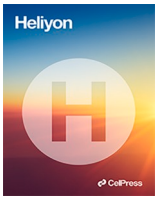
Heliyon 10 (2024) e34107

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Case report

Refractory pruritus caused by sintilimab and its clinical management: A case report

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ARTICLE INFO

Keywords:
Case report
Sintilimab
Naloxone
Refractory pruritus
Immune checkpoint inhibitors

ABSTRACT

Several immune related adverse events (irAEs) were reported with the wide application of immune checkpoint inhibitors (ICIs) in tumors. ICI-related skin reactions are the most common, which are manifested as maculopapules, rash, pruritus, vitiligo, psoriasis, and lichenoid rash. Among them, the incidence of pruritus is second only to maculopapule/rash, but both often coexist. The severity of pruritus is mostly mild to moderate and can be relieved after symptomatic treatment with antihistamines. Symptoms are slightly relieved after conventional treatment in patients with severe pruritus, but it easily recurs and eventually develops into refractory pruritus.The patient's quality of life may be affected and may also be life-threatening.

We report a case of a patient with postoperative recurrence of gallbladder neuroendocrine carcinoma,who developed refractory pruritus after sintilimab use, which was relieved after naloxone infusion after unsuccessful conventional drug therapy. By analyzing the treatment plan of this typical case of immune-related refractory pruritus after using sintilimab, this report discusses how clinical pharmacists can provide individualized treatment of patients by using their expertise and clinicians' cooperation and complementation in treating clinically difficult cases. This case report may be used as a reference in treating patients with refractory pruritus after the clinical use of sintilimab.

1. Background

Neuroendocrine tumors are rare tumors originating from peptidergic neurons and neuroendocrine cells [1]. Gallbladder neuroendocrine carcinoma account for only 0.5 % of neuroendocrine carcinoma [2]. Radical surgery is performed to remove early-stage gallbladder neuroendocrine carcinoma [3]. Most patients are diagnosed in the advanced stage (losing the chance of surgical

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https://doi.org/10.1016/j.heliyon.2024.e34107
Received 9 December 2023; Received in revised form 3 July 2024; Accepted 3 July 2024
Available online 4 July 2024

intervention) because early symptoms of neuroendocrine carcinoma are inconspicuous, and they are dependent on chemotherapy and local radiotherapy to improve their quality of life and prolong their life. With the continuous discovery of therapeutic methods besides radiotherapy and chemotherapy, ICIs have become one of the important means to treat advanced gallbladder neuroendocrine carcinoma. ICIs mainly include CTLA-4, PD-1, and PD-L1, with PD-1 and PD-L1 being currently used in advanced neuroendocrine carcinoma [4], which are antitumors that activate tumor immune response. However, ICIs may influence tissues and organs besides tumor cells, causing a series of adverse reactions (ADR) of different types and degrees. Some ADR may seriously affect the patient's quality of life and may even be life-threatening if not promptly diagnosed and treated. IrAEs are common in skin reactions, which are manifested as skin rashes, maculopapules, etc., and pruritus is usually symptomatic. Among these patients who experience IrAEs, the severity of pruritus is mostly mild to moderate and can be relieved after symptomatic treatment with antihistamines. Symptoms are slightly relieved after conventional treatment in patients with severe pruritus, but it easily recurs and eventually develops into refractory pruritus. Currently, although most patients with severe pruritus can benefit from NK-1 receptor antagonist or omalizumab, due to drug price and accessibility, patients often experience insufficient treatment, and few patients with severe pruritus are difficult to cure.

Therefore, feasible and inexpensive treatment methods for severe pruritus in patients using ICIs are necessary.

2. Case presentation

In December 2021, a previously healthy 55-year-old female patient was admitted because of abdominal pain, and cholecystectomy was performed after relevant examinations and consideration of gallbladder tumor lesions. The patient was diagnosed with stage III (pT4N2M0) gallbladder neuroendocrine carcinoma after surgery. In February 2022, a reexamination of the enhanced CT scan of the upper abdomen indicated possible postoperative recurrence and metastasis. On March 10, 2022, she underwent local radiotherapy of the gallbladder and concurrent chemotherapy (sintilimab 200 mg d1 + etoposide 80 mg d1–3 + cisplatin 30 mg (thoracic perfusion) d1–3). Because of abdominal infection and nausea and vomiting caused by cisplatin after the first cycle, she temporarily stopped sintilimab use and was only administered etoposide 80 mg d1–3 + carboplatin 400 mg d1 chemotherapy. However, the second cycle of etoposide infusion was not successfully completed because of IV myelosuppression. On April 17, 2022, she developed a systemic punctate rash with pruritus after 39 days of chemotherapy with sintilimab. Subsequently, the rash subsided after treatment with methylprednisolone, loratadine, calamine lotion, and mometasone furoate cream, but pruritus recurred intermittently. Additionally, the patient purchased aprepitant for further treatment, but the pruritus was still not significantly relieved.

