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Pembrolizumab-Induced Autoimmune Bullous Eruption in a Neutropenic Patient With Triple-Negative Breast Cancer: A Diagnostic and Therapeutic Dilemma

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Abstract:

Immune checkpoint inhibitors such as pembrolizumab have revolutionized cancer treatment but can trigger severe cutaneous immune-related adverse events, including autoimmune bullous disorders. Most reported cases of pembrolizumab-associated bullous pemphigoid involve hemodynamically stable patients suitable for confirmatory skin biopsy with direct immunofluorescence. However, data are limited regarding critically ill, neutropenic patients where invasive diagnostic procedures and aggressive immunosuppression pose substantial risks. We report a 72-year-old woman with stage IIIB triple-negative breast cancer receiving neoadjuvant carboplatin, paclitaxel, and pembrolizumab who presented with febrile neutropenia and septic shock. She rapidly developed widespread bullae and erosions on both pressure-bearing and non-pressure-bearing sites. Given profound neutropenia and hemodynamic instability requiring vasopressor support, skin biopsy was deferred. Clinical diagnosis of pembrolizumab-induced autoimmune bullous eruption was based on temporal association with drug exposure, characteristic morphology, and distribution beyond typical pressure points. Pembrolizumab was discontinued, and empiric high-dose intravenous corticosteroids were initiated, but the cutaneous eruption progressively worsened. The patient developed refractory septic shock and died on hospital day 6. This case illustrates the profound diagnostic and therapeutic challenges of managing suspected immune checkpoint inhibitor-induced bullous disease in critically ill, neutropenic patients, where clinicians must balance the risks of invasive diagnostics and further immunosuppression against the morbidity of untreated immune-related adverse events. Heightened clinical suspicion and multidisciplinary collaboration are essential in such complex scenarios.

Keywords:

pembrolizumab, bullous pemphigoid, immune checkpoint inhibitor, immune-related adverse event, neutropenia, sepsis

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Introduction

Background

Immune checkpoint inhibitors (ICIs) targeting programmed cell death-1 (PD-1), such as pembrolizumab, have transformed the treatment landscape for advanced malignancies, including triple-negative breast cancer [1]. Despite

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remarkable therapeutic benefits, ICIs can induce diverse immune-related adverse events (irAEs) affecting virtually every organ system. Cutaneous irAEs are among the most frequent, ranging from mild exanthematous eruptions to severe autoimmune blistering disorders resembling bullous pemphigoid or pemphigus [2,3]. Most reported cases of pembrolizumab-associated bullous pemphigoid involve hemodynamically stable patients who can undergo confirmatory skin biopsy with direct immunofluorescence [4]. However, data are scarce regarding patients who develop suspected ICI-related bullous eruptions in the context of neutropenic sepsis, where invasive diagnostic procedures and aggressive immunosuppression may pose prohibitive risks. We present such a case to highlight the diagnostic and therapeutic dilemmas encountered in this challenging clinical scenario.

Case Presentation

A 72-year-old woman with stage IIIB triple-negative breast cancer was undergoing neoadjuvant treatment with carboplatin, paclitaxel, and pembrolizumab and presented on day 1 of cycle 4 of this regimen. She was admitted from a skilled nursing facility with acute altered mental status, febrile neutropenia, and septic shock requiring vasopressor support. Initial evaluation revealed toxic metabolic encephalopathy, urinary tract infection, and possible pneumonia. Broad-spectrum antimicrobial therapy with vancomycin and meropenem was initiated.

Early dermatologic assessment documented sacral maceration and lower-extremity erythema, initially attributed to moisture-associated skin damage and pressure-related injury. Within the first 24 hours of hospitalization, wound-care evaluation identified incontinence-associated dermatitis involving the sacrum with macerated, fragile skin and multiple erosions. Additionally, scattered intact and deflated bullae developed on the sacrum, bilateral gluteal regions, lower extremities, and dorsal feet **(Figure 1)**. The bullae were dry, non-draining, and notably distributed beyond typical pressure points—a finding atypical for routine pressure injury or moisture-related dermatitis.

Given the patient's recent exposure to pembrolizumab, including three completed neoadjuvant cycles and presentation on day 1 of cycle 4, the clinical team raised suspicion for an ICI-related autoimmune blistering disorder such as bullous pemphigoid or a pemphigus-spectrum disease. Over the subsequent days, the cutaneous eruption progressively worsened with expansion of erosions and development of denuded plaques on both dependent and non-pressure-bearing anatomic sites, including the back, chest, and bilateral lower extremities **(Figure 2)**.

