Clinical Case Report

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A challenging diagnosis of late-onset tumefactive multiple sclerosis associated to cervicodorsal syringomyelia: doubtful CT, MRI, and bioptic findings

Case report and literature review

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Abstract

Background: Tumefactive multiple sclerosis (MS) is an unusual variant of demyelinating disease characterized by lesions with pseudotumoral appearance on radiological imaging mimicking other space-occupying lesions, such as neoplasms, infections, and infarction. Especially when the patient's medical history is incompatible with MS, the differential diagnosis between these lesions constitutes a diagnostic challenge often requiring histological investigation. An older age at onset makes distinguishing tumefactive demyelinating lesion (TDL) from tumors even more challenging.

Methods: We report a case of brain TDL as the initial manifestation of late-onset MS associated with cervico-dorsal syringomyelia. A 66-year-old Caucasian woman with a 15-day history headache was referred to our hospital because of the acute onset of paraphasia. She suffered from noncommunicating syringomyelia associated to basilar impression and she reported a 10-year history of burning dysesthesia of the left side of the chest extended to the internipple line level.

Results: Computed tomography (CT) and magnetic resonance imaging (MRI) examinations revealed a left frontal lesion with features suspicious for a tumor. Given the degree of overlap with other pathologic processes, CT and MRI findings failed to provide an unambiguous diagnosis; furthermore, because of the negative cerebrospinal fluid analysis for oligoclonal bands, the absence of other lesions, and the heightened suspicion of neoplasia, the clinicians opted to perform a stereotactic biopsy. Brain specimen analysis did not exclude the possibility of perilesional reactive gliosis and the patient, receiving anitiedemigen therapy, was monthly followed up. In the meanwhile, the second histological opinion of the brain specimen described the absence of pleomorphic glial cells indicating a tumor. These findings were interpreted as destructive inflammatory demyelinating disease and according to the evolution of MRI lesion burden, MS was diagnosed.

Conclusion: TDL still remains a problematic entity clinically, radiologically, and sometimes even pathologically. A staged follow-up is necessary, and in our case, it revealed to be the most important attitude to define the nature of the lesion, confirming the classic MS diagnostic criteria of disseminate lesions in time and space. We discuss our findings according to the recent literature.

Abbreviations: CNS = central nervous system, CSF = cerebrospinal fluid, CT = computed tomography, Cy = cyclophosphamide, FLAIR = fluid attenuation inversion recovery, MET-PET = ^{1}C-methionine PET, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, MS = multiple sclerosis, NCS = noncommunicating syringomyelia, TDL = tumefactive demyelinating lesion, TMS = tumefactive multiple sclerosis.

Keywords: brain biopsy, magnetic resonance spectroscopy, multiple sclerosis, syringomyelia, tumefactive demyelinating lesion, tumefactive multiple sclerosis

Editor: Song Liu.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2016) 95:36(e4585)

Received: 8 November 2015 / Received in final form: 8 March 2016 / Accepted: 21 July 2016

http://dx.doi.org/10.1097/MD.0000000000004585

1. Introduction

Tumefactive multiple sclerosis (TMS) is an unusual variant of demyelinating disease characterized by lesions with pseudotumoral appearance on radiological imaging.[1,2] Its prevalence is reported to be 1 to 2 cases per 1000 cases of multiple sclerosis (MS), more often in patients aged 10 to 30 years, without a clear predominance of gender.[2–4] Imaging findings include a single intracranial tumefactive demyelinating lesions (TDL) greater than 2 cm in diameter with associated mass effect, perilesional edema, and ring enhancement after contrast medium administration.[2,5–7] TDL can be observed during a relapse of a known SM or may represent the acute initial manifestation of a presumed inflammatory demyelinating disease without history of an earlier demyelinating event.[7] The radiographic features of large TDL often mimic those of other space-occupying lesions such as neoplasms, infections, and infarction.[1,2,4–6,8] Moreover, the clinical features of TMS and brain tumors, such as malignant glioma, metastasis, or lymphoma, are similar. Especially when the patient's medical history is incompatible with MS, the differential diagnosis between these lesions constitutes a diagnostic challenge for both the clinicians and the radiologists and diagnostic solution may require histological investigation. An older age at onset makes distinguishing TDL from tumors even more challenging.[1–6,9]

