Annals of Clinical and Medical Case Reports

Case Report ISSN 2639-8109 | Volume 14

Successful Desensitization to Pembrolizumab in Patients with Severe Hypersensitivity Reactions, one of Them with Mastocytosis: Report of Three Cases and Review of The Literature

Borras Cuartero J[1], Viedma Ayllon P[2*], Pesántez Mendez CG[2], Torres Gorriz MC[2,3], Stein Coronado CI[2] Germán Sánchez A[2] and Enrique E [2,3]

[1]Allergy Department, Castellon Provincial Hospital Consortium, Castellon, Spain

[2]Allergy Department, Castellon University General Hospital, Castellon, Spain

[3]Department of Medicine, Jaume I University (UJI), Castellón, Spain

[*]Corresponding author:

Paula Viedma Ayllon,
Allergy Department, Castellon University General Hospital, Castellon, Spain

Received: 30 Jan 2025
Accepted: 24 Feb 2025
Published: 05 Mar 2025
J Short Name: ACMCR

Citation:

Viedma Ayllon P, Successful Desensitization to Pembrolizumab in Patients with Severe Hypersensitivity Reactions, one of Them with Mastocytosis: Report of Three Cases and Review of The Literature. Ann Clin Med Case Rep. 2024; V14(4): 1-3

Keywords:

Pembrolizumab; Desensitization; Anaphylactic shock; Mastocytosis hypersensitivity reaction; Monoclonal Abs

1. Case Report

Pembrolizumab is a humanized IgG4 monoclonal antibody targeting the PD-1 receptor, approved for immunotherapy in advanced cancers (melanoma, non-small cell cancer, Hodgkin lymphoma, bladder cancer, etc.) [1]. Standard dosing includes 200 mg every 3 weeks or 400 mg every 6 weeks via continuous intravenous infusion over 30 minutes. Common adverse effects involve hypothyroidism, gastrointestinal disorders, fatigue, myalgia, and respiratory issues. Furthermore, severe non-immediate hypersensitivity reactions, like toxic epidermal necrolysis/Stevens-Johnson syndrome, erythema multiforme and acute generalized exanthematous pustulosis have been described [2]. On the other hand, four cases of immediate hypersensitivity reactions (HR) to pembrolizumab have been reported, but only one patient presented a severe reaction [3-6]. In these cases, skin tests were performed in two patients showing a positive result in intradermal tests (IDT), and in one case a post-reaction tryptase determination was carried out with significant increase of tryptase value [3,6]. Consequently, different Rapid Drug Desensitization (RDD) protocols were employed [3-6]. We present three cases of advanced-stage lung cancer patients experiencing severe immediate HR after the 9th and 15th dose of pembrolizumab. All of them developed dizziness, generalized pruritus, urticaria, and bronchospasm, and two patients also showed hemodynamic instability with hypotension and oxygen desaturation. After stopping the administration of this drug and providing oxygen, intravenous fluids, corticosteroids, and antihistamines in the Oncology Day Unit (ODU), the symptoms were completely resolved. Two hours after the reaction, analytical determination of tryptase and IL-6 values were performed (Supplementary Table). The results of post-reaction analysis showed normal IL6 levels (25 pg/ml and 22.9 pg/ml) and elevated tryptase (36.9 µg/l and 50.7 µg/l) in two patients with an elevated baseline tryptase in one of them (34.4 µg/l). Tryptase determination could not be performed in the other patient due to technical issues. According to these results, the patient with increased baseline tryptase was referred to the Hematology department because of a high suspicion of mast cell activation syndrome, supported by a high score on the Spanish Mastocytosis Network (REMA score 2 points). Skin tests were performed in prick-test (25 mg/ml) and IDT (0.025, 0.25, and 2.5 mg/mL), with saline and histamine as negative and positive controls, two weeks after the reaction by the Allergy department. The results showed a clear positive result in the three patients in IDT at concentration of 0.025 mg/ml, with wheal surrounded by erythema, and intense itching. Given these outcomes, all patients were given the final diagnosis of severe immediate IgE-mediated HR to pembrolizumab, one of them with a high suspicion of mastocytosis. Therefore, a rapid drug desensitization (RDD) with 3-bags (12-steps) protocol was scheduled for all three patients in order

