


Treatment of PD-1 Inhibitor-Associated Toxic Epidermal Necrolysis: A Case Report and Brief Review

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Background: Sintilimab is a fully human monoclonal antibody targeting PD-1, which has been considered well tolerated among patients and widely applied in malignancies.

Case Presentation: We present a case report of a patient with gallbladder carcinoma treated with sintilimab who developed toxic epidermal necrolysis (TEN). A 72-year-old female presented with fever and maculopapular rash after receiving one dose of sintilimab for metastatic gallbladder carcinoma. Widespread maculopapular rashes with progressive skin detachment occurred within one week. Early skin biopsy of the patient showed apoptotic keratinocytes along with interface dermatitis. She was initially treated with escalating methylprednisolone (from 0.8 to 1.6 mg/kg/d) and subsequently in the combination of intravenous immunoglobulin. Her skin lesions significantly improved, and satisfying re-epithelialization was achieved after 43 days of hospitalization.

Conclusion: Because of the high mortality of grade four immune related adverse event (irAE) on skin, we recommend early monitoring and recognition of symptoms. During management, high-dose glucocorticoids with combined intravenous immune globulin and supportive care may be helpful.

Keywords: sintilimab, anti-PD1, programmed death-1 inhibitor, immune checkpoint inhibitor, toxic epidermal necrolysis, TEN, skin toxicity, immune-related adverse events, irAE

Introduction

Sintilimab is a fully human monoclonal IgG4 antibody that directly binds to programmed cell death receptor-1 (PD-1).¹ In malignancies, overexpression of PD-1 receptor ligand (PD-L1) anergizes T cells and thus inhibits anti-tumor immunity. PD-1 inhibitors block PD-L1 from binding to T cells and result in enhancement of immunity and tumor control. Immune checkpoint inhibitors (ICIs) are deemed well tolerated and exhibiting durable anti-tumor activity when compared with cytotoxic agents. Nevertheless, administration of ICIs could cause a group of immune-related adverse events (irAE) due to immune upregulation, of which dermatologic toxicity has been reported as the most frequent manifestations.² Maculopapular and morbilliform eruptions may occur in 15% of patients during therapy and barely cause significant consequences.² Life-threatening reactions, namely acute Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), may occur as well, with an incidence of less than 1%.³ We report a case of toxic epidermal necrolysis (TEN) associated with sintilimab in gallbladder carcinoma, which was successfully treated during hospitalization.

Case Presentation

A 72-year-old female presented with fever (T_{max} 38.0°C) and maculopapular rash after receiving one dose of sintilimab as gallbladder carcinoma systemic therapy (T₃N₂M₁, Stage IV_B).

The patient received surgical procedures including cholecystectomy, en bloc hepatic resection, and portal lymphadenectomy 55 days prior to this visit. The lesion histologically contained low-differentiated adenocarcinoma together with signet-ring cell carcinoma. Test identified high microsatellite instability (MSI-H) in the tumor. After surgery, an elevated CEA level (65.4ng/mL) and a re-staging scan using PET-CT showed suspicious mesenteric metastasis. The patient started receiving sintilimab in combination with anlotinib on day-13 as tentative systemic therapy. Written informed consent was obtained from the patient.

