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CASE REPORT

Natalizumab and HSV meningitis

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Abstract Natalizumab (Tysabri, Biogen Idec and Elan Pharmaceuticals) is a monoclonal antibody approved for use in patients with relapsing multiple sclerosis (MS) as well as moderate to severe Crohn's disease. We report the first case of a patient with a history of MS, on monthly natalizumab, who developed HSV-2 meningitis. We discuss the mechanism of action of natalizumab and review what is known about the reactivation of herpes infection in association with this medication. The question of herpes simplex virus (HSV) and varicella zoster virus (VZV) prophylaxis for patients is raised.

Introduction

Natalizumab (Tysabri, Biogen Idec and Elan Pharmaceuticals) is a monoclonal antibody approved for use in patients with relapsing multiple sclerosis (MS) and moderate to severe Crohn's disease (CD). We report the case of a 51-year-old woman with MS, on natalizumab, who presented with fevers, headaches, and neck stiffness.

Three days prior to admission, she developed a headache and neck discomfort. The following day, she felt fatigued with worsening headache and nuchal rigidity. On the day prior to admission, she developed chills and fever to 38.7°C (101.7°F) and presented to the Emergency Department (ED) at our hospital.

She had been diagnosed 4 years prior to admission with MS when an evaluation for headaches revealed evidence of demyelinating disease on brain MRI and a lumbar puncture demonstrated oligoclonal bands and mild lymphocytosis. Initial treatment included glatiramer acetate (Copaxone, Teva Pharmaceuticals), which was complicated by extreme site reactions. Interferon beta-1a (Avonex, Biogen Idec) was complicated by depression, chills, and fever and discontinued in favor of monthly natalizumab, approximately a year prior to her admission. Her other past medical history was significant for depression and asthma. She had no history of sexually transmitted diseases and specifically no history of genital herpes.

In the ED, she was found to be febrile to 38.3°C (101°F). She received parenteral ceftriaxone and vancomycin, and oral oseltamivir for suspected bacterial meningitis and possible H1N1 infection. Analysis of cerebrospinal fluid (CSF) obtained by lumbar puncture (LP) revealed 25 white blood cells with 4% neutrophils, 52% lymphocytes, and 40% monocytes, glucose of 59 mg/dl, and total protein of 52 mg/dl. The Gram stain showed rare mononuclear cells, a few red blood cells, and no organisms. Infectious disease was consulted: ampicillin and acyclovir were added for empiric coverage of *Listeria monocytogenes* and herpes simplex virus (HSV).

She was afebrile and complained of photophobia. She was unable to flex her neck. She had no oral lesions. She was sleepy but arousable and oriented to time and place. Her speech was slowed without paraphrasic errors. Cranial nerve exam was intact. She had diminished sensation of light touch and vibration and impaired coordination bilaterally. Her gait was unsteady. A pelvic and genital exam was not performed.

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Brain MRI revealed no evidence of encephalitis. Repeat LP studies are shown in Table 1. CSF cryptococcal antigen was negative, as were bacterial cultures. The CSF was not tested for syphilis. On the third day, herpes simplex virus 2 (HSV2) PCR returned positive.[1] She was continued on acyclovir with slow clinical response.

The patient was seen in follow-up infectious disease clinic as well as neuro-infectious disease clinic: after approximately 4 weeks of IV acyclovir, she was switched to valacyclovir. At the time, an LP was negative for HSV, JC virus, and syphilis, and a brain MRI was stable. Neuropsychological testing revealed mild cognitive sequelae. Three months after her acute illness, she resumed natalizumab. It was recommended that she continue on HSV prophylaxis though she had difficulties with adherence to various prophylactic regimens due to gastrointestinal intolerance and she self-discontinued therapy. A clear understanding of the cognitive sequelae of the HSV-2 meningitis versus MS-related manifestations has been limited by lack of baseline neuropsychiatric testing.

Table 1 CSF Findings

	Hospital day 1	Hospital day 2
WBC	25	88
%PMN	4	2
%Lymphs	52	50
%Monos	40	48
Glucose	59	72
Total protein	52	37
HSV PCR	+HSV2	Not tested
Cultures	No growth	No growth

Discussion

Natalizumab is a monoclonal antibody targeted at two specific α4 integrins, α4β1 (also known as very late antigen 4 or CD49d–CD29) and α4 β7(also known as lamina propria-associated molecule 1), present on the surface of T lymphocytes. The interaction of these receptors with cell adhesion molecules on the vascular endothelium of the blood–brain barrier allows activated T lymphocytes to penetrate the brain. Natalizumab disrupts this interaction. The decrease in lymphocyte-induced inflammation is believed to be responsible for the clinical benefit (Von Andrian and Engelhardt 2003).

Natalizumab use has been infrequently associated with brain infections since its use was approved by the FDA and introduced in the USA in 2004 (Miller et al. 2003; Ghosh et al. 2003) Progressive multifocal leukencephalopathy (PML), caused by the JC virus, was reported in patients treated with natalizumab for MS and for Crohn's disease in the months following its introduction (Van Assche et al. 2005; Langer-Gould et al. 2005).

