Case Report

Recurrent tumefactive demyelinating lesions in an elderly woman

Erika L. Weil, MD, Mohammad Obadah Nakawah, MD

Stanley H. Appel Department of Neurology, Houston Methodist Neurological Institute, 6560 Fannin St, Scurlock Suite 802, Houston, TX 77030 USA

Article history:
Received 10 June 2022
Revised 29 August 2022
Accepted 4 September 2022

Keywords:
Tumefactive demyelination
Neuroimaging

Abstract

Here we describe a 72-year-old Caucasian woman who presented with progressive left hemiparesis and hemisensory deficits due to a pathology-confirmed tumefactive demyelinating lesion in the right frontoparietal region. Symptoms improved with glucocorticoids and plasmapheresis, but five months following initial presentation, the patient developed right visual field deficits and acute encephalopathy. Brain imaging revealed near resolution of the initial lesion with interval development of new multifocal tumefactive demyelinating lesions. This case highlights several atypical features associated with tumefactive demyelinating disease, including an older age of onset and recurrent, treatment-resistant lesions. Clinical and neuroimaging features which may be helpful in diagnosing this rare disorder are reviewed.

© 2022 The Authors. Published by Elsevier Inc. on behalf of University of Washington. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

Introduction

Tumefactive demyelinating lesions (TDL) are described as large (>2 cm in diameter), tumor-like demyelinating lesions in the central nervous system (CNS). TDL represent a rare subtype of CNS inflammatory demyelinating disorders, though multiple sclerosis (MS) accounts for the majority of cases [1]. Often, TDL present a diagnostic challenge as the radiographic appearance can mimic other space-occupying lesions, including neoplasm or abscess. Patients with TDL may experience a fulminant course with need for aggressive management [2]. While the majority of patients with TDL later follow a typical relapsing-remitting MS course, a small subset exhibit a tendency for recurrent tumefactive demyelinating attacks [1,3]. Due to the overall rarity of this disorder, the immunopathogenesis remains poorly understood. Herein, we describe a case of relapsing TDL which highlights atypical features and an aggressive clinical course.

Case description

A 72-year-old right-handed Caucasian woman presented with a 5-week history of progressive left-sided weakness and numbness. Symptoms started approximately 1 week after receiving a second dose of mRNA COVID-19 vaccine
Past medical history included obesity, hypertension, hyperlipidemia, nonalcoholic steatohepatitis and erythema nodosum. Neurologic examination revealed mild dysarthria, left facial weakness and moderate left-sided hemiparesis with hemisensory loss. Brain magnetic resonance imaging (MRI) demonstrated a large, right frontoparietal mass with partial ring-enhancement and mild local mass effect (Fig. 1).

Serological studies for infectious causes (including syphilis, HIV, and JC virus) and autoimmune etiologies (including aquaporin-4 and myelin oligodendrocyte glycoprotein “MOG” antibodies) were unremarkable. Spinal fluid analysis revealed normal opening pressure, cell count, cytology, infectious studies, IgG Index, and no oligoclonal bands. Histopathology of the lesion biopsy demonstrated areas of reactive gliosis with dense infiltration of foamy, CD-68 positive macrophages (Luxol fast blue-periodic acid Schiff immunostain positive) predominately involving the white matter with relative preservation of axons identified with neurofilament immunostain. Findings were overall consistent with a non-neoplastic, demyelinating process.

Following biopsy, a 7-day course of intravenous methylprednisolone was initiated followed by oral prednisone taper. The patient also received 5 sessions of plasmapheresis. She underwent 6 weeks of inpatient rehabilitation resulting in modest improvement of left hemiparesis; estimated Expanded Disability Status Scale (EDSS) was 6. Multiple sclerosis disease-modifying therapy was considered, but unfortunately the patient developed progressive confusion and right visual field deficits prior to starting any disease-modifying therapy, approximately 5 months from initial hospitalization. Repeat MRI showed decreased size of the right frontoparietal lesion with interval development of three new, partial rim-enhancing lesions involving the right frontal centrum semiovale, right occipital lobe and left anterior temporal lobe (Fig. 2).

Spinal fluid studies showed mildly elevated white cell count of 21 (74% monocytes, 26% lymphocytes), with normal protein, IgG index and no identified oligoclonal bands.