The patient presented with a sporadic mild rash (grade 1, SCORTEN score 2) on body trunk and proximal lower extremities two weeks after receiving one dose of sintilimab. Intravenous infusion of 40 mg of methylprednisolone (0.8mg/kg/d) was applied on the first day. The patient still had a low-grade fever and developed a more extensive rash on day 2, and thus she was given a higher dose of methylprednisolone (1.2 mg/kg/d) in the next two days and admitted to hospital on day 3. Within one day during hospitalization, the rashes connected into large-area maculopapular skin rash with bullae (SCORTEN score 3), and epidermal detachment appeared, in which direct Nikolsky's sign was present (Figure 1). Skin biopsy revealed karyopyknotic keratinocytes in the epidermis and interface dermatitis with lymphocyte infiltration in the dermo-epidermal junction (Figure 2). Immunoassay showed anti-Dsg1, anti-Dsg3, anti-BP180, anti-BP230 antibodies were negative in patient's serum. Dosage of methylprednisolone was increased to 80 mg (1.6 mg/kg/d). Meanwhile, intravenous immunoglobulin was added. The skin rash and bullae continued to progress, and around 70% body surface area of skin and mucosa was affected on day 13 (Figure 1). Intravenous immunoglobulin was increased to 800 mg/kg/d for three days, along with albumin infusion and encapsulation therapy (topical halometasone, erythromycin, and epidermal growth factor spray). The score of toxic epidermal necrolysis (SCORTEN)⁴ achieved five, and thus the patient was referred to a specialized care unit. We utilized an isolation room and bed with horizontal laminar airflow for infection control. Dressing of skin and mucosa lesions was changed once a day, and medical pain management was applied. It significantly improved her skin lesion within one week (Supplementary Figure 1). Blood and exudate cultures reported negative throughout the course. Fungal infection in the oral cavity appeared and subsequently improved with tapering of glucocorticoid (started on day 20, as SCORTEN decreased to 2) and application of oral nystatin. She was



Figure 1 Maculopapular rash with bullae and skin detachment. Changes in skin lesions. **(A)** Day 5 shows maculopapular rash covering 30% BSA and appearance of epidermal detachment. **(B)** Day 13 shows progressive detachment affecting mucosa, along with massive dermis exposure and exudation.

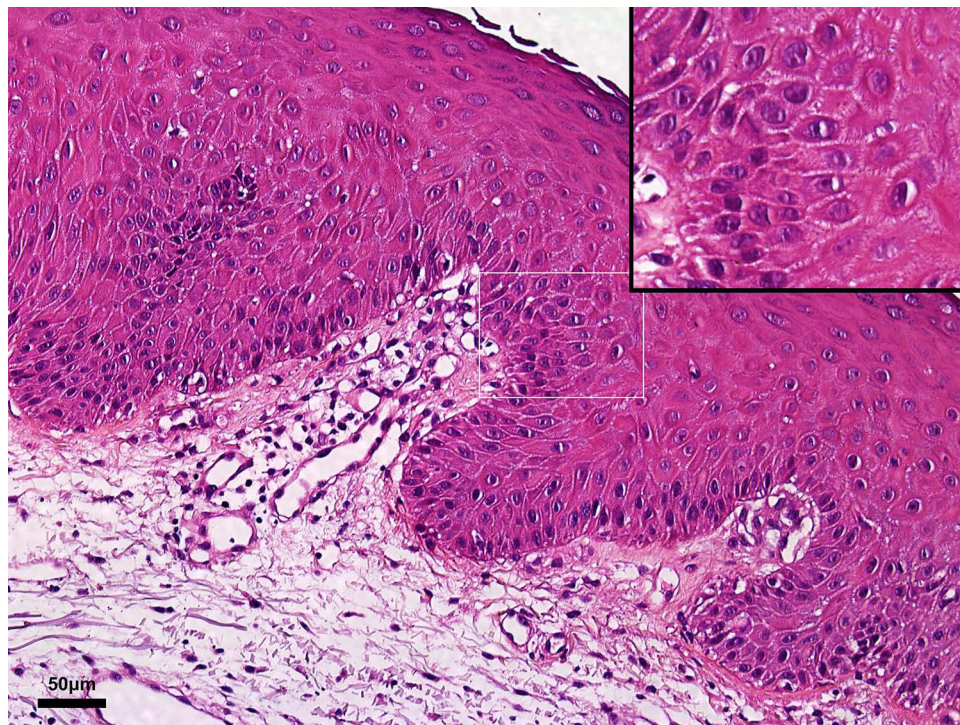


Figure 2 Skin biopsy histopathology. Karyopyknosis was observed in keratinocytes, indicating an early stage of irreversible necrosis or apoptosis of cells. Lymphocyte infiltration and vessel edema appeared in the dermo-epidermal junction.

dismissed after 43 days of hospitalization with satisfying re-epithelialization and no infection signs (Figure 3). The patient did not receive further anti-tumor medications. Imaging showed no signs of tumor recurrence at the primary site. A mildly elevated CEA was observed during hospitalization (75.57 ng/mL, 3 weeks after sintilimab administration).

