Immune-Related Dermatologic Reactions in Cancer Patients Undergoing Immunotherapy: A Case Series

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Ind J Med Paediatr Oncol 2025;46:615–620.

Abstract

Immune checkpoint inhibitors (ICIs) have transformed the treatment paradigm across various malignancies by reactivating T cell responses against tumor cells. These agents function by blocking inhibitory checkpoint pathways, thereby preventing immune downregulation and enhancing antitumor immunity. Despite their clinical success and relatively favorable safety profile, ICIs are associated with immune-related adverse events (irAEs), which can impact multiple organ systems. Among these, cutaneous irAEs are some of the most common, owing to the skin's immunologic sensitivity. These manifestations range from mild conditions—such as pruritus, maculopapular rashes, and inflammatory dermatoses including eczema, psoriasis, and lichenoid reactions—to more severe immunobullous disorders (such as bullous pemphigoid, pemphigus vulgaris, and Stevens–Johnson syndrome). While most cutaneous irAEs can be effectively managed without interrupting immunotherapy, certain cases may require prompt, multidisciplinary intervention to prevent serious complications. This case series presents four diverse malignancies complicated by dermatologic irAEs, highlighting atypical presentations, critical warning signs, and evidence-based strategies for management. Through these cases, we aim to raise awareness about less common cutaneous toxicities and offer practical guidance to ensure safe continuation of cancer immunotherapy.

Keywords
- dermatology
- immune checkpoint inhibitors
- immune-related adverse events

Introduction

Immunotherapy has transformed cancer treatment, with immune checkpoint inhibitors (ICIs) at the forefront. These agents—targeting inhibitory receptors such as CTLA-4, LAG-3, PD-1, and PD-L1—restore antitumor immunity by blocking immune checkpoints that suppress T cell activity. This reinvigorates immune surveillance, enabling the recognition and elimination of malignant cells, and has led to durable responses across various cancers. Compared with traditional chemotherapy, ICIs generally have a more favorable toxicity profile. However, by enhancing immune function, they can trigger immune-related adverse events (irAEs).[1,2] Among these, cutaneous irAEs are common and range from mild rashes to severe, potentially life-threatening dermatologic conditions. With the growing use of ICIs across malignancies—including melanoma, hematologic, and gynecologic cancers—clinicians must remain alert to these skin manifestations. Early recognition, prompt dermatologic consultation,

article published online
September 8, 2025

DOI https://doi.org/10.1055/s-0045-1811565.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

and coordinated management are essential to reduce morbidity and allow patients to continue life-prolonging therapy.

Case History

Case 1: Severe Immune-Related Exfoliative Dermatitis Mimicking Toxic Epidermal Necrolysis Following Dual Checkpoint Inhibition in Metastatic Non–Small Cell Carcinoma Lung

A 52-year-old female, chronic smoker with no prior autoimmune disease, was diagnosed with metastatic squamous cell carcinoma of the lung, complicated by pleural effusion and bone metastases. Molecular profiling revealed no actionable mutations, and PD-L1 expression was <1%. She was started on a combination regimen of nivolumab (PD-1 inhibitor), ipilimumab (CTLA-4 inhibitor), and paclitaxel–carboplatin chemotherapy. The initial cycles were well tolerated. However, by day 11 posttherapy, the patient developed extensive erythematous and exfoliative skin lesions involving the back, trunk, and abdomen, characterized by diffuse desquamation, scaling, and epidermal detachment, without mucosal involvement initially (►**Fig. 1A–C**). She became systemically unwell, with hypotension and signs of toxicity, prompting urgent intensive care unit admission. The clinical picture was highly suggestive of a severe immune-related cutaneous adverse reaction (grade 4), closely mimicking toxic epidermal necrolysis (TEN). Dermatology consultation confirmed the diagnosis of severe exfoliative dermatitis, likely immune-mediated, possibly compounded by chemotherapy. Laboratory workup (including complete blood count, liver function tests, eosinophil count, and inflammatory markers) was initiated to rule out drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome and assess systemic involvement. Immunotherapy was immediately discontinued, and the patient was started on IV methylprednisolone (1 mg/kg/day) along with topical corticosteroids, skin barrier repair agents, and comprehensive supportive ICU care. Over the following 2 weeks, her skin lesions gradually stabilized, with early signs of re-epithelialization. Due to the severity of the grade 4 toxicity, immunotherapy was permanently discontinued, and alternative systemic treatment options were initiated. At the 6-month follow-up, hypopigmented facial patches and alopecia showed partial repigmentation, although some residual depigmentation remained. No new lesions developed, and the patient remained in oncologic remission, continuing alternative therapy without further irAEs.

