

Favourable response to plasma exchange in tumefactive CNS demyelination with delayed B-cell response

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Abstract

We report a case of multiple sclerosis-associated fulminant tumefactive demyelinating lesion (TDL) with the special feature of delayed humoral immune response. Plasma exchange (PE) yielded significant benefit in two consecutive steroid-unresponsive relapses, while signs of an intrathecal B-cell response were only present 2 years later at the second relapse. Remission was achieved and sustained thereafter with natalizumab. Our case indicates that PE might be a therapeutic option even when the B-cell response is not fully developed. This delay in the development of a humoral immune response may reflect the step-wise B-cell colonization of the CNS and represent an attractive therapeutic window of opportunity.

Keywords

humoral immune response, immunopathogenesis, multiple sclerosis, plasma exchange, treatment, tumefactive demyelination

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Introduction

Tumefactive demyelinating lesions (TDLs) are defined as solitary demyelinating areas greater than 2 cm and frequent neuroimaging features include mass effect, oedema and atypical contrast enhancement. Clinical manifestations are mostly acute with rapid progression of symptoms.¹ Acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS) account for some cases of TDL,² although the diagnosis remains a challenge in spite of the knowledge of typical neuroimaging features.

inversion recovery (FLAIR) images but only a discrete peripheral contrast enhancement was present. No other pathologies, particularly no other white matter lesions, were found on brain and spinal cord MRI. The examination of the cerebrospinal fluid (CSF) revealed a cell count in the normal range and lack of evidence for blood–brain barrier (BBB) disruption. Flow-cytometric (FACS) analysis verified that the majority of cells were T-cell subsets and CD14⁺ monocytes (23.7%), whereas the rate of CD19⁺ B

Patient history

A 29-year-old male post-graduate student was admitted with incremental worsening of a right-sided weakness and speech disturbances over the last 2 weeks. Upon neurological examination, a non-fluent aphasia and a moderate right-sided sensorimotor hemisindrome were observed. The Expanded Disability Status Scale (EDSS) score at this time point was 4.5 (Figure 1a). Brain MRI showed a large mass lesion (3.2 cm × 3.1 cm × 2.6 cm) in the left parietal lobe (semioval centre) (Figure 1b), which was circular and accompanied by cytotoxic oedema and mild local mass effect. Hyperintensive rims peripherally on fluid attenuated

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cells (0.07%) and CD19+/CD138+ plasma blasts (0.18%) was low (Figure 1c). Neither intrathecal IgG production nor CSF-specific oligoclonal bands (OCBs) were detected. Furthermore, there was no serum antibody response to native myelin oligodendrocyte glycoprotein (MOG antibody). The clinical examination and serological testing did not provide any evidence for vasculitis or infection.

A 7-day course of high-dose intravenous methylprednisolone (1 g), added to the 3-day course he received in another hospital, did not halt further progression of clinical symptoms; accordingly, treatment escalation with seven courses of plasma exchange (PE) every second day was performed, which led to a marked improvement of the clinical syndrome. Three months later and following rehabilitation, only slight aphasia and hemiparesis persisted. In

contrast to the course of signs and symptoms, the MRI showed a progression of the lesion with increasing contrast enhancement (Figure 1b, II). At this time a malignancy could not be ruled out. Subsequently, a brain biopsy was scheduled and revealed an inflammatory demyelinating process with oligodendrocyte pathology defined by the presence of oligodendrocytes in the lesion.³ Details of the histological examination are explained in the legend of Figure 2.

The diagnosis of TDL was established, and a subtotal remission was observed on examination 3 months later (EDSS 2.5). At this time a slight regression of the lesion was seen on MRI. Immunomodulatory treatment was recommended but refused by the patient. Regular clinical and MRI follow-ups did not reveal any new disease activity.