On May 10, 2022, the patient was admitted for further treatment due to abdominal pain and pruritus of the limbs and back. Physical examination after admission showed multiple scratches and scaling on the backs and palms of both hands and feet (Fig. 1). Moreover, no rash or pain upon palpation was noted. Laboratory investigations, including complete blood count, liver, and renal function tests were normal. Abdominal CT showed a significantly smaller focus, and the efficacy evaluation was partial clinical remission(Fig. 2-3). On May 11, 2022, pruritus and scaling of limbs and back worsened and affected sleep, but no rash was noted. The patient was administered 0.4 mg naloxone intravenous drip once daily for 8 h. After 2 days of treatment, the patient's pruritus significantly improved. The dose of naloxone was adjusted to 0.2 mg intravenous drip every 6 h as maintenance treatment. On May 15, 2022, the patient was slightly nauseous after naloxone infusion but did not complain of pruritus, and naloxone was stopped. Subsequently, the patient was discharged for recuperation. At the 2-week follow-up, she had no pruritus. In this admission, the patient regularly took

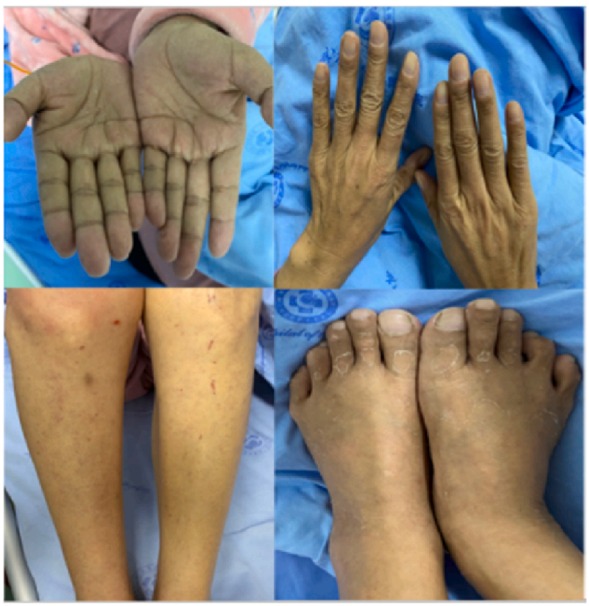

Fig. 1. Multiple scratches and scaling on the backs and palms of both hands and feet.

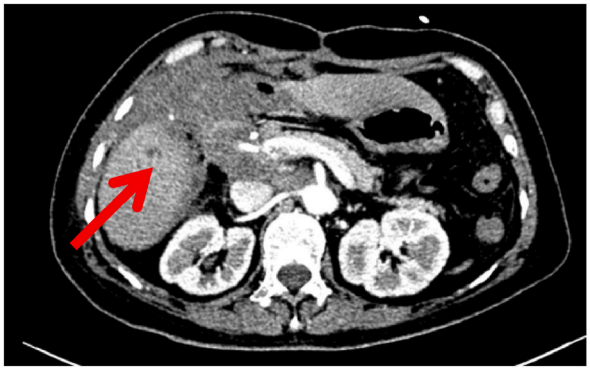

Fig. 2. 2022.02 Upper abdominal CT without treatment.

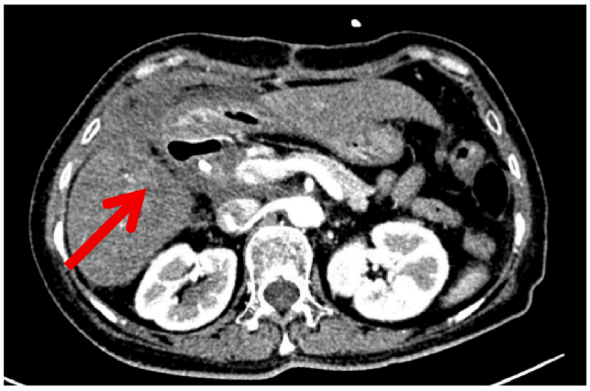

Fig. 3. 2022.05 Upper abdominal CT after immunotherapy combined with chemotherapy.