Case 2: Maculopapular Rash Following Tremelimumab and Durvalumab in Advanced Hepatocellular Carcinoma

A 60-year-old male with hepatocellular carcinoma involving portal vein thrombosis (Barcelona Clinic Liver Cancer [BCLC] Stage C, Child-Pugh A, Eastern Cooperative Oncology Group 1 [ECOG]) underwent transarterial chemoembolization (TACE) followed by systemic immunotherapy with tremelimumab (CTLA-4 inhibitor) and durvalumab (PD-L1 inhibitor), as per the HIMALAYA regimen. The patient tolerated the initial infusion well; however, on day 7 posttreatment, he developed a diffuse erythematous, pruritic maculopapular rash (MPR) over the trunk and back (►**Fig. 2A, B**), without systemic symptoms or mucosal involvement. The rash involved ~10 to 30% of body surface area (BSA). The dermatologic toxicity was categorized as a grade 2 immune-related MPR according to Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0). He was managed conservatively with topical corticosteroids (mometasone 0.1%), oral antihistamines, and close clinical monitoring. Immunotherapy was continued without interruption, and systemic corticosteroids were not required. The rash gradually resolved, with complete clearance by 4 weeks. At the 4-month follow-up, there was no recurrence or post-inflammatory pigmentation, and immunotherapy continued without further cutaneous adverse events.

Case 3: Triple-Negative Breast Cancer with Cutaneous Immune-Related Adverse Event

A 40-year-old woman with a history of hypothyroidism presented with a 6-month history of a painless, immobile lump in the upper outer quadrant of her left breast. Over time, the lesion became painful, accompanied by bloody nipple discharge. Positron emission tomography–computed tomography (PET-CT) revealed a 1.5×1.7 cm FDG-avid, irregular, spiculated lesion without skin or chest wall involvement. FDG-avid left axillary and subpectoral lymphadenopathy

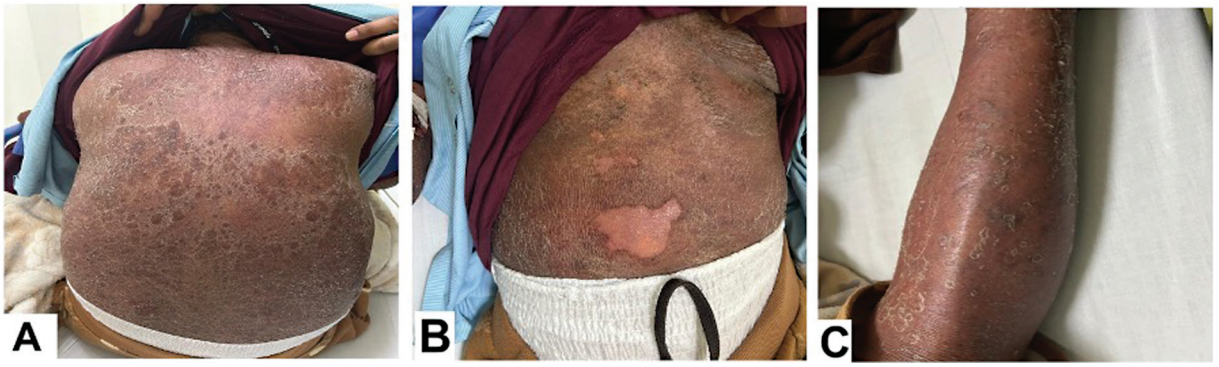

Fig. 1 (**A–C**) Clinical images show extensive erythematous and exfoliative skin lesions involving the back, trunk, and abdomen. Clinical images demonstrate diffuse desquamation, scaling, and areas of epidermal detachment without initial mucosal involvement, consistent with a severe immune-related cutaneous adverse event mimicking toxic epidermal necrolysis.

