Original Research

# Safety of Immune Checkpoint Blockade in Patients with Cancer and Preexisting Autoimmune Diseases and/or Chronic Inflammatory Disorders

**Mohsin Shah[1], Mazen N. Jizzini[1], Imad E. Majzoub[1,2], Aiham Qdaisat[1], Cielito C. Reyes-Gibby[1], Sai-Ching J. Yeung[1]**

*[1]Department of Emergency Medicine, Unit 1468, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Department of Emergency Medicine, American University of Beirut Medical Center, Beirut, Lebanon*

## Abstract

**Background:** Checkpoint blockade therapy, in the form of immune checkpoint inhibitors (ICIs), is increasingly being used to prolong survival in cancer patients, but its use is limited by the occurrence of immune-related adverse events (irAEs). These can be serious and occasionally fatal. However, the safety of ICIs is currently unknown in cancer patients with preexisting autoimmune diseases (PADs) and/or chronic inflammatory disorders (CIDs) such as eczema. **Aim:** The aim of this study is to evaluate the safety of ICIs in cancer patients with PAD and/or eczema at our institution. **Patients and Methods:** A retrospective study of cancer patients who presented to the Emergency Department between March 1, 2011, and February 29, 2016, after ICI therapy was previously conducted. Among these patients, those with PAD and/or eczema were further evaluated for safety by determining the occurrences of de novo irAEs or preexisting disease exacerbation. **Results:** Twenty-two cancer patients with PAD and/or eczema who received ICIs were reviewed, in which 15 were male (68%). Their median age was 63 years (range: 40–78 years). Most patients received anti-PD-1drugs (68%). Melanoma was the most common malignancy (45%). Autoimmune thyroiditis/primary hypothyroidism was the most common PAD. Four patients were receiving treatment for PAD at baseline using systemic corticosteroids, anti-inflammatory agents, and other immunosuppressants. Nineteen patients experienced de novo irAEs and/or PAD exacerbation. In three patients, the irAE was severe (grade ≥3). In six patients, the irAE or exacerbation was managed with systemic corticosteroids. Twelve patients experienced resolution of the de novo irAE or PAD exacerbation without the need to withhold or discontinue ICI therapy. The median time to last follow-up or death from the first dose of ICI was 16.8 months (range: 2–80 months). Death due to cancer progression was reported in 17 patients. **Conclusion:** Although de novo irAEs and PAD exacerbation were common, most patients with PAD and/or CIDs tolerated ICI therapy well.

**Keywords:** *Cancer, checkpoint inhibitors, immune checkpoint blockade, immune-related adverse events, oncologic emergency, preexisting autoimmune diseases*

## Introduction

Checkpoint blockade therapy functions by blocking 1 of 2 immune inhibitory mechanisms: the cytotoxic T-lymphocyte antigen-4 (CTLA-4) (ipilimumab) pathway and the programmed cell death protein 1 (PD-1) (nivolumab, pembrolizumab, and cemiplimab)/programmed death ligand-1-associated pathways (PD-L1) (avelumab, atezolizumab, and durvalumab) pathway. An increasing number of combinations and indications of these immune checkpoint inhibitors (ICIs) have been approved by the US Food and Drug Administration, transforming the therapeutic landscape for many malignant neoplasms.[1-9]

Although ICIs have been shown to confer significant clinical benefits across multiple malignancies by removing the brakes on these regulatory pathways and overcoming immune tolerance to enhance T-cell expansion, they also produce complex immune-mediated side effects, commonly known as immune-related adverse events (irAEs), which are not triggered by conventional cytotoxic anticancer agents.[10] An extensive range of irAEs has been documented in the literature, with their rates and types varying with respect to organs, agent class, and tumor type.[11-13] These irAEs are wide encompassing in terms of the target organs affected and their severity: almost every organ or system is involved, with dermatologic, neurologic,

***Address for correspondence:***
*Dr. Sai-Ching J. Yeung, Department of Emergency Medicine, Unit 1468, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA. E-mail: syeung@mdanderson.org*

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endocrine, gastrointestinal, respiratory, and musculoskeletal toxicities occurring alone or in conjunction.[11] Depending on severity, these irAEs may require systemic immunosuppression or treatment cessation.