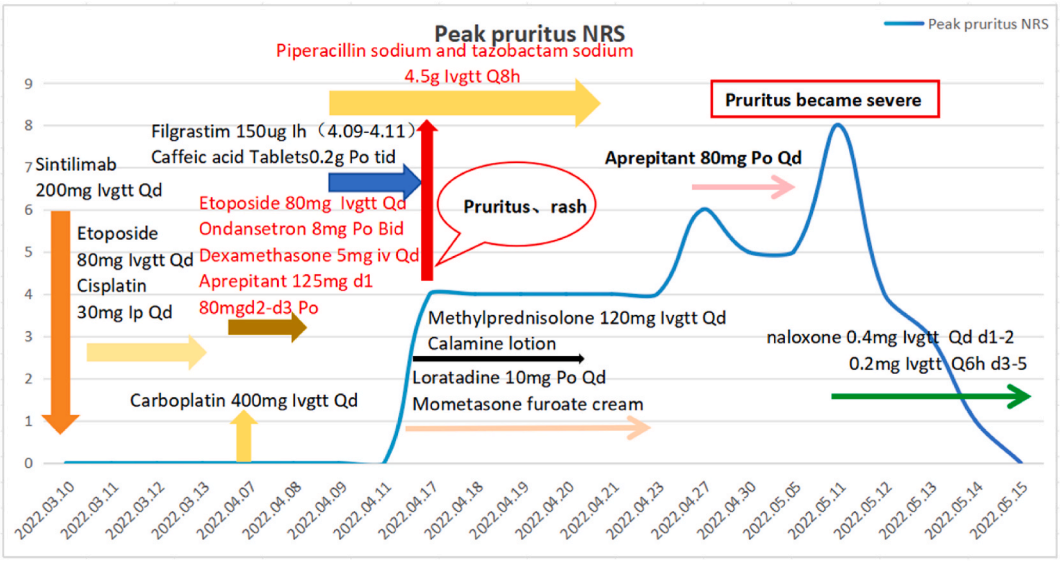

Fig. 4. Peak pruritus NRS Changes in intensity of pruritus over time.

morphine sustained-release tablets at 30 mg every 12 h to relieve abdominal pain.Evaluate the degree of pruritus in patients using the Peak pruritus NRS Scale,as shown in Fig. 4.

3. Discussion

3.1. Refractory pruritus causes

On April 17, 2022, the patient developed multiple systemic punctate rashes with pruritus. Previously, the drugs used included Sintilimab, Etoposide,Cisplatin, Carboplatin,Ondansetron, Dexamethasone,Aprepitant, Filgrastim,Caffeic acid Tablets, Piperacillin sodium and tazobactam sodium.Based on relevant literature, these drugs have been reported to cause pruritus, but except for sintilimab, the pruritus can be resolved after drug withdrawal and can generally be completely relieved through routine treatments such as antihistamines and glucocorticoids [5–8]. These drugs except for sintilimab can be excluded because the patient stopped the intake of these drugs before this admission and cannot be relieved through routine treatments. The patient's pruritus occurred on the 39th day after the discontinuation of sintilimab, which is an anti-PD-1 monoclonal antibody, but studies have shown that ICI-related pruritus generally occur after 4–6 weeks, which is time-related [9–11]. In addition, pruritus is also a common symptom of disease. However, the patient had no previous history of skin disease and denied a history of food or drug allergies. In addition, her liver and kidney functions were normal during hospitalization, so it can be ruled out that her pruritus was caused by disease. Therefore, the possibility of pruritus caused by sintilimab is high.

In summary, drugs and disease factors were excluded, and Naranjo's scale was used to evaluate the causal relationship between sintilimab use and the occurrence of pruritus [12]. The causal relationship between the drug and adverse reactions is positive, likely to be related, possible, and suspicious if the total score is ≥ 9, 5–8, 1–4, and ≤ 0, respectively. The patient's final score was 6, indicating a likely to be related causal relationship. Table 1 shows Naranjo's probability scale for assessing sintilimab-associated pruritus.