In 2005, natalizumab was withdrawn from the market, returning in 2006 after an FDA advisory committee recommended it for patients with relapsing MS, with restrictions and mandatory monitoring required.[2] As of December 2010, a total of 79 cases of PML and 16 deaths associated with Tysabri use have been reported by Biogen Idec.[3,4]

In MS and Crohn's disease studies of natalizumab, the incidence of herpes-like symptoms was greater in the treatment group than the placebo.[5] In 2006, the labeling of natalizumab was modified to include the warning that

[1] HSV PCR testing in our clinical lab is completed using the LightCycler® FastStart DNA Master HybProbe (Roche). Nucleic acid extracted from 200 μl of CSF fluid was tested for the presence of herpes simplex viral DNA type 1 and/or 2 using LightCycler real-time PCR on a LightCycler 1.2 instrument with FRET hybridization probes. Primers and probes are sequence-specific for the DNA polymerase gene of HSV-1/2. A 215-bp fragment of the DNA polymerase gene (Genebank accession nos. M12356 and M16321) was amplified with specific primers for HSV-1/2. The amplicon is detected by fluorescence using a specific pair of hybridization probes. The hybridization probes consist of two different short oligonucleotides that hybridize to an internal sequence of the amplified fragment during the annealing phase of the PCR cycle. One probe is labeled at the 5′-end with LightCycler® Red 640-*N*-hydroxy-succinimide ester (Red 640-NHS ester) or LightCycler® 705-phosphoramidite and, to avoid extension, modified at the 3′-end by phosphorylation. The other probe is labeled at the 3′-end with fluorescein. Only after hybridization to the template DNA do the two probes come in close proximity, resulting in fluorescence resonance energy transfer (FRET) between the two fluorophores. During FRET, fluorescein, the donor fluorophore, is excited by the light source of the LightCycler® 1.2 Instrument, and part of the excitation energy is transferred to LightCycler® Red 640-NHS ester or the LightCycler® 705-phosphoramidite, the acceptor fluorophore. The emitted fluorescence of LightCycler® Red 640-NHS ester is then measured by the LightCycler® 1.2 Instrument. A melting curve analysis was performed after the PCR run to differentiate positive samples in HSV-1 or HSV-2. Melting points for HSV-1 and HSV-2 are reproducible and significantly different and allow clear determination of the HSV subtype (REF no. 03315177001). An internal control is used in this process to control for substances that may interfere with DNA amplification. Detail courtesy of JS Eversly and ES Rosenberg, Massachusetts General Hospital Molecular Laboratory.

[2] Patients receiving natalizumab are required to participate in the TOUCH Prescribing Program which requires baseline MRI prior to initiation of therapy.

[3] Reuters Health News. Biogen reports more PML cases with natalizumab (Tysabri), 17 December 2010.

[4] Reuters. Biogen CEO says Tysabri added 1,700 patients in Q4, 11 January 2011.

[5] Natalizumab label, Sec 6.3, Post-Marketing Experience, US Food and Drug Administration (Accessed 22 November 2009 at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125104s0067lbl.pdf). No data are provided on statistical significance.

there was one case of fatal herpes encephalitis in a patient receiving the product. A second patient with herpes meningitis survived.[6] Unfortunately, none of the publicly available documents comment on whether or not these cases represent infection with HSV-1 or HSV-2.[7] Over 56,000 patients are currently being treated with natalizumab, and given the incidence of HSV reported among this population, our case study represents a rare event.

Recently, researchers have shown that oral herpes eruptions were three times more likely in MS patients taking natalizumab than in MS patients not taking natalizumab (Scheiss et al. 2009). In this observational study, researchers compared patient reports of symptoms of herpes simplex 1 (HSV1), HSV2, varicella zoster virus (VZV) and Epstein–Barr virus among healthy controls, patients with MS on natalizumab, and MS patients receiving interferon. They found that patients treated with natalizumab were more likely than healthy controls (p=0.005) and than MS patients not receiving natalizumab (p=0.05) to develop oral herpes. They also found that saliva VZV titers were higher in the week following natalizumab infusion (p=0.06).

HSV infection has been associated with another monoclonal antibody. Alemtuzumab (Campath, Ilex Pharmaceuticals) is used in the treatment of B cell chronic lymphocytic leukemia (CLL), and non-Hodgkin's lymphoma and T cell malignancies (CTCL). It binds to the CD52 receptor site on lymphocytes. In patients with CLL and CTCL treated with alemtuzumab, up to 45% had reported viral infections (Thursky et al. 2005). A recent study of alemtuzumab for early MS reported that about 8% of patients suffered herpes simplex infections, and viral meningitis was reported in one patient (CAMMS223 Trial Investigators et al. 2008). Given the documented increased risk, famcyclovir or acyclovir prophylaxis is recommended for patients on therapy and for up to 6 months after the last treatment (Worth et al. 2005).

In conclusion, we report the first case of HSV-2 meningitis associated with the use of natalizumab. While aseptic meningitis occurs in more than a third of women coincident with primary HSV-2 genital infection (Berger and Houff 2008), in our case, the patient had no history of oral or genital HSV. Though the available data cannot support a causal relationship between natalizumab and HSV, given the increased frequency of oral herpes in patients on natalizumab, its mechanism of action, and the experience with PML, there is a need for increased awareness and research to define the relationship between HSV and natalizumab. Clinicians prescribing natalizumab may consider initiating prophylaxis in particularly high-risk patients and at the very least early treatment of patients with active or recurrent herpes.

Competing interest None declared.

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[6] Natalizumab label, updated October 2008, Sec 6.3, Post-Marketing Experience, US Food and Drug Administration. (Accessed 15 February 2011 at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125104s0067lbl.pdf).

[7] The labeling of Tysabri does not included details regarding whether or not cases of herpes encephalitis and meningitis were related to HSV-1 or HSV-2.