The time to toxicity onset is variable but most often occurs within the initial 12–16 weeks of therapy; however, it may not occur until after several months of therapy and thus not follow the cyclical pattern that is normally seen with conventional cytotoxics.[3,14-17]

Overall, severe irAEs (Grade 3 or higher) are less common with anti-PD-1 (about 11%–20%)[18-20] or anti-PD-L1 agents (1%–9%)[6,16,21-23] than with anti-CTLA-4 therapy (10%–42%),[3,24-26] and serious ones may require urgent care or emergency center evaluation and management. Previously, cancer patients with preexisting autoimmune diseases (PADs) were excluded from clinical efficacy trials because of concerns that their underlying autoimmunity would increase their risk for serious irAEs.[19,21,27-29] Because patients with PADs are already at increased risk of developing several different types of malignancy,[30,31] few studies have evaluated the safety of ICIs in this population. The limited studies that have been performed have suggested that ICI therapy in patients with melanoma or non-small cell lung cancer and PAD is safe.[31-33] However, these studies only focused on two types of cancer; the results may not be generalizable to other cancers, as irAEs have been shown to vary by the type of malignancy.[13] Similarly, no studies have evaluated safety in cancer patients who underwent ICIs and had PAD with/or without chronic inflammatory disorders (CIDs) such as eczema.

There is an urgent need to identify patients with predisposed conditions who are more likely to develop irAEs to enable personalized management and to provide early or prophylactic intervention to help mitigate these events. To address this gap, we conducted a single-institution retrospective review of a series of cancer patients with PAD and/or CIDs such as eczema who received ICIs.

## Patients and Methods

### Settings and participants

We searched The University of Texas MD Anderson Cancer Center (Houston, Texas) institutional databases to identify adult cancer patients who had undergone therapy with ICI (ipilimumab [anti-CTLA-4], nivolumab [anti-PD-1], or pembrolizumab [anti-PD-1], alone or in combination) between March 1, 2011, and February 29, 2016, to allow adequate follow-up. The earliest dispensing date was referenced as the initiation of ICI. This information was then cross-tabulated with patients who presented to MD Anderson's Emergency Department (ED) between March 2, 2011 (1 day after the earliest immune checkpoint therapy initiation date), and February 29, 2016, to identify those who had visited the ED after the initiation of therapy. We identified 628 patients. Patients with ED visits (at least one) were then reviewed manually and retrospectively for irAEs. We then identified patients with PAD and/or eczema by reviewing charts and physician notes. Secondary causes of PAD, such as drug-induced autoimmune diseases, were excluded.

### Data collection and analysis

Data extracted from the electronic health records included patient demographics, comorbidities, treatments, and subsequent ED visits; ICI agents and dosages; first and last infusion dates; number of infusions; time to de novo irAE or preexisting condition exacerbation/flares; other ICI-associated irAEs; laboratory data; discontinuation or withholding of ICI therapy; and patients' reported clinical outcomes. The severity of irAEs was graded on the basis of the Common Terminology Criteria for Adverse Events (grading scale: 0–5, where 0 is no adverse event or within normal limits and Grade 5 is a fatal adverse event).[34] This study was approved by the Institutional Review Board.

Eczema is a CID that is considered to be systemically immune driven similar to psoriasis;[35,36] in a clinical study of eczema using an antibody that targeted interleukin-4 (IL-4) receptor-α/IL-13 receptor, the clinical efficacy and correlative transcriptomic data showed it to be modulating a TH2 response.[37] Therefore, we have included eczema as being a preexisting chronic inflammatory condition of interest, and we provide the summary statistics including and excluding eczema.

Descriptive statistics were used to describe the characteristics of the cohort. Categorical variables were reported as counts and percentages, and continuous variables as means and standard deviations (if normally distributed) or as medians and ranges. The software used for data analysis was R (R Core Team, Vienna Austria), available online at https://www.R-project.org.