Herein we report a case of brain TDL as the initial manifestation of late-onset MS with confounding clinical history, imaging findings, and histological features that made MS diagnosis doubtful until magnetic resonance imaging (MRI) showed typical multiple lesions disseminated in time and space.

2. Case report

A 66-year-old Caucasian woman with a 15-day history of left occipital pain radiating to the frontal region was referred to our hospital because of the acute onset of paraphasia. She suffered from noncommunicating syringomyelia (NCS) associated to basilar impression and she reported a 10-year history of burning dysesthesia of the left side of the chest extended to the internipple line level. On admission, neurological examination was normal except for a deficit of the right inferior VII cranial nerve, slight hypopallesthesia (upper limbs: 7/8, right lower limb: 7/8 and left lower limb: 6/8), and accentuated osteotendinous reflex to the 4 limbs (more evident were the left upper limb and the right knee jerk reflexes). ESR and D-dimer were elevated (respectively 25 mm/h and 1.54 mg/L), whereas the other routine blood chemistries were normal. Electroencephalogram (EEG), somatosensory evoked potentials (SSEPs), and visual evoked potentials (VEPs) were normal. Head computed tomography (CT) scan—without contrast medium administration—showed a large (axial diameters: 57 × 65 mm) hypodense lesion in the left frontal region involving both cortical and subcortical areas with peripheral finger-like edges, exerting mass effect with midline shift, compression of the left ventricular frontal horn and of the surrounding subarachnoid spaces (Fig. 1A). According to these CT findings, the patient was hospitalized and underwent brain MRI study. The lesion in the left frontal lobe appeared hyperintense on T2-weighted (w) and fluid attenuation inversion recovery (FLAIR)-w images with an incomplete hypointense peripheral rim (Fig. 1B and C), while it was hypointense on T1-w images. The lesion also involved the corpus callosum and exercised a mass effect on the ventricular system that was displaced toward the opposite side. Diffusion-w images (DWI) showed restriction of water diffusivity with reduced apparent diffusion coefficient (ADC) values in the peripheral areas (Figs. 1D) of the lesion which presented a mild peripheral contrast enhancement more appreciable in the posterior–inferior side (Fig. 1E). MRI exam also confirmed the presence of cervicodorsal syringomyelia and excluded other brain and spinal cord lesions (Fig. 1F). Cerebrospinal fluid (CSF) analysis showed 1 nucleate cell, normal glucose (59 mg/dL) and protein (31 mg/dL) levels, normal Link index, and the absence of oligoclonal band. CSF virological analysis was negative for viral infections (EBV, CMV, HS1–2, VZV, JCV). Blood tumor markers (CEA, AFP, CA 15–3, CA 125, CA 19–9, CA 72–4, CYFRA 21–1), inflammatory and rheumatologic tests were negative. Because these findings could not exclude malignancy, the patient was moved to neurosurgical department in order to perform a stereotactic biopsy of the lesion. During hospitalization, the patient started antiedemigen therapy consisting in intramuscular dexamethasone (4 mg × 2/ day) and intravenous mannitol (150 cc × 3/day). She was discharged on a tapering dose of oral prednisone. The histological analysis of the sample (1 cm) revealed a hypercellular white matter lesion with predominant macrophages (CD 68+) mixed with hypertrophic astrocytes (GFAP+) presenting moderate atypic nuclei and rare lymphocytes (LCA+ and CD3+). The findings were related more likely to a reactive condition than a neoplastic one, but did not exclude the possibility of perilesional reactive gliosis. One month after the biopsy, the patient underwent MRI examination with spectroscopy study, which revealed reduction of sizes and mass effect of the frontal lesion associated to a reduction of *N*-acetylaspartate (NAA)/creatine (Cr) ratio with a slight increase of choline (Cho)/Cr ratio (Fig. 2A and B). Moreover, the left frontal lesion did not show contrast enhancement any more (Fig. 2C). At further monthly follow-up MRI studies, a new enhancing lesion appeared in the right temporal lobe and other lesions were appreciable in both frontal lobes and in periventricular regions similar to typical MS plaques (Fig. 3A–D). In the meanwhile, the second histological opinion of the brain specimen described an increased cell number, numerous macrophages infiltrating the lesion, loss of myelin, and reactive astrocytes with swollen cell bodies. No major T-cell infiltrates were seen and pleomorphic glial cells indicated that tumors were not present (Fig. 4A and B). These findings were interpreted as destructive inflammatory demyelinating disease and according to the evolution of MRI lesion burden, MS was the most reliable diagnosis. Then, the patient started immunosuppressive therapy with cyclophosphamide (Cy) (800 mg/m^2; 1500 mg) and after 1-year of follow-up she had no side effects and her clinical condition remained stable.

