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Characterization and evaluation of dermatological immune-mediated reactions associated with checkpoint inhibitors: an observational, longitudinal and retrospective study in an oncology service in Salvador/BA

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Abstract

Objective: To evaluate dermatological immune-mediated reactions in patients treated with checkpoint inhibitors at an oncology center in Salvador-BA. **Method:** An observational, longitudinal, retrospective, descriptive, and uncontrolled study was carried out in patients undergoing treatment with checkpoint inhibitors, during the period from Jan/2021 to Dec/2021. After applying the exclusion criteria, the study's sample size resulted in 69 patients. Electronic spreadsheets from the Excel tool (Microsoft®) were used for data processing and statistical analysis. The identification and measurement of the severity of toxicities followed the Common Toxicity Criteria, as defined by the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. **Results:** The investigation found 84 immune-mediated dermatological reactions occurring in 44 patients (63.77%), with the most frequent being dry skin (37%), maculopapular rash (26%), and itching (20%).The regimen with the highest incidence of reactions was the one that included pembrolizumab, with 47 occurrences. The severity of dermatological immune-mediated toxicities ranged from grade 1 to grade 2, indicating a good safety profile for these medications. Key management strategies included the use of emollients, increased fluid intake, and administration of antihistamines and corticosteroids. **Conclusion:** The findings of this study are aligned with the evidence from the clinical literature and highlight the importance of in-depth understanding of factors related to immunotherapy toxicity, in order to detect these reactions prematurely, optimizing management and preventing more serious complications.

Key words: cancer, immunotherapy, monoclonal antibodies. adverse events.

Caracterização e avaliação de reações imunomediadas dermatológicas associadas a inibidores de checkpoint: um estudo observacional, longitudinal e retrospectivo em um serviço de oncologia de Salvador/BA

Resumo

Objetivo: Avaliar as reações imunomediadas dermatológicas em pacientes tratados com inibidores de checkpoint em um centro oncológico de Salvador-BA. **Método:** Foi realizado um estudo observacional, longitudinal, retrospectivo, descritivo e não controlado, em pacientes submetidos ao tratamento com inibidores de checkpoint (n = 72), durante o período de jan/2021 até dez/2021. Após os critérios de exclusão, o tamanho amostral do estudo resultou em 69 pacientes. Planilhas eletrônicas da ferramenta Excel (*Microsoft*®) foram utilizadas para tratamento dos dados e análise estatística. A identificação e mensuração da gravidade das toxicidades seguiram os Critérios Comuns de Toxicidade, conforme definidos pelo *Common Terminology Criteria for Adverse Events* (CTCAE), versão 5.0. **Resultados:** A investigação constatou 84 reações imunomediadas dermatológicas ocorridas em 44 pacientes (63,77%), com maior frequência para pele seca (37%), rash maculopapular (26%) e prurido (20%). O regime com maior incidência de reações foi aquele que incluía o pembrolizumabe, com 47 ocorrências. A gravidade das toxicidades imunomediadas dermatológicas variou de grau 1 a grau 2, indicando um bom perfil de segurança para esses medicamentos. As principais estratégias de gerenciamento incluíram o uso de emolientes, aumento da ingestão de líquidos e a administração de anti-histamínicos e corticosteroides. **Conclusão:** Os achados deste estudo são consonantes com as evidências da literatura clínica e destacam a importância da compreensão aprofundada dos fatores relacionados à toxicidade da imunoterapia, de maneira a detectar prematuramente essas reações, otimizando o manejo e prevenindo complicações mais graves.

Palavras-chave: câncer, imunoterapia, anticorpos monoclonais, eventos adversos.

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Introduction

Over the centuries, cancer has been a disease that significantly affects the quality of life of afflicted patients. Despite advances in various treatment approaches such as radiotherapy, surgery, and conventional chemotherapy, the multifactorial complexity, drug resistance, and rapid spread of neoplastic cells have limited the effectiveness of these traditional strategies. With the advent of new pharmaceutical technologies and a deeper understanding of antitumor immunity, new therapies have been implemented, including immunotherapy, which has revolutionized antineoplastic treatment[1-2].

