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Progression of tumefactive demyelinating lesion in a child demonstrated with MRI

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ABSTRACT

Tumefactive demyelinating lesions (TDLs) are atypical presentations of various demyelinating diseases. They can mimic brain tumors in their clinical and radiological features and usually respond favorably to corticosteroid therapy. We report a case of a 17-year-old girl with a single TDL suddenly increasing in size even under steroid therapy. She underwent very strict follow-up examinations with conventional magnetic resonance and diffusion-weighted imaging, perfusion-weighted imaging, proton-magnetic resonance spectroscopy. The behavior of the lesion during the different follow-up sessions posed a diagnostic challenge as it expanded its size during the final examination, in stark contrast to what we forecast. Diagnosis of TDL was initially hypothesized, but the aggressive behavior of the lesion required biopsy.

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Introduction

Tumefactive demyelinating lesions (TDLs), also named “demyelinating pseudotumors,” are rare subsets of demyelinating manifestations. The exact pathogenesis of TDLs is not clearly understood [1–4]. They can occur in isolation, as part of multiple sclerosis (MS), acute disseminated encephalomyelitis

(ADEM), or neuromyelitis optica spectrum disorder (NMOSD) [5]. MS accounts for most cases of TDLs [3,6]. TDLs might be single or multiple and may appear simultaneously at onset or sequentially. When they appear as single mass lesion, they might be mistaken for brain tumors [1–3]. Clinical manifestations vary from asymptomatic lesions to headache, cognitive abnormalities, mental confusion, impaired consciousness, aphasia, apraxia, cerebellar symptoms, visual field defects, or

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seizures [1,2,4]. Usually, there is no previous history of similar episodes and they may appear as the first demyelinating event in the course of MS [4,7,8]. Magnetic resonance imaging (MRI) is a critical tool in the diagnosis of this entity, although the overlapping similarities between the imaging appearances of TDLs with the imaging appearances of brain neoplasms, such as primary central nervous system (CNS) lymphoma and high-grade glioma, often leads to surgical biopsy [1,2,9,10]. In general, TDLs respond well to steroids, reducing in size on follow-up imaging [6,11,12]. However, in many cases, the diagnosis remains uncertain and, therefore, biopsy is indicated [9–12].

Subject and methods

A 17-year-old Caucasian girl came to the emergency room of our hospital with vertigo, aphasia, and a difficulty in moving her right leg, first experienced 5 days earlier. A neurologic examination revealed right brachiorural hemiparesis (MRC2/5), reduction of right tendon reflexes, and hypoesthesia of the right lower limb. She had no medical history and mentioned a tetanus vaccine 3 months earlier. Brain computed tomography showed a large hypodense lesion, without mass effect, in the left periventricular and paratrigoal zone. A brain MRI was immediately performed, which showed a left large periventricular and paratrigoal area of signal abnormality, hypointense on T1-weighted images, hyperintense on T2-weighted and fluid-attenuated inversion recovery images, measuring 40 × 50 × 30mm, with minimal perifocal edema and no mass effect (Fig. 1A). Diffusion-weighted imaging (DWI) revealed areas of restricted diffusion within the lesion, with low apparent diffusion coefficient (ADC) values (Fig. 1B and C). After Gd-contrast administration, no enhancement was seen; only on a very delayed scan (after 15 minutes) a faint enhancement could be appreciated (Fig. 1D). Dynamic susceptibility contrast and perfusion-weighted imaging (PWI) revealed an augmented relative cerebral blood volume (rCBV) (Fig. 2A and B), relative cerebral blood flow (rCBF), and reduction of mean transit time. Proton multivoxel magnetic spectroscopy (PMRS) showed an increase in Gln/Cr, GSH/Cr, a peak of lactate, and reduction of ml/Cr (Fig. 2C). Suspecting a demyelinating lesion, the study was extended to the spine, which revealed a small, peripheral non-enhancing, medullary lesion at D5 level. Based on these imaging features, a diagnosis of TDL was carried out. Low-grade glioma was considered a less probable differential diagnosis. A screen for against aquaporin 4-IG, GAD-SSA-SSB, N-methyl-d-aspartate (NMDA) myelin oligodendrocyte glycoprotein-IG, anti-nuclear, anti-neutrophil cytoplasmic as well as anti-cardiolipin antibodies, angiotensin-converting enzyme, lysozyme, and C-reactive protein yielded negative results or normal values. An infection screen, including human immunodeficiency viruses, treponemal, and Borrelia serology tests yielded negative results or results within the normal ranges. The cerebrospinal fluid (CSF) was clear and showed normal biochemistry and cell counts. Fluorescence-activated cell-sorting analysis revealed no atypical cells. Oligoclonal bands were positively restricted to CSF. Somatosensory and visually evoked potentials were normal. Under the presumptive diagnosis of TDL, treatment with methylprednisolone (1000 mg/d,

