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Case report

A case report of hemophagocytic lymphohistiocytosis induced by toripalimab plus chemoradiotherapy in cervical cancer

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ABSTRACT

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening clinical syndrome characterized by immune hyperactivation. Unlike primary HLH, immune checkpoint inhibitor (ICI)-triggered HLH is not well described, and there is a lack of theranostic guidelines. Herein, we first reported the successful management of PD-1 inhibitor-associated HLH in locally advanced cervical cancer.

Case presentation: We report a case of HLH in a 47-year-old patient with International Federation of Gynecology and Obstetrics (FIGO) IIIC1r cervical cancer who received toripalimab, a programmed cell death-1 receptor inhibitor, combined with chemoradiotherapy. The patient developed pyrexia, splenomegaly, leukopenia, anemia, thrombocytopenia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, reduced NK cell activity, elevated sCD25 levels, and hemophagocytosis in a bone marrow aspirate. Our patient was successfully treated with methylprednisolone, indicating that immune-induced HLH might respond to glucocorticoids, and is still alive with a complete response of the tumor.

Conclusion: Considering the possibility of HLH is needed in patients receiving ICIs to detect rare toxicities at an early stage when the patient develops uncontrollable fever, cytopenia, and splenomegaly, our multidisciplinary treatment modality contributed to the early diagnosis and successful management of HLH, avoiding progressive tissue damage and organ failure. Whether glucocorticoids are used alone or not for immune-associated HLH needs further investigation.

1. Introduction

Although accumulating evidence has revealed the efficacy of immune checkpoint blockade in the management of various tumors [1], immune-related adverse events have attracted the attention of clinicians [2,3]. Hemophagocytic lymphohistiocytosis (HLH), induced by excessive immune activation, is a rare but life-threatening clinical syndrome with a 1-year overall survival rate of less than 40 % according to large retrospective studies [4].

HLH is broadly classified into primary (genetic HLH) and secondary (acquired HLH). The former manifests as an immunodeficiency syndrome driven by genetic mutations, whereas the latter is triggered by various predisposing factors, including malignancy, infection,

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rheumatological disorders, and acquired immunodeficiency. Notably, immune checkpoint inhibitor (ICI) therapy is an emerging cause of treatment-associated HLH and is becoming a cornerstone in the treatment of numerous cancer types. The prevalent targets of ICI therapy include Programmed Death-1/Programmed Death-Ligand 1 (PD-1/PD-L1) and Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4), which are primarily expressed on the surface of T and Natural Killer (NK) cells and negatively regulate their functions. However, blockade of the PD-1/PD-L1 or CTLA-4/CD80/CD86 pathways by ICI treatment leads to hyperactivation of T cells and NK cells, precipitating immune-related adverse reactions. These conditions include dermatitis, ophthalmological disorders, endocrinopathies, myocarditis, pericarditis, vasculitis, colitis, hepatitis, nephritis, and pneumonitis. HLH is an immune-related adverse reaction that is rare and often fatal. An analysis based on the World Health Organization (WHO) database revealed 38 cases of HLH among 49,883 ICI-related adverse events as of September 30, 2018 [5]. With the generalization of ICIs in various tumor treatments, an increasing number of immune-associated HLHs have been reported [6]. Herein, we report a case of toripalimab-induced HLH in a patient with locally advanced cervical cancer (LACC). Intensive chemotherapy based on HLH-1994 can be fatal in secondary HLH with severe cytopenia, especially in heavily pretreated chemoradiotherapy, advanced age, or critical conditions [7]. Therefore, corticosteroids alone were administered as the initial treatment in this case. The recent KEYNOTE-A18 and CALLA studies [8,9] have reported the results of immunotherapy for the treatment of LACC, but no serious adverse events have been reported. Therefore, this case reminds clinicians to pay attention to the identification of severe immune-related adverse reactions and provide suggestions for early diagnosis and treatment of ICI-HLH in the future.