One of the essential components of this contemporary therapeutic arsenal is immune checkpoint inhibitors, which have demonstrated significant benefits in the approach to cancer. These agents are proteins that restrict regulatory immune components and play a fundamental role in reactivating immune responses against cancer cells. Among them, the inhibition of programmed cell death protein 1 (PD-1) and its ligands (PD-L1 and PD-L2), as well as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), stands out. This therapeutic approach represents an important milestone in cancer treatment, expanding the available treatment options[3].

The main checkpoint inhibitors approved by the Food and Drug Administration (FDA) are Ipilimumab, Nivolumab, Pembrolizumab, Toripalimab, Retifanlimab, Dostarlimab, Atezolizumab, Durvalumab, and Avelumab[4-8]. Despite their broad applicability to various types of cancer and promising results in extending survival, it is important to highlight that the use of these medications has been associated with the occurrence of some events known as immune-mediated adverse reactions. These events can affect any organ system, primarily the cutaneous, musculoskeletal, endocrine, intestinal, and pulmonary[1,9] tissues. It is reported that the most common events are dermatological and are usually the first to manifest. Most of these reactions tend to range from mild to moderate according to the Common Terminology Criteria for Adverse Events (CTCAE)[16]. Furthermore, they occur more frequently with CTLA-4 inhibitor monotherapy compared to PD-1/PD-L1[10] inhibitors.

These immune-mediated adverse reactions profoundly impact the quality of life of patients and can affect the efficacy of checkpoint inhibitor treatment due to dose-limiting effects. Cutaneous immune-mediated adverse reactions are the most frequent and the first to arise in patients receiving this class of medication. Therefore, understanding their clinicopathological characteristics and developing targeted and effective management strategies is crucial for successful[10] oncodermatology practice. After all, many of these checkpoint inhibitors are relatively new, and there is concern about the long-term effects of these agents, including the potential for late-onset immune-mediated reactions and the impact on overall immune function.

In this context, the present study aims to conduct a comprehensive evaluation of dermatological immune-mediated reactions in patients undergoing checkpoint inhibitor treatment. It seeks to identify the main associated dermatological adverse reactions, measure the most incident ones, outline the patient profiles when these reactions occur, and record the primary management strategies for these events. With such information, it will be possible to better understand the challenges associated with dermatological reactions and implement appropriate management strategies to optimize treatment efficacy and minimize adverse impacts on the patient experience.

Methods

This is an observational, longitudinal, retrospective, descriptive, and uncontrolled study conducted on adult patients of both sexes with cancer who underwent checkpoint inhibitor treatment at an oncology center in Salvador, Bahia.

Sociodemographic information, the existence of other comorbidities, the use of other medications (which could be confounding factors), possible drug interactions, treatment protocol information, toxicity screening, their gradations and management, as well as the type of neoplasia and lifestyle habits were analyzed. Patients diagnosed with cancer and undergoing checkpoint inhibitor treatment between January 2021 and December 2021 were investigated. Those patients who had already started the protocol before the period in question, as long as they continued treatment throughout 2021, were also selected. This approach was adopted to ensure a consistently relevant temporal analysis. Patients without sufficient data for identifying and measuring reactions were excluded. Additionally, the sample size was determined by convenience due to the availability of the number of participants per treatment protocol and available resources. To minimize potential biases, comparisons were made considering similar characteristics between groups.

Electronic spreadsheets from Microsoft Excel, version 2308, were used for data processing and statistical analysis. The study began with a review of the main adverse effects of the medications used by the patients to reduce the chance of statistical interference from polypharmacy. Furthermore, regarding potential research biases, other studies associating the use of checkpoint inhibitors with dermatological reactions have shown a lower incidence for other treatments or protocols, particularly from the mechanistic standpoint through which this occurs.

To analyze the incidence, relative risk was calculated based on the participants who presented the outcome in relation to the total number of participants following the protocol. The reaction rate was determined by the number of participants who experienced the event compared to the total number of study participants. The identification and measurement of the severity of toxicities followed the Common Terminology Criteria for Adverse Events (CTCAE) – version 5.0, developed by the National Cancer Institute (NCI) and the National Institutes of Health (NIH) of the United States. This version was published in November 2017 (CTEP, 2017). The grading of adverse events according to the CTCAE occurs on a scale of 1 to 5, where grade 1 represents mild toxicities and grade 5 corresponds to death.