3. Discussion

Late onset of MS is very rare with a reported frequency of 0.6% to 0.75% of MS cases diagnosed past age 60 years.[3] In our case, the demyelinating disease presented as late-onset TMS with an isolated TDL. Clinical presentations of TMS are variable and include headache, cognitive abnormalities, mental confusion, aphasia, apraxia and/or seizures, according to lesion location and size.[1,3] These symptoms cannot be differentiated from those of a brain tumor especially in the absence of previous demyelinating episodes as in our patient, whose symptoms were associated with a history of dysesthetic pain related to her known cervicodorsal NCS.[1,3,10] Unlike our case, NCS has been described as an incidental finding of spinal pathology in patients who undergo MRI not for clinically suspected syrinx but spinal cord involvement of MS.[11,12] NCS could partially justify some

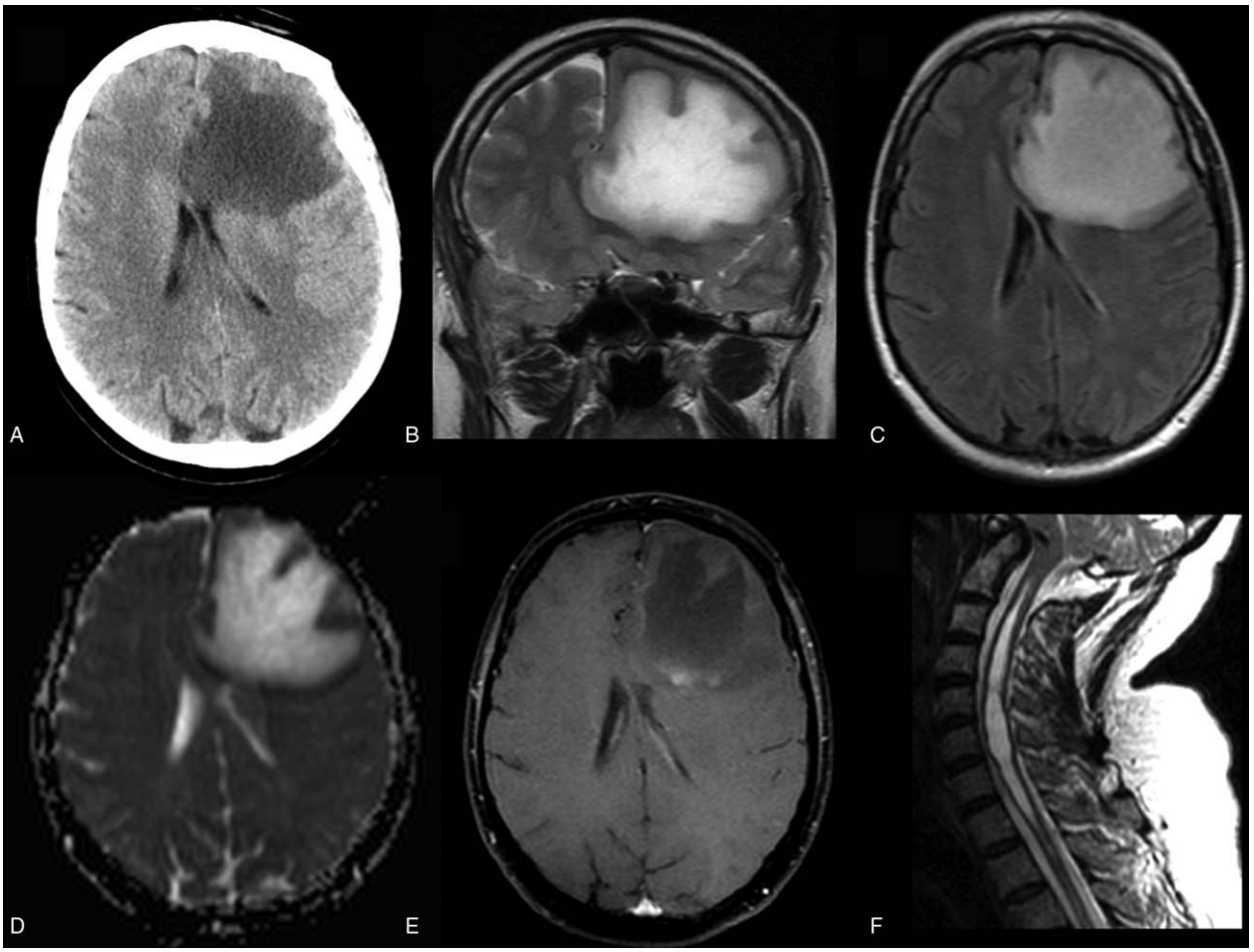

Figure 1. (A) Unenhanced CT axial image: hypodense tumefactive lesion in the left frontal lobe with mass effect. (B) Coronal T2-w and (C) axial FLAIR MRI images: the hyperintense lesion has an incomplete peripheral hypointense rim. (D) ADC map: peripheral areas of diffusion restriction appearing hypointese. (E) Postcontrast axial T1-w MRI image: mild peripheral enhancement with nodular foci directed toward the basal ganglia. (F) T2-w sagittal MRI image of the spinal cord: the tip of the odontoid process projects above the foramen magnum and is associated to a syrinx extending from C2 to T1 level. ADC = apparent diffusion coefficient, CT = computed tomography, FLAIR = fluid attenuation inversion recovery, MRI = magnetic resonance imaging.

symptoms and signs of her neurological examination, but the onset of paraphasia and deficit of the right inferior VII cranial nerve indicated a left hemispheric involvement confirmed by CT examination. As described by several previous studies, TDL was hypodense on unenhanced CT, but brain tumors also frequently had CT hypoattenuation, and it was not possible to exclude malignancy also considering its mass effect.[3,13] In comparison with tumors and abscesses, mass effect and edema in TDL are

