

Delayed Allergic Reaction to Natalizumab Associated With Early Formation of Neutralizing Antibodies

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Background: Natalizumab is a new therapeutic option for relapsing-remitting multiple sclerosis. As with other antibody therapies, hypersensitivity reactions have been observed. In the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) trial, infusion-related hypersensitivity reactions developed in 4% of patients, usually within 2 hours after starting the infusion.

Objective: To report a significant, delayed, serum sickness–like, type III systemic allergic reaction to natalizumab.

Design: Case report describing clinical follow-up and the serial measurement of antinatalizumab antibodies.

Patient: A 23-year-old man with relapsing-remitting multiple sclerosis developed a fever, arthralgias, urticarial

exanthema, and a swollen lower lip during several days after his second infusion of natalizumab.

Results: The patient developed a delayed, serum sickness–like, type III systemic allergic reaction to natalizumab. Five weeks after initiation of this therapy, he tested positive for antinatalizumab antibodies and exhibited persistent antibody titers 8 and 12 weeks later. His symptoms completely resolved with a short course of oral glucocorticosteroids.

Conclusion: Clinicians and patients should be alert not only to immediate but also to significantly delayed substantial allergic reactions to natalizumab.

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NATALIZUMAB IS A MONOCLONAL antibody targeting α_4 integrin. It is highly effective in reducing the relapse rate and disease progression in patients with relapsing-remitting multiple sclerosis¹ and was approved by the US Food and Drug Administration in June 2006 as monotherapy given intravenously every 4 weeks. Adverse effects include progressive multifocal leukoencephalopathy in about 0.1% and systemic allergic reactions in about 4% of treated patients. Hypersensitivity reactions usually occur within 1 hour after the infusion of natalizumab and frequently concur with the second infusion.

Here we describe a patient who presented to us 6 days after the second dose of natalizumab with a substantial systemic allergic reaction. Subsequently, he tested permanently positive for antibodies against natalizumab.

REPORT OF A CASE

A 23-year-old white man was treated with natalizumab for severe relapsing-remitting multiple sclerosis with recurrent myelitis

resulting in severe gait ataxia (Expanded Disability Status Scale, 5.5). Previous treatments included steroid pulses for relapses and 44 μ g of interferon beta-1a 3 times weekly. Interferon therapy was discontinued after 1 year because of insufficient efficacy. The first dose of natalizumab was given 24 days later. The patient did not report any adverse reactions within 2 hours after the first and second infusions. On both occasions there were no immediate adverse effects and the patient returned home. Eight hours after the second infusion, however, he collapsed and developed a fever of up to 39.4°C. Initially, he thought he had acquired a viral infection and therefore did not seek medical advice. His body temperature returned to normal, but 3 days later an itching rash appeared on his thighs and chest. Another 3 days later, his lower lip swelled and the general practitioner referred the patient back to our outpatient clinic.

The patient reported arthralgias and a feeling like he had a swollen tongue and throat. On examination, there was an urticarial erythema accentuated on his thighs and chest. His lower lip was swollen (**Figure 1**). His concurrent medications had been unchanged during the past

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Figure 1. Swollen lower lip (A) and erythema on the right thigh (B) documented in a 23-year-old patient with multiple sclerosis 6 days after his second dose of natalizumab.

weeks. He had no history of allergic reactions. After excluding infectious causes, we started treatment with 60 mg of prednisolone orally for 2 days; all symptoms disappeared in the subsequent days. We diagnosed a delayed allergic reaction, discontinued natalizumab, and initiated mitoxantrone therapy after 8 weeks instead.

Evaluation of antinatalizumab antibodies by standard sandwich enzyme-linked immunosorbent assay¹ revealed that the patient had seroconverted after the second dose of natalizumab. The number of antibodies rose further during the following 8 weeks until the first dose of mitoxantrone, when they started to decrease slightly (**Figure 2**). The order of magnitude of the antinatali-

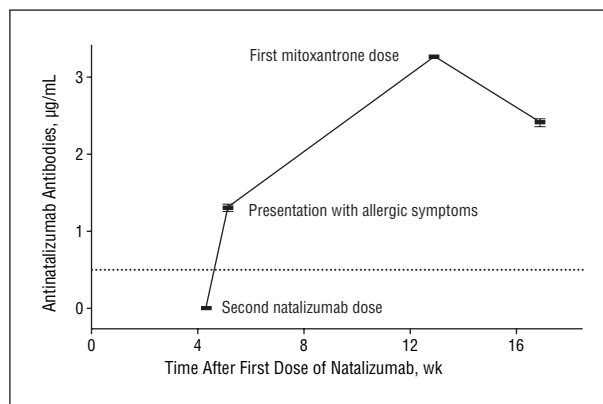


Figure 2. Time course of antibodies against natalizumab. Antibodies were measured by sandwich enzyme-linked immunosorbent assay in serum samples obtained as indicated immediately before the second dose of natalizumab, at peak of symptoms when the patient presented in our outpatient clinic (6 days after the second dose of natalizumab), immediately before the first dose of mitoxantrone, and 21 days after mitoxantrone. Whiskers indicate SDs of triplicates. The dotted line indicates the cutoff for antibody-positive samples at 0.5 µg/mL.

zumab antibodies in this patient was similar to other patients who have tested positive for antibodies against natalizumab.