intravenously) was started, which prompted a clinical response. After 1 week of therapy, a follow-up MRI revealed consistent, unchanged dimension of the lesion, although the values of the ADC seemed widely increased and there was no enhancement (even 1 hour after injection). PWI continued to show an increase in rCBV and rCBF but on a less significant scale than the previous examination. PMRS confirmed higher Gln/Cr, GSH/Cr, Cho/Cr with the reduction of ml/Cr and N-Acetylaspartate/Cr. The results of the neurologic examination improved (brachiorural hemiparesis MRC 4/5), and oral prednisone therapy was continued (50 mg/d for 2 weeks, after 25 mg/d), although it must be noted the MRI performed 6 weeks later showed an unexpected progression of the lesion. As a matter of fact, it had increased in size, extending to the parietal and in the temporal lobe, with mass effect and midline shift. Also, the perilesional edema was extended (Fig. 3A). The lesion showed necrotic components and intense, inhomogeneous enhancement (Fig. 3B). ADC values (Fig. 3C) were high, and PWI showed a reduction of perfusion parameters (Fig. 3D). PMRS confirmed the spectral profile of the previous examinations. (All results are reported in Table 1.) At this point, a biopsy was necessary to make a certain diagnosis because a neoplastic nature of the lesion could not be excluded. Histology showed demyelination, extensive macrophage invasion (CD68+), gliosis, and necrosis. The patient is currently under interferon β 1a (44 μ g 3 times for week). The last follow-up MRI showed no new lesions, and the neurological examination is stable.

Discussion

A TDL is defined on MRI by the presence of large brain mass (≥ 2.0 cm in diameter) with edema and mass effect. The lesion more commonly involves the supratentorial compartment, mainly white matter tracts, in a periventricular distribution [1,2,4]. When there are multiple periventricular white matter lesions involving the major white matter tracts, such as corpus callosum or brachium pontis, associated to the presence of spinal cord lesions, the diagnosis of MS is straightforward [13]. However, a solitary, inhomogeneous lesion can pose a considerable diagnostic challenge. The use of a contrast agent is of limited benefit because any pathologic process associated with disruption of the blood-brain barrier can result in enhancement on MRI [12–17]. Primary and metastatic tumors often manifest as rounded, well-circumscribed, nodular ring enhancement lesions with different sizes, surrounded by a variable amount of vasogenic edema [16]. In comparison with tumors, TDLs have lesser mass effect and edema, relating to plaque size with incomplete or open ring enhancement [12] but the conventional MRI appearance cannot be specific. Advanced MRI techniques, such as DWI, PWI, PMRS, may improve the diagnosis of solitary brain lesions [11,12]. In this study, we have observed and analyzed the evolution of a TDL, under corticosteroid therapy, with conventional and advanced MRI techniques. In the case analyzed, the initial MRI showed areas of restricted diffusion, with decreased ADC in the left paratrigoal and periventricular areas, without the classical peripheral distribution [12]. Several recent case studies have reported reduced ADC values in acute demyelinating lesions