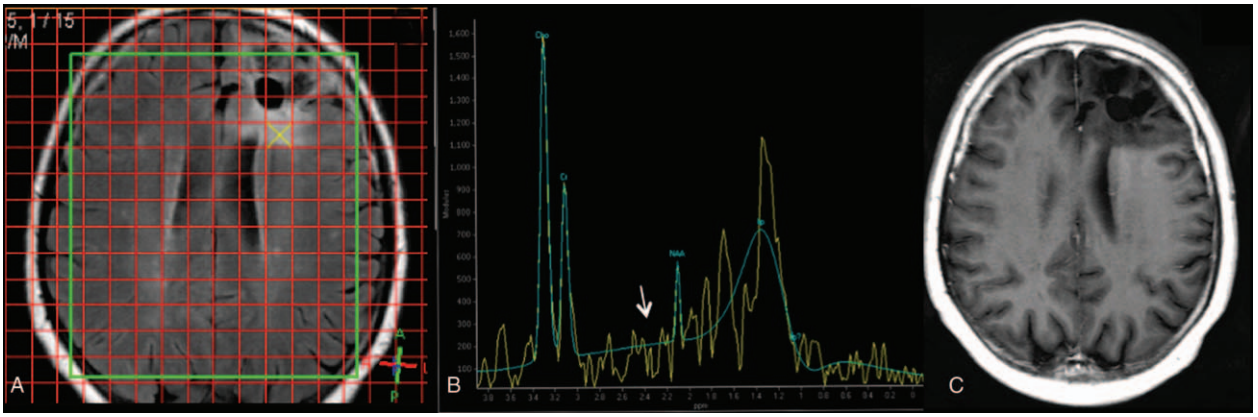

Figure 2. (A) FLAIR localizing image for proton MR spectroscopy: shrinking of the lesion which shows inner postbioptic air bubble and reduced compression on the left ventricle. (B) Proton MR spectrum of the lesion: elevated Cho value, decreased NAA value, evidence of lip-lac peak caused by the necrosis component, and the absence of -Glx peaks (*arrow*). (C) Postcontrast axial T1-w MRI image: the lesion is not enhanced. FLAIR = fluid attenuation inversion recovery, MRI = magnetic resonance imaging, NAA = *N*-acetylaspartate.