The temporal relationship between pembrolizumab exposure and the onset of bullae, combined with the characteristic lesion morphology and distribution pattern extending beyond pressure points, strongly supported a diagnosis of pembrolizumab-associated autoimmune bullous eruption. Ideally, definitive diagnosis requires histopathologic confirmation via punch biopsy demonstrating subepidermal cleavage with an eosinophil-predominant infiltrate, complemented by direct immunofluorescence studies showing linear IgG and C3 deposition at the dermal-epidermal junction [4,5].

However, in this case, skin biopsy and immunofluorescence studies were deferred after multidisciplinary discussion involving dermatology, oncology, infectious disease, and critical care teams. The decision was based on several factors: (1) profound neutropenia with absolute neutrophil count persistently <100 cells/μL, significantly increasing infection risk from any invasive procedure; (2) hemodynamic instability requiring continuous vasopressor support, precluding safe positioning for biopsy; (3) coagulopathy secondary to sepsis, increasing bleeding risk; and (4) patient-centered goals of care prioritizing infection management and comfort over aggressive diagnostic workup. Clinical diagnosis was therefore favored based on morphology, distribution, temporal association with pembrolizumab administration, and the absence of an alternative unifying etiology.

Following multidisciplinary consultation, both pembrolizumab and ongoing chemotherapy were immediately discontinued. Empiric high-dose intravenous methylprednisolone was initiated for suspected immune-mediated dermatologic toxicity, while broad-spectrum antimicrobial therapy and vasopressor support were maintained for management of septic shock.

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Standard management protocols for ICI-induced bullous pemphigoid typically include systemic corticosteroids with gradual taper over weeks to months, and in refractory cases, escalation to steroid-sparing immunosuppressive agents such as mycophenolate mofetil, azathioprine, or rituximab [6,7]. However, in this profoundly neutropenic, septic patient, the initiation of additional immunosuppressive therapies beyond corticosteroids posed a substantial risk of worsening the underlying infection, presenting a critical therapeutic dilemma with no clear evidence-based resolution.

Despite aggressive supportive care measures and empiric immunosuppressive therapy with corticosteroids, the patient's cutaneous lesions persisted and progressively worsened over the following days. Her overall clinical condition continued to deteriorate, with the development of refractory septic shock unresponsive to escalating doses of multiple vasopressors and maximal medical intervention. She ultimately suffered fatal cardiac arrest on hospital day 6.

Discussion

Pembrolizumab-induced bullous pemphigoid typically manifests weeks to months after treatment initiation, presenting with tense bullae on erythematous or normal-appearing skin, most commonly affecting the trunk and extremities [4,8]. The condition usually responds favorably to discontinuation of the offending agent and systemic corticosteroid therapy [9]. However, management becomes profoundly challenging in the subset of critically ill, neutropenic patients where standard diagnostic and therapeutic approaches carry substantial risk.

This case underscores several critical clinical considerations. First, clinicians must maintain a high index of suspicion for ICI-related bullous eruptions when bullae arise in atypical distributions—particularly beyond typical pressure points—in patients receiving PD-1 inhibitors, even when competing diagnoses such as pressure injury, moisture-associated dermatitis, or sepsis-related skin changes are present [10]. The distribution pattern beyond pressure-bearing sites was a key discriminating feature in this case that heightened suspicion for an immune-mediated process rather than a simple pressure injury.

Second, the decision to defer skin biopsy in hemodynamically unstable, profoundly neutropenic patients represents a reasonable clinical judgment when the risks of bleeding, infection, and procedural complications outweigh the diagnostic benefits, provided the clinical presentation is sufficiently characteristic to support empiric treatment [11]. In this case, the temporal relationship with pembrolizumab exposure, characteristic morphology, and distribution pattern provided adequate clinical evidence to support the diagnosis and guide management decisions without histopathologic confirmation.

Third, this case highlights the profound therapeutic dilemma inherent in balancing irAE treatment with infection control in the setting of neutropenic sepsis. While high-dose systemic corticosteroids represent first-line therapy for ICI-induced bullous disease, they carry the potential to exacerbate underlying infections and impair immune reconstitution in neutropenic patients [12]. In this case, despite the initiation of empiric high-dose corticosteroids, both the cutaneous eruption and the patient's septic condition progressively worsened, ultimately proving fatal. Whether earlier intervention with more aggressive immunosuppression would have altered the trajectory of the cutaneous disease remains unknown, but the infection risks associated with further immunosuppression in the context of profound neutropenia were deemed prohibitive by the multidisciplinary team.

Furthermore, the differential diagnosis of bullous eruptions in critically ill patients is broad and includes drug-induced reactions, infections, autoimmune blistering diseases, and pressure-related injuries. The co-existence of multiple risk factors in this patient—including chemotherapy-induced neutropenia, septic shock, pressure exposure from prolonged immobility, and recent ICI therapy—made diagnostic certainty challenging without histopathologic confirmation. Nevertheless, the clinical features most consistent with an ICI-related autoimmune bullous eruption included the temporal relationship to pembrolizumab, the distribution extending well beyond pressure points, and the morphologic appearance of the lesions.

