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EDITORIAL

Pembrolizumab autoimmune related diabetes: Moving forward, keep learning

Jose Angel Garcia, Diego Alcaraz, Esther Holgado, Felipe Couñago

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Abstract

Immune checkpoint inhibitors (and more specifically programmed cell death 1/programmed cell death ligand 1 inhibitors as Pembrolizumab) initiated a revolution in the field of melanoma and have now expanded to several tumor subtypes and in increasingly broader clinical contexts, including the adjuvant and neoadjuvant setting, with potentially curable patients and prolonged survival. The side effects related to these drugs include a wide spectrum of manifestations, with endocrinological adverse events being some of the most frequent. Pembrolizumab-induced type 1 diabetes mellitus is an infrequent but potentially serious and not clearly reversible side effect that possesses characteristic clinical features and has high morbidity and mortality, with a chronic impact on quality of life. The etiopathogenesis of this phenomenom needs to be further investigated and a collaborative effort through the involvement of oncologists and other medical specialists is necessary for the correct identification and management of patients at risk.

Key Words: Immune checkpoints; Pembrolizumab; Immunotherapy; Side effects; Endocrine system; Diabetes mellitus

Core Tip: Pembrolizumab-induced type 1 diabetes mellitus is a rare and potentially serious adverse event of immunotherapy, with a significant number of cases debuting abruptly and in a state of diabetic ketoacidosis without clear predisposing factors. Further research and strict follow-up by oncologists are fundamental tools for prevention and early treatment focusing on reducing the morbidity and mortality associated with this side effect.

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INTRODUCTION

The study published by Bhanderi *et al*[1] in 2023 presents a case report of an oncologic patient on immunotherapy who debuts in a state of rapidly developing diabetic ketoacidosis with low HbA1c levels suggestive of autoimmune diabetes mellitus 1 (DM1) with negative autoantibody studies, which differs from the clinical presentation of classic DM1. This publication suggests that the identification of patients at risk from a genotypic point of view remains unclear based on current literature, highlighting the need for future research to define prognostic biomarkers that may help in the management of these patients.

Immune checkpoint inhibitors (ICI) are currently a standard in daily practice. In the last ten years we have witnessed a revolution that has changed the treatment paradigm for many solid tumors, initiated in 2011 with the Food and Drug Administration (FDA) approval of Ipilimumab (anti-CTLA4) and continued further with the approvals in 2014 of the anti-programmed cell death 1 (PD1)/programmed cell death ligand 1 (PDL1) drugs (Pembrolizumab, Nivolumab). Since the FDA approval in 2014 of Pembrolizumab for advanced melanoma, its use has expanded to more than 20 treatment indications in different solid tumors in 2023, consolidating its position as one of the standard treatments in monotherapy or combined with other drugs, in both disseminated and localized disease (adjuvant and/or neoadjuvant setting)[2,3]. The adverse effect profile of immunotherapy has changed the perspective established by conventional chemotherapy treatments and poses a clinical challenge. In this context endocrinological toxicities are frequent and probably underdiagnosed. Pembrolizumab-induced DM1 is a rare and potentially serious adverse event described in the literature that can have relevant consequences in terms of quality of life.

PD1 inhibitors are associated with approximately 95% of cases of ICI-induced DM1, although incidence is < 1%[4-6]. Pathogenically, it is caused by destruction of insulin-producing pancreatic beta cells, with reports suggesting a deeper and more rapid destruction than in classic DM1. It is unresponsive to corticosteroids and hardly reversible when established[7,8]. The average time to debut varies between 7-17 wk, although there are cases of late development (even months after the end of immunotherapy)[9,10]. It is important to note that 38%-70% of patients who develop this type of DM1 debut in a state of diabetic ketoacidosis with high (but lower than expected) hemoglobin A1C levels, suggesting a rapid development with a sharp drop in insulin secretion[4]. The clinical features of Pembrolizumab-induced DM1 involve acute onset of hyperglycemia, increased frequency of ketosis, rapid decline in C concentrations, and high glycemic variability consistent with the absence of residual beta-cell function[10].