## Results

### Study population

In a previous study,[38] our research group identified 628 patients who underwent ICI therapy and presented to the ED during the 5-year study period. These patients made 1026 visits to the ED after starting ICI therapy. Of these 628 patients, our present study identified 22 who had PAD using the institutional databases for further review and analysis.

Patients' demographics and clinical characteristics are summarized in Table 1. Twenty-two cancer patients with PAD who received ICIs were reviewed. The male-to-female ratio is about 2:1, which is reflecting the prevalence of lung cancer and melanoma rather than the female dominance in the incidence of autoimmune diseases. Their mean age was 59.5 years (standard

**Table 1: Summary of demographic features, clinical characteristics, and reported adverse events in cancer patients with preexisting autoimmune disease and/or eczema**

| | *n*=22 patients PAD + eczema | *n*=19, excluding eczema only |
|---|---|---|
| Age (years) | 63 (40–78) | 59 (40–78) |
| Sex, *n* (%) | | |
| Male | 15 (68) | 12 (63) |
| Female | 7 (32) | 7 (37) |
| CCI | 9.5 (5–13) | 9 (5–13) |
| PAD*, *n* (%) | | |
| Psoriasis | 2 (9) | 2 (10.5) |
| Vitiligo | 2 (9) | 2 (10.5) |
| Primary hypothyroidism | 8 (36.4) | 8 (42.1) |
| Graves' disease | 2 (9) | 2 (10.5) |
| Type I diabetes | 1 (4.5) | 1 (5.3) |
| Ankylosing spondylitis | 1 (4.5) | 1 (5.3) |
| Systemic lupus erythematosus | 1 (4.5) | 1 (5.3) |
| Ulcerative colitis | 2 (9) | 2 (10.5) |
| Nephropathy | 1 (4.5) | 1 (5.3) |
| CID, *n* (%) | | |
| Eczema | 4 (18.2) | |
| PAD management*, *n* (%) | | |
| Hormone regulation[#] | 8 (36) | 8 (42) |
| Anti-inflammatory drugs | 2 (9) | 2 (10.5) |
| Systemic corticosteroids | 2 (9) | 2 (10.5) |
| Other immunosuppressants | 1 (4.5) | 1 (5.3) |
| Primary cancer for which the ICIs were intended, *n* (%) | | |
| Melanoma | 10 (45) | 9 (47) |
| Lung cancer | 4 (18) | 3 (16) |
| Others | 8 (37) | 7 (37) |
| ICI agent*, *n* (%) | | |
| Ipilimumab | 10 (45) | 9 (47) |
| Pembrolizumab | 9 (41) | 8 (42) |
| Nivolumab | 6 (27) | 4 (21) |
| PAD exacerbation | 4 (18) | 4 (21) |
| De novo irAEs* | | |
| Pulmonary | 10 | 8 |
| Hepatic | 5 | 5 |
| Renal | 3 | 3 |
| Primary hypothyroidism[@] | 2 | 1 |
| Hypophysitis | 1 | 1 |
| Gastrointestinal | 6 | 6 |
| Dermatological | 2 | 2 |
| Musculoskeletal | 2 | 2 |
| No irAEs | 3 | 2 |
| Time to irAE (months) | 1 (0.1–37.9) | 1.2 (0.1–37.9) |
| irAE management*, *n* (%) | | |
| Interruption of ICI | 4 (18.2) | 4 (21) |
| Discontinuation of ICI | 3 (13.6) | 3 (15.8) |
| Topical corticosteroid | 1 (4.5) | 1 (5.3) |
| Systemic corticosteroid | 6 (27.3) | 4 (21) |
| Other immunosuppressants | 1 (4.5) | 1 (5.3) |
| Other anti-inflammatory agents | 2 (9) | 2 (10.6) |
| Other immune modulators | 1 (4.5) | 1 (5.3) |

