Natalizumab-Associated Primary Central Nervous System Lymphoma

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Key words
- Central nervous system
- Craniotomy
- Crohn disease
- Lymphoma
- Multiple sclerosis
- Natalizumab
- Tsyabri

Abbreviations and Acronyms
EBV: Epstein-Barr virus
FDA: Food and Drug Administration
HHV: Human herpesvirus
HIV: Human immunodeficiency virus
Ig: Immunoglobulin
LPD: Lymphoproliferative disorder
MS: Multiple sclerosis
PCNSL: Primary central nervous system lymphoma
PML: Progressive multifocal leukoencephalopathy

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OBJECTIVE: **Natalizumab, a selective adhesion molecule inhibitor binding to an α-4 subunit of integrin, has emerged to be an effective immunomodulator, especially in the treatment of relapsing-remitting multiple sclerosis and Crohn disease. Recent reports documenting the development of primary central nervous system lymphoma (PCNSL) as a result of its administration have been concerning, and they trigger a debate about a possible causal association. In our report, we provide a comprehensive review of the literature on lymphoma development after natalizumab use, and we report an additional case of PCNSL development in a young woman who received natalizumab for her Crohn disease.**

METHODS: **A systematic (qualitative) review of literature on lymphoma development after natalizumab therapy was performed by use of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Data on patient characteristics, indication for drug therapy, dosages, radiologic findings, potential risk factors for PCNSL, and tumor markers were synthesized. Additionally, we present the findings from the case of a young woman who received natalizumab therapy (4 doses, 300 mg each) for Crohn disease and in whom PCNSL developed.**

RESULTS: **Overall, 8 reports including our index case document lymphoma development after natalizumab use. Our case finding revisits the debate suggesting a remote possibility of association that warrants further evaluation and validation.**

CONCLUSIONS: **Evidence documenting a causal association of natalizumab and PCNSL is weak. Considering the potential benefits of using natalizumab for current indications, we recommend vigilant monitoring of patients receiving the drug for PCNSL outlook.**

INTRODUCTION

Primary central nervous system lymphomas (PCNSL) are rare tumors and constitute approximately 2.4% of all primary intracranial neoplasms.[1] Immunodeficiency, congenital or acquired, has been implicated in its genesis. Recent reports documenting a drug-induced association of PCNSL after the use of a human recombinant monoclonal immunoglobulin (Ig)G4 antibody, natalizumab (Tysabri), have been concerning, albeit widely debated.[2-8] Natalizumab is an approved therapy for the management of relapsing multiple sclerosis (MS) in both the United States and Europe, and for Crohn disease in the United States alone.[9-11]

Our report, describing the development of PCNSL in a young woman who received natalizumab therapy for her Crohn disease, revisits the widely debated association of natalizumab with PCNSL. Additionally, we provide our findings from a systematic review of literature, documenting the clinicopathologic characteristics of patients reported to have experienced PCNSL after treatment with natalizumab.

METHODS

A systematic review of the literature was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] Relevant peer-reviewed articles up to July 2017 were searched by the use of electronic databases: MEDLINE, Web of Science, and Google Scholar. The primary search terms included "natalizumab" and "Tysabri" in the article titles. The extracted citations were then screened for duplicates, after which boolean operators "and" and "or" were applied on the extracted records by use of the terms "lymphoma," "central," "central nervous system," and "primary" in various combinations to narrow the scope of the review. The resulting citations were screened in detail for further eligibility in their entirety by 2 authors independently (P.K. and K.S.). Screening was performed by reviewing article titles, abstracts, or full texts. To ensure completeness of the