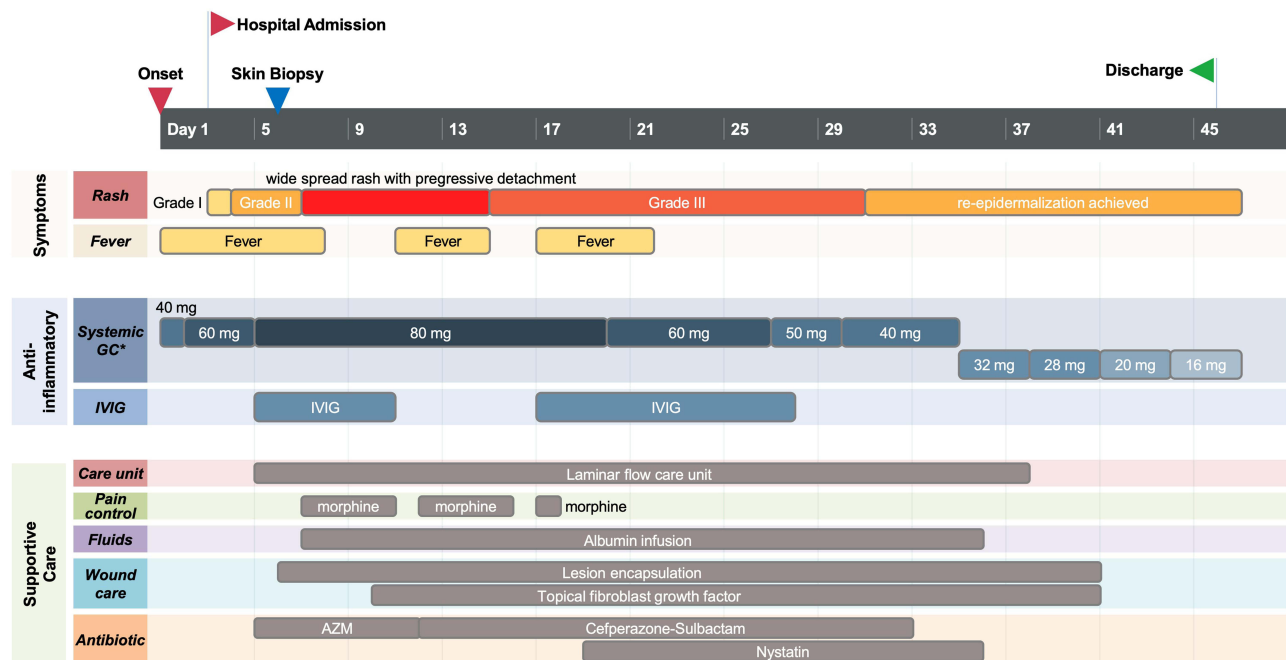


Figure 3 Clinical timeline of major interventions. Graph conclusion of major interventions in patient management, *Intravenous methylprednisolone was initially applied as systemic GC and was converted to oral tablets since 32 mg per day. Body weight of the patient was 50 kg. **Abbreviations:** GC, glucocorticoid; IVIG, intravenous immune globulin.

The co-medication of the patient includes calcium antagonists for hypertension treatment (switching from amlodipine to nifedipine on day-4). We evaluated the drug causality using method of ALDEN,⁵ according to which sintilimab was very probable cause (ALDEN 6'), anlotinib was a possible cause (ALDEN 2'), while nifedipine was an unlikely cause (ALDEN 0') of the disease. All three drugs were classified as possible causes according to Naranjo's Scale (sintilimab 3'; anlotinib 1'; nifedipine 1').⁶ The detailed algorithms were listed in [Supplementary Tables 1](#) and [2](#).

