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CORRESPONDENCE

Natalizumab-associated complication? First case of peripheral T cell lymphoma

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Natalizumab (TYSABRI, Biogen Idec) is a therapeutic monoclonal antibody approved in 2004 for treatment of patients with the relapsing form of multiple sclerosis (MS). The drug reduces MS relapses, as well as new inflammatory lesions on MRI, and is highly clinically effective. Unfortunately, soon after approval, occurrence of progressive multifocal leukoencephalopathy (PML), due to reactivation of JC virus was reported with use of drug in two MS patients [6, 8] and one with inflammatory bowel disease [15]. Natalizumab was temporarily removed from the market. Availability resumed in 2006 with monitoring programs in place, including serological testing for JC virus exposure [3, 4]. As of 31 December 2011, over 95,300 patients have used natalizumab worldwide and, despite cautious use, 207 PML cases have occurred (https://medinfo.biogenidec.com). Other rare neoplastic [13] and infectious [2] complications seen in immunosuppressed patients are also starting to be reported.

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A 39-year-old woman with relapsing-remitting MS presented at age 36 (August 2007) with left hemisensory syndrome 5 weeks postpartum after her forth pregnancy. MRI was consistent with demyelination. On her second relapse (January 2008), multiple new MRI lesions were found and she met McDonald Criteria for definite MS. She had three more relapses over the next several months and was started on glatiramer acetate (October 2008). Due to relapses and an active MRI, she was switched to natalizumab (March 2009). She received 17 consecutive infusions. In August 2010, she noted left scalp tenderness, and in October 2010 had onset of vertigo, nausea without vomiting, and confusion. Emergent brain MRI in October 2010 revealed a new extra-axial mass overlying the left parietal convexity. The mass encircled the inner and outer tables of skull, with an enhancing intracranial part and smaller enhancing subgaleal component (Fig. 1a). JC virus serology was negative. Neurosurgical resection material revealed peripheral T cell lymphoma, unspecified, with severe cytological atypia, brisk mitotic rate (Fig. 1b), diffuse immunoreactivity for CD3 (Fig. 1c), and exceedingly high MIB-1 labeling (Fig. 1d). Lymphoma was negative for CD4, CD7, CD8, CD20, CD30, TdT, CD1a, and ALK-1 by immunohistochemistry, negative for Epstein Barr virus (EBV) by in situ hybridization, and clonal by gene rearrangement (Fig. 1e). Flow cytometry of tissue confirmed negativity for CD4, CD7, and CD8. This aggressive subtype represents about half of all peripheral T cell lymphomas in Western countries and is of unknown etiology.

Initial bone marrow biopsy was positive for lymphoma cells. She was treated with Hyper-CVAD chemotherapy (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and received donor stem cell transplant. Core biopsy of L2 vertebral body remained

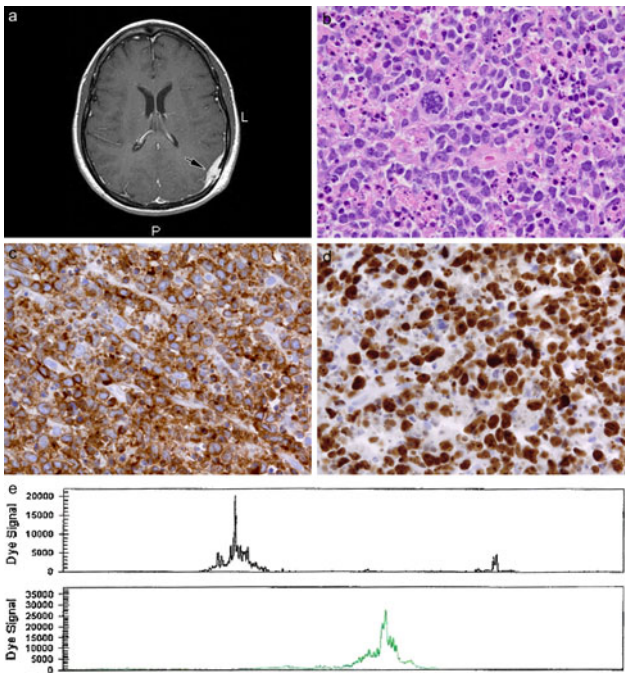

Fig. 1 **a** Peripheral T cell lymphoma first manifested as an extra-axial enhancing mass overlying the left parietal convexity (*arrow*). **b** The lymphoma showed severe cytological atypia and brisk mitotic rate. **c** Diffuse immunoreactivity for CD3 verified T cell origin; this was corroborated by flow cytometry. **d** Lymphoma demonstrated an exceedingly high MIB-1 rate. **e** Detection of monoclonal T cell population via PCR of *TCRG* gene with multiple primer sets

positive 11 months later despite aggressive therapy; she survives in guarded condition. She has not had any new neurological symptoms suggestive of MS relapse since stem cell transplant.

While PML remains the greatest risk associated with natalizumab use, other disorders possibly linked to natalizumab treatment have been reported, including primary central nervous system lymphoma (PCNSL) [13], ocular toxoplasmosis [17], melanoma [1, 5, 9–12, 16], and hepatosplenic T cell lymphoma [7], conditions identified in other immunosuppressed populations. We report the first peripheral T cell lymphoma in an MS patient after natalizumab treatment, but like the case of PCNSL [13], without evidence of EBV-driven etiology. Thus, clear definitive cause and effect cannot be established from this case, or any single example. Nevertheless, pathologists and clinicians need continual vigilance for "the unexpected" [14] in natalizumab-treated individuals.

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