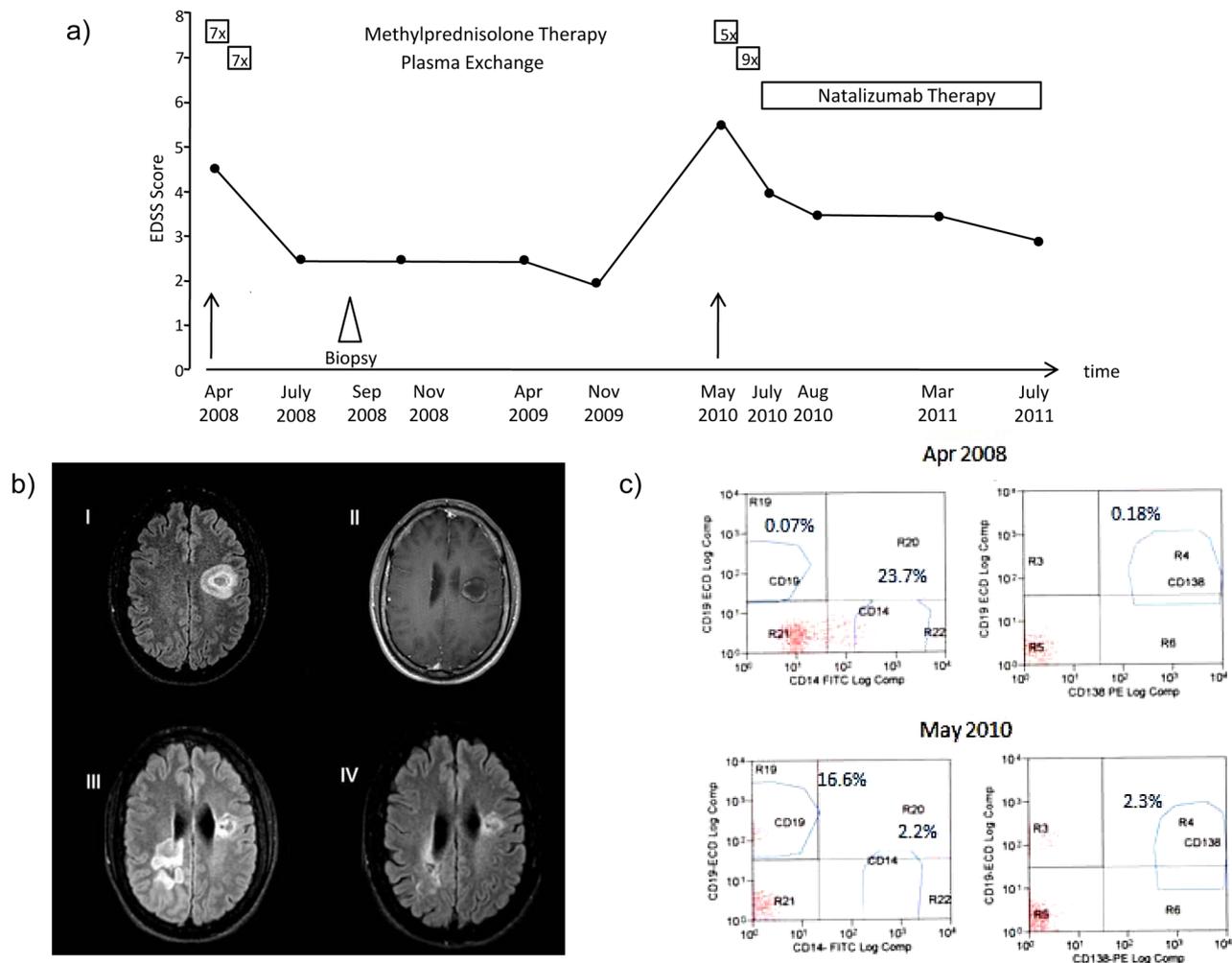


Figure 1. Clinical course, neuroimaging and flow cytometric findings in multiple sclerosis (MS)-associated tumefactive demyelinating lesion (TDL) with the special feature of delayed B-cell response. (a) Clinical course indicated by Expanded Disability Status Scale (EDSS) over time. (b) I. Initial axial fluid attenuated inversion recovery (FLAIR) brain MRI (May 2010) showing a lesion in the left parietal lobe (semioval centre). II. T1-weighted contrast-enhanced axial MRI 6 months later. III. Axial FLAIR brain MRI (May 2010) at the time of the second relapse with a new right-sided concentric lesion (2.2 cm × 2.5 cm) and contrast enhancement (not shown) close to the lateral posterior ventricle. IV. Axial FLAIR brain MRI after 8 months of natalizumab treatment (March 2011) with evidence for regression of the lesions. (c) Flow cytometric analysis of cerebrospinal fluid (CSF) lymphocyte subsets at the initial episode and the second relapse.