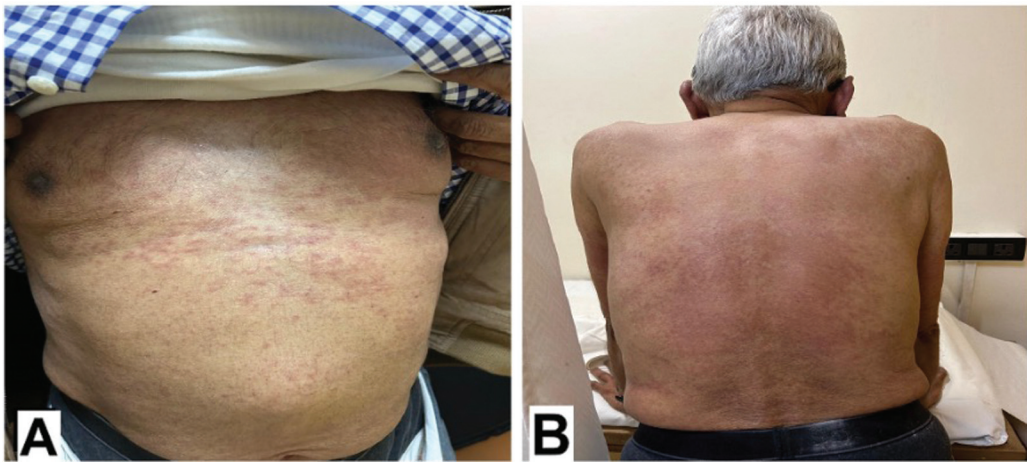

Fig. 2 (**A**, **B**) Clinical images showing diffuse erythematous, pruritic maculopapular rash over the trunk and back, involving 10–30% of BSA.

was noted, with the largest node measuring 2.4 × 2.3 cm (SUVmax: 11.5), along with perinodal fat stranding. Core biopsy confirmed triple-negative breast cancer (ER-, PR-, HER2-). The patient was initiated on neoadjuvant chemo-immunotherapy with pembrolizumab and carboplatin. After three cycles of pembrolizumab, she developed asymptomatic, non-scaly hypopigmented patches over her face and frontal scalp, with associated diffuse alopecia (►**Fig. 3A**). These lesions were consistent with vitiligo-like depigmentation, a recognized cutaneous irAE associated with anti-PD-1 therapy. Based on CTCAE v5.0, this event was categorized as grade 2 vitiligo, given the multifocal involvement and cosmetic impact. The patient was managed conservatively with topical corticosteroids (clobetasol: 0.05%), calcineurin inhibitors (tacrolimus: 0.1%) on facial areas, strict photoprotection, and dermatologic follow-up. No systemic immunosuppression was required, and pembrolizumab therapy was continued without interruption. Following completion of eight cycles of therapy, she underwent a left modified radical mastectomy with axillary clearance. Histopathology revealed a pathological complete response to the neoadjuvant regimen. Postoperative PET-CT showed no evidence of metabolically active residual or recurrent disease. At the 3-month follow-up, the patient had developed post-inflammatory hyperpigmentation over previously affected areas, particularly the back and trunk. No active desquamation was seen, but skin fragility persisted. She remained off immunotherapy and was transitioned to alternative systemic therapy.

Fig. 3 Clinical image showing asymptomatic hypopigmented facial patches with diffuse frontal scalp alopecia, consistent with vitiligo-like depigmentation.

Case 4: Immune-Related Lichenoid Dermatitis Following Nivolumab-Based Therapy in Recurrent Tongue Carcinoma

A 59-year-old woman with recurrent squamous cell carcinoma of the tongue, previously treated with multiple chemotherapy lines, was started on oral metronomic chemotherapy (methotrexate, erlotinib, and celecoxib) combined with nivolumab (100 mg every 2 weeks). After two cycles, she developed pruritic, hyperpigmented, scaly plaques on her lower limbs, predominantly the shins, with associated linear excoriations, superficial erosions, and post-inflammatory crusting (►**Fig. 4A, B**). The morphology and distribution were consistent with lichenoid dermatitis, an irAE associated with PD-1 inhibition. Initially categorized as grade 1 toxicity, the condition was managed with topical corticosteroids and oral antihistamines. However, following the third cycle, the skin lesions significantly worsened, with more extensive excoriation and superficial ulceration, leading to an upgraded classification of grade 3 dermatitis (CTCAE v5.0). Nivolumab was temporarily withheld, and the patient was started on