It is because of the high risk of morbidity and mortality that it is important for physicians to be aware of this situation and act accordingly in an early manner[8]. In this context, the European Society for Medical Oncology recommends the monitorization of blood glucose in patients receiving (ICI)[11], while the American Society of Clinical Oncology guidelines recommend measuring it at baseline and with each treatment cycle for 12 wk, and then every 3-6 wk[12].

Since the publication of the first cases of Pembrolizumab-induced DM1 in 2015 we have witnessed a marked increase in reported cases, with > 90 in recent years[13,14]. In our opinion, the growing interest in this field and the efforts of clinicians and researchers should aim towards a stricter follow-up and a better identification of patients with immune-mediated adverse events. However, which group of patients at risk could benefit from a stricter follow-up remains unclear. The work of Magis *et al*[15] in 2018 shows us a prospective study based on the glycemic follow-up of 163 patients under anti-PD1 with a median follow-up of 5.6 months. This study shows the low incidence of this adverse effect (only three patients developed diabetes mellitus with anti-PD1 plus two additional patients in a parallel study with anti-PD1 *vs* Ipilimumab) and also evidences that, in all cases, glycemia prior to treatment was normal, reflecting that glycemia monitoring during treatment may not be sufficient to anticipate this phenomenon. This publication also suggests the potential role of human leukocyte antigen (HLA) determination given that four of the five affected patients were DRB01 03 or 04, (which are known to increase the risk of type 1 diabetes in the general population), noting the role of risk haplotyping to aid in the comprehensive follow-up of these patients. In 2019, Tsang *et al*[16] conducted a retrospective study of 538 melanoma patients treated with anti-PD1 (Pembrolizumab monotherapy and Ipilimumab-Nivolumab combination) over a 3-year period, with ten patients (1.9%) developing potentially immunotherapy-induced diabetes mellitus with Pembrolizumab (six patients) or the combination therapy (four patients). In the ten affected patients a DM1-associated autoantibody test (including anti-glutamic acid decarboxylase antibody, anti-insulin antibody, islet antigen 2 antibody and zinc transporter 8 antibody) was performed, with GADA (20%) being the only positive result in two patients. In addition, HLA typing was performed on the ten affected patients showing that three patients expressed high-risk HLA haplotypes (two patients had DRB104-DQB103:02-DQA103:01, one patient had DRB103:01-DQB102:01-

DQA105:01) , while three patients had an HLA haplotype previously associated with protection against DM1 (one had DRB107:01-DQB103:03-DQA102:01, one had DRB13:01, and one had DRB111-DQB103:01-DQA105:01). This publication concludes that the absence of autoantibodies and lack of clear association with high-risk HLA typing might suggest an entity with its own characteristics. The work of Wu *et al*[17] in 2021 is consistent with the data presented previously and again shows the genetic variability in DM1 cases associated with ICI, including a review of 200 patients of whom 10% had protective haplotypes. This suggests that the association with risk HLA haplotypes appears to be weaker than in DM1 cases and that other factors may be at play, although it appears that the presence of these protective haplotypes was associated with a delayed onset (18 *vs* 9 wk). To note, other authors (Akturk *et al*[18], Clotman *et al*[19]) have reported contradictory results regarding the role of autoimmunity and HLA typing in this under-represented population.

In light of these results and given the low incidence in the published case series, it is difficult to establish with certainty which predisposing factors and the mechanisms are involved. This makes early identification difficult considering that glycemia monitoring as an isolated tool may not be enough. These uncertainties reinforce the idea that joint and collaborative efforts are necessary to understand these mechanisms, correctly identify patients at risk and develop tools that allow for effective follow-up to be established in order to reduce the risk of serious side effects.

CONCLUSION

AntiPD1-PDL1 drugs represent a widely used treatment in oncology, with a different profile of adverse events compared to conventional chemotherapy. DM1 is a rare and potentially serious side effect, with a variable development time and different clinical presentations. The identification of patients at risk remains unclear and more collaborative research is needed due to the small number of subjects affected. According to the main clinical practice guidelines in the world, thorough surveillance by treating oncologists is necessary for early management to help reduce morbidity and mortality, as well as the participation of other medical specialists for an integral management of affected patients.

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FOOTNOTES

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