Lupus-like disease and progressive multifocal leukoencephalopathy following etanercept treatment: just a coincidence?

Sirs,

Tumour necrosis factor (TNF) inhibitors have revolutionised the treatment of chronic inflammatory disorders. Nevertheless, adverse reactions have been recognised including demyelination and, rarely, progressive multifocal leukoencephalopathy (PML) (1). PML is a rare, severe demyelinating disease resulting from reactivation of John Cunningham-virus (JCV) (1). We describe a case of anti-TNF-induced lupus in a psoriatic arthritis patient who later developed PML and immune reconstitution inflammatory syndrome (IRIS).

A 65-year-old female presented with right hemianopsia and behavioural changes starting a year earlier. Neurological examination revealed right plantar extensor reflex, right homonymous hemianopsia and cognitive dysfunction. CSF values including IgG-index were within normal limits. Type-2 CSF oligoclonal bands were detected, compatible with intrathecal IgG production. Immunophenotyping showed reduction of $CD4^+$/$CD8^+$ T-cells, and increase of NK-cells. Brain-MRI showed a T2-hyperintense, parieto-occipital subcortical lesion of the left hemisphere, (Fig. 1A), with ependymal gadolinium enhancement at the left lateral ventricle. MRI-spectroscopy revealed increased concentration of choline and presence of lactate (data not shown). Antiphospholipid antibodies were not detected.

Her past medical history was significant for psoriatic arthritis treated with a five-year etanercept monotherapy, followed by development of photosensitivity, hair loss, and anti-Ro/SSA and anti-La/SSB autoantibodies, a finding which was not present at initial diagnosis. Complement levels and anti-DNA antibodies were within normal limits. With a presumable diagnosis of anti-TNF-induced lupus, etanercept was replaced by hydroxychloroquine. One year later, following behavioral symptoms, hydroxychloroquine was discontinued.

Differential diagnosis includes anti-TNF-induced demyelination; however, this entity rarely resembles with tumour-like lesions (2). CNS involvement due to lupus-like disease was also considered due to cognitive impairment, a symptom with varying prevalence in systemic lupus erythematosus (SLE), often in association with antiphospholipid or neurotoxic antibodies (3). Nevertheless, imaging of SLE-CNS involvement differs, involving small white matter lesions (3). Finally, a tumour diagnosis was compatible with the imaging/spectroscopy findings, thus a biopsy was performed. A demyelinating lesion with axonal sparing, stained with anti-SV-40 and anti-p53 antibodies, distinctive for PML, was revealed (Fig. 1 E-H). Diagnosis was confirmed by JCV detection in CSF by PCR.

Mirtazapine (60 mg qd) was administered, as it has been associated with increased survival through occurrence of IRIS (4). A month later, worsening of symptoms occurred (apraxia, aphasia, disorientation) attributed to a lesion enlargement (Fig. 1B) and multifocal contrast enhancement, compatible with IRIS (Fig. 1C). 5 grams of intravenous methylprednisolone (1gr qd) were administered followed by oral steroids (1mg/kg, subsequent tapering). One month later, a remarkable improvement was observed. There was no contrast enhancement in a brain-MRI (Fig. 1D) and CSF-PCR for JCV was negative.

Taken together, we present a PML case with IRIS induction and a favourable outcome, developing in a setting of anti-TNF-induced lupus following etanercept treatment in a psoriatic arthritis patient. Though etanercept could be directly related to PML development, as in previous isolated cases of rheumatoid arthritis (5, 6), anti-TNF-induced lupus seems more likely to be related