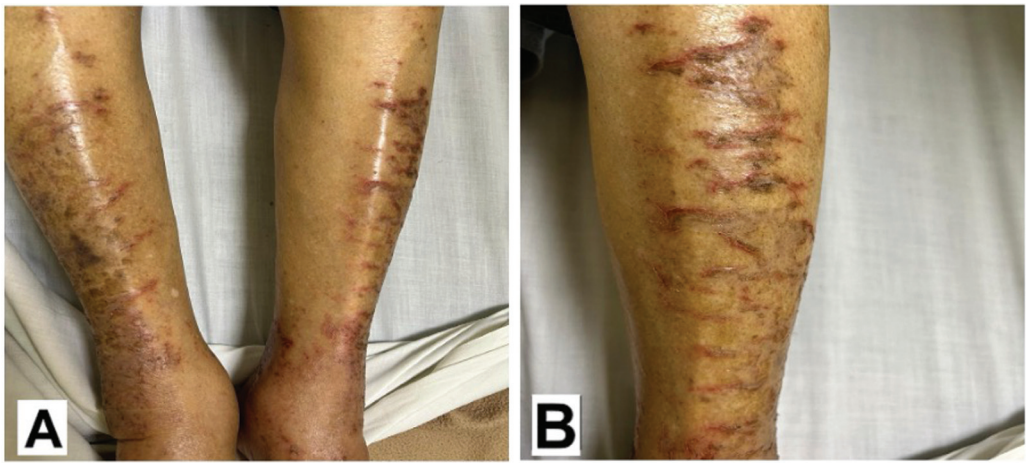

Fig. 4 (**A, B**) Clinical images showing pruritic, hyperpigmented, scaly plaques with excoriations and superficial erosions on the lower limbs, consistent with lichenoid dermatitis.

systemic corticosteroids (prednisolone 1 mg/kg/day), to which she responded favorably. The patient achieved gradual lesion resolution with systemic steroids, and skin changes continued to improve over 3 weeks during steroid tapering. At the 6-month follow-up, only mild post-inflammatory hyperpigmentation and occasional pruritus persisted. Given the improvement, she was considered for immunotherapy reinitiation and was successfully rechallenged under close dermatologic supervision, with no recurrence to date.

Discussion

Dermatologic irAEs are among the most common and often the earliest manifestations of ICI therapy, typically occurring within the first 2 to 4 weeks after treatment initiation. These cutaneous toxicities can serve as early indicators of systemic immune dysregulation, underscoring the importance of prompt recognition and management. The incidence and severity of immune-related cutaneous adverse events (irCAEs) vary by the type of ICI administered. Skin-related adverse events of any grade occur in ~26 to 43.5% of patients receiving CTLA-4 inhibitors, 7.6 to 34% with PD-1 inhibitor monotherapy, and around 40 to 41% with combined CTLA-4 and PD-1 blockade.[3,4] Some studies report even higher rates, with cutaneous toxicities seen in up to 70% of patients on PD-1/PD-L1 inhibitors and nearly all patients on combination regimens. Most irCAEs are mild to moderate in severity (grades 1–2) and are reversible with timely intervention. Grade 1 involves less than 10% BSA with mild symptoms such as pruritus or burning. Grade 2 includes 10 to 30% BSA involvement, or more than 30% with only mild symptoms not affecting self-care. Grade 3 is defined by more than 30% BSA with moderate to severe symptoms impacting activities of daily living. Grade 4 reactions are life-threatening and require immediate medical attention.[4] Severe (grade 3 or higher) skin toxicities remain relatively uncommon, affecting ~1 to 3% of ICI-treated patients.[5,6] However, when they occur, they may necessitate temporary interruption or even permanent discontinuation of therapy, potentially affecting overall cancer outcomes. Clinically, irCAEs frequently present as nonspecific MPRs, pruritus, or inflammatory dermatoses such as psoriasiform, eczematous, or lichenoid eruptions. Less common manifestations include vitiligo-like depigmentation, alopecia, and autoimmune blistering disorders like bullous pemphigoid. Although most cases are self-limiting, rare but serious dermatologic toxicities—such as Stevens–Johnson syndrome (SJS), TEN, and drug reaction with eosinophilia and systemic symptoms—can arise and require urgent, aggressive management.

In Case 1, a patient receiving a combination of nivolumab, ipilimumab, and chemotherapy developed extensive exfoliative dermatitis with epidermal detachment, suggestive of a TEN-like immune-mediated reaction. This severe and rare event required immediate discontinuation of ICIs, intensive care unit admission, and systemic immunosuppression, emphasizing the importance of early recognition and intervention in rapidly evolving skin toxicities. Case 2 featured a patient with hepatocellular carcinoma treated with tremelimumab and durvalumab who developed a grade 2 MPR—an irAE that typically arises within the first 2 weeks of treatment. Symptoms were effectively managed with topical corticosteroids and antihistamines, allowing immunotherapy to continue without interruption. In Case 3, a woman with triple-negative breast cancer developed vitiligo-like facial depigmentation following pembrolizumab-based immunotherapy. Although this pigmentary change is more commonly observed in melanoma, it is increasingly recognized in non-melanoma malignancies. While not medically harmful, such changes often persist and may carry prognostic significance, potentially reflecting sustained immune activation. Case 4 involved a woman receiving metronomic chemotherapy alongside nivolumab who presented with pruritic, reticulated, and ulcerated plaques on her lower limbs, characteristic of lichenoid dermatitis. Initially mild, the condition progressed to grade 3 toxicity after subsequent treatment cycles, necessitating systemic corticosteroids. This case highlights the importance of regular dermatologic assessment and a stepwise approach to management based on severity.