3.2. Analysis of treatment plan for patients with refractory pruritus

Several irAEs were reported with the wide application of ICIs in tumors. ICI-related skin reactions are the most common and the earliest, with a median time of 3.6 weeks. The incidence rate is as high as 70 %, and most cases are mild to moderate and can be relieved within 2 weeks [13]. The main manifestations include maculopapules, rash, pruritus, vitiligo, psoriasis, and lichenoid rash. The incidence of bullous dermatitis, Stevens Johnson, and toxic epidermal necrolysis(TEN) are rare. Among them, the incidence of pruritus is second only to maculopapule/rash [14], but both often co-exist. Currently, studies have shown that drug-related skin reactions, such as rash and vitiligo, may be positively related to drug therapy efficacy [15–17]. However, studies on the relationship of pruritus to drug therapy efficacy need to be further explored. The median occurrence time of ICI-related pruritus is 4–6 weeks, although most of them are mild to moderate. If not promptly treated, for special populations with weakened immunity, such as cancer patients, this can not only affect the patient's quality of life and exacerbate their anxiety but can also lead to skin rupture and even infection, which can be life-threatening [9–11]. Histamine-mediated pruritus is the main pathway, and a few are mediated by non-histamine pathway, such as neuropeptide, protease, cytokine, opioid receptor, etc. [16]. Currently, ICI-related pruritus is mainly treated by grading clinical symptoms through CTCAE 5.0 and formulating different treatment strategies based on different grading reference guidelines (e.g., the European Society of Clinical Oncology [ESMO], National Comprehensive Cancer Network [NCCN], and the Chinese Society of Clinical Oncology[CSCO]). Grade 1 is generally mild or localized. Grade 2 usually accompanies skin changes (e.g., edema, papulation, oozing/crusts). Moreover, antihistamines and external medium strong glucocorticoids can be administered for grades 1–2. A grade of 3 may affect sleep quality and even limit self-care activity of Daily Living (ADL). Suspension of ICI administration and administration of medium-effect glucocorticoids, such as prednisone or methylprednisolone at 0.5–1 mg/kg/day, as well as the administration of gabapentin, pregabalin, or γ-aminobutyric acid receptor agonist therapy, are the main strategies for grade 3. Aprepitant can be used to treat refractory pruritus, and serum lgE values should be measured. Omalizumab can be used if the lgE value is high [9–11].

Table 1
Naranjo's probability scale for assessing sintilimab-associated pruritus.

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.				
	Yes	No	Do not know	Score
1 Are there previous conclusive reports on this reaction?	+1	0	0	+1
2 Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2
3 Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4 Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	0
5 Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	+2
6 Did the reaction reappear when a placebo was given?	−1	+1	0	0
7 Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8 Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
9 Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10 Was the adverse event confirmed by any objective evidence?	+1	0	0	0
			Total score	6

The patient's limbs and back pruritus seriously affected sleep, which can be evaluated as grade 3 ICI-related pruritus. Thus, glucocorticoid is currently the main therapeutic drug [16]. Considering the influence of hormone therapy on immunotherapy efficacy, the occurrence of most of the irAEs may be due to over-activation of the immune system. Additionally, the treatment dose of hormones plays a role in regulating the immune system; thus, the therapeutic efficacy of ICIs will not be reduced [18]. The rash subsided after treatment with methylprednisolone, loratadine, calamine lotion, and mometasone furoate cream when the first ICI-related skin reaction occurred, but the pruritus was only slightly relieved. Subsequently, the patient's pruritus worsened, and she purchased aprepitant for symptomatic treatment, but the pruritus was still not significantly relieved. Although current guidelines recommend omalizumab use in treating ICI-related pruritus, the patient's serum lgE was not measured, and its therapeutic effect cannot be predicted. In China, omalizumab is expensive and has poor accessibility. Currently, omalizumab is mainly used to treat allergic asthma but is less used in refractory ICI-related pruritus.

Because of the difficulties in the treatment, the clinical pharmacist suggested naloxone for treatment after consulting the relevant literature. After 5 days of treatment, the patient's pruritus did not recur. Some researchers have recently confirmed that naloxone can antagonize respiratory depression caused by opiates and has good efficacy and safety in treating different kinds of pruritus, such as uremic pruritus [19], elderly refractory pruritus [16], and pruritus caused by systemic sclerosis [20]. The occurrence of pruritus in this patient may be due to μ-opioid receptor activation in the central nervous system, which can inhibit the activity of Vgat interneurons in the spinal cord, relieving inhibition of the pruritus signal pathway, leading to pruritus [21]. Naloxone is an opioid receptor antagonist, which can inhibit pruritus by antagonizing μ-opioid receptor upregulation [22]. Kwatra et al. [23] reported the development of a pruritic rash in a patient with lung adenocarcinoma with bone metastasis after 6 months of treatment with pembrolizumab. The rash gradually aggravated despite the administration of antihistamine, glucocorticoid intravenous infusion, and topical use. After 2 days of continuous intravenous drip of naloxone 50 mL/h for 8 h, the route was changed to oral naltrexone 50 mg once daily for maintenance for 1 month, and pruritus did not recur. In 2019, Singh et al. [24] also reported the development of refractory pruritus in a patient with anorectal squamous cell carcinoma after the second cycle of pembrolizumab. The patient was treated with naloxone using the same scheme by Kwatra et al. After 2 days of treatment, the patient's pruritus was rapidly relieved. Pruritus did not recur after 2 weeks of maintenance naltrexone.