COMMENT

This patient showed a delayed allergic reaction that developed during several days after the second infusion of natalizumab. Tests were persistently positive for antinatalizumab antibodies as early as 5 weeks after the first dose. Most previously reported hypersensitivity reactions to natalizumab occurred within in the first 2 hours after infusion. By contrast, our patient developed symptoms gradually during several days. Because we could not detect any other cause for this hypersensitivity reaction, a causal relationship with the second natalizumab infusion is very likely.

So far, typical infusion-related allergic reactions after natalizumab treatment include anaphylactoid hypersensitivity reactions with urticaria,² allergic dermatitis,² flushing, headache, and hypotension. These symptoms occurred within 2 hours after infusion and would be classified as type I allergic reactions. However, in our case, the clinical course points to a serum sickness–type reaction (type III), because symptoms progressed during several days. Three cases (2 patients in treatment groups, 1 patient in a placebo group, each at a single study center) of serum sickness were noted in the phase 2 trial of natalizumab in multiple sclerosis,³ but no further information about the time course, symptoms, or treatment of these patients was provided. Serum sickness has also been described in association with other monoclonal antibody therapies, including chimeric antibodies, such as infliximab⁴ and rituximab,⁵ as well as humanized antibodies, such as alemtuzumab.⁶ In one study with infliximab in patients with Crohn disease, serum sickness occurred in 2.8% of patients, indicating that type III allergic reactions may be more frequent with chimeric monoclonal antibodies than with humanized monoclonal antibodies.⁷

Data from the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) trial point to an association of infusion-related reactions with the presence of antinatalizumab antibodies, as 68% of natalizumab-treated patients who had hypersensitivity reactions were persistently positive for antibodies,² whereas the incidence of persistent antibodies was 6% in the entire treatment cohort.

Antinatalizumab antibodies in patients with multiple sclerosis have already been detected in 2 former studies as early as 4 weeks after a single natalizumab infusion.^{8,9} However, there are no data reported about adverse events or infusion-related reactions in these patients.

Our observation supports the view that hypersensitivity reactions are associated with antibody formation and that these antibodies can occur early in the treatment course with natalizumab. So far, testing is recommended within 6 months after the beginning of natalizumab therapy in patients who show evidence for therapy failure and/or infusion-like reactions. We believe that the antibody status can add important information and should therefore be tested early during natalizumab treatment in all patients who present with any type of hypersensitivity reaction.

In conclusion, patients and treating physicians should be aware that delayed hypersensitivity reactions, such as serum sickness, can develop during treatment with natalizumab. If unusual symptoms consistent with an allergic reaction occur during the first days after infusion, patients should contact their neurologists to initiate appropriate medical treatment. In such patients, early testing for natalizumab antibodies is advised.

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Pellkofer, Gold, and Kümpfel. *Analysis and interpretation of data:* Krumbholz and Kümpfel. *Drafting of the manuscript:* Krumbholz and Kümpfel. *Critical revision of the manuscript for important intellectual content:* Pellkofer, Gold, Hoffmann, and Hohlfeld. *Administrative, technical, and material support:* Krumbholz. *Study supervision:* Hohlfeld and Kümpfel.

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REFERENCES

1. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006;354(9):899-910.
2. Phillips JT, O'Connor PW, Havrdova E, et al. Infusion-related hypersensitivity reactions during natalizumab treatment. *Neurology*. 2006;67(9):1717-1718.
3. Miller DH, Khan OA, Sheremata WA, et al; International Natalizumab Multiple Sclerosis Trial Group. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2003;348(1):15-23.
4. Gamarra RM, McGraw SD, Drelichman VS, Maas LC. Serum sickness-like reactions in patients receiving intravenous infliximab. *J Emerg Med*. 2006;30(1):41-44.
5. Schutgens RE. Rituximab-induced serum sickness. *Br J Haematol*. 2006;135(2):147.
6. Blisard D, Nation D, Khan A, et al. Serum sickness in pancreas transplantation with campath-1h induction. *Am J Transplantation*. 2006;82(1)(suppl 6):528.
7. Colombel JF, Loftus EV Jr, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology*. 2004;126(1):19-31.
8. Vollmer TL, Phillips JT, Goodman AD, et al. An open-label safety and drug interaction study of natalizumab (Antegren) in combination with interferon-beta (Avonex) in patients with multiple sclerosis. *Mult Scler*. 2004;10(5):511-520.
9. Tubridy N, Behan PO, Capildeo R, et al. The effect of anti-alpha4 integrin antibody on brain lesion activity in MS: The UK Antegren Study Group. *Neurology*. 1999; 53(3):466-472.

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