Discussion

Gallbladder carcinoma has a low-incidence and poor-prognosis.^{7,8} Nevertheless, it is the most common biliary tract carcinoma (BTC) worldwide. In 2017, the BiCap study reported the benefit of adjuvant capecitabine in overall survival and relapse-free survival,⁹ thus capecitabine has been considered as a preferred adjuvant option following potentially curative resection of BTC since then. Advanced BTC displayed limited efficacy upon chemotherapy, of which most studies were negative over the past 20 years, and clinical practice has barely changed.¹⁰ As for first-line treatment, cisplatin/gemcitabine was recommended as a reference regimen. However, there is no evidence supporting second-line chemotherapy usage in advanced BTC hitherto.¹¹ The main problem lies in the poor physical status of patients due to disease progression during first-line therapy and complications, such as biliary obstruction. Hence, the application of novel therapeutic targets and the development of practice-changing regimes are in urgent need to improve the prognosis of BTC patients.

Tumors with high mutational load are considered more immunogenic and receive better effect upon immunotherapies.¹² Mismatch-repair (MMR) deficiency and microsatellite instability (MSI) are classic indicators that are related to tumor mutational load and thus contribute to the efficacy of checkpoint inhibitors.¹³ MMR and MSI status have been explored in BTCs, yet the results vary from studies. MMR and MSI are uncommon (3.2%) in BTC patients without hereditary nonpolyposis colorectal cancer.¹⁴ According to publications, high-level MSI was reported in 5% of gallbladder carcinoma¹⁵ while MMR status (MLH1 and MSH2 negative staining) was observed, respectively, in 51.3% and 59% (N = 39) of gallbladder carcinoma.¹⁶ Companion diagnostic approaches using next-generation sequencing, such as tumor mutational burden (TMB), have been newly developed to estimate mutational and predict clinical benefit of anti-PD-1 therapy.^{17,18} The overall mutational load was reported relatively high in BTCs. The median count of non-silent somatic mutations in gallbladder cancer was 64 (N = 28), which is significantly higher than other kinds of BTCs (39 and 35 in intrahepatic and extrahepatic cholangiocarcinoma, respectively).¹⁹ Increased expression of PD-1 and PD-L1 (40% and 15%, respectively) was identified in BTC samples.²⁰ In the KEYNOTE-28 study, 37 of 89 (42%) patients with advanced BTC were identified as PD-L1-positive tumors. Among the pembrolizumab-treated group (N = 24), four patients (17%) achieved partial responses, with another four acquiring stable diseases.²¹ These results are highly encouraging, and studies are in progress to validate the efficacy of checkpoint inhibitors in BTCs.

Currently, SJS and TEN are considered as a continuous spectrum of disease and are differentially diagnosed according to the extent of skin detachment, measured with the percentage of body surface area (BSA) involved.²² TEN have been reported in nivolumab therapy²³⁻²⁵ while SJS was described more frequently in multiple ICIs, namely nivolumab, ipilimumab, and pembrolizumab²⁶⁻³⁰ (Table 1). Most cases develop SJS/TEN after the first or second infusion of ICI therapy, including the present case. Two cases of three TEN related to nivolumab were fatal^{24,25} while the other one patient died four months later,²³ and the presented case enriched the experience of treating PD-1 antibody-related extensive TEN.

Diagnosis of SJS/TEN is based on clinical features and histopathological findings. Initial manifestations may appear as rapidly progressing macules or papules at body trunk and extremities, along with mucosal involvement and fever. Extensive necrosis and detachment of epidermis follow subsequently. Biopsy of early lesions could manifest as scattered apoptotic keratinocytes in the basal layer of the epidermis. While full-thickness epidermal necrosis and subepidermal bullae may be observed in advanced lesions.³¹

As for the management of immunotherapy-related grade 4 exfoliative skin toxicity, permanent discontinuation of ICI, and immediate hospitalization are required. Systemic corticosteroid is recommended and initiated at 1.0 to 2.0 mg/kg/d. Dosage tapering after symptom improvement should last 4 to 6 weeks. One could consider a combination of cyclosporine or intravenous immunoglobulin in corticoid non-responders.^{28,32} Supportive care, including nutrition, pain management,