The management of irCAEs generally involves topical corticosteroids and symptomatic care in mild cases, while more severe or persistent cases may require systemic corticosteroids or additional immunosuppressive therapies such as tumor necrosis factor-α (TNF-α) inhibitors. However, it is important to note that the early use of systemic corticosteroids, particularly around the initiation of ICI therapy, may attenuate the antitumor immune response and should be considered judiciously. The variation in immune-related side effects among different checkpoint inhibitors is believed to arise from how these drugs function within the immune system. CTLA-4 inhibitors mainly influence T cell activation in the lymph nodes and other lymphoid tissues, while PD-1 and PD-L1 inhibitors exert their effects more directly at the tumor site. This difference contributes to the distinct patterns and timing of irAE associated with each class of drug.

Distinguishing between preexisting or unrelated skin conditions and irCAEs can be challenging, especially when symptoms appear long after immunotherapy has begun. A thorough clinical evaluation is essential, focusing on the rash's distribution, appearance, type, estimated BSA involvement, any mucosal lesions, and the presence of lymph node enlargement. Furthermore, these cutaneous toxicities are graded based on severity using the CTCAE. The choice of initial investigations depends on how severe the presentation is and may include vital sign monitoring, urine dipstick testing, swabs from any ulcers or erosions for bacterial or viral cultures, and routine blood work such as complete blood count, kidney and liver function tests, inflammatory markers, thyroid function, blood glucose, and muscle enzyme levels. While most skin reactions can be diagnosed based on clinical appearance, more severe, unusual, or persistent cases may require skin biopsy and histopathological analysis for confirmation. MPRs, pruritus, and depigmentation resembling vitiligo are among the most frequently observed cutaneous immune-related side effects. In contrast, more uncommon but serious manifestations include SJS, TEN, and autoimmune blistering skin disorders.

A pruritic MPR is the most common skin-related adverse event associated with CTLA-4 inhibitors, occurring more frequently than with PD-1/PD-L1 therapies. It affects 49 to 68% of patients on anti–CTLA-4 treatment compared with around 20% on anti-PD-1/PD-L1.[7,8] The rash usually appears within 3 to 6 weeks of treatment initiation and tends to be dose dependent. Commonly affecting the trunk and extensor limbs, it presents as faint erythematous macules and papules that may merge into plaques. Most cases are mild to moderate (grades 1–2), involving less than 30% of the BSA, while ∼4% develop severe (grades 3–4) rashes. Koebner phenomenon may occur due to trauma or scratching. Management of grades 1 to 2 MPR includes mid- or superpotent topical corticosteroids with continued immunotherapy. Grade 3 requires systemic corticosteroids (prednisone: 1–2 mg/kg/day) alongside topical treatment, and immunotherapy should be paused until improvement. For grade 4, therapy must be discontinued and high-dose methylprednisolone (2 mg/kg/day) initiated.

Vitiligo occurs in ∼11% of patients on anti-CTLA-4 therapy and up to 25% with anti-PD-1 treatment.[8,9] In the latter, the immune response involves CD8+ cytotoxic T cells targeting melanoma-associated antigens—such as MART-1/MelanA, gp100, and tyrosinase-related proteins—that are also found in healthy melanocytes. This can result in asymmetrical depigmentation patterns, ranging from large patches to fine, confetti-like spots. When nivolumab is combined with ipilimumab, depigmentation tends to be more widespread and may appear earlier. These pigment changes usually persist after therapy ends and do not require stopping or pausing ICIs. While not medically necessary, interventions like high-SPF sun protection and cosmetic camouflage can help address aesthetic concerns. Topical corticosteroids or calcineurin inhibitors may be used cautiously, though they offer limited clinical benefit.

