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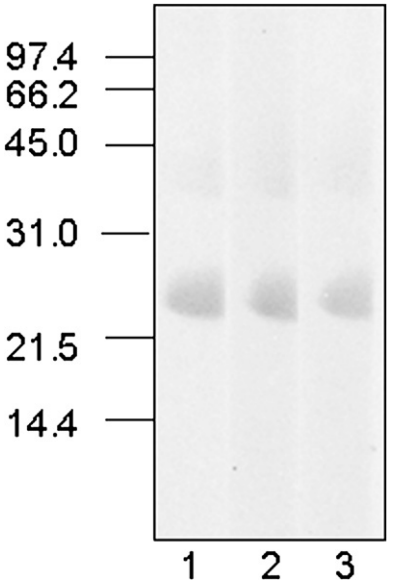

FIG 1. Natalizumab immunoblotting (40 μg per lane). Serum dilutions: 1:5 *(lane 1)*, 1:10 *(lane 2)*, and 1:20 *(lane 3)*. A 28-kd band is recognized in all lanes. The molecular marker (Low Range, Bio-Rad) contains 6 different proteins with the following molecular weights: lysozyme, 14.4 kd; trypsin inhibitor, 21.5 kd; carbonic anhydrase, 31.0 kd; ovalbumin, 45.0 kd; serum albumin, 66.2 kd; and phosphorylase b, 97.4 kd.

Biological agents: New drugs, old problems

To the Editor:

Monoclonal antibodies are innovative drugs used to treat different human diseases. Adverse events related to these drugs are typically mild but can be life-threatening. Potential adverse reactions also include IgE-, IgG-, or T cell–mediated hypersensitivity reactions.[1] Natalizumab is a recombinant humanized IgG4κ mAb anti–α_4-integrin produced in murine myeloma cells and used in multiple sclerosis treatment. It consists of 2 heavy and 2 light chains connected by 4 interchain disulfide bonds with a molecular weight of 146 kd. Several cases of hypersensitivity reactions to natalizumab have been reported, but no IgE-mediated mechanism has been demonstrated to date.

We describe the case of a 46-year-old woman with multiple sclerosis who was receiving intravenous treatment with natalizumab monthly (Tysabri; Biogen Idec SL, Cambridge, Mass). Immediately after the second dose of the drug, the patient experienced a generalized, pruritic, maculopapular rash with palmoplantar involvement and shortness of breath requiring treatment with corticosteroids and antihistamines. The patient had no prior personal history of rhinitis, food allergy, urticaria, or anaphylactic episodes. She was referred to our allergy unit to rule out a possible case of hypersensitivity to natalizumab.

Cutaneous tests were performed according to the European Network for Drug Allergy recommendations,[2] resulting in a negative skin prick test response (20 mg/mL) to natalizumab but a positive result (20 × 20 mm) on the intradermal test (0.002 mg/ml). After obtaining written informed consent, a healthy control subject was also tested, with negative results.

The protein profile was analyzed by means of SDS-PAGE with reducing and nonreducing conditions and stained with Coomassie Blue (Bio-Rad Laboratories, Hercules, Calif). Specific IgE to natalizumab was detected by using the UniCAP 100 system (Phadia, Uppsala, Sweden), according to the manufacturer's instructions. Briefly, natalizumab was labeled with biotin (Roche Diagnostics GmBH, Mannheim, Germany) and afterward conjugated with commercial streptavidin ImmunoCAP (Phadia). The allergenic profile of the patient's serum was studied by means of immunoblot (dilution 1:2) by using reducing and nonreducing conditions with the natalizumab in the solid phase. Serum samples from 4 subjects treated with natalizumab and without clinical symptoms were analyzed in parallel and used as negative controls. After reducing conditions, 2 different bands at 28 and 48 kd were identified. The immunoblot studies demonstrated the IgE-binding capacity of both previously described bands. However, only the 28-kd band was vividly recognized (Fig 1). In nonreducing conditions one band in the high-molecular-weight range was intensely visualized (Fig 2). No band was identified in control subjects who tolerated natalizumab. The level of specific IgE to natalizumab in serum was 16.5 kUI/L. No specific IgE to carbohydrate determinants[3] was detected. This assay was performed by using ImmunoCAP with both bromelain and epithelia (Phadia) extracts. Specific IgE levels to epithelia extracts (Phadia) were also negative, recently associated with sensitization to carbohydrates determinants.[3]

The detection of a positive intradermal test result together with the specific IgE to natalizumab suggests that an IgE-mediated mechanism could be responsible for the patient's reaction. The immunoblot supports these findings because the patient's serum recognized a 28-kd band that corresponds, as previous studies have demonstrated, to the Fab fragment of natalizumab.[4] The Fab fragment corresponds to the murine fraction of this humanized mAb and contains a glycosylation site.[4] However, no sensitization to glycoproteins or carbohydrate determinants was detected. Therefore these results suggest that our patient was sensitized to protein epitopes.