The present study was approved by the Research Ethics Committee of the Faculty of Pharmacy at the Federal University of Bahia, with the opinion numbered 5.756.057, CAAE: 62083922.5.0000.8035.

Results

The sample consisted of 72 patients. Of these, 3 were excluded due to the absence of data in medical records or the performance of protocol cycles at another institution. The study patients were between 30 and 94 years old, with over 50% diagnosed with malignant melanoma of the skin, malignant neoplasm of the bronchi and lungs, and malignant melanoma of the skin. The majority were male, representing 55.07% (38), while 44.93% (31) were female. The average age of the total population was 67.90 years (SD = 12.64). Analyzing the sex groups separately, the average

age for the female population was 67.81 years (SD = 13.48), and for the male population, it was 65.84 years (SD = 12.11).

Most patients had comorbidities, around 78.26% (54) of the cases, with a higher prevalence among the elderly population (≥ 65 years). The most recurrent comorbidities included hypertension, diabetes, and dyslipidemia. In the context of polypharmacy (concurrent use of ≥ 5 medications), 60.87% (42) of the patients fell into this category, which can be attributed to the fact that individuals with comorbidities often require specific treatments for each of their health conditions. No clinically significant adverse reactions were found that associated other medications used by patients with dermatological adverse events.

During the study period, 84 immune-mediated dermatological reactions related to checkpoint inhibitors were identified, as illustrated in Figure 1. The most prominent events included dry skin, which represented 37% (31 cases), maculopapular rash with 26% (22 cases), and pruritus with 20% (17 cases).

Three treatment regimens had a higher number of patients (Figure 2), the protocol with pembrolizumab (n = 44), nivolumab (n = 12), and durvalumab (n = 5). Additionally, they resulted in a higher frequency of adverse events.

Table 1 shows the frequency of reactions in these main protocols, where the most common included maculopapular rash, dry skin, and pruritus. Notably, the treatment line with pembrolizumab presented the highest incidence of reactions, recording 47 occurrences. Of these, 38.30% were identified as dry skin, followed by 29.79% maculopapular rash.

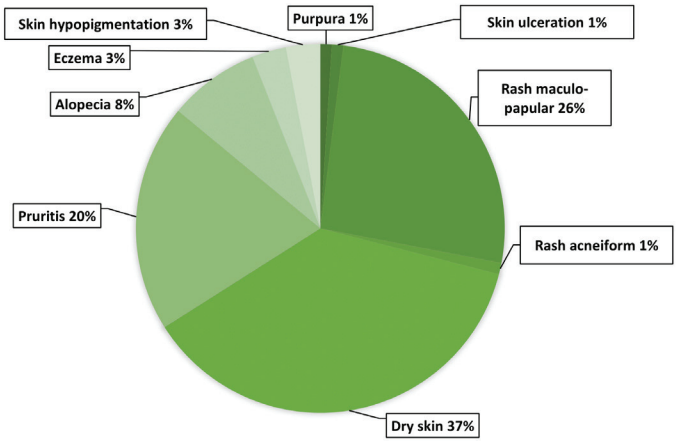
The treatment lines with nivolumab monotherapy and/or nivolumab + ipilimumab presented 21 records, with only 3 of these reactions associated with combination therapy. Finally, nine reactions were recorded for the agent durvalumab, with 44.45% of them related to dry skin and 33.33% associated with alopecia.

The severity of immune-mediated dermatological toxicities ranged from grade 1 to grade 2, as shown in Table 2. No higher complexity toxicities were identified.

The main strategies for managing immune-mediated dermatological reactions are listed in Table 3. A total of 152 approaches were adopted to manage these toxicities. Some of these measures were not employed in isolation; in some cases, strategies were combined to optimize the response, with emphasis on the application of emollients and the recommendation to increase water intake.

