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## IgE-mediated Allergy to Pembrolizumab and Successful Desensitization

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Pembrolizumab is a humanized monoclonal IgG4  $\kappa$  antibody that targets programmed cell death protein 1 (PD1). PD1 is a T-cell receptor array expressed on prolonged antigenic stimulations that negatively regulate cytotoxic activity, rendering them unable to clear pathogens or eliminate neoplastic cells [1].

Pembrolizumab has been approved for treating several malignant tumors. It has also been tested for off-label use in patients with progressive multifocal leukoencephalopathy caused by the JC virus, although study results are contradictory [2].

Pembrolizumab can be used as monotherapy or in combination with chemotherapy. The most frequently reported adverse reactions to this drug in monotherapy were fatigue, nausea, and diarrhea, although many other adverse reactions affect various body systems, and skin and subcutaneous tissue disorders, rash and pruritus are very common [3].

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

To our knowledge, only 1 previous report covers successful desensitization to pembrolizumab in a patient presenting an immediate IgE-mediated reaction to the drug. The patient was diagnosed based on a positive result in intradermal testing.

A 69-year-old man was diagnosed with non-small-cell lung carcinoma (NSCLC) in April 2020 and initially treated with 4 cycles of chemotherapy (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 switched to pembrolizumab, starting in October 2020 and applied every 21 days. Tolerance was good.

In September 2021, immediately after the 17th dose of intravenous pembrolizumab 200 mg, the patient developed generalized pruritus, palmar erythema, and eyelid and

**Table.** Pembrolizumab 1-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 h			

labial angioedema. The symptoms fully resolved some 3 hours after treatment with intravenous corticosteroids and antihistamines.

The patient was referred to our allergy department for evaluation and an allergology study. Since, to our knowledge, the concentration for pembrolizumab skin tests has not been assessed in the literature, we used serial dilutions, taking those used with nivolumab as a reference [5]. One month after the reaction, prick testing (25 mg/mL) and intradermal testing (0.25 mg/mL) were performed with pembrolizumab. The result was positive for the intradermal test in the immediate reading. A control group comprising 3 patients diagnosed with lung carcinoma treated with pembrolizumab and 4 healthy patients never exposed to pembrolizumab underwent intradermal testing. The results were neither positive nor irritative in the tests performed up to 2.5 mg/mL.

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

A second desensitization following the same protocol and premedication was completed with no reactions 21 days later. The third desensitization was performed 21 days later, increasing the final infusion rate to 140 mL/h with good tolerance. Again, premedication with intravenous dexchlorpheniramine was administered.

Pembrolizumab has been widely used in recent years since its approval for treatment of several types of malignant neoplasm. Although pruritus and maculopapular exanthema have been described as the most prevalent adverse events [3],

no underlying IgE-mediated mechanism has been demonstrated to date.

Other severe cutaneous diseases related to a possible—albeit undemonstrated—allergological mechanism have also been described and include toxic epidermal necrolysis–Stevens-Johnson syndrome, erythema multiforme, and acute generalized exanthematous pustulosis [3].

Desensitization has proven to be a safe and effective procedure for patients with drug hypersensitivity reaction and enables the most effective treatment to be maintained [4,7]. It has also proven to be more cost-effective than standard administration [6].

The results of a desensitization procedure in a patient diagnosed with ovarian cancer were unable to confirm an IgE-mediated mechanism underlying the reaction, as no skin testing data were available [7,8]. Similarly, Kim et al [9] describe a 12-step desensitization protocol using 1 bag with pembrolizumab, although skin tests were not performed (or not shown).

Data have been reported after successful desensitization with 1 bag of pembrolizumab [10]. The patient presented with a suspicious IgE-mediated reaction, and skin tests showed a possible IgE-mediated mechanism. However, since the authors did not perform skin tests on controls, an irritant mechanism cannot be ruled out. Given that we used the same concentration and obtained negative results for all controls, we can affirm that neither result was irritant.

In the present case, the symptoms reported during the administration of pembrolizumab were compatible with an allergic IgE-mediated reaction, as demonstrated by the positive immediate intradermal test result. The patient successfully underwent a standard 12-step desensitization protocol with a single dilution after premedication with intravenous dexchlorpheniramine. There were no breakthrough reactions, and the patient was able to achieve a better response to his disease.

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### Conflicts of Interest

The authors declare that they have no conflicts of interest.

### References

1. Kwok G, Yau TC, Chiu JW, Tse E, Kwong YL. Pembrolizumab (Keytruda). *Hum Vaccin Immunother*. 2016;12(11):2777-89.
2. Cortese I, Muranski P, Enose-Akahata Y, Ha SK, Smith B, Monaco M, et al. Pembrolizumab Treatment for Progressive Multifocal Leukoencephalopathy. *N Engl J Med*. 2019;380(17):1597-605.
3. Simonsen AB, Kaae J, Ellebaek E, Svane IM, Zachariae C. Cutaneous adverse reactions to anti-PD-1 treatment-A systematic review. *J Am Acad Dermatol*. 2020;83(5):1415-24.
4. Vega A, Jimenez-Rodriguez TW, Barranco R, Bartra J, Diéguez MC, Doña I, et al. Hypersensitivity Reactions to Cancer Chemotherapy: Practical Recommendations of ARADyAL for Diagnosis and Desensitization. *J Investig Allergol Clin Immunol*. 2021;31(5):364-84.
5. Sáenz de Santa María García M, Noguero-Mellado B, Rojas-Pérez-Ezquerro P, Prieto-García A, Bartolomé-Zavala B, Tornero P. First case of allergy to nivolumab. *J Allergy Clin Immunol Pract*. 2017;5(4):1140-1.
6. Sloane D, Govindarajulu U, Harrow-Mortelliti J, Barry W, Hsu FI, Hong D, et al. Safety, Costs, and Efficacy of Rapid Drug Desensitizations to Chemotherapy and Monoclonal Antibodies. *J Allergy Clin Immunol Pract*. 2016;4(3):497-504.
7. Isabwe GAC, García Neuer M, de Las Vecillas Sanchez L, Lynch DM, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes. *J Allergy Clin Immunol*. 2018;142(1):159-70.e2.
8. Labella M, Castells M. Hypersensitivity reactions and anaphylaxis to checkpoint inhibitor-monoclonal antibodies and desensitization. *Ann Allergy Asthma Immunol*. 2021;126(6):623-9.
9. Kim HH, Seo J, Ahn YH, Kim H, Yoon JE, Suh JH, et al. Analysis of Breakthrough Reactions in 1,143 Desensitization Procedures in a Single Tertiary Hospital Using a One-Bag Desensitization Protocol. *Front Allergy*. 2022;3:786822.
10. Collin L, Babin M, de Chabot G, Lhuissier M, Beauvillain C, Urban T, et al. Successful one- bag desensitization protocol in a patient with pembrolizumab hypersensitivity. *European-Academy-of-Allergology-and-Clinical-Immunology Digital Congress (EAACI)*, Jun 2020, London, United Kingdom. pp.603.

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