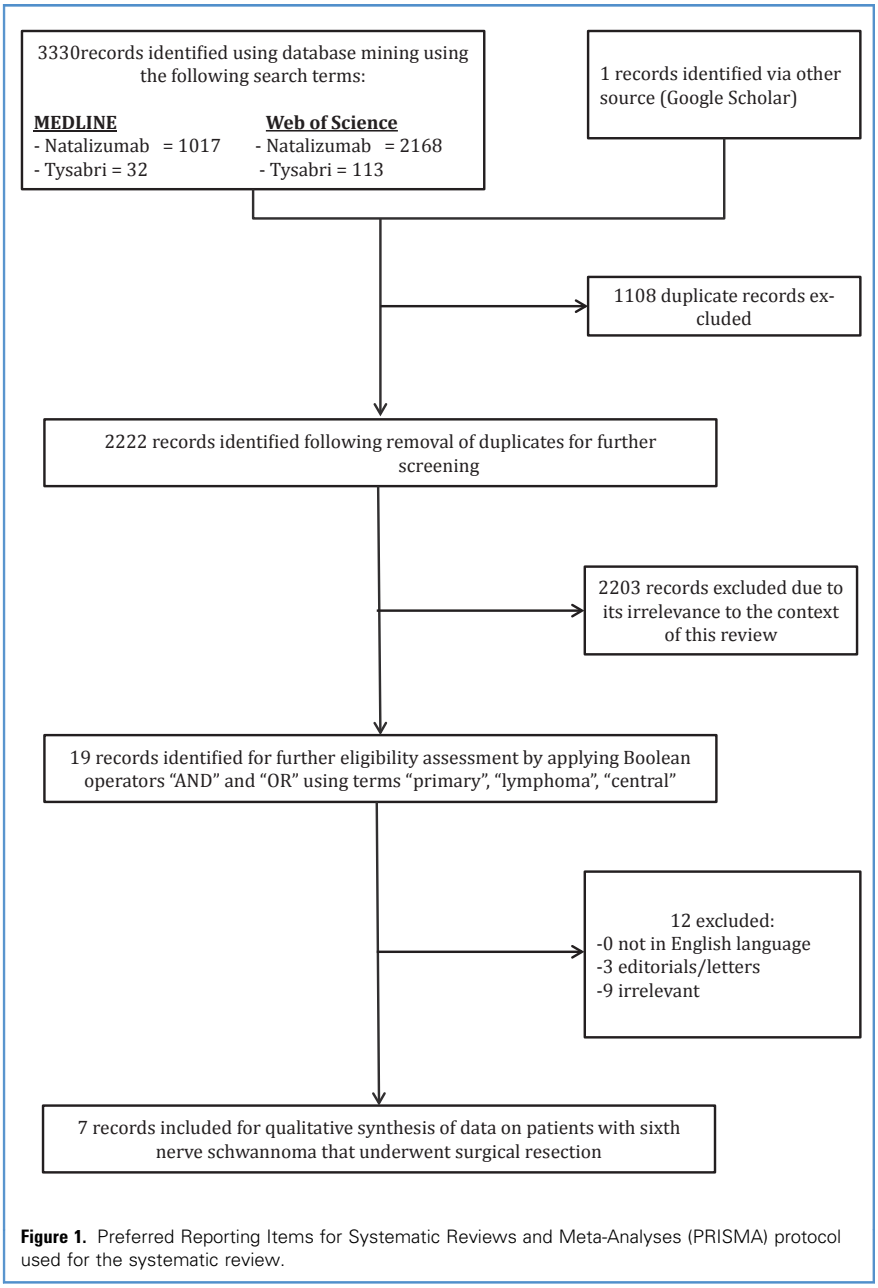

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol used for the systematic review.

review, bibliographies of the identified publications and articles citing them were also scrutinized.

The criteria implemented for screening included 1) articles documenting an association of the drug with PCNSL development; 2) articles limited to human subjects. Articles documenting the development of progressive multifocal leukoencephalopathy (PML) and other adverse effects after natalizumab administration, and those not in English languages, were excluded. Any potential conflict arising on article selection was mitigated by discussion and mutual consensus. The final list of identifiable papers for data synthesis was reviewed and approved by the senior author (B.G.). Relevant information including patient characteristics, indication of drug therapy and dosages, radiologic findings, potential risk factors for PCNSL, and tumor markers was extracted. A glimpse of our search strategy algorithm is presented in Figure 1. A summary of our findings is tabulated in Table 1.[2-8] In addition, we present the findings of our index case of a patient in whom PCNSL developed after she received the monoclonal antibody.

CASE ILLUSTRATION

History and Examination

A 27-year-old woman presented to our neurosurgical clinic because of 2 weeks of worsening headaches and visual disturbances, primarily diplopia. Her past medical history was significant for Crohn disease and fibromyalgia. Upon further questioning about her chronic conditions, she stated that she had received a total of 4 doses of natalizumab for Crohn disease, although she was currently not taking any other medications or immunomodulators. She did not describe experiencing fever, nausea or vomiting, weight loss, night sweats, cough, seizures, vertigo, or tinnitus. A review of systems gave negative results. A comprehensive metabolic profile and complete blood count did not reveal any abnormalities. The results of her physical examination were remarkable for diplopia on left lateral gaze. No other motor or sensory deficits were noted. A noncontrast computed tomographic (CT) scan of the head demonstrated a region of hyperdensity in the right temporal lobe with surrounding edema, measuring approximately 2.6 cm in its maximal diameter, suggestive of a brain neoplasm (Figure 2A). A brain abscess was the other differential diagnosis that was considered at this point. Magnetic resonance imaging of the brain with and without contrast material was subsequently obtained. The findings were consistent with a gadolinium ring-enhancing lesion in the right temporal tip with a hypointense area of necrotic center with surrounding vasogenic edema, consistent with a brain neoplasm (Figures 2B, C). Diffusion-weighted imaging revealed a low intensity signal (Figure 3A) and an apparent diffusion coefficient image revealing a high-intensity signal (Figure 3B) within the necrotic center, confirming our suspicion of a brain neoplasm as opposed to an abscess. The results of an evaluation for immunocompetency, including testing for human immunodeficiency virus (HIV) and human herpesvirus (HHV), were negative, except for Epstein-Barr virus (EBV)