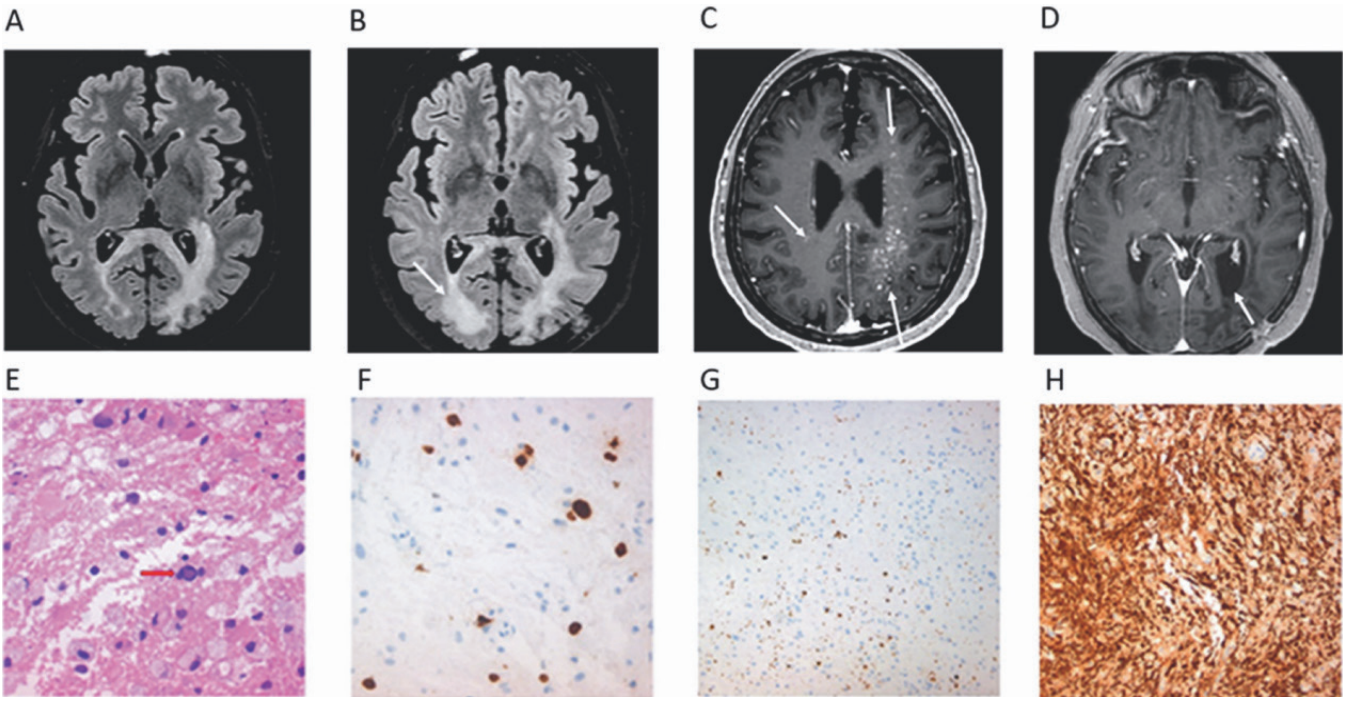

Fig. 1. Brain imaging. and histopathological findings.
A: Axial-FLAIR image reveals a hyperintense lesion extending bilaterally in the occipital lobes and the corpus callosum.
B: FLAIR image shows lesion enlargement on the right occipital lobe (arrow) two months later.
C: Multiple areas of enhancement on T1 images post gadolinium (arrows), attributed to PML-IRIS.
D: Two months later, there was no enhancement on T1 with contrast. Dilatation of the left lateral ventricle (arrow) due to parenchymal volume loss and gliosis.
E: Nuclear inclusions of the infected oligodendrocytes (H&E, x400).
F: Immunohistochemical staining of the infected nuclei with the monoclonal antibody SV-40 (clone Pab101, BioSB) (IHC, x400).
G: Complete loss of sheaths of myelin (IHC Myelin Basic Protein, MONOSAN, polyclonal, x200) with residual myelin granules within the cytoplasm of the macrophages.
H: Neurofilaments (IHC DAKO, clone 2F11, x200) with complete axonal sparing in the same area as in (G).

to this complication, since SLE itself seems to increase susceptibility for PML (7). Induction of type I interferon (IFN) responses and B-cell activation previously shown to be induced by anti-TNF treatment (8) and found to be upregulated in peripheral blood of our patient as well (data not shown), could lead to mobilisation of $CD34^+$ B-cell precursors harbouring JCV, a mechanism postulated for PML development (9). A contribution of decreased toll-like receptor signalling and dampened plasmacytoid dendritic cell activation following hydroxychloroquine seems less decisive, given the heightened expression of IFN-inducible genes found in our patient (10).

In summary, this case highlights the need for careful evaluation and close neurological surveillance in patients receiving TNF-inhibitors. Whether PML resulted directly from TNF-induced compartmentalised immunosuppression or from activation of the type I IFN/B-cell activation axis remains to be explored.

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V.E. Papadopoulos[1], *MD, PhD*
G. Velonakis[2], *MD, PhD*
T. Argyrakos[3], *MD*
M. Anagnostouli[1], *MD, PhD*
L. Stefanis[1], *MD, PhD*
C.P. Mavragani[4], *MD, PhD**
M.-E. Evangelopoulos[1], *MD, PhD**

**These authors contributed equally.*

[1]1st Department of Neurology, National and Kapodistrian University of Athens, Eginition Hospital, Athens;
[2]Research Unit of Radiology, 2nd Department of Radiology, National and Kapodistrian University of Athens, Eginition Hospital, Athens;
[3]Department of Pathology, Evaggelismos General Hospital, Athens;
[4]Departments of Physiology and Pathophysiology, School of Medicine, Greece & Joint Academic Rheumatology Program, National and Kapodistrian University of Athens, Greece.

Please address correspondence to:
Clio P. Mavragani,
M. Asias 75,
11527 Athens, Greece.
E-mail: kmauragan@med.uoa.gr

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