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Letter to the Editor

Long-term follow-up of immunotherapy-unresponsive recurrent tumefactive demyelination

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Dear Editors,

Recurrences of tumefactive demyelinating lesions (TDL) are very infrequent, and most of them occur in the context of multiple sclerosis (MS) [1]. Hence, the initial diagnosis, and prediction of the subsequent course and therapeutic strategy of isolated TDL are challenging. We report a patient with biopsy-proven idiopathic TDL who presented with seven tumefactive relapses over eleven years of follow-up despite the use of several types of immunotherapy.

In 2003, a 44-year-old woman presented with progressive mental confusion and memory impairment. A brain MRI demonstrated a tumefactive lesion in the temporal lobes extending through the splenium of the corpus callosum, with perilesional edema and gadolinium enhancement (Fig. 1). Oligoclonal bands were absent in cerebrospinal fluid (CSF) and there was no evidence of other brain or spinal cord lesions. A brain biopsy was suggestive of a demyelinating origin (extensive demyelination with astrocytosis and a prominent infiltration by vacuolated macrophages in addition to perivascular B and T mature lymphocytes. No atypical cells were observed and infectious agents could not be demonstrated), and the patient was treated with IV methylprednisolone (IVMP). Two years later she suffered a second relapse of a large left capsulo-thalamic lesion. Due to the appearance highly suggestive of primary central nervous system lymphoma (PCNSL), we decided to treat her with a standard chemotherapy regimen (one cycle of CHOD and two of BVAM) [2] (Fig. 1). Shortly after starting the therapy, the clinical and MRI findings worsened, a new tumefactive lesion appeared (Fig. 1), and the second cycle of BVAM was not administered. A new biopsy revealed macrophage infiltration with reactive gliosis and no tumoral cells. She had only mild recovery despite IVMP, plasma exchange (PLEX), and IV cyclophosphamide (1 g). Six months later the neurologic examination had improved remaining a right hemiparesis (Expanded Disability Status Scale, EDSS: 4.0). Five years later she presented with a left homonymous hemianopsia associated with a fourth tumefactive relapse. Immunomodulatory therapy with subcutaneous interferon-beta 1 a was started to prevent new episodes (EDSS: 4.0). After 3 years under interferon, she experienced two new tumefactive relapses in a 3 month period and remained with residual non-fluent aphasia despite IVMP administration. NMO-IgG/AQP4 tested several times and MOG-IgG were negative [3]. Interferon-beta was discontinued and switched to IV cyclophosphamide (1 g) and rituximab (1 g administered 2 weeks apart). Three months later (peripheral CD20+ cells count of 0%), the patient suffered a status epilepticus, worsening of the aphasia, and right hemianopsia associated with a new large lesion (Fig. 1). After IVMP and PLEX she recovered only partially. At that point, we decided to initiate natalizumab off-label, and she has remained relapse-free for 9 months and neurologically stable with slight improvement of the aphasia after rehabilitation (Fig. 1).

Patients who experience isolated relapses of TDL outside the context of MS are uncommon [1]. TDL are lesions larger than 2 cm, located mainly in white matter, with perilesional edema, hypointense rim on T2-weighted images and often incomplete ring enhancement on T1-weighted images (Fig. 1). Those MRI characteristics as well as the finding of increased cell-membrane metabolism and decreased neuro-axonal integrity on magnetic resonance spectroscopy [4] (Fig. 1) are suggestive of a demyelinating origin. However, none of them are pathognomonic and a biopsy can be necessary to exclude other causes including neoplasm [1]. In the current case, the absence of typical asymptomatic dissemination in space, the lack of oligoclonal bands in the CSF (analyzed twice), and the unresponsiveness to disease-modifying therapy and immunosuppressive drugs which have demonstrated beneficial effects in MS [5], suggest that this and other cases of TDL are not a variant of conventional MS but a distinct subtype of demyelinating disease. It is important to note that the patient did not complete the standard chemotherapy regimen used for the treatment of PCNSL. The therapy is similar, but the doses much lower, to BEAM, the conditioning for autologous haematopoietic stem cell transplantation in MS. Nevertheless, if this regimen was enough to halt the acute inflammatory process, it is unlikely that it was responsible for the absence of relapses for 5 years. In the setting of recurrent TDL, the potential positive effect of natalizumab, reported in few individual cases [6], remains to be proven.