2. Case presentation

2.1. Clinical history

In August 2022, a 47-year-old female patient was admitted complaining of irregular vaginal bleeding for 1 year. Magnetic resonance (MR) with contrast revealed a 5.5 × 4.0 × 4.9 cm soft tissue mass in the cervix with lesions invading the uterus upwards and the upper third of the vagina, several mass lymph nodes in paraaortic regions, and external iliac regions. A vagino-recto-abdominal physical examination revealed that the lesion involved both sides of the uterus, with the right side reaching the pelvic wall and the left side near the pelvic wall. After completing the systematic evaluation, the patient was diagnosed with FIGO stage IIIC1r cervical squamous carcinoma (Fig. 1A and B, Table 1).

The patient was enrolled in our clinical study (NCT04368273), which evaluated the safety and efficacy of toripalimab concurrent with chemoradiation therapy (CCRT) in LACC. The patient received six cycles of weekly cisplatin (40 mg/m^2) chemotherapy, concomitant with a dose of 50.4 Gy local irradiation with intensity-modulated radiotherapy, a dose of 30 or 36 Gy intraluminal brachytherapy, and four doses of toripalimab every 2 weeks. One month after the initiation of external beam radiotherapy (EBRT), pelvic MR was performed to evaluate the tumor response, indicating a 64 % tumor shrinkage (Fig. 1C and D, Supplementary Fig. 1).

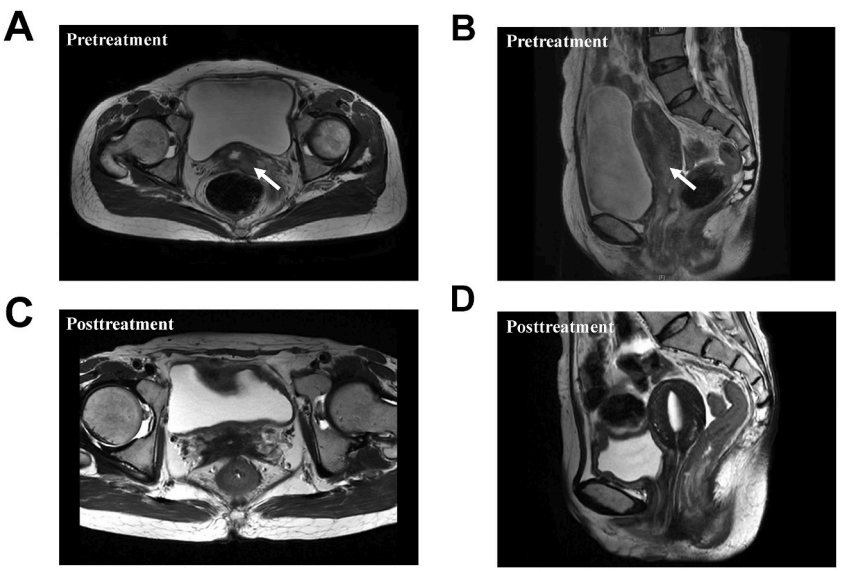

Fig. 1. (A) and (B) Pelvic MRI images before treatment. Irregular T2 slightly high signal shadow can be seen on the upper end of the cervix and vagina, the boundary of the lesion is unclear, and the range is about 50*23mm (White arrow). (C) and (D) Pelvic MRI images 2 months after the treatment. The slightly longer T2 signal of the cervix and upper vaginal end was significantly reduced. Axial image (A) and (C). Sagittal image (B) and (D).

Table 1
Summary of patient demographics.

Characteristics	Status
Age, years	47
Sex	Female
ECOG, PS.	0
PD-L1 expressions	Unknown
FIGO 2018 stage	IIIC1r
Maximum tumour diameter, cm	5.5
Local invasion	Uterus upwards, upper third of the vagina
Nodal involvement	Paraaortic, external iliac
Sites of metastases	No
Histological type	Squamous carcinoma
HPV status	16 Positive
Ethnicity	Chinese Han
Education	Unknown
Occupation	Peasant
Previous medical history	Hemorrhoid, abortion.
Tobacco smoking	Never
Family history	None cancer-related history
Marital status	Married
Previous therapy	None
Finished Treatment	
EBRT	24 fractions of 43.2Gy
Brachytherapy	5 fractions of 30 Gy
Chemotherapy	Cisplatin 40 mg/m2 weekly for 4 cycles
Immunotherapy	Toripalimab, 240mg for 3 doses
Response	Complete response
Follow up	18.6 months up to now
Recurrence	No

Note: abbreviation: FIGO, International Federation of Gynecology and Obstetrics; EBRT, external beam radiotherapy.