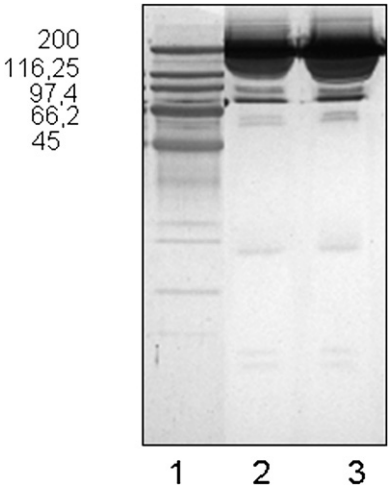

FIG 2. Natalizumab SDS-PAGE under nonreducing conditions: standard high molecular weight (Bio-Rad; *lane 1*), 20 μg of natalizumab *(lane 2)*, and 40 μg of natalizumab *(lane 3)*. One band in the high-molecular-weight range is intensely visualized.

IgG hypersensitivity reactions to natalizumab have been described previously, and IgG against natalizumab is present in up to 12% of patients receiving natalizumab.[5] Other immunologic events, such as serum sickness–like delayed hypersensitivity reactions, have also been reported.[6] IgE-mediated reactions have been described with other mAbs, such as cetuximab[7] or omalizumab.[8] Chung et al[7] observed that these patients had IgE against cetuximab before therapy. These IgE antibodies were specific for an oligosaccharide, galactose-α-1,3-galactose, which is present in the Fab portion of the cetuximab heavy chain.[6] However, this mechanism could be discarded in omalizumab hypersensitivity reactions because it is grown in a Chinese hamster ovary cell line that does not express the enzyme α-1,3-galactosyl transferase and thus has a different glycosylation pattern. A positive skin prick test response to polysorbate has been demonstrated in some patients allergic to omalizumab, but the mechanism has not been elucidated in many other cases.[8]

To our knowledge, we are describing the first case of a probable IgE-mediated hypersensitivity reaction to natalizumab diagnosed by means of an *in vitro* and *in vivo* study.

Monoclonal antibody and fusion protein therapy is rapidly increasing. Because of the complex molecular structure of immunoglobulins, a variety of heterogeneous immunologic reactions is possible. Assessing reactions to these therapies is a growing challenge to allergists.

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Infants aged 12 months can mount adequate serotype-specific IgG responses to pneumococcal polysaccharide vaccine

To the Editor:

Streptococcus pneumoniae is a major cause of bacterial pneumonia, meningitis, bacteremia, and otitis media leading to an estimated 1 million deaths per year worldwide in children younger than 5 years. The capsule of *S pneumoniae* is the major virulence

TABLE I. Serotype-specific IgG GMC before and after 23vPPV immunization in infants at 12 months of age

	Pre-23vPPV	2 Weeks post-23vPPV	
Serotype	GMC μg/mL (95% CI)	GMC μg/mL (95% CI)	*P* value*
1	0.17 (0.13-0.22)	2.04 (1.49-2.80)	<.0001
2	0.28 (0.23-0.35)	12.48 (9.66-16.12)	<.0001
3	0.37 (0.26-0.53)	13.74 (10.55-17.91)	<.0001
4	0.08 (0.06-0.10)	2.37 (1.76-3.20)	<.0001
5	0.26 (0.20-0.34)	2.77 (2.15-3.57)	<.0001
6B	0.14 (0.12-0.17)	0.31 (0.23-0.42)	<.05
7F	0.10 (0.08-0.14)	2.58 (1.98-3.37)	<.0001
8	0.26 (0.20-0.32)	13.59 (10.72-17.23)	<.0001
9N	0.12 (0.09-0.15)	3.06 (2.18-4.30)	<.0001
9V	0.09 (0.07-0.12)	1.21 (0.90-1.62)	<.0001
10A	0.20 (0.16-0.24)	0.87 (0.65-1.17)	<.0001
11A	0.10 (0.08-0.13)	2.21 (1.58-3.08)	<.0001
12F	0.06 (0.05-0.08)	0.39 (0.28-0.54)	<.0001
14	0.20 (0.16-0.25)	0.41 (0.29-0.59)	NS
15B	0.17 (0.14-0.22)	0.79 (0.59-1.05)	<.0001
17F	0.11 (0.09-0.13)	1.39 (0.98-1.97)	<.0001
18C	0.07 (0.05-0.08)	1.23 (0.88-1.72)	<.0001
19A	0.29 (0.24-0.36)	0.79 (0.55-1.12)	<.05
19F	0.47 (0.36-0.62)	1.15 (0.81-1.62)	NS
20	0.10 (0.08-0.12)	0.90 (0.61-1.34)	<.0001
22F	0.36 (0.29-0.46)	5.23 (3.47-7.88)	<.0001
23F	0.19 (0.15-0.25)	0.42 (0.30-0.57)	NS
33F	0.14 (0.11-0.17)	2.01 (1.44-2.80)	<.0001

No. of infants = 56.
NS, Not significant.
*Comparison of serotype-specific IgG before and 2 weeks after 23vPPV immunization (paired *t* test).