*Adding up not equal to 22 patients or 100% because some patients have multiple conditions, multiple treatments or no treatment, [#]Including thyroid hormone replacement, inhibitor of thyroid hormone synthesis, insulin, etc., [@]two cases were documented as Hashimoto thyroiditis; no evidence of secondary causes of primary hypothyroidism in the remaining cases. CCI: Charlson Comorbidity Index, ICI: Immune checkpoint inhibitor, irAE: Immune-related adverse event, PAD: Preexisting autoimmune disease, CID: Chronic inflammatory disorder

deviation: 11.6 years), and the median age was 63 years (range: 40–78 years). The median Charlson Comorbidity Index was 9.5 (range: 5–13). Most patients received anti-PD-1 drugs (68%). Melanoma was the most common malignancy (45%). Autoimmune thyroiditis/primary hypothyroidism was the most common PAD, and endocrine disorders were present in 40% of the patients. Thirty-two percent of patients had a dermatologic disorder, 12% had inflammatory bowel disease, etc., [Table 1]. Three patients had >1 autoimmune disease. Four patients were receiving treatment for PAD at baseline using systemic corticosteroids, anti-inflammatory agents (mesalamine and sulfasalazine), and other immunosuppressants (rituximab). Nineteen patients experienced de novo irAEs and/or PAD exacerbation. In three patients, the irAE was severe (grade ≥3). In six patients, the irAE or exacerbation was managed with systemic corticosteroids. Twelve patients experienced resolution of the de novo irAE or PAD exacerbation without the need to withhold or discontinue ICI therapy. The median time to last follow-up or death from the first dose of ICI was 16.8 months (range: 2–80 months). Death due to cancer progression was reported in 17 cases.

## Immune-related adverse events

Patients' irAEs are summarized in Table 1. Of the 22 patients with PAD, 19 experienced a de novo irAE or PAD exacerbation (any grade). Thirteen had gastrointestinal symptoms, three had dermatological symptoms, two had pneumonitis, and two had new-onset hypothyroidism. Three patients had irAEs of Grade 3–4 that were classified as severe. Only six patients were treated with systemic corticosteroids (prednisone or equivalent: 1–2 mg/kg/day). Some patients tapered their corticosteroid dose within a couple of weeks. Patients with multiple irAEs also received intravenous immunoglobulins after systemic corticosteroids. None of the patients were treated with tocilizumab. In 12 patients, resolution of the de novo irAE or PAD exacerbation was achieved without the need to

withhold or discontinue immunotherapy. No deaths were attributable to irAEs.

## Discussion

ICIs are increasingly being used in multiple malignancies that take advantage of their immune-related antitumor effects. However, their use can be hindered by the development of various inflammatory and immune-mediated events that may be severe and occasionally fatal.[10] A growing number of irAEs have been documented; these affect nearly every organ and system and present complex management challenges.[11] However, the use of ICIs is limited in patients with autoimmunity or previous episodes of severe immunotherapy toxicity, as they are mainly excluded from clinical trials; most data come from observational studies and case reports.[32,33,39]

In the present study, we analyzed the outcomes of 22 cancer patients with PAD and/or CIDs such as eczema who presented to the ED after ICI therapy. Our study sample was heterogeneous, encompassing a wide range of PADs affecting various organ systems, including endocrine, rheumatic, gastrointestinal, and dermatological. Patients presented with a range of typical and atypical clinical irAE symptoms, ranging from mild fatigue and dyspnea to more serious complications resulting from the exacerbation of underlying preexisting disease (type I diabetes) leading to diabetic ketoacidosis.