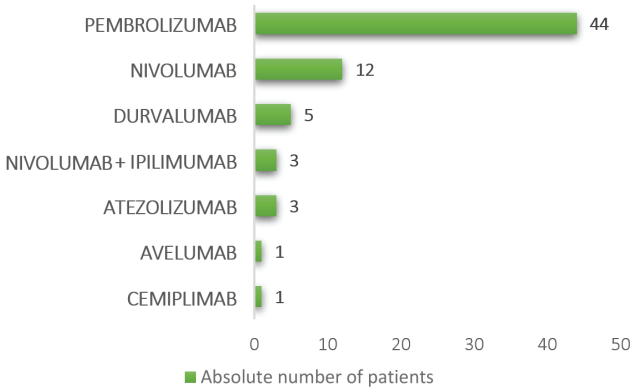
For grade 1 severity reactions, emollients were predominantly used in 43.44% of cases, followed by the recommendation to increase water intake in 31.96%, and the administration of antihistamines in 13.11%. Most therapeutic interventions were directed at reactions such as maculopapular rash, dry skin, and pruritus, which manifested more frequently. Regarding antihistamines, a variety of options were observed, with loratadine and fexofenadine being the most employed, especially in managing reactions like maculopapular rash and pruritus. Prednisone was the most used corticosteroid. Other important measures included the use of sunscreen, antiseptic soaps, and thermal caps.

Figure 1. Quantitative analysis of patients by treatment protocol (n = 84).



Source: Own authorship

Figure 2. Quantitative relationship between the number of patients and Protocol (n = 69).



Source: Own authorship

Table 1. Profile of immune-mediated dermatological reactions among protocols with a high frequency of adverse events.

Immune-Mediated Reaction	Protocol		
	Pembrolizumab	Nivolumab (monotherapy) and/or Nivolumab + Ipilimumab	Durvalumab
Maculopapular rash	14 (29.79%)	7 (33.33%)	1 (11.11%)
Dry skin	18 (38.30%)	6 (28.57%)	4 (44.45%)
Pruritus	11 (23.40%)	5 (23.82%)	1 (11.11%)
Alopecia	1 (2.13%)	1 (4.76%)	3 (33.33%)
Purpura	-	1 (4.76%)	-
Hypopigmentation	1 (2.13%)	1 (4.76%)	-
Eczema	2 (4.26%)	-	-
Total reactions	47 (100%)	21 (100%)	9 (100%)

Source: Own authorship

Table 2. Distribution of severity according to toxicity grading by CTCAE 5.0.

Immune checkpoint inhibitors	Grade 1	Grade 2
Anti-PD-1 agents	53 (63.10%)	14 (16.67%)
Anti-PD-L1 agents	12 (14.28%)	2 (2.38%)
Anti-CTLA-4/PD-1 agents	2 (2.38%)	1 (1.19%)
Total	**67 (79.76%)**	**17 (20.24%)**

Source: Own authorship

For grade 2 severity reactions, the use of emollients (26.66%) and approaches directed at managing skin ulcerations and eczema (23.33%) were the most prominent, due to their moderate severity. These interventions included the application of topical bacteriostatic antibiotics, creams for recovery from scaling and dryness, and sunscreen. In 5 cases (3.29%), no description of management approaches for both severity grades was found. **

Table 3. Therapeutic measures adopted for the management of dermatological immune-mediated reactions.

Severity level	Antihistamines	Corticosteroids	Emollients	Hydration	Other measures	Undescribed approach
1[1]	16 (13.11%)	4 (3.29%)	53 (43.44%)	39 (31.96%)	8 (6.56%)	2 (1.64%)
2[2]	5 (16.67%)	5 (16.67%)	8 (26.66%)	2 (6.67%)	7 (23.33%)	3 (10.00%)

[1]Data presented in absolute numbers and percentage (Total interventions = 122). [2]Data presented in absolute numbers and percentage (Total interventions = 30). Source: Own authorship

Discussion

In the present study, the results suggest that more than 20% of the immune-mediated dermatological reactions associated with the use of checkpoint inhibitors were characterized as dry skin, maculopapular rash, and pruritus. These findings are consistent with Geisler et al. (2020), who described commonly reported cutaneous manifestations as non-specific maculopapular rash (MPR) and pruritus. Additionally, other adverse events such as dry skin, alopecia, and hypopigmentation were also well documented by the author. It is important to note that these cutaneous complications generally present as self-limiting and easily manageable, although some rare events may occur, such as Stevens-Johnson syndrome, ulcerations, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS)[10].