Kwatra et al. [23] used low-dose naloxone for continuous infusion to achieve a stable and long-term blood concentration and then shifted to naltrexone orally to avoid the patient's compliance reduction due to continuous infusion. For this patient, the specific administration plan by the clinical pharmacist was the initial administration of 0.4 mg naloxone intravenous drip for 8 h for 2 days, followed by 0.2 mg naloxone intravenous drip every 6 h (1–2 h per intravenous drip) as maintenance for 3 days. Subsequently, the patient's pruritus did not recur. Currently, although a standard dose of naltrexone has been used to treat pruritus [23], naltrexone is strictly controlled in China because it is used to treat opioid addiction and only supplied to drug rehabilitation centers. Thus, the administration methods of Kwatra et al. were not fully implemented in this case [23]. Some studies have shown that naloxone exceeding 2 μg/kg/h may have an antagonistic effect on opioid analgesic use [25,26]. The patient took morphine sustained-release tablets to relieve abdominal pain. If the maintenance program of naloxone is adjusted to 0.4 mg intravenous drip every 6 h, hourly naloxone concentration is 4.5 μg/kg, antagonizing the analgesic effect of morphine. In addition, the half-life of naloxone is 0.5–1.5 h, and the body's metabolism is fast. The therapeutic effect may also be affected if the infusion time is too short at this time. Therefore, based on the above analysis, the patient was administered 0.4 mg naloxone intravenous drip for 8 h and adjusted to 0.2 mg intravenous drip every 6 h (1–2 h per intravenous drip) for maintenance treatment. The patient complained of nausea after naloxone infusion after 3 days of maintenance treatment. Consequently, naloxone administration was stopped after significant relief from pruritus. After symptomatic treatment, the patient's nausea symptoms improved. During pruritus treatment, the dose of morphine sustained-release tablets was not increased in this patient, indicating that the maintenance dose of naloxone did not affect the analgesic effect of morphine. The patient's pruritus did not recur during the 2-week follow-up period.

4. Conclusion

The patient developed refractory pruritus after sintilimab use. Despite intake of loratadine, glucocorticoids, aprepitant, and other symptomatic treatments, the pruritus was not significantly alleviated, and the patient's quality of life was seriously affected. However, the pruritus was significantly relieved after naloxone treatment. Based on this case, we can fully recognize that although most of the ICI-related pruritus is mild to moderate and can be alleviated by conventional antihistamines, a small number of patients may develop intractable pruritus due to μ-opioid receptor upregulation. Currently, we can administer low-dose naloxone to relieve pruritus. In clinical work, clinical pharmacists should share their professional expertise with patients with ineffective conventional treatment or poor accessibility of treatment plans, correlate with the patient's condition, consider pharmacokinetic characteristics, accessibility, and economy of drugs, and assist clinicians in formulating appropriate treatment plans and conduct pharmaceutical monitoring to ensure effectiveness and safety of drug use.

Ethics approval and consent to participate

Informed consent was obtained from the patient for the publication of all images, clinical data and other data included in the manuscript.

Consent for publication

The authors obtained informed consent from the patient to publish information on his disease and clinical course.

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Data availability statement

No datasets were generated or analyzed during the current study.

CRediT authorship contribution statement

Li Chen: Writing – original draft, Validation, Investigation, Formal analysis. **Xin Cao:** Validation, Supervision, Conceptualization. **Xing Luo:** Validation, Methodology, Conceptualization. **Ting Jiang:** Writing – review & editing, Visualization, Software, Project administration, Methodology, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Journal of Heliyon for providing a platform for sharing case reports. Written informed consent was obtained from the patient for publication of this case report and accompanying images. The authors thank the patient for his participation and his agreement to publication of the report.

Abbreviations

ICIs	immune checkpoint inhibitors
IrAEs	Immune related adverse events
ADR	adverse reactions
TEN	toxic epidermal necrolysis
ESMO	the European Society of Clinical Oncology
NCCN	National Comprehensive Cancer Network
CSCO	the Chinese Society of Clinical Oncology
ADL	activity of Daily Living

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