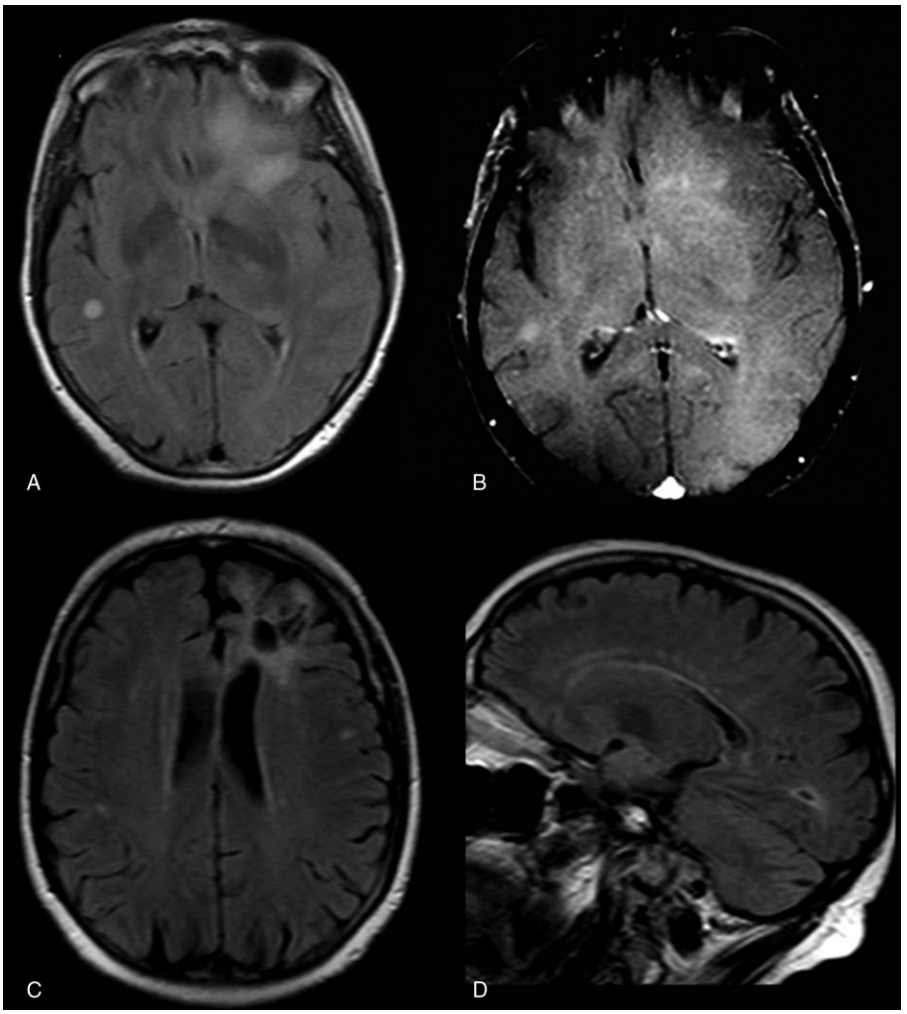

Figure 3. Axial FLAIR (A) and postcontrast T1-w (B) MRI images: new enhancing lesion in the right temporal lobe. Axial (C) and coronal (D) FLAIR MRI images: multiple small lesion with MS plaque appearance. FLAIR = fluid attenuation inversion recovery, MRI = magnetic resonance imaging.

reported to be proportionally minor relative to plaque size, suggesting that lack of mass effect differentiates MS plaques from other space-occupying lesions.[3,13] In contrast, in our case TDL presented significant mass effect with initial subfalcine herniation, and although this was in agreement with the result of a recent large study larger study, CT findings were most likely suspicious for brain tumor, given also the age of the patient who then underwent contrast-enhanced MRI exam.[3]

In the literature, MRI features suggestive of TDL include large white matter lesions with little mass effect or vasogenic edema,

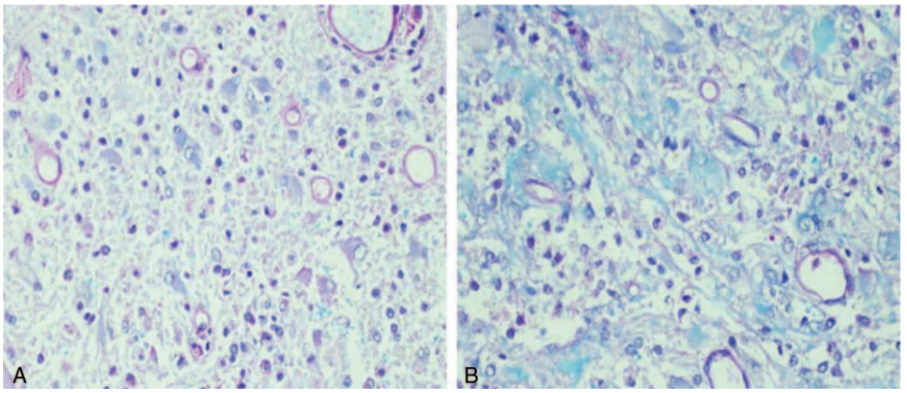

Figure 4. Hematoxylin and eosin (A) and Luxol Fast Blue-Periodic Acid Schiff (B) stains: hypercellular lesion with infiltrating macrophages and reactive astrocytes with swollen cell bodies; the tissue structure is loosened.