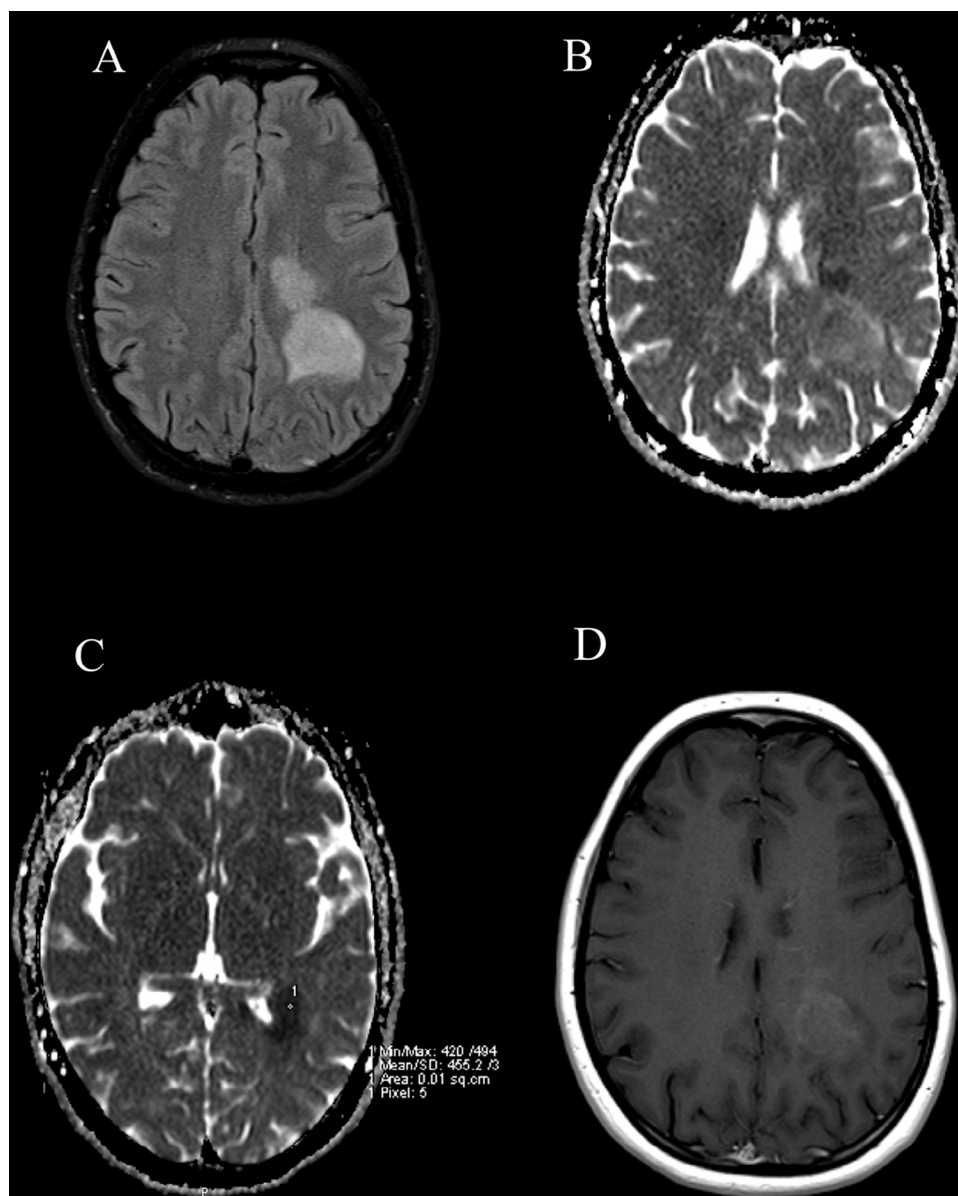


Fig. 1 – MRI study at baseline: Hyperintense alteration signal in the periventricular area on FLAIR image (A); ADC map showed a periventricular (B) and (C) paratrigonal areas with low ADC; faint enhancement appreciated after contrast administration (D).

and have emphasized their stroke-like ADC appearance [15,17–19]. Thus, in the early phase, those findings may reflect pathophysiological mechanisms, such as cytotoxic edema or localized hypercellularity and this is in keeping with the DWI lesion behavior during the follow-up. In fact, afterward, we saw a progressive elevation in ADC values, probably as a consequence of steroid therapy, inducing a decrease in inflammation and transition from the acute to the subacute phase. The ADC evolution reflects pathologic substrates like inflammatory vasogenic edema, axonal loss, and demyelination. The steroid-induced pathophysiological changes may be the key to understand the perfusion parameters behavior, too. In fact, in the first study, we found increased rCBV and rCBF ratios, probably because of the vasodilatation of the inflammatory very acute phase [12,15,17]. At this stage, the lesion was

non-enhancing, because no blood-brain barrier damage had occurred, whereas the faint enhancement found in a very delayed phase is most likely a venous engorgement [19].

Previous studies [11,13,20] reported that PWI might help in the differential diagnosis of brain tumors and TDLs because the latter usually displays lower rCBV values. This did not happen in our case as we observed high rCBV and rCBF values on the first examination (probably because of the high inflammatory activity). These parameters gradually decreased during the following weeks, an unexpected trend in a glioma under steroid therapy, perfectly plausible in an inflammatory setting [13,20].