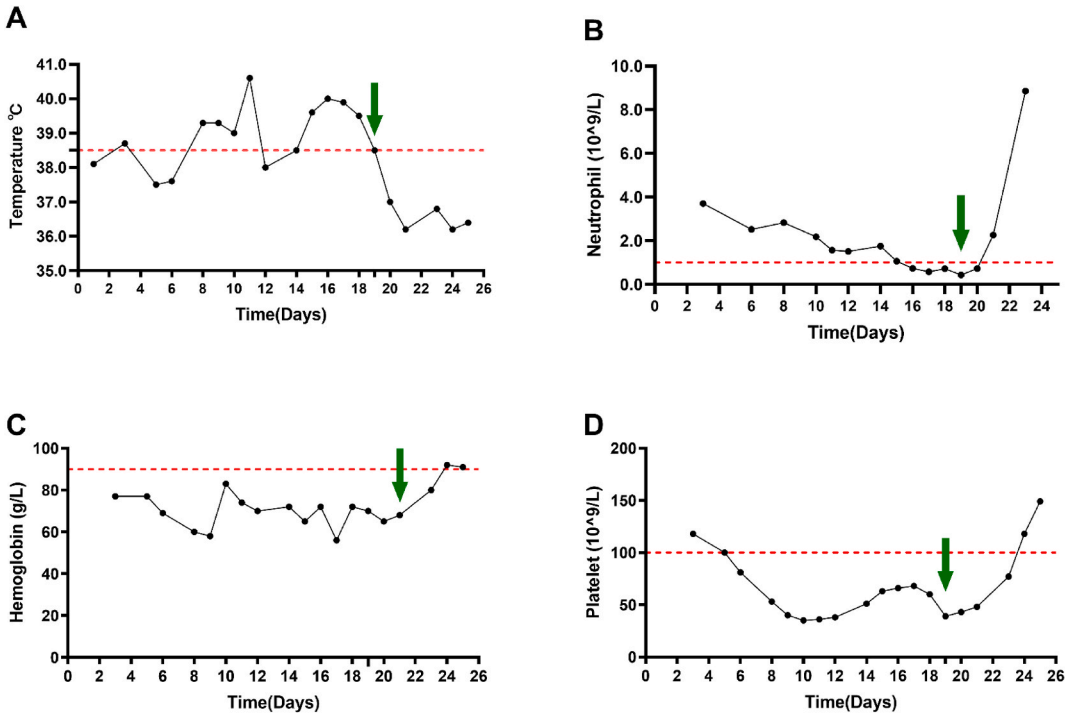

Fig. 2. The changing trend of temperature (A), the absolute number of neutrophils (B), hemoglobin (C) and blood platelets (D). The green arrow denotes time points for the initiation of steroids. The red line denotes the diagnostic criteria of HLH. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.2. Clinical findings

On Day 46, when 24 fractions of EBRT, five fractions of intraluminal brachytherapy, four cycles of cisplatin-based chemotherapy, and three doses of toripalimab were completed, this patient developed a fever with a maximum temperature beyond 38.5 °C for more than 7 days (Fig. 2A). Given the patient's poor physical condition, treatment was discontinued. Hence, the entire course of treatment started on August 15, 2022, and concluded on September 30, 2022. Physical examination revealed slight breath sounds in both lungs, no obvious dry or wet rales, and no pleural friction sounds.

2.3. Laboratory test results

Blood tests revealed severe pancytopenia, including grade 4 leukopenia, grade 4 neutropenia, grade 3 thrombocytopenia, grade 4 anemia (CTCAE, version 5.0) [10], hypertriglyceridemia (3.63 mmol/L), elevated ferritin (161347 ng/mL), