided weakness and numbness over 6 week's duration. Neurological examination confirmed a mild right hemiparesis and neuropsychological examination further revealed a clinical tetrad of right-left disorientation, finger agnosia, agraphia and acalculia, constituting Gerstmann's syndrome.	CT scan: hypodense lesion without significant enhancement or mass effect in the superior left parietal subcortical white matter. MRI: 3 cm rounded, well-defined T1 hypointense, T2 hyperintense mass with an incomplete rim of enhancement in the post-contrast scans. No other similar mass lesion or focal signal change. No encroachment into the grey matter. Accompanying oedema was disproportionately mild. Despite its mass-like appearance, the rim enhancement and relative little perilesional oedema were thought to favour a demyelinating lesion over a low grade glioma.	Myelin loss associated with relative preservation of axons. Immunoperoxidase for neurofilaments showed disruption of white matter tracts with relative preservation of neurofibrils whereas Luxol fast blue stain revealed dissolution of myelin in the affected areas. No giant astrocytic changes or oligodendroglial inclusions to suggest PML. Reported to be an astrocytoma on histology. The finally confirmed a demyelinating process.	
3.	M.E.Evan-gelopoulos et al., 2009 ⁷	1	23 M. 3/52 Hx of blurred vision and instability, lasting for 5 days. Left homonymous hemianopsia. Tendon reflexes equally elicited on both sides for upper and lower limbs and a Babinski sign detected on the left side.	MRI: a large lesion at the right parietal lobe extending till the temporal lobe with consequent edema, compressing the posterior aspect of the right ventricle. Few small periventricular lesions in both cerebral hemispheres, cerebellum. No gadolinium enhancement. No spinal lesions.		Received cortisol IV, intravenous methylprednisolone, neurological status gradually improved.
4.	A.Fallah et al., 2010 ⁸	3	50 F. 3/7 Hx of headaches and generalized tonic-clonic seizures	A computed tomography (CT) scan: large right frontal ring enhancing lesion with central necrosis, peritumoral edema and a mild midline shift, most consistent with a malignant brain tumour.	Postoperative pathology: extensive inflammatory cell reaction, both acute and chronic, with focal necrosis predominantly through the white matter areas. Luxol fast blue staining showed an absence of myelin.	

			43 F.,4/7 Hx of left facial droop and left arm weakness, more pronounced distally. Physical examination confirmed these symptoms, including gait ataxia. Medical history included a diagnosis of MS 3 years ago when had transverse myelitis.	MR obtained 3 years earlier showed transverse myelitis from T4 to T7 with unremarkable intracranial pathology. A new CT scan of head showed a large solitary right frontal hypodense white-matter lesion. It was unclear whether this represented a tumefactive multiple sclerotic lesion or a low-grade cystic neoplasm.	The diagnosis of MS was confirmed	
			35 F. New-onset generalized tonic-clonic seizures and headaches	MRI: a large right frontal mass with surrounding edema and a mild midline shift	Lowgrade glioma and reactive gliosis were among the likely differential diagnoses. Permanent section showed a demyelinating lesion.	
5.	M. Van Lan-digham et al, 2010 ²¹	3	Child. 3/52 Hx of ataxia and diplopia	MRI: asymmetric T2/fluid-attenuated inversion recovery hyperintensity within the pons		Improved with corticosteroid therapy
			Child. Sudden onset of coma. Elevated ICP	A large heterogeneously enhancing temporal lobe mass, with extensive edema	cortical biopsies revealed ADEM	Improved with corticosteroid therapy
			Child. 4/12 Hx of increasing lethargy and clumsiness in all extremities	Multiple small brain lesions with occasional ring enhancement	cortical biopsies revealed ADEM	Improved with corticosteroid therapy
6.	MK Sinha, 2010 ¹⁷	2	23 F. Recurrent right focal tonic-clonic seizures with secondary generalization of three-month duration. Normal neurological examination	A rounded well-defined lobulated T1 hypointense mass measuring about 5 cm in left fronto-parietal region, which was hyperintense in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, with a mild incomplete rim of enhancement in the post-contrast scans. Reported to be an astrocytoma elsewhere. Repeat neuroimaging demonstrated an increase in the mass effect and edema. No encroachment into the adjacent grey matter. Though the mass was large in size, the surrounding edema and mass effect were disproportionately mild		Rapid clinical improvement after intravenous methylprednisolone

		48 M. Right homonymous hemianopia 1/12, difficulties reading	An irregular well-defined mass measuring 4.8 cm in the left parieto-temporal region involving splenium of corpus callosum with mass effect on adjacent structures. The lesion was hyperintense on T2-weighted and FLAIR images with incomplete rim of enhancement in the post-contrast images. Initially, a diagnosis- brain tumor	Perivascular lymphocytic infiltrate and aggregates of foam cells in white matter with relatively uninvolved grey matter, suggestive of tumefactive demyelinating lesion	Rapid clinical improvement after intravenous methylprednisolone
7.	V.Puri et al., 2004 ¹⁵	13 F. Episodes of hemiplegia and hemianopia involving opposite sides, each time associated with seizures.	MR: a giant demyelinating, peripherally enhancing lesion with mass effect. MR spectroscopy (MRS) was indistinguishable from a tumor	Histopathology revealed an acute demyelinating lesion with no evidence of tumor	Partial clinical recovery after corticosteroids
8.	S.Yama-shita et al. 2006 ²²	27 F. Clumsiness of right hand followed by progressive right hemiparesis within several days. Physical examination: severe weakness and hyperreflexia in the right upper and lower extremities	MR: a large ring-enhancing lesion with surrounding edema and mass effect in the left frontal lobe	A macrophage-rich lesion with gliosis of reactive astrocytes. Klüver-Barrera stain: total myelin loss. Bodian stain: relative axonal preservation, consistent with demyelinating disease. No evidence of cell neoplasia.	Recovery after corticosteroids
9.	S.Navarro et al, 2005 ¹²	31 F. 48/24 Hx of a progressive aphasia and a sensory parietal syndrome	A hyperintense in T2 lesion 3.6 cm in diameter with perilesional edema and minimal gadolinium uptake, along with other images that revealed increased signal intensity in the periventricular subcortical white matter on the right-hand side and in the left-hand frontal subcortical region. Was not possible to distinguish between a demyelinating disease and a high grade glioma.	demyelinating pseudotumoral lesion	
10.	T.Takeuchi et al., 2008 ¹⁸	87 F. 2/52 Hx of right-sided progressive hemiparesis, slurred speech. Previous Hx of uterine cancer 35 yrs ago.	Tumor-like lesion with little mass effect and edema		
11.	MA.Taricco et al., 2002 ²⁰	31 M. Rapid onset of right side weakness and loss of vision. A diagnosis of MS confirmed by CSF analysis and MRI. Nine years later developed progressive tetraparesis, leading initially to suspicion of illness relapse and a demyelinating plaque in the spinal cord	MR: a large spinal cord lesion with isointense signal on T1 weighed MR between the second and seventh cervical vertebrae, with a cystic nodule at the C3 level. Brain MR: T2 weighed MR exhibited small lesions suggestive of demyelination plaques	Revealed an ependimoma	

Case report as an illustrative example from Latvian MS data base:

28 years old female presented with acute onset and progressive right sided leg weakness and pain. In 2/52 period lower paraparesis and urine frequency developed. MR imaging scans showed large rounded T2 and FLAIR hyperintense tumor-like lesion in the left frontal lobe with incomplete ring enhancement and mild perifocal edema, and one small enhancing periventricular lesion (Fig.1). Nonenhancing hyperintense lesions in both optic nerves and two T2 hyperintense enhancing lesions with edema in the cervical and thoracic spinal cord were found as well.

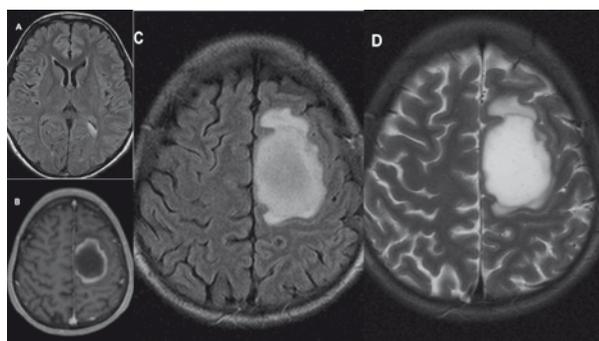


Fig. 1. Representative samples of TDL in MR imaging: A.FLAIR axial, B.T1-weighted axial post contrast, C.FLAIR axial, D.T2-weighted axial

The most likely working diagnosis was neoplasm. Patient underwent stereotactic surgery and histology results from brain biopsy reported features typically to demyelination. Patient was sent for further investigations to MS centre. Detailed retrospective clinical history clarified previous optic neuritis. No other relevant symptoms related to possible demyelinating disease were found. Diagnosis of MS was established. The full clinical recovery after intravenous prednisolone course was observed.

CONCLUSIONS

There is a high importance of obtaining a detailed neurological history in all adult patients with presenting tumor-like lesions. The particular attention to prior episodes of transient neurological dysfunction for which the patient may not have sought medical attention may be very helpful specifying features more characteristic to demyelinating disease.

In some cases when a brain biopsy may be necessary, it is important for clinician to have a consideration of a demyelinating lesion so as standard tumor histopathological protocols do not include staining with Luxol fast blue used for detecting myelination.

However, a pre-existing diagnosis of multiple sclerosis does not exclude the possibility of a coexisting tumor, or other additional pathology.

Conflict of interest: None

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