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This case also emphasizes the critical importance of multidisciplinary collaboration involving dermatology, medical oncology, infectious disease, and critical care specialties when managing suspected irAEs in the intensive care setting. Shared decision-making regarding diagnostic approaches, treatment intensity, acceptable risk thresholds, and overall goals of care is essential when competing clinical priorities exist. In this case, the consensus approach prioritized infection control and patient comfort while attempting empiric immunosuppression at a level deemed unlikely to worsen the septic picture significantly.

Finally, this case contributes to the limited but growing literature on the management of severe irAEs in critically ill patients, a population often excluded from clinical trials of ICIs and therefore underrepresented in the evidence base guiding irAE management. Further research and case series are needed to develop evidence-based guidelines for this challenging clinical scenario.

Conclusion

This case illustrates the diagnostic and therapeutic complexity of probable pembrolizumab-induced autoimmune bullous eruption in a critically ill neutropenic patient with triple-negative breast cancer. Clinicians must carefully balance the need for timely immunosuppression to control severe immune-related adverse events against the heightened risk of infection and impaired immune recovery in the setting of neutropenic sepsis. Multidisciplinary collaboration is essential to individualize decisions about biopsy, treatment intensity, and goals of care when standard irAE management algorithms may not be safely applicable.

Take Home Messages

Maintain high clinical suspicion for immune checkpoint inhibitor-related autoimmune bullous eruptions when bullae develop in atypical distributions, particularly beyond typical pressure points, in patients receiving PD-1 inhibitors such as pembrolizumab.

In critically ill, neutropenic patients with suspected ICI-induced bullous disease, deferring invasive diagnostic procedures such as skin biopsy may be justified when procedural risks (bleeding, infection) outweigh diagnostic benefits and clinical features are sufficiently characteristic.

Managing suspected ICI-related bullous eruptions in the setting of neutropenic sepsis presents a profound therapeutic dilemma, as systemic corticosteroids (first-line therapy for irAEs) may worsen underlying infections and impair immune recovery.

Multidisciplinary collaboration involving dermatology, oncology, infectious disease, and critical care is essential for balancing competing priorities of irAE management and infection control in vulnerable patient populations.

Further research is needed to develop evidence-based guidelines for managing severe immune-related adverse events in critically ill, neutropenic patients—a population often excluded from clinical trials but increasingly encountered in real-world practice.

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Figure Legends

Figure 1. Clinical photographs from hospital day 2 demonstrating the initial cutaneous presentation of the patient. Multiple well-circumscribed erosions and shallow ulcers, some with overlying hemorrhagic crust, on a background of xerotic, lichenified hyperpigmented skin of the (A) Gluteal cleft, (B) Lower extremities, (C) Sacrum, (D) Dorsal feet.

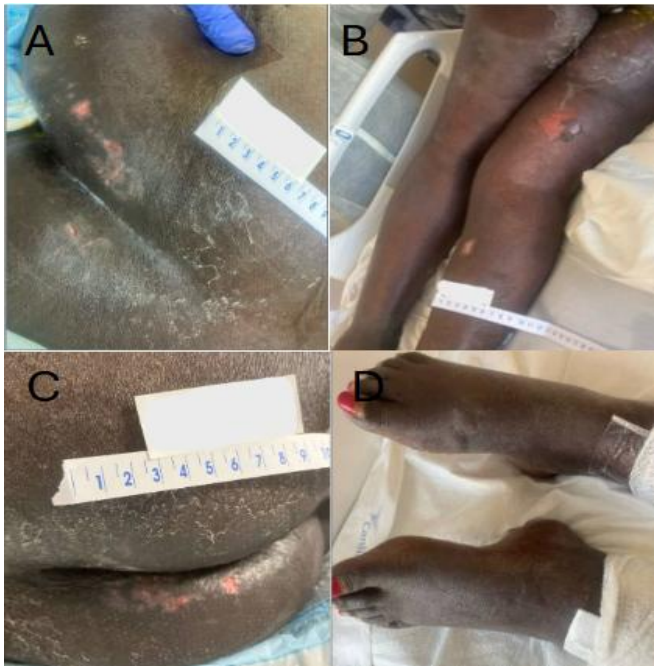

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Figure 2. Clinical photographs from hospital day 5 demonstrating the evolution of cutaneous findings with progression to large erosive patches after epidermal sloughing on the (A) Back, (B) Chest, (C) Right leg, (D) Left leg.