The protocol with the highest incidence of reactions was pembrolizumab, with nearly 60% of the events, primarily dry skin and pruritus. This profile is also recurrent in Naidoo et al. (2015), where a safety analysis revealed that rash, pruritus, and vitiligo were the most prevalent toxicities in isolated anti-PD-1 agents, observed in 39% of patients who received pembrolizumab and 34% of those treated with nivolumab[11]. Monotherapy with nivolumab and/or nivolumab + ipilimumab accounts for 25% of the reactions. It is crucial to highlight the possibility of bias in inferring these data, given the limited number of patients undergoing treatment with combined agents, which prevents robust comparisons. However, this result is corroborated by the findings of Wolchok et al. (2016), where combined nivolumab + ipilimumab therapy for advanced melanoma showed a 55% incidence of reactions related to rash and 47% associated with pruritus, results very similar to those of the current[12] study. For durvalumab, the highest percentage of alopecia was observed, about 33.33%, a more frequent event for this treatment line, corroborated by Al-Salama (2022), where 32% of patients presented this reaction in a phase III study conducted in patients treating advanced[13] stage small cell lung cancer.

The severity of adverse reactions ranged from mild to moderate. This scenario is supported by the literature, with a reduced incidence of reactions classified as grade 3 or higher. According to observations by Sibaud (2017) and Villadolid and Amin (2015), these reactions occur in about 40% of patients undergoing monotherapy with anti-CTLA-4 or anti-PD-1 and in 60% of those receiving combined therapy with both types of agents[14-15]. Although only 2.38% of reactions were recorded in patients undergoing combined therapy, it is crucial to highlight the limitation of the number of patients who underwent this specific type of treatment during the study period.

Regarding the management strategies for immune-mediated dermatological reactions, the consensus of the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group establishes some system-based toxicity management strategies. For the treatment of maculopapular rash and grade 1 dermatitis, characterized by lesions covering less than 10% of body surface area, with or without symptoms of pruritus, burning, and tightness, interruption of immunotherapy is not necessary. Additionally, oral antihistamines such as cetirizine or loratadine (10 mg/day) or hydroxyzine (10-25 mg/day) are suggested. For the body, the use of class I topical corticosteroids such as clobetasol, halobetasol, betamethasone cream, or ointment is recommended. For the face, class V or VI corticosteroids such as alclometasone, desonide, and 2.5% hydrocortisone cream are indicated. In cases of grade 2 severity, with lesions covering 10% to 30% of the body surface area and possible limitations in daily activities, continuation of immunotherapy remains, and the suggested management includes antihistamines and corticosteroids used in grade 1. Referral to a dermatologist is also recommended, though not urgently. For grade 3 severity, with lesions covering more than 30% of the body surface area, with or without limiting symptoms in daily activities, immunotherapy may be continued, immediate dermatological follow-up is needed, systemic hypersensitivity ruled out, and management with oral antihistamines as per grades 1 and 2. Additionally, the use of systemic corticosteroids, such as prednisone (0.5 to 1 mg/kg/day) or an equivalent dose of methylprednisolone, is recommended until the event reaches grade 1[1] severity or lower.

Regarding the management of pruritus, in cases of grade 1 severity, characterized as mild or localized, topical intervention is indicated. Unscented emollients in cream or ointment form are recommended. Class I topical corticosteroids for the body and class V or VI for the face are also appropriate, as well as the incorporation of oral antihistamines as described for rash. For grade 2 severity, where pruritus is intense or generalized, potentially

causing skin changes, intervention with topical corticosteroids and oral antihistamines is recommended. In some cases, oral corticosteroids (prednisone 0.5 to 1 mg/kg/day or an equivalent of methylprednisolone) may be gradually used over two weeks. At this severity level, referral to a dermatologist for follow-up is also suggested, though not urgently. In grade 3 severity situations, defined as intense or generalized pruritus, constant and limiting self-care activities or sleep, the use of oral corticosteroids or immunosuppressive therapy is recommended, as described earlier, along with immediate dermatological follow-up. GABA agonists such as pregabalin and gabapentin, 100-300 mg, three times a day may also be management[1] options.