A study from Australia by Johnson et al. reviewed thirty PAD patients who underwent CTLA-4 therapy for the treatment of advanced melanoma; Grade 3–5 irAEs occurred in 33% and were reversible in only two cases using corticosteroids or infliximab therapy.[33] Similarly, Menzies et al. reported on 119 patients with underlying autoimmune disease or major ipilimumab toxicities who were being treated with pembrolizumab or nivolumab therapy. Of the 52 patients with PAD, only 38% developed disease exacerbation or flare-ups, and there was a trend toward more flare-ups in patients who required immunosuppressive therapy at initiation for the management of their underlying autoimmune disorder. Leonardi et al. studied patients with non-small cell lung cancer and concurrent PAD.[32] A minority (13%) developed an exacerbation of their underlying PAD, while 55% experienced an irAE or both. Patients who experienced a disease flare-up did not require permanent discontinuation of immunotherapy; however, 11% of patients who experienced an irAE did. Interestingly, patients who were symptomatic from their baseline PAD were more likely to experience a disease flare-up on anti-PD-1/PD-L1 therapy. Toi et al.[40] assessed the safety and efficacy of anti-PD-1 therapy in cancer patients with subclinical disease and advanced non-small cell lung cancer, including or excluding PAD markers at baseline. Interestingly, they reported an independent association between preexisting autoantibodies and irAEs. Further, dermatologic reactions, such as preexisting rheumatoid factor (47% vs. 24%) and thyroid dysfunction, were more common with preexisting thyroid antibodies (20% vs. 1%). Abdel-Wahab et al., in a systematic review studying the fate of patients with PAD, found that of 127 patients with >30 different autoimmune and/or auto-inflammatory diseases who underwent either CTLA-4 or PD-L/L-1 therapy, about 75% developed a de novo irAE or had a PAD exacerbation/flare.[12] Overall, ICI therapy in patients with PAD has a very high incidence of de novo irAE or PAD exacerbation/flare, but whether these complications are manageable and not outweighing the benefit of ICI therapy remains to be closely examined.

The majority of the PADs in our cohort involve the skin or the thyroid. This is perhaps due to risk–benefit assessment of the irAE/PAD flare versus antineoplastic benefit. Almost all of these patients with PADs of the skin or the thyroid do not require systemic corticosteroid or immunosuppressant therapy, and worsening of these PADs (in only about 20% of cases in our cohort) is usually manageable by medication adjustments. The time to de novo irAEs or PAD flare-ups varied in our study, but in most patients, these events occurred early, after a few doses, emphasizing the need to adequately assess patients after ICI therapy. In addition, patients who have undergone multiple ICI therapies, as seen in three of our patients, and those who have undergone combination therapy require close monitoring. Several of our patients presented with multiple irAEs; most were elderly and had multiple comorbidities, posing a complex challenge. Nevertheless, patients responded well to corticosteroids; other immune modulators and anti-inflammatory agents were also occasionally used. These results demonstrate that the cautious management of irAEs (especially early detection and treatment) can help in achieving the maximum antitumor clinical benefit.

There is an urgent clinical need for irAE risk stratification. Greater emphasis on personalized management strategies aimed at providing prophylactic interventions may be needed to help mitigate such events. Predictors or biomarkers for the risk of irAEs after ICI have not been well investigated, although there is growing evidence that IL-17, the clonal expansion of CD8-positive T-cells, eosinophil counts, and neutrophil activation markers are linked to specific irAEs.[40-43] Other risk factors include a family history of autoimmune disease, prior viral infections, and the use of drugs with known autoimmune toxicities.[40,44,45]

Our retrospective review has several limitations. Our study population was heterogeneous in terms of cancer type, which may influence the frequencies of various de novo irAEs. The retrospective nature of our study limits the ability to collect data on autoantibodies or in many cases details about the pharmacological management of the PADs. Our sample size is relatively small and not allowing us to examine whether the differing types and

severities of PADs may have played a role in the risk of de novo irAEs or disease flare-ups. Our series also remained underpowered for the subgroup analysis, which limited our ability to assess survival or irAE risk.

## Conclusion

Studies have suggested assessing clinical biomarkers that are predictive of irAEs, performing pretherapy evaluations, and performing close monitoring in cancer patients with PAD; however, because of the limited number of studies, these recommendations should be interpreted with caution.[46] Prospective studies with larger and more homogeneous samples are required to assess the risk–benefit profile of ICI therapy in patients with PAD.

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### Conflicts of interest

The authors disclosed no conflicts of interest related to this article.

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