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Fatal natalizumab-associated progressive multifocal leukoencephalopathy with initial low JCV antibody index in a multiple sclerosis patient

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Progressive multifocal leukoencephalopathy (PML) is a rare, oligodendroglial infection, caused by Polyomavirus JC (JCV), and a serious complication of natalizumab. We report here the case of a 62-year-old woman who presented a fatal PML developed after 50 months of natalizumab exposure, with initial low JCV index-value < 0.5 but with prior use of dimethyl fumarate (DMF).

This patient had a relapsing-remitting multiple sclerosis diagnosed in 2005. She received first immunomodulatory therapies, before switching to immunosuppressive therapies with DMF from 2014 to 2017 (lymphocyte nadir: 664/mm³) and fingolimod for 4 months in 2018. Natalizumab was introduced in September 2018 because of side effect under fingolimod (macular oedema). JCV serology was positive at baseline, with a low index-value at 0.67 and remained below 0.5 from October 2018 to June 2022. Patient neurological condition remained stable during this period with residual left hemiparesis predominating in the upper limb, hypoesthesia and dysmetria (EDSS score 5.5).

In September 2022, two new hyperintensities were identified on a systematic brain MRI (*Figure 1*). One month later, the patient complained of a worsening of her left hemiparesis (EDSS 6.5). Because of an initial suspicion of relapse, a 3-day course of oral 1 g/day methylprednisolone was administered. On the follow-up MRI two weeks later, hyperintensities had progressed. The JCV index-value was at 2.39 on October 17th, 2022, but the patient received a last natalizumab infusion mid-November 2022. The JCV index-value was controlled stable one month later at 2.53 on November 8th, 2022 and the patient was then referred to our department in December 2022. At admission, she presented a severe clinical worsening with left hemiparesis, aphasia and frontal syndrome. When reviewing retrospectively MRI scans, it appeared that the radiological pattern of hyperintensities was suggestive of PML, with marked T1 hypointensity involving subcortical U-shaped fibres with diffusion restriction particularly at the leading edge and no enhancement.

CSF JCV PCR was positive, with a high viral load, confirming the PML diagnosis. The patient received 4 courses of plasma exchange (PLEX) but the treatment was interrupted because of poor tolerance. Follow-up MRI in January showed progression of the lesions, without enhancement. The patient died on February 19th, 2023.

Risk stratification algorithm for PML under natalizumab treatment is based on (1) JCV serological status with index-value, (2) duration of treatment (> 24 months), and (3) prior

immunosuppressant use with residual effect (Plavina et al., 2014; Ho et al., 2017; Vukusic et al., 2020). Our patient had a long exposure to natalizumab, with a total duration of 50 months. However, because of low JCV index-value <0.5 throughout treatment period, she was not considered to be at high risk of PML. In the initial retrospective analysis of risk stratification (Plavina et al., 2014), a list of immunosuppressive drugs with residual effect was reported and included mainly mitoxantrone, mycophenolate mofetil, cyclophosphamide, methotrexate and azathioprine. In her past drug history, our patient had never been exposed to any of these drugs, but she received DMF, another immunosuppressive therapy. A recent review showed that the PML incidence in DMF treated patients was around 0.02/1000 patients (Jordan et al., MSJ 2022). Older age also appears to increase this risk.

In conclusion, this case highlights the special attention that should be paid to old MS patients previously exposed to more recent immunosuppressive therapies, such as DMF or fingolimod. In this specific population, positivity of JCV should prompt reconsideration of natalizumab start or continuation. And, given the 5% annual risk of seroconversion, any neurological event occurring under natalizumab treatment should raise the possibility of PML (Dwyer et al., 2021).

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Figure 1 legend

Figure 1 - Clinical and radiological evolution according to JCV index-value

(A) axial FLAIR: last stable routine surveillance brain MRI. – (B) axial FLAIR. Apparition of two new FLAIR white matter hyperintensities (right precentral and left frontal) (red arrows) – (C) axial FLAIR. Progression of the hyperintensities involving the U-fibers, with extension to left temporal lobe. – (D) and (E) axial FLAIR. Progression of the hyperintensities, with crossing of median line and slight mass effect on left frontal ventricular horn.

JCV: JC virus; NTZ: Natalizumab; PML: progressive multifocal leukoencephalopathy; MS: multiple sclerosis; PLEX: plasma exchange; FLAIR: fluid-attenuated inversion recovery

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