

Clinical Communications

First case of allergy to nivolumab

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Clinical Implications

- Nivolumab (Opdivo) is a humanized IgG4 anti-PD-1 monoclonal antibody used to treat different types of cancer. There are no previously reported cases of suspected mast cell-mediated adverse reactions. This is the first reported case with a positive skin test and a desensitization protocol.

TO THE EDITOR:

Nivolumab (Opdivo) is a humanized IgG4 anti-PD-1 monoclonal antibody used to treat different types of cancer, mainly metastatic skin and lung tumours,¹ and, more recently, metastatic liver cancer as part of some clinical trials. Nivolumab works as an inhibitor, blocking the binding of the PD-1 T-receptor to its ligands, PD-L1 and PD-L2. This blocking derepresses T cells that can then effectively attack the tumor. Some psoriasiform eruptions have been described in relation to this drug, but there are no cases of any IgE-mediated adverse reactions previously described.²

We present the case of a 57-year-old woman diagnosed with hepatocellular carcinoma in 2015. Previous treatment with sorafenib was well tolerated. In January 2016, because of progression of her disease, she started treatment with nivolumab and ipilimumab, as part of a new clinical trial. In the third cycle, at the end of intravenous infusion of nivolumab, she immediately developed facial flushing, hives on her face and neck, and eyelid angioedema. Vital signs demonstrated blood pressure 110/75 mm Hg, pulse rate 70 bpm, and pulse oximetry 99% on room air, with no other systemic symptoms. No tryptase levels were taken at that time. The infusion was stopped and the symptoms disappeared spontaneously in approximately 45 minutes. After that, she received ipilimumab and tolerated it well.

The patient was referred to our allergy department. *In vivo* testing was undertaken after informed consent was signed. The skin prick test with nivolumab at a concentration of 1 mg/mL (1/10) was negative on immediate reading. The intradermal (ID) test with nivolumab at 0.1 mg/mL (1/100) elicited a positive reaction (8 mm wheal) at 15 minutes. Negative and positive controls were carried out with saline and histamine, respectively. Identical skin tests in 5 patients included in the same clinical trial receiving treatment with nivolumab but without symptoms were all negative.

In vitro testing, including basal tryptase levels, was normal (1.4 mg/L). Moreover, anti-nivolumab IgE antibodies measured by SDS-PAGE immunoblotting, according to the Laemmli technique in reducing and nonreducing conditions

(with and without 2-mercaptoethanol, respectively), with serum dilutions of 1/5, 1/10, and 1/20, and the enzyme allergosorbent test were undetectable.

Because of the excellent response of the patient to nivolumab, the oncologists decided that she needed to continue receiving the same drug. We performed the first desensitization of 240 mg of nivolumab with a 12-step protocol in 3 bags: bag A at a concentration of 0.01 mg/mL, bag B at 0.1 mg/mL, and bag C at 0.5 mg/mL, premedication with oral aspirin 300 mg, montelukast 10 mg, intravenous dexchlorpheniramine 5 mg, ranitidine 50 mg, and hydrocortisone 200 mg.³⁻⁵ During the infusion of bag C, at 160 mL/h, after 50 minutes, she presented with right eyelid pruritus and angioedema, without other symptoms. The infusion was stopped and she received intravenous dexchlorpheniramine 5 mg and hydrocortisone 200 mg, and her symptoms resolved in less than 30 minutes. We finished the desensitization at 160 mL/h with no additional reactions. After that, we performed further desensitizations using a desensitization protocol^{3,6} with more modifications (Table I), adding steps in bag C (80 mL/h, 120 mL/h, 140 mL/h, and 160 mL/h), and adding pretreatment with dexchlorpheniramine at the step before the step with symptoms. Despite those modifications, the patient always had the same eyelid angioedema at 120 mL/h. Then we decided to administer desloratadine 5 mg every 24 hours for the 3 days before the treatment, and she has had no reactions since the 11th desensitization and has tolerated 9 desensitizations with the same modified protocol as of this report.

To our knowledge, there is no previous literature published about an immediate hypersensitivity reaction to nivolumab. This is the first case with a positive skin test and a desensitization protocol reported. In this case, the symptoms and the positive ID test suggest that there is an IgE-mediated mechanism, although we could not prove this hypothesis by the *in vitro* test. This reaction was amenable to rapid desensitization as previously reported for other biologic agents.^{3,5,6} We recommend performing *skin* tests in patients with reactions to new biologic

TABLE I. Desensitization protocol used

Step	Bag		Flow (mL/h)	Time (min)
	A: 0.01 mg/ML	B: 0.1 mg/ML		
	C: 0.5 mg/ML			
1	A		2	15
2	A		5	15
3	A		10	15
4	A		20	15
5	B		5	15
6	B		10	15
7	B		20	15
8	B		40	15
9	C		20	15
10	C		40	15
11	C		80	30
12	C		120	60
13	C		140	60
14	C		160	Rest

agents, even if there is no previous information about the sensitivity and specificity of such tests.

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