An acute giant demyelinating plaque could mimic a glioma on PMRS, too. In fact, acute demyelinating plaque may show elevated Cho and decreased NAA signal [21–23]. However, the

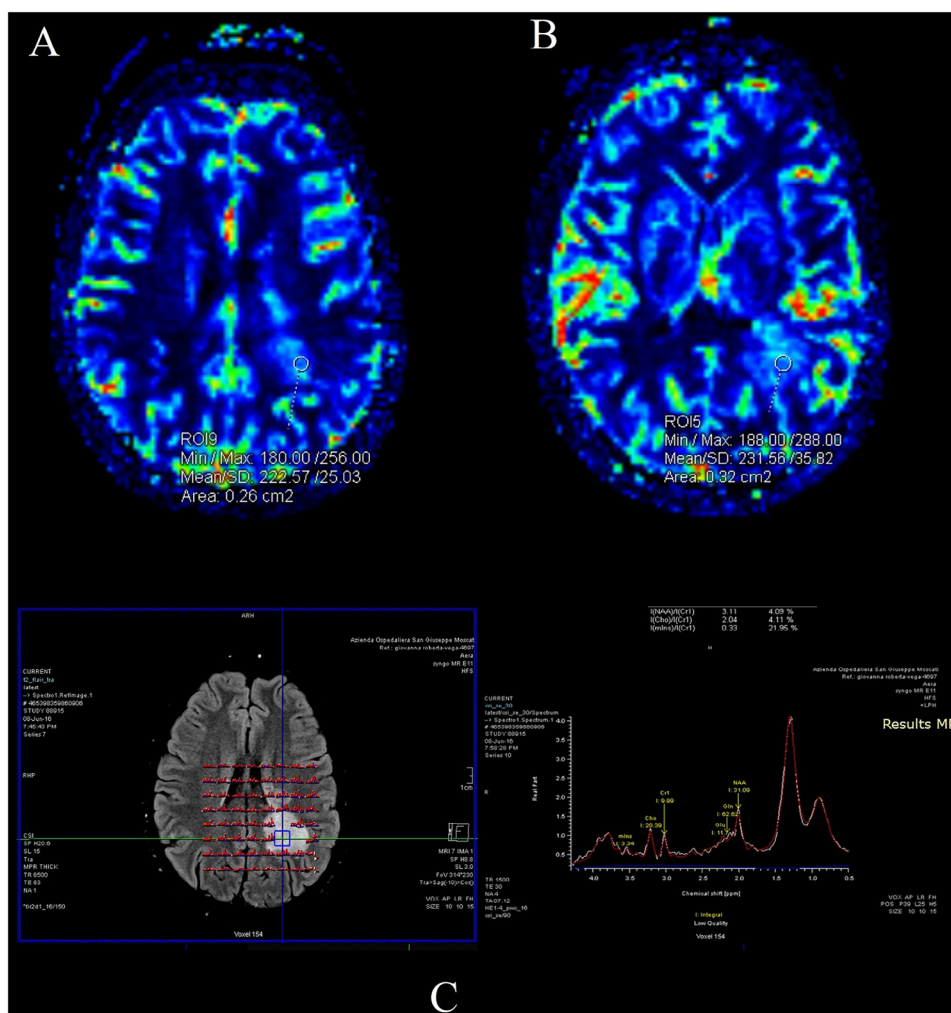


Fig. 2 – CBV map showed increased relative cerebral blood volume (A,B); multivoxel spectroscopy (C) study with higher GLN/Cr, GSH/Cr ratios, peak of lactate, reduction of ml/Cr.

cell breakdown of both glial and neural elements occurring in a demyelinating plaque leads to high concentration of glutamate and glutamine, which are not seen in gliomas [21,23]. This was observed in the case. Recently, a few works [24,25] have underlined the role of glutathione (GSH) as an important indicator of oxidative status in a human brain, and oxidative stress has been strongly suggested to play an important role in the early, active phase of MS. The trend of GSH values in TDLs has not been yet studied; however, in our case we found an increase in GSH/Cr ratio compared with the normal appearing white matter, and this ratio further increased in follow-up studies.