Regarding other reactions, including those affecting other systems, according to the general guidelines for managing immune-mediated toxicities from SITC, in grade 1 toxicities, corticosteroids are generally not indicated. From grade 2, suspension of immunotherapy during corticosteroid use is suggested, inclusion of proton pump inhibitors for gastrointestinal prophylaxis, and resumption of immunotherapy when the event resolves to grade 1 or lower. From grade 3 severity, prednisone is adopted at a dose of 1-2 mg/kg/day (or an equivalent dose of methylprednisolone). If no improvement is seen within 3 days, the inclusion of an immunosuppressant such as infliximab is indicated. After achieving improvement to grade 1 or lower, a gradual tapering of steroids over 6 weeks is advisable. Additionally, the continuation of immunotherapy can be maintained, provided symptoms improve within this period. Consideration should also be given to the use of proton pump inhibitors for gastrointestinal prophylaxis and the prescription of prophylactic antibiotics for pneumonia, especially if immunosuppression is expected to last more than three weeks. In grade 4 severity cases, management follows a similar approach to grade 3. However, it is recommended to consider discontinuation of immunotherapy in these cases[1].

The approaches used for managing immune-mediated dermatological reactions were consistent with the guidelines established by the SITC consensus. However, since these provided guidelines are based on case reports and series, as well as expert consensus, it is valid for each institution to implement discussions with the medical oncology team, taking into account the particularities of each patient. Another crucial aspect lies in the effective management of adverse reactions, making early recognition and immediate intervention vital through appropriate strategies for the affected organ and toxicity severity. The contribution of the multidisciplinary team, including the pharmacist, is essential in this regard and involves familiarization with such immune-mediated reactions, expediting investigations and preventing potentially fatal complications. Evaluating drug interactions and promoting health education with the patient, emphasizing active participation in treatment, in addition to practicing pharmacovigilance in these events, also represent important measures that should be implemented. These actions aim to prevent the progression of immune-mediated reactions to severity stages that compromise treatment while seeking to improve the patient's quality of life.

It is important to highlight some limitations of the investigation, mainly because it is a retrospective observational study. Given the limited number of participants for certain protocols, there is a chance of generalizing the results to other populations or clinical settings. Therefore, the study's findings may not be fully representative. Additionally, since the study was conducted in a specialized clinic, there may be location bias, including differences in patient characteristics, which could complicate the interpretation of the results and their applicability. To mitigate these limitations, multicenter studies with a significant number of participants, including a variety of populations and clinical settings, would be necessary. Furthermore, a thorough data analysis considering confounding factors and bias is essential to correctly interpret the results and make relevant clinical recommendations.

These directions for future research can provide valuable insights into the management and understanding of immune-mediated dermatological reactions associated with the use of checkpoint inhibitors, contributing to a more effective and personalized approach in clinical practice.

Conclusion

The study analyzed the incidence and profile of immune-mediated dermatological reactions in patients undergoing treatment with checkpoint inhibitors, in addition to investigating the approaches adopted for their management. The results reflect the data presented in both national and international clinical literature. Likewise, treatment practices were aligned with guidelines for managing immune-mediated reactions associated with checkpoint inhibitors. A deeper understanding of the factors related to immunotherapy toxicity may allow for the early identification of patients more prone to these reactions. In this way, providing aspects for the early detection of these events, accelerating the management of reactions, and preventing more severe complications.

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Contributors

Almeida LB: 1. Conception and design of the study. 2. Data analysis and interpretation. 3. Drafting the article.

Wingert NR: 1. Critical review of methodological content.

Barbosa IA: 1. Assistance in study design. 2. Review of data interpretation and intellectual content.

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Conflict of Interest Statement

The authors declare no conflicts of interest regarding this article.

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