Despite treatment with high-dose intravenous methylprednisolone and plasmapheresis, the patient continued to decline and ultimately required mechanical ventilation for somnolence and respiratory distress. Continuous EEG monitoring over 4 days demonstrated fiewright frontotemporal epileptiform discharges, but no definitive seizures were captured. A repeat MRI brain demonstrated expansion of the multifocal lesions (Fig. 3). Despite a trial of intravenous immunoglobulins followed by rituximab 1000 mg infusion, there was no neurologic improvement. Therefore, per the patient’s
advanced directive, family elected to forgo further treatments and deferred further life-sustaining measures. The patient was transitioned to comfort care and passed away 2 weeks later.

Discussion

TDL often present a diagnostic dilemma and may be mistaken for other space-occupying lesions. Patients with TDL commonly have no prior history of demyelinating disease making diagnosis even more challenging [4]. Presentation is typically subacute with multiple symptoms reflective of lesion location and mass effect [1–3,5]. The estimated prevalence of TDL is 1-3 per 1000 cases of MS and the annual incidence approximately 0.3/100,000 [3,4]. Lucchinetti et al. reported a median age of onset of 37 years in the largest series of biopsy proven TDL; only 4% (n = 7) of patients were older than 65 years at clinical onset [1]. Though uncommon, TDL can occur in older individuals as demonstrated in the present case. When atypical clinical features are present, biopsy of TDL to rule out alternative etiologies may be unavoidable. Despite aggressive management, patients with TDL may experience a fulminant course [1–3].

The underlying immunopathogenesis of this rare disorder remains unclear. These lesions may be seen in association with a spectrum of other neuroinflammatory disorders such as acute disseminated encephalomyelitis (ADEM), neuromyelitis optica, MOG antibody disease, or tumefactive variant of MS [3,5]. The Marburg subtype is a particularly aggressive MS variant which is often treatment-resistant and leads to a fatal outcome within 1 year [2,5]. It is possible that our patient succumbed to this subtype, though lesions in Marburg variant tend to appear quite destructive and necrotic on histology [5].

Although there is not a pathognomonic radiographic appearance of TDL, certain neuroimaging features may suggest tumefactive demyelination over radiologically similar lesions. TDL are classically 2 to 6 cm in size, and multiple lesions can occur simultaneously [1]. A frontoparietal predilection has been observed [1,6]. Perilesional edema is observed in most cases [1], but relative to lesion size, the edema and mass effect are often much less prominent than what is seen in association with neoplasm or abscess [3]. White matter lesions in a distribution typical for MS can be a helpful clue, if present [3,5]. A hypointense rim on T2 weighted imaging is another supportive radiographic feature [3,5,7].

Fig. 2 – Brain MRI, 5 months following initial hospitalization, demonstrating interval development of multiple tumefactive demyelinating lesions. Axial brain MRI with T2-weighted, fluid inversion recovery imaging, postcontrast, diffusion weighted and apparent diffusion coefficient images (labeled columns) showing interval decrease in size of the previous right frontoparietal lesion (A, arrowhead) but development of three hyperintense lesions involving the right frontal centrum semiovale, right occipital lobe and left anterior temporal lobe which have associated edema but exhibit relatively little mass effect. All lesions show partial rim-enhancement on postcontrast images (A–C, arrows). The lesions show peripheral, but not central, restricted diffusion (A, stars).
Contrast enhancement is mostly present, though patterns vary. An incomplete ring enhancement with an open rim facing the cortical (pial) or ventricular (ependymal) surfaces may be observed (Figs. 1 and 2, arrows). If present, this is a highly specific sign useful to distinguish TDL from other space-occupying lesions [8,9]. Although nonspecific, closed-ring enhancement is also a commonly observed pattern [1]. Hypoattenuation on a noncontrast CT corresponding to enhancing regions on MRI is another specific sign seen more commonly with TDL than primary central nervous system lymphoma (PCNSL) or primary glioma [9].

Advanced MRI sequences can be of additional value. Blood-sensitive MRI sequences may demonstrate presence of a central vein within an inflammatory demyelinating lesion (Figs. 3 D and E) [7]. Diffusion weighted imaging often demonstrates low apparent diffusion coefficient values along the periphery of TDL with high apparent diffusion coefficient values centrally [3,7], whereas abscesses more commonly show restricted diffusion centrally rather than peripherally.

Recurrence of TDL, as in the present case, is unusual. The majority (70%) of patients with TDL have future demyelinating episodes classic for relapsing-remitting MS after a median of 4.8 years [1]. Similar to this case, a small subset of patients exhibit a tendency for relapsing tumefactive demyelinating episodes [1,3]. No specific determinants for recurrence have been identified [1]. Case reports have described recurrent TDL occurring in patients up to 50-70 years of age [10–12].