incomplete or open-ring enhancement, vessel-like structures running through the center of lesions on dynamic T2*-w images and marked reduction in blood flow perfusion compared with normal white matter.[3,13,14] In our case, the TDL showed some of other conventional MRI features including an ill-defined or irregular border, mass effect, perilesional edema, central necrosis, variable enhancement, variable T2-w signal intensity, and involvement of gray matter or corpus callosum, which are nonspecific and shared by gliomas.[2,13] Some studies reported that in contrast to neoplasia and infections, the pattern of ring enhancement associated with demyelination is more often open, the incomplete portion abutting cortical gray matter or the basal ganglia.[2,3] In our case, the lesion showed a thin irregular complete peripheral enhancement with foci of nodular hyperintensity directed toward the basal ganglia; these enhancing nodular areas corresponded to hypodense regions on unenhanced CT. A recent study showed that comparing the MRI-enhancing regions with the respective areas on CT, corresponding hypoattenuation was specific for distinguishing TDL from primary glioma or central nervous system (CNS) lymphoma; however, its results cannot be generalized to brain tumors other than gliomas and lymphomas.[13,15] T1-w or T2-w signal intensities of MRI-enhancing TDLs are reported to be variable and not significantly different from those of tumors.[13] In our case, the lesion was characterized by an incomplete rim of hypointensity on T2-w sequences.[3] T2-w hypointense rims are described in various ring-enhancing lesions, most commonly abscesses, but are also associated with intracranial hematoma, vascular malformations, neoplastic hemorrhage, and granulomatous disease. Abscesses have the highest percentage of complete hypointense rims, whereas metastases and gliomas more often feature hypointense arcs; MS lesions equally show rims and arcs.[3] Furthermore, MS-demyelinating lesions are more often centrally homogenous on T2-w compared with abscesses, as observed in our case;[3] however, abscess was also excluded according patient's clinical condition and CSF tests. It is reported that most TDLs demonstrate increased DWI signals and ADC on MRI, allowing differentiation from lymphoma that are highly cellular tumors, with a restriction of water diffusivity making them appear hyperintense on DWI and hypointense on ADC maps.[9,16,17] Occasionally, acute demyelinating lesions may have areas of diffusion restriction with reduced ADC values in the periphery of the lesion.[9,16] When these tumefactive lesions are large, such as in our case, may be indistinguishable from neoplasms as both can lead to mass effect/edema, a hypointense rim on T2-w scans, variable degree of ring-enhancement and restriction on DWI associated to reduced ADC values.[7,9,14,17] Given the degree of overlap with other pathologic processes, CT and MRI findings failed to provide an unambiguous diagnosis; furthermore, because of the negative CSF analysis for oligoclonal bands (positive in up to 30% of cases of TMS), the absence of multiple lesions on MRI at the time of the biopsy (present in up to 70% of patients with TMS) and the heightened suspicion of neoplasia, the clinicians opted to perform a stereotactic biopsy.[2,18] Histological findings in demyelinating disease might be misinterpreted as a neoplasm given the hypercellularity, gliosis, and the frequent observation of atypical reactive astrocytes with mitotic figures and the presence of permeating lymphocytes.[2,3,9] Two main causes for error in histological diagnosis are described: biopsies performed in areas of intense gliosis, with atypical astrocytes, favor a misdiagnosis of glioma; tissue samples from the center of the lesion, due to the presence of a large number of macrophages, can be misdiagnosed as cerebral infarction.[2] In our case, hypercellularity and hypertrophic astrocytes with atypic nuclei did not allow the first histological analysis to exclude a neoplastic condition.

Recently, it has been reported that some TMS cases were diagnosed without biopsy thanks to advanced imaging techniques such as MRS, positron emission tomography (PET), in addiction to careful follow-up to assess the response to steroid treatment.[1,7] In our case, MRS was not available at the time of hospitalization, and then it was performed at another institution after the histologic report because of the patient's misgiving and clinicians' diagnostic doubts. Literature reports, studying the potential utility of proton MRS in differentiating TDLs from neoplasms, have focused on the classical metabolites of *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr), lactate (Lac), and mobile lipids (Lip).[19,20] In our case, although affected by postbioptic artifacts, it was observed a significative decrease of NAA peak reflecting the neuronal destruction and axonal damage, and a slight elevation of the Cho level.[20,21] Our findings were in agreement with recent studies underlying the need for the cautious interpretation of spectroscopic findings, which reported that MRS may not allow a sure differentiation of TMS from neoplasms, because of the overlap in decreased NAA/Cr ratio, increased Cho/Cr ratio, and the variable and nonspecific presence of Lac and Lip in both of these entities.[19,20,22] Moreover, it was not appreciable an abnormal elevation of the glutamate/glutamine peak described—even if lacking of statistical significance—as a more specific MRS finding in differentiating TDL from brain tumors.[9,20,23]1C-methionine PET (MET-PET) is widely used as a standard diagnostic modality for detecting brain tumors, but low-grade gliomas sometimes cannot be differentiated from non-neoplastic lesions using only MET-PET, and a combination of contrast-enhanced MRI and MET-PET is required.[8,24] Although we did not perform MET-PET study, its result could not be useful in differential diagnosis given the atypical features of TDL on MRI.