Table I Summary of Immune Checkpoint Inhibitor Induced SJS/TEN Case Reports

	Characteristics	Disease	ICI	Time to Onset	Severity	Intervention	Outcome
[23]	64 F	Melanoma	Nivolumab	14 days	TEN, 40% BSA	GC + Cyclosporine	Improved, deceased in 4 months
[24]	50 F	Melanoma	Nivolumab	During cycle 1	TEN, 90% BSA, SCORTEN 5	Infliximab + GC + IVIG	Deceased on hospital day 6
[25]	54 M	Follicular lymphoma	Nivolumab	10 days	TEN, 70–80%BSA, SCORTEN 3	GC + antibiotics	Deceased on hospital day 58
[26]	76 F	NSCLC	Nivolumab	40 days (cycle 2)	SJS, <1% BSA	GC + Aprepitant	Improved
[27]	55 F	Melanoma	Pembrolizumab	6 months (cycle 9)	SJS, <1% BSA	GC	Improved
[28]	50 F	Nasopharyngeal carcinoma	Pembrolizumab	140 days (cycle 5)	SJS, 4–5% BSA	GC + Cyclosporine	Improved
[28]	53 M	Renal cell carcinoma	Pembrolizumab	77 days (cycle 2)	SJS, 3% BSA	Cyclosporine	Improved
[29]	69 M	NSCLC	Pembrolizumab	12 days	SJS, <1% BSA	GC	Improved

Note: Table conclusion of reported cases of PD-1 antibody.

Abbreviations: GC, glucocorticoid; IVIG, intravenous immune globulin; NSCLC, non-small cell lung cancer.

and infection prevention, also plays a pivotal role during treatment. To this aspect, we applied encapsulation of corticoid, antibiotics, and epidermal growth factor on exposed dermis for better re-epithelialization and lower risk of infection. Furthermore, specialized wards, including burn units, can help maintain hydration and control sources of infection, especially in patients having lesions of extensive BSA involvement or patients with SCORTEN score ≥ 2 .³³

The specific mechanism underlining ICI-related toxic epidermal necrolysis remains controversial. Generally, SJS/TEN was related to massive apoptosis of keratocytes due to cell-mediated cytotoxic reaction.³⁴ Studies have shown that the cytotoxic T cells involved are drug specific and directed against the native form of the drug.³⁵ However, irAEs caused by immune check point inhibitors are considered being associated with over-activation of the whole immune system rather than a hypersensitive reaction against the drug. It is hypothesized that blockade of immune checkpoint molecules could cause imbalances in immunologic tolerance that lead to severe immune response as TEN, which is mainly mediated by T cells.³⁶ In melanoma, common antigen that co-expressed on both tumor cells and skin has been reported, indicating the role of autologous antigen specific cytotoxic T cells during the development of irAEs.³⁷ We deem that the pathomechanism of the disease might relate both to overall immune system activation and tumor-related autologous antigens, further investigations are required for verification.

Incomplete evaluation of skin lesions is the major limitation of the presented case. We deem that direct and indirect immunofluorescence, serology and pathology tests should be performed when available for diagnosis confirmation and exclusion of other conditions that may mimic SJS/TEN.

Conclusions

This study reported the first case of sintilimab-related toxic epidermal necrolysis that was successfully treated. Further studies are needed to clarify the mechanisms of severe skin toxicity following PD-1 blockade. On the whole, we highlight the necessity of early recognition, timely intervention, and supportive care during management of grade 4 skin toxicity of immune therapy.

Data Sharing Statement

Additional data and materials related to the lab tests, pathologic reports, treatment information, and images are available from the corresponding author upon reasonable request.

Consent

This research was approved by the ethics committee of Changshu NO.2 People's Hospital. Written informed consent including a patient perspective for publication of clinical details and photographs was obtained from the patient.

Disclosure

The authors report no conflicts of interest in this work.

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