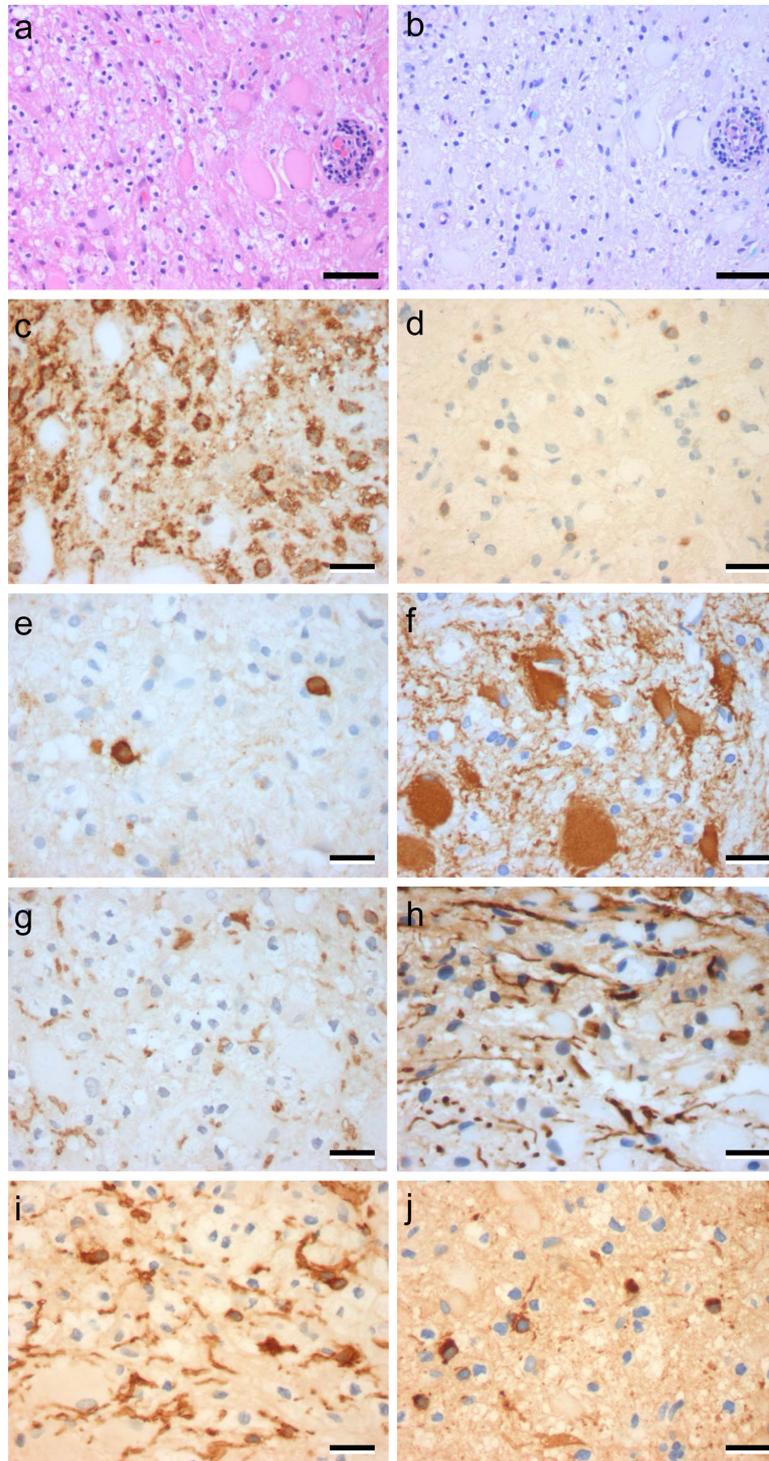


Figure 2. Histological evaluation of the biopsy revealed an inflammatory demyelinating lesion. Hematoxylin and eosin (H&E) staining showed white matter with increased cell density, whereby several foamy macrophages and reactive astrocytes were detected (a). Focal perivascular lymphocytes were also observed. Demyelination was seen in these areas on Luxol Fast Blue and Periodic Acid Schiff (LFB-PAS) stained sections (b). Immunohistochemical stainings for inflammatory cells revealed diffuse infiltration with KiM1P-positive macrophages (c), scattered CD3-positive T cells (d), and individual CD138-positive plasma cells (e). CD20-positive B cells were not observed within the lesion (data not shown). Reactive hypertrophic astrocytes were detected in the lesion with antibodies against glial fibrillary acidic protein (f). The lesion appeared demyelinated on stainings using antibodies against myelin proteins such as proteolipid protein (g). The axonal density appeared reduced in the lesion, but remaining axons could still be detected using antibodies against neurofilaments such as phosphorylated neurofilaments (SMI31) (h). CNPase-positive (i) and NogoA-positive (j) oligodendrocytes were still present within the demyelinated lesion. The first two images (a) and (b) were taken at 200 \times original magnification (scale bars: 50 μ m) and the remaining immunohistochemical images (c)–(j) were taken at 400 \times original magnification (scale bars: 20 μ m).