to continue their first line therapy. Taking this into account, we adjusted the pembrolizumab dose to 200 mg, using 50-ml and 100-ml bags according to the drug's pharmacostability indicated by the Pharmacy department (Table 1). The RDD was successfully performed at the ODU in two patients, preceded by domiciliary premedication (montelukast, acetylsalicylic acid, and ebastine) two days before and hospitalary premedication (dexchlorpheniramine, famotidine, and diazepam), taking approximately 4 hours with a final infusion rate of 32 ml/h. Subsequently, four additional desensitizations were performed every three weeks, gradually increasing the final infusion rate to 64 ml/h with good tolerance. Based on the positive RDD tolerance, the second patient transitioned to one-bag (12-steps) protocol after the fourth session with successful tolerance. Nevertheless, the other patient couldn't undergo planned one-bag desensitization owing to disease progression. The third patient had a change of therapeutic line due to disease progression and didn't receive the RDD. Additionally, the Hematology department confirmed the diagnosis of systemic mastocytosis in the patient with elevated baseline tryptase. The study revealed a bone marrow infiltration of >15 aggregated mast cells, c-kit D816V mutation, and positive CD2 and CD25 expression. Patients with systemic mastocytosis have a higher risk of developing anaphylaxis compared to the general population (prevalence of 22% to 49%), often triggered by pharmacological induction or hymenoptera bites. This condition constitutes a diverse group of cellular disorders characterized by the clonal proliferation and accumulation of mast cells in various tissues and organs [7]. To date, there have been limited publications on the tolerance and the safest RDD protocol in patients diagnosed with mastocytosis. Tolerance has been reported in RDD to different chemotherapy regimens in four mastocytosis-diagnosed patients (two patients were diagnosed after their DHR) who experienced reactions (Brown's grade 2) during standard administration. Subsequently, these patients underwent a one-bag desensitization protocol, although all of them had experienced mild reactions during their first RDD [8]. A study by Hutten *et al.* reported a successful case of isatuximab desensitization in a patient previously diagnosed with mastocytosis and multiple myeloma. The patient had experienced a severe reaction after the first cycle retreatment. Following, a successful RDD with isatuximab was performed using a 3-bags (12-steps) protocol, although during the first and fourth desensitization, the patient presented mild allergic symptoms which resolved with antihistamines [9]. In summary, we report three cases of severe IgE-immediate HR (Brown's grade 2-3) induced by pembrolizumab, one of them subsequently diagnosed with systemic mastocytosis. We describe the first successful RDD to pembrolizumab in a patient with severe HR diagnosed with mastocytosis after their DHR. Although specific desensitization protocols are needed for patients at risk of severe HR, especially with mastocytosis, other comorbidities, positive prick tests, and elevated tryptase levels, initial consideration of 3-bag desensitization protocols can be a safe approach to minimize reactions during desensitization.

	Total Doses (mg)	**mg/ml**	**0.9% NaCl (ml)**
Solution A: 1/100	1	0.02	50
Solution B: 1/10	10	0.2	50
Solution C: 1/1	198.5	1.985	100

Table 1: Pembrolizumab Desensitizations 3-Solutions Protocol (200mg).

	Step	**Rate (ml/h)**	**Time (min)**	**Total Volume Infused (ml)**	**Doses (mg)**
SOLUTION A	1	0.8	15	0.2	0.004
	2	2	15	0.5	0.01
	3	4	15	1	0.02
	4	8	15	2	0.04
		Total	60	3.7	0.074
SOLUTION B	5	2	15	0,5	0,1
	6	4	15	1	0,2
	7	8	15	2	0,4
	8	16	15	4	0,8
		Total	60	7,5	1,5
SOLUTION C	9	4	15	1	1,99
	10	8	15	2	3,97
	11	16	15	4	7,94
	12	32	61,8	93	184,61
		Total	106,8	100	198,5
		Total Hours=	3 h 48 min	**Total mg=**	200,07

Supplementary Table: Patients Characteristics with Drug Hypersensibility Reaction by Pembrolizumad.

CASE	1	2	3
Sex	Male	Male	Female
Age	65	55	50
Disease	Lung cancer	Lung cancer	Lung cancer
Cycle number during DHR	9º and 10º	15º	9º
Symptoms	Dizziness, profuse sweating, pruritic erythema on palms and feet hypotension and bronchospasm	Dizziness, nausea, flushing, generalized pruritic erythema, urticaria	Dizziness, flushing of the neck and face, tachycardia, bronchospasm and hypotension
DHR (Brown Classification)	3 (Severe)	2 (Moderate)	3 (Severe)
Skin Test	Positive IDT 0.025 mg/ml	Positive IDT 0.025 mg/ml	Positive IDT 0.025 mg/ml
Tryptase postreadicción (ug/l) BST	36,9 7,8	Unknown	50,7 34.4
REMA score	+1 points	-3 points	+2 points
RDD	Discontinued RDD due to disease progression	1st-3rd RDD 3-bags(12-steps) with home premedication 4th RDD one-bag (12-steps) with hospitalary premedication	1st-2nd RDD 3-bags(12-steps) with home premedication

DHR: Drug Hypersensibility Reaction; BST Baseline Serum Tryptase; RDD Rapid Drug desensitization; IDT Intradermal Test.

References

1. Kwok G, Yau TC, Chiu JW, Tse E, Kwong YL. Pembrolizumab (Keytruda). Hum Vaccin Immunother. 2016; 12(11): 2777-89.
2. 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.
3. Collin L, Babin M, De Chabot G, Lhuissier M, Beauvillain C, Urban T. Successful one-bag desensitization protocol in a patient with pembrolizumab hypersensitivity. European-Academyof-Allergology-and-Clinical-Immunology Digital Congress (EAACI). 2020; 603.
4. Isabwe GAC, Garcia Neuer M, de Las Vecillas Sanchez L, Lynch DM. Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes. J Allergy Clin Immunol. 2018; 142(1): 159-70.
5. Kim HH, Seo J, Ahn YH, Kim H, Yoon J-E, Suh JH. 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.
6. Torrado I. IgE-mediated Allergy to Pembrolizumab and Successful Desensitization." Journal of investigational allergology & clinical immunology. 2023; 33(4): 304-306.
7. Bonadonna P, Lombardo C. Drug allergy in mastocytosis. Immunol Allergy Clin North Am. 2014; 34: 397-405.
8. Solano E, Madrigal R, Carpio LV, Bernal L, Berges MP, Alvarez E. Chemotherapy in Mastocytosis: Administration Issues, Hypersensitivity, and Rapid Drug Desensitization. J Investig Allergol Clin Immunol. 2017; 27(5): 315-317.
9. Hutten E. Successful ISATUXIMAB desensitization in a patient with refractory multiple myeloma and indolent systemic mastocytosis. Journal of Investigational Allergy and Clinical Immunology. 2023; 34(3).