In our case, follow-up was crucial to define the nature of the TDL; the first MRI exam after steroid therapy showed the shrinking of the lesion then making unlikely most of the brain tumors, but as both CNS lymphoma and TDLs are steroid responsive, a differential diagnosis between these 2 diseases was necessarily required. Although we excluded lymphoma on the basis of T2-w and DWI signal intensity and the histological confirmation, since primary central nervous system lymphoma may present within 12 months after a sentinel demyelinating lesions, it is important to stress the need to undertake postbiopsy surveillance imaging, particularly in the elderly.[3,7,25] During the following months, our 66-year old patient developed new enhancing lesion in right temporal lobe, multiple ovoid lesions in frontal and temporal lobes and within periventricular white matter oriented perpendicular to the long axis of the ventricular system.[3] According to the new McDonald criteria, which require objective evidence of lesions disseminated in time and space depending largely on the results of the MRI examinations, our patient was diagnosed with MS.[26–28]

There are no standardized guidelines for immunomodulatory treatment for people with TMS and their management can be a challenge.[17,29] Treatment choices generally include methylprednisolone, β-interferons, plasma exchange, rituximab, and natalizumab.[17] Although most of TDLs are reported to respond favorably to corticosteroid therapy, in some tumefactive diseases that fail to improve following treatment with steroids, or plasma exchange, cytotoxic agents such as Cy, an alkylating agent, or B cell-depleting regimens such as rituximab may be consid-

ered.[30,31] Intravenous Cy is described as an effective treatment in patients with rapidly worsening, treatment refractory, relapsing-remitting MS, or in an early secondary progressive phase of the disease.[32] Despite the other agents that are currently approved for patients with MS have no or very limited bioavailability in CNS, Cy penetrates the blood—brain barrier and has a good bioavailability within the CNS.[33] Thus, Cy may induce local immunomodulation and immunosuppression even after the formation of lymphatic tissues in the brain and spinal cord, potentially stabilizing the disease and preventing further progression.[33] In our patient, despite the initial response of TDL to the steroid treatment, new multiple enhancing plaques appeared on further MRI examinations. According to the conception that in patients presenting higher T2-w lesion load and enhancing lesions, the early treatment with a potent agent as Cy may freeze and stabilize the disease, our patient gave informed consent to intravenous Cy (starting with 800 mg/m^2) administration.[32] Unlike in our case, many studies suggest that acute episodes of TDL are usually isolated and rarely progress to more typical MS, and that the presence of TDL does not affect the prognosis and could potentially protect against long-term disease progression.[19,26,34,35]

4. Conclusions

Our report illustrates how challenging is the correct diagnosis of TMS for neurologists, neurosurgeons, neuroradiologists, and neuropathologists. Despite the past few years have witnessed major advancements in our ability to diagnose MS, demyelinating diseases presenting with TDL still remains a problematic entity clinically, radiologically and sometimes even pathologically.[35,36] A staged follow-up is necessary and in our case it revealed to be the most important attitude to define the nature of the lesion, confirming the classic MS diagnostic criteria of disseminate lesions in time and space.[37]

Acknowledgments

The authors would like to thank the patient's relatives for their cooperation and support, and their center colleagues and the devotion of the patients.

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