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Conflicts of interest

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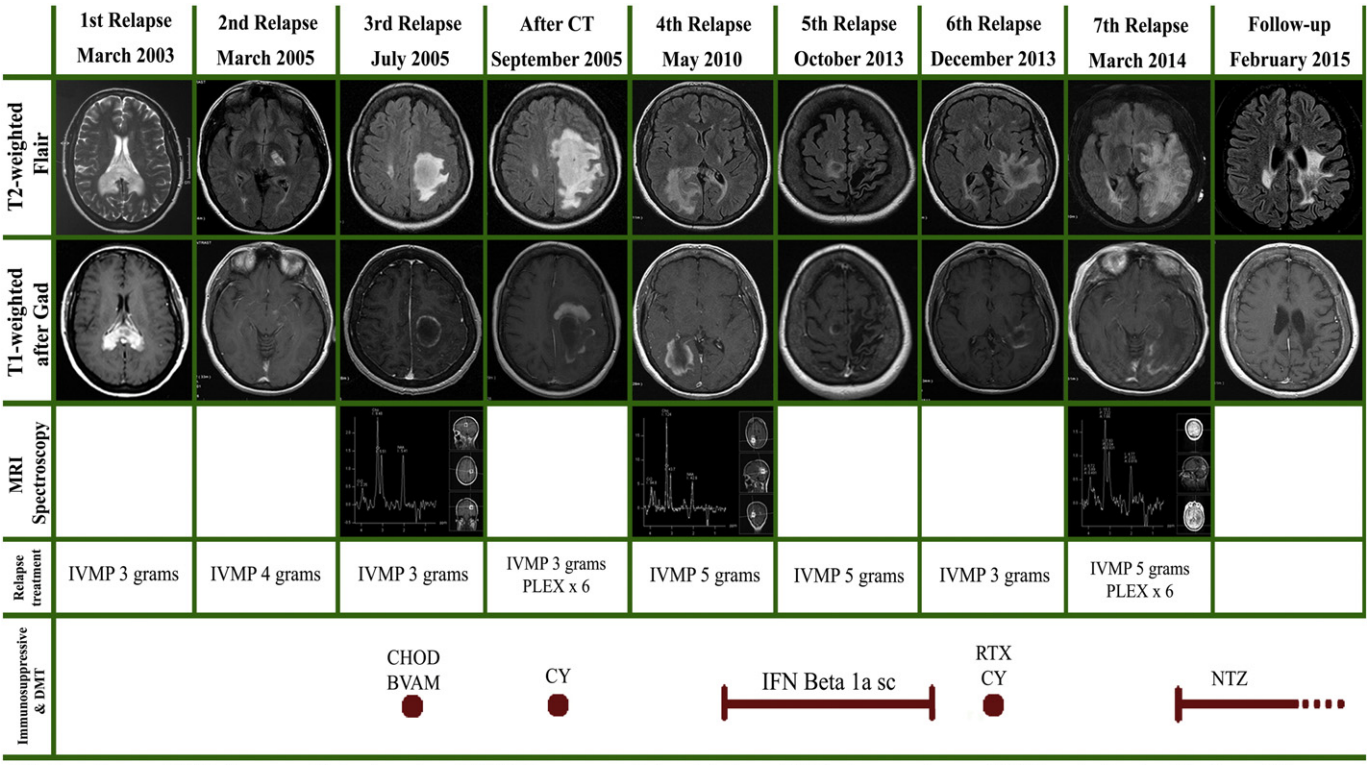

Fig. 1. Evolution of the relapsing tumefactive demyelinating disease. Images of the lesions on T2-weighted or FLAIR and T1-weighted after gadolinium injection and treatment details are included. Magnetic resonance spectroscopy showed decreased N-acetylaspartate/creatine ratio, increased choline/creatine ratio and double lactate pick, indicating increased cell-membrane metabolism and decreased neuro-axonal integrity.

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A signed informed consent was obtained from the patient for the publication of the clinical data.

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