Rarely, immunocompetent patients with PCNSL may present initially with TDL, the so-called ‘sentinel demyelinating lesion’ [3]. Typical neuroimaging features of non-AIDS PCNSL include a solitary homogeneously enhancing parenchymal mass with diffusion restriction due to high cellularity [13], however, this was absent on our patient’s imaging (Fig. 2). Additionally, incomplete ring enhancement and other radiographic findings as described above, were more suggestive of TDL.

**Conclusion**

This case highlights several clinical complexities associated with tumefactive demyelination. Though uncommon, elderly patients can develop TDL. Helpful neuroimaging clues for the diagnosis of TDL include incomplete ring enhancement and
disproportionately mild surrounding vasogenic edema and mass effect relative to the lesion size. Despite aggressive management, a subset of patients with TDL may experience relapses or a fulminant course.

**Ethics approval**

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Authors’ contributions**

All authors contributed to the study conception and design. Data collection, drafting of manuscript and figure preparation were performed by ELW. Interpretation of data and critical revisions of the manuscript were performed by MON. All authors have approved the final manuscript.

**Patient consent**

Written informed consent for publication was obtained from the patient’s husband.

**Acknowledgments**

We thank the patient’s family for consent to publish this case report.

**REFERENCES**

[1] Lucchinetti CF, Gavrilova RH, Metz I, Parisi JE, Scheithauer BW, Weigand S, et al. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. Brain 2008;131(Pt 7):1759–75. doi:10.1093/brain awn098.

[2] Rahmlow MR, Kantarci O. Fulminant demyelinating diseases. Neurohospitalist 2013;3(2):81–91. doi:10.1177/1941874412466873.

[3] Hardy TA, Chataway J. Tumefactive demyelination: an approach to diagnosis and management. J Neurol Neurosurg Psychiatry 2013;84(9):1047–53. doi:10.1136/jnnp-2012-304498.

[4] Algahtani H, Shirah B, Alassi R. Tumefactive demyelinating lesions: a comprehensive review. Mult Scler Relat Disord 2017;14:72–9. doi:10.1016/j.msard.2017.04.003.

[5] Frederick MC, Cameron MH. Tumefactive demyelinating lesions in multiple sclerosis and associated disorders. Curr Neurol Neurosci Rep 2016;16(3):26. doi:10.1007/s11910-016-0626-9.

[6] Altintas A, Petek B, Isik N, Terzi M, Bolukbasi F, Tavsanli M, et al. Clinical and radiological characteristics of tumefactive demyelinating lesions: follow-up study. Mult Scler 2012;18(10):1448–53. doi:10.1177/1352458512438237.

[7] Nakayama M, Naganawa S, Ouyang M, Jones KA, Kim J, Capizzano AA, et al. A review of clinical and imaging findings in tumefactive demyelination. AJR Am J Roentgenol 2021;1–12. doi:10.2214/AJR.20.23226.

[8] Masdeu JC, Quinto C, Olivera C, et al. Open-ring imaging sign: highly specific for atypical brain demyelination. Neurology 2000;54(7):1427–33. doi:10.1212/wnl.54.7.1427.

[9] Kim DS, Na DG, Kim KH, Kim J, Kim E, Yun BL, et al. Distinguishing tumefactive demyelinating lesions from glioma or central nervous system lymphoma: added value of unenhanced CT compared with conventional contrast-enhanced MR imaging. Radiology 2009;251(2):467–75. doi:10.1148/radiol.2512072071.

[10] Selkirk SM, Shi J. Relapsing-remitting tumefactive multiple sclerosis. Mult Scler 2005;11(6):731–4. doi:10.1111/j.1352-5805.2005.01244.x.

[11] Häne A, Bargetzi M, Hewer E, Bruehmeier M, Khamis A, Roelcke U. Recurrent tumefactive demyelination without evidence of multiple sclerosis or brain tumour. Journal of neurology 2011;258(2):318–20.

[12] Vakratou AG, Tzametakis D, Argyrakos T, Koutsis G, Evangelopoulos ME, Andreadou E, et al. Recurrent fulminant tumefactive demyelination with marburg-like features and atypical presentation: therapeutic dilemmas and review of literature. Front Neurol 2020;11(536):536. doi:10.3389/fneur.2020.00536.

[13] Haldorsen IS, Espeland A, Larsson EM. Central nervous system lymphoma: characteristic findings on traditional and advanced imaging. AJNR Am J Neuroradiol 2011;32(6):984–92. doi:10.3174/ajnr.A2171.