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Natalizumab-related progressive multifocal leukoencephalopathy in Greece

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Abstract
Background & objectives: Progressive multifocal leukoencephalopathy (PML) may complicate natalizumab treatment in multiple sclerosis patients. We sought to characterize the clinical and laboratory features of natalizumab-related PML (NR-PML) cases from Greece.
Methods: Pharmaceutical industry, national drug authorities and all neurology departments within the Greek territory were asked to provide data for cases of NR-PML until October 2012. Collected cases were classified according to their level of diagnostic certainty using the five-level system introduced by Mentzer et al. (2012).
Results: Thirteen NR-PML cases were identified by the neurology departments. Data were provided for only 9 cases. PML manifestations appeared after a median number of 40 (21–52) natalizumab infusions. All but two patients were treated with plasma exchange and some were treated adjunctively with mirtazapine while the others were treated with mefloquine. IRIS developed in 6 cases after a median time of 6 (2–10) weeks from PML presentation and were treated with different regimens of corticosteroids. PML was fatal in 3 cases. The median EDSS after a median follow-up time of 12 (8–23) months in the surviving cases was 4.75 (2–8.5).
Conclusions: Outcomes for collected NR-PML cases varied from death to returning to baseline. Close surveillance is essential for early diagnosis and treatment of NR-PML patients.

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1. Introduction

Natalizumab is a humanized IgG_4 monoclonal antibody that works against the α4 subunit of the VLA4 integrin; licensed for the treatment of highly active relapsing-remitting multiple sclerosis (MS). Its primary mechanism of action is thought to be the prevention of leukocyte migration from the lumen of the cerebral vessels into the brain parenchyma. Natalizumab binds to the VLA-4 molecules on the surface of the leukocytes and prevents interaction of the VLA-4 molecules with their ligands (VCAM1 and fibronectin) on the endothelial surface, which is essential for leukocyte adhesion to the endothelial wall (Engelhardt and Briskin, 2005). Two phase III clinical trials (AFFIRM and SENTINEL) and a post-hoc analysis of the AFFIRM trial have provided evidence of natalizumab's remarkable efficacy as an immunomodulator (Polman et al., 2006; Rudick et al., 2006; Havrdova et al., 2009). Unfortunately, despite its very satisfactory overall safety profile, natalizumab treatment in MS has been complicated with the development of progressive multifocal leukoencephalopathy (PML), which is an opportunistic infection of the central nervous system (CNS) associated with severe morbidity and mortality due to re-activation of latent John Cunningham virus (JCV). PML occurs in the context of HIV infection, immunosuppressive treatments, chemotherapy and organ and bone marrow transplantation.

Natalizumab-related PML (NR-PML) was reported for the first time in 2005 in two multiple sclerosis patients receiving natalizumab in combination with interferon beta-1a in the SENTINEL trial and shortly after in a third patient participating in a natalizumab trial for Crohn's disease (ENACT-1 & 2) (Kleinschmidt-DeMasters and Tyler, 2005; Van Assche et al., 2005). Nevertheless, the first post-marketing case occurred in July 2008 and 323 PML cases have been reported among 110,000 patients treated with natalizumab worldwide as of the end of 2012. PML has also been reported in association with other monoclonal antibodies including rituximab, alemtuzumab, efalizumab, adalimumab, bevacizumab, cetuximab and infliximab, used to treat conditions other than MS (Keene et al., 2011). Interestingly, NR-PML in MS patients exhibits several clinical and radiological differences compared to PML seen under different circumstances (Hellwig and Gold, 2011; Yousry et al., 2012). This study presents 9 cases of NR-PML from Greece focusing on their clinical and radiological features, treatments and outcomes.

2. Methods

Biogen Idec, Genesis Pharma SA (the representative of Biogen for natalizumab distribution in Greece), the Greek National Organization for Medicines, and all Neurology Departments within the Greek territory were asked to provide data for cases of NR-PML up to October 2012. Contacts were made via email (Biogen Idec), personal and official letters (Genesis Pharma SA) or official letters only (National Organization for Medicines). Neurology Departments were approached via telephone. Units performing plasma exchange were also contacted. Treating neurologists had to fill a datasheet with demographic, clinical, MRI, laboratory and treatment data prior, during and after PML presentation for each NR-PML case. Demographic and clinical data included age, gender, disease duration to PML presentation, comorbid conditions, disease-modifying treatments (DMTs) prior to natalizumab, other medications, EDSS at natalizumab treatment onset, number of natazizumab courses at PML presentation, PML presenting manifestations, presence of seizures, EDSS at PML diagnosis and at latest follow-up and time to PML diagnosis. MRI data sought included lesion localization, presence of Gadolinium enhancement, DWI signal abnormalities and presence of edema. All MRI scans were reviewed by a neuroradiology specialist (PT). Laboratory data including CSF analysis (cell counts, protein levels, JCV PCR), brain biopsy and anti-JCV ELISA antibody status were collected. Information on plasma exchange (PLEX), treatment of IRIS and its manifestations, other treatments used for PML (mefloquine, mirtazapine or cidofovir), intensive care requirement, the disease-modifying treatments used after PML-IRIS and MS disease activity after PML-IRIS were collected. IRIS was defined as the clinical deterioration following immune reconstitution with or without MRI changes (Hellwig and Gold, 2011).

Given the heterogeneous clinical presentations and the range of paraclinical investigations (MRI, PCR, CSF vs. serum anti-JCV antibody levels, histopathology) that complicate PML diagnosis, a standard 5-level system for defining diagnostic certainty of monoclonal antibody treatment-associated PML was recently proposed based on the clinical, imaging and laboratory findings suggestive of the diagnosis (Mentzer et al., 2012). Our group of NR-PML cases were categorized according to the above system for future reference and data comparability.

Correlations between EDSS at follow-up and a number of variables (number of natalizumab courses, patient age, time from PML presentation to diagnosis, time from PML presentation to PLEX, duration of DMTs prior to natalizumab, MS disease duration, EDSS at onset, JCV CSF PCR DNA copies, CSF cell counts, CSF protein levels) was calculated with the Spearman's rank correlation coefficient. The GraphPad Prism version 5 software was used for statistical analysis.

3. Results

Biogen Idec, Genesis Pharma SA and the National Organization for Medicines did not provide data. Only treating neurologists provided data. Thirteen NR-PML cases were identified by October 2012. Relevant data were collected for 9 NR-PML cases and are summarized in Tables 1-3. Four more NR-PML cases from Greece have been reported before and will not be dealt with here in detail (Travasarou et al., 2012). All data in the text are presented as a median (range) unless otherwise stated.

3.1. Demographic and epidemiological data

The median age at PML presentation was 42 years and ranged between 31 and 64 years. Seven of the 9 patients were female. The median disease duration from MS diagnosis to PML was 11 (8-24) years. All but one patient had