Although systemic corticosteroids remain the mainstay for managing moderate to severe cutaneous irAEs, a subset of patients may exhibit inadequate response or develop steroid-related toxicity. In such cases, emerging immunomodulatory agents are being explored. Janus kinase (JAK) inhibitors such as tofacitinib and ruxolitinib have shown efficacy in small series and case reports, likely due to their ability to downregulate proinflammatory cytokine signaling. Similarly, targeted biologics including IL-17 and IL-23 inhibitors (e.g., secukinumab, guselkumab)—traditionally used in psoriasis—have demonstrated benefit in selected patients with immune-related psoriasiform or lichenoid eruptions. Other agents such as mycophenolate mofetil, azathioprine, and rituximab may also be considered based on individual presentation and multidisciplinary input. These therapies offer promising steroid-sparing options and may allow reintroduction of immunotherapy in patients with previously severe reactions under careful monitoring.

Among the most serious cutaneous irAEs are SJS and TEN, which are characterized by widespread epidermal necrosis and detachment, often accompanied by mucosal involvement. These conditions are increasingly recognized in association with ICIs such as pembrolizumab, nivolumab, and ipilimumab. Clinically, SJS and TEN may begin with nonspecific targetoid macules that progress to dusky plaques, bullae, widespread epidermal sloughing, and a positive Nikolsky sign. The extent of BSA involvement differentiates the conditions: SJS involves less than 10% BSA, TEN involves more than 30%, and overlap syndromes affect between 10 and 30%. Management requires the permanent discontinuation of ICIs. Treatment involves hospital admission with intensive supportive care to maintain fluid balance and reduce the risk of infection through appropriate wound care. Therapeutic strategies may include administering high-dose corticosteroids, such as methylprednisolone at 2 mg/kg per day, along with the possible use of intravenous immunoglobulin, TNF-α inhibitors, mycophenolate mofetil, or cyclosporine, depending on the severity and clinical judgment.

This case series offers several strengths, including a diverse representation of malignancies and a broad spectrum of dermatologic irAE associated with different ICI regimens. The detailed clinical descriptions, visual documentation, and treatment strategies presented can serve

as a practical reference for oncologists and dermatologists encountering similar presentations in real-world practice. The inclusion of both mild and severe cutaneous reactions enhances clinical relevance and educational value. However, the study is limited by its small sample size, and the absence of long-term follow-up data in some cases. Additionally, the reliance on clinical diagnosis without histopathologic confirmation in all cases may limit diagnostic precision, especially in distinguishing overlapping or atypical presentations. Future research should focus on larger, prospective multicenter studies to better characterize the incidence, risk factors, and treatment responses of cutaneous irAEs across cancer types and ICI combinations. Biomarker-driven approaches to predict susceptibility or severity of irAEs may enable more personalized immunotherapy regimens. The findings, while informative, may not be fully generalizable due to the small number of patients and single-institution setting. However, the diverse clinical contexts represented here do reflect real-world scenarios in oncology practice. Gray areas that warrant further exploration include optimal management strategies for steroid-refractory cutaneous irAEs, long-term dermatologic sequelae post-ICI therapy, and the prognostic significance of skin toxicities in non-melanoma cancers. Additionally, standardized algorithms for rechallenge decisions following high-grade irAEs remain an unmet need.

Conclusion

ICIs have transformed cancer therapy, but their use is often accompanied by irAE, with cutaneous toxicities being among the most common. This case series highlights the clinical diversity of skin-related irAEs, ranging from mild, self-limiting rashes to severe reactions requiring systemic immunosuppression or even treatment discontinuation. Prompt recognition, accurate grading, and individualized management are essential to minimize morbidity and maintain continuity of life-saving cancer treatment. Notably, dermatologic manifestations can serve as early indicators of immune dysregulation and should be carefully evaluated, as they may influence therapeutic decisions and overall outcomes.

Authors' Contributions

Conceptualization was performed by R.C., C.D., S.R., A.V., V.K., and M.A.O.. Data curation was performed by R.C., M.A.O., and V.K. Project administration was managed by C.D., S.R., and A.V. Original draft preparation was undertaken by R.C., C.D., S.R., A.V., V.K., and M.A.O. All authors—R.C., C.D., S.R., A.V., V.K., and M.A.O.—contributed to the review and editing of the manuscript and provided final approval of the version to be submitted. The corresponding author is the guarantor of the submission.

Ethical Approval

For this case series, formal consent from a local ethics committee is not required.

Patients' Consent

The authors certify that they have obtained the appropriate consent from the patients. The patients have given their consent for the images and other clinical information to be reported in the journal. The patients understand that the name and initials will not be published, and due efforts have been made to conceal the same.

Funding

None.

Conflict of Interest

None declared.

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