However, more than 2 years after the initial episode, the second relapse occurred with vertigo, left-sided hemiataxia and hemianopsia towards the left (EDSS 5.5). The patient now fulfilled the criteria for clinically definite MS. The MRI showed a new right-sided concentric lesion (2.2 cm × 2.5 cm) next to the lateral posterior ventricle with pathological contrast enhancement (Figure 1b, III). Spinal MRI now visualized a few small non-contrast-enhanced lesions at the C4, Th4, Th7 and Th9 levels. A repeat spinal tap revealed a lymphocytic pleocytosis (65 cells/μl) with evidence for BBB disruption and CSF-specific oligoclonal bands. The CSF FACS analysis detected a significant B-cell response with presence of CD19+ B-cells (16.6% of all CD45+ cells) and plasma blasts (2.2 % of all CD45+ cells) (Figure 1c). Serum MOG-antibodies remained negative. Since intravenous treatment with methylprednisolone (1 g) over 5 days was again unable to alleviate the symptoms, another course with a total of nine PEs every second day was completed. The latest follow-up MRI revealed a decline of the size of both lesions (Figure 1b, IV). The clinical condition improved moderately and remained stable over a period of 1 year since he was started on monthly infusions of natalizumab.

Methods

FACS of CSF lymphocyte subsets was performed as described previously.⁴ Antibodies to native MOG were evaluated with a cell-based assay.⁵ Rating of PE effects: mild (subjective or minimal, but no effect on function); moderate (gain in neurological status that affects function); marked (important difference from baseline).⁶

Discussion

The main differential diagnoses of solitary TDL include high-grade glioma, lymphoma and infectious CNS disease. Typical but non-specific neuroimaging features of TDL are ill-defined borders, mass effect, perilesional oedema, cystic degeneration, contrast enhancement, and variable involvement of the grey matter. However, the clinical course with deteriorating aphasia and the only discrete contrast enhancement of the lesion at onset, and normal CSF findings had raised concerns regarding the validity of a diagnosis of autoimmune CNS inflammation.

Most importantly, this case illustrates two consecutive steroid-unresponsive relapses of MS clinically clearly responding to PE. Treatment escalation with PE in patients with steroid-unresponsive CNS demyelination achieved a moderate to marked response in 59% within 6 month of treatment.⁷ In that study, short disease duration and preserved deep tendon reflexes were clinical predictors of treatment response. These features were present in our case together with radiological predictors of beneficial response including ring-enhancement and mass effect of the lesion.⁷

No evidence of a humoral immune response was present in the CSF (e.g. B cells, intrathecal IgG synthesis and OCBs) when the first relapse occurred and hence, the favourable response to PE is intriguing. Humoral immune responses are believed to develop gradually with initial B-cell activation in the periphery and later colonization of the meninges and the CSF compartment.⁸ In this regard, PE might have targeted the peripheral B-cell response prior to colonization of the CNS. The clinical effects might also be partly explained by the removal of pathogenic factors beyond antibodies (e.g. interleukins, amino acids or toxins). Alternatively, the marginal BBB disruption and the distance of the lesion to meninges or ventricles might have contributed to a low efflux of inflammatory cells to the CSF.

PE was effective for relapse treatment but had no preventive effect for the development of new lesions. Since starting the therapy, natalizumab has been having a sustained impact on the clinical course and the lesions (over 1 year). It is very unlikely that this can be regarded as a natural course, following the rapid development of new and extensive lesions mounting in the second relapse and given the profound effect of this antibody on immune cell subsets within the CNS.⁹

This report supports the concept of a gradual formation of the B-cell and antibody response in the immunopathogenesis and disease evolution of MS. This clinical case implies that obvious signs of a humoral immune response and intrathecal inflammation do not seem to be prerequisites for a clinical response to PE in patients with steroid-unresponsive demyelination. Another explanation could be the more advanced demyelinating activity of the lesion since criteria for an early active demyelinating lesion were not observed. Only in these earliest stages of lesion development can antibody and complement deposits be detected.¹⁰ To this end, stereotactic brain biopsy remains the method of choice to confirm the diagnosis in cases where MRI and CSF analysis are unable to distinguish between neoplasia and TDL.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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