In this case, the restriction of oligoclonal bands to CSF and the presence of a small, peripheral spinal lesion indicated an MS-like demyelinating process. In neuromyelitis optica (NMO), spinal lesions are more often extensive than those of MS, and they often have central cord involvement. Optic nerve lesions have a tendency to be more extensive in length. In our case, optic nerve sheaths did not show any impairment [5]. Although the lack of prompt response to the corticosteroid therapy could not exclude atypical demyelinating

syndromes such as Neuromyelitis Optica Spectrum Disorder, these entities are usually positive for a serum marker against aquaporin 4-IgG and are less likely to have CSF-restricted oligoclonal bands [5,26]. Important autoantigens are also antibodies against myelin oligodendrocyte glycoprotein-IgG that are produced by the oligodendrocytes and are recognized in atypical demyelinating lesions such as in NMSOD, ADEM, and in a selected subgroup of adult type II MS (antibody-mediated demyelination) [5,26]. Other autoantigens are anti-NMDA-R autoantibodies that are seen in autoimmune anti-NMDA-R encephalitis [5,27]. Very few patients with anti-NMDA-R encephalitis can have concurrent, or later-developed, TDL [5]. All of these autoantibodies were absent in our patient. Not all patients with a TDL require stereotactic brain biopsy [28]. Despite the positive analysis of CSF for oligoclonal band (positive in up to 30% of cases of TDLs in MS), the absence of multiple lesions on MRI at the time of the biopsy (present in up to 70% of patients with MS), and the suspicion of a coexistent tumor [12], the clinicians decided to perform a stereotactic biopsy [28]. It has been reported that lymphoma and malignant neoplasm can be inside TDLs and can also coexist [9,12,28].

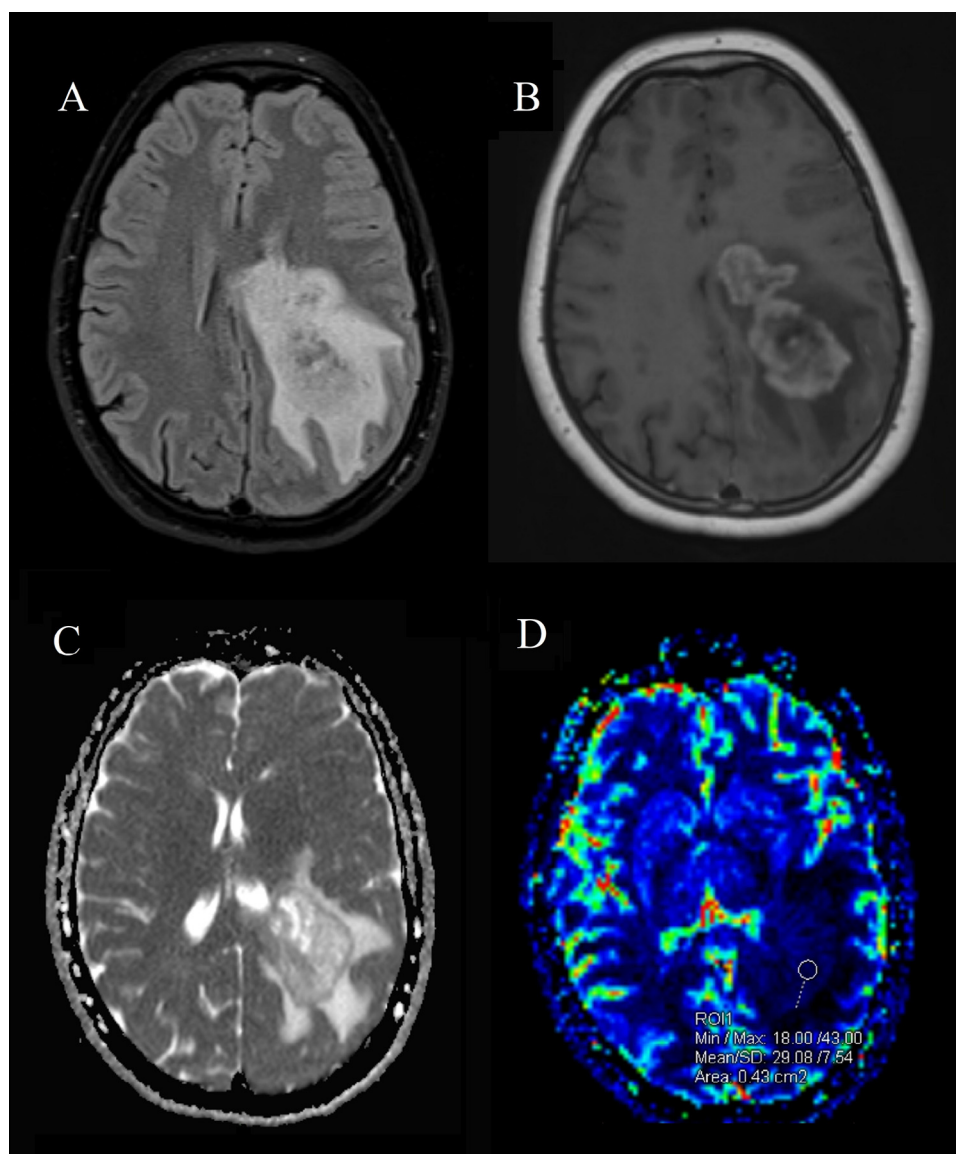


Fig. 3 – FLAIR image showed lesion progression with increased edema and mass effect (A); The lesion appeared with diffuse and inhomogeneous enhancement (B) and high value of ADC (C); CBV map with areas of decreased rCBV ratio (D).

A fluoro-deoxyglucose positron emission tomography (FDG-PET) scan might be useful in the investigation of a TDL [28]; however, because of the patient's young age, we decided not to perform this kind of study.

The histopathological examination revealed the absence of Creutzfeldt-Peters cells. These cells are frequently but not universally found in active MS lesions, and they were absent in NMO/NMOSD biopsies [5,29]. Creutzfeldt-Peters cells in MS may reflect astrocyte proliferation, whereas their absence in NMO may reflect astrocyte death or their endangerment [29].

In our case, the presence of a brain-enhancing lesion with a small un-enhancing spinal lesion indicated a clinically isolated syndrome and it can be the first manifestation of MS. Treatment recommendations advise that patients be treated as early as possible after a first clinical demyelinating event. It has been reported that in this case, early treatment with

interferon β could reduce the risk of developing MS and has beneficial effects on patients [30].

The pathogenesis of TDLs may be associated with infections or vaccinations [2,4]. In the study of Qui et al [2], 1 case of TDLs was reported, which was associated with a history of hepatitis B vaccination. In our report, the history of tetanus vaccination might be correlated to TDLs although there is a lack of previous reports supporting this hypothesis. Previous vaccinations are more reported in ADEM. ADEM is an acute multifocal monophasic inflammatory demyelinating disorder of the brain and spinal cord, which should not progress beyond 3 months [4]. In the present case, we excluded this entity from the differential diagnosis because the characteristic MRI features of ADEM include multifocal and diffuse hyperintense lesions, in the gray and white matter of the brain and spinal cord, on T2-weighted and fluid-attenuated inversion recovery images and no gadolinium enhancement [4,31,32].

Table 1 – Main results of each MR examination.

	Gd enhancement	ADC VALUES (mm ² /s)	PWI	PMRS		
				Ratio	P	N
T0	Faint	0.57071 × 10 ⁻³	rCBV 4.7 rCBF 5 rMTT 0.3	NAA/Cr	3.28	2.8
				Cho/Cr	1.86	1.18
				mI/Cr	0.33	1.33
				Gln/Cr	6.27	2.04
				GSH/Cr	2.28	1.43
				Lac	H	A
1 W	Absent	0.69793 × 10 ⁻³	rCBV 2.5 rCBF 4 rMTT 0.9	NAA/Cr	1.77	2.8
				Cho/Cr	2.92	1.16
				mI/Cr	1.01	1.16
				Gln/Cr	3.71	2.11
				GSH/Cr	4.0	1.23
				Lac	H	A
6 W	Inhomogeneous	0.150025 × 10 ⁻³	rCBV 1.02 rCBF 1.3 rMTT 0.0	Naa/Cr	3.04	2.33
				Cho/cr	8.38	1.22
				mI/Cr	2.38	1.36
				Gln/cr	6.15	1.06
				GSH/cr	4.16	0.9
				Lac	H	A

The first row shows contrast behavior (faint enhancement; absent; irregular), the second ADC values, the third PWI values, and the fourth PMRS data (P = pathologic side, N = normal side, H = high, A = absent).

The columns report the time of follow-up studies (T0 first control; 1 W = after a week of therapy; 6 W = after 6 weeks of therapy).

Conclusions

Currently, there is not a single and absolute parameter or threshold that might define the diagnosis. Advanced MRI can be considered a valuable tool for defining “pseudotumoral lesions” finding. In this case, the presence of glutamate and also of glutathione addressed the diagnosis more for a demyelinating process than for a tumoral lesion. Nevertheless, recent reports underline the needs for prudent interpretation of spectroscopic findings [12,21] because they may not allow a reliable differentiation of TDLs from brain tumors. So, the synthesis of conventional and advanced MRI studies together with the careful evaluation of follow-up variations should be considered in a single case to suggest the best diagnosis. A systematic study of TDLs with advanced MRI techniques is necessary to standardize their behavior to reduce the necessity of brain biopsy.

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