Allergy IgE-mediated to Pembrolizumab and Successful Desensitization

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Pembrolizumab is a humanized monoclonal IgG4 kappa antibody which targets programmed cell death protein 1 (PD1). PD1 is one of the arrays of receptors on T cells that are expressed on prolonged antigenic stimulations that negatively regulate their cytotoxic activity, making them unable to clear pathogens or eliminate neoplastic cells [1].

It has been approved for treating several malignant tumors. Pembrolizumab has also been tested on an off-label use for treating patients with progressive multifocal leukoencephalopathy caused by the JC virus, with conflicting results between different studies [2].

Pembrolizumab can be used as a monotherapy or in combination with chemotherapy. The most frequently reported adverse reactions to this drug used as a monotherapy were fatigue, nausea and diarrhea. Many other adverse effects affecting different body systems have also been described. Regarding skin and subcutaneous tissue disorders, rash and pruritus have been reported as very common [3].

Immediate drug hypersensitivity reactions, IgE and non-IgE mediated, have been treated with drug desensitization, which has been proved to be safe and highly effective procedure [4].

As far as we know, there are just a single previous report on successful pembrolizumab desensitization in A patient presenting an immediate reaction IgE mediated to this drug, diagnosed with a positive intradermal test, also performed on controls.

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Case report

A 69-year-old man was diagnosed with a non-small-cell lung carcinoma (NSCLC) on April 2020 and initially treated with 4 cycles of chemotherapy with carboplatin and taxol, followed by radiotherapy sessions (up to a total dose of 60 Gy).

As there was no response at that time, treatment was modified to pembrolizumab, started on October 2020 and applied every 21 days with a good tolerance.

On September 2021, just after finishing the 17th administration of 200 mg intravenous pembrolizumab, he developed a generalized pruritus, palmar erythema and eyelid and labial angioedema. The symptoms disappeared completely in approximately 3 hours after treatment with intravenous corticosteroids and antihistamines.

He was referred to our Allergy Department for evaluation and allergological study. As far as we knew, the concentration for pembrolizumab skin tests was not previously described on the literature, so we used serial dilutions, taking as a reference those used with nivolumab [5]. One month after the reaction prick (25 mg/ml) and intradermal (ID) (0.25 mg/ml) tests with pembrolizumab were performed, achieving a positive ID test in the immediate reading. A control group was reunited (three patients diagnosed with lung carcinoma, treated with pembrolizumab and four healthy patients, never exposed to pembrolizumab). None of them showed neither positive nor irritative result on the tests performed up to 2.5 mg/ml in ID test.

A standard 12-step desensitization protocol, based on the one described by the Brigham and Women's Hospital group [6], modified using a single dilution, with pembrolizumab 200 mg was scheduled. We used a one 100 ml bag solution to solve chemical integrity problems, as indicated by the Pharmacy Department. Patient's desensitization was performed in an outpatient basis at the allergy day care unit, after premedication with IV dexchlorpheniramine (prescribed by the oncologist), with a final infusion rate of 120 ml / h, in a total time of 3.17 hours (Table 1). There were no adverse events.

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A second desensitization was completed with no reactions 21 days later following the same protocol and premedication. The third desensitization was performed 21 days later, increasing the final infusion rate to 140 ml/h with a good tolerance, also premedicated with IV dexchlorpheniramine.

Pembrolizumab has been widely used these past years since its approval as the treatment for several malignant neoplasms. Although pruritus and maculo-papular exanthema have been described as the most prevalent adverse events [3], to date, there is no demonstration on an underlying IgE mediated mechanism.

Other severe cutaneous diseases related to a possible, although non-demonstrated, allergological mechanism are also described: toxic epidermal necrolysis / Stevens-Johnson syndrome / erythema multiforme and an acute generalized exanthematous pustulosis [3].

Desensitization procedures have shown to be a safe and effective procedure for patients presenting a drug hypersensitivity reaction and allows maintaining patients on their most effective treatments [4,7]. It has also shown to be cost-effective when compared to standard administration [6].

Castells and their group [7,8] describe a desensitization procedure in a patient diagnosed with an ovarian cancer but an IgE-mediated mechanism underlying the reaction cannot be confirmed as there is no report about cutaneous tests performed on this patient. In the same line, Kim [9] communicates a 12-step desensitization protocol using one bag with pembrolizumab, but cutaneous tests are not performed (or not shown).

In the other hand, there is a case report published [10] that describes a patient successfully desensitized with one bag of Pembrolizumab. This patient presents with a suspicious IgE-mediated reaction and cutaneous tests are performed showing a possible IgE mechanism. Unfortunately, they didn't perform cutaneous tests on controls, so an irritant mechanism at that moment couldn't be ruled out. As far as we have used the same concentration, and we got negative results on all controls, we can affirm that both results are not irritative.

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In the present report, symptoms during the administration of pembrolizumab were compatible with an allergic reaction IgE-mediated, demonstrated on the positive immediate ID test. Our patient underwent successfully a standard 12-step desensitization protocol with one single dilution, premedicated with IV dexchlorpheniramine with no breakthrough reactions, and achieved a sustained mayor response of the disease.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Table. Pembrolizumab one solution protocol

Step	Rate (ml/h)	Time (min)	Volume infused per step (ml)	Dose infused per step (mg)	Cumulative dose (mg)
1	0.1	15	0.03	0.0500	0.05
2	0.2	15	0.05	0.1000	0.15
3	0.4	15	0.10	0.2000	0.35
4	0.8	15	0.20	0.4000	0.75
5	1.6	15	0.40	0.8000	1.55
6	3.2	15	0.80	1.60	3.15
7	7.0	15	1.75	3.50	6.65
8	15.0	15	3.75	7.50	14.15
9	30.0	15	7.50	15.00	29.15
10	60.0	15	15.00	30.00	59.15
11	80.0	15	20.00	40.00	99.15
12	140.0	21.61	50.43	100.85	200.00

Total time (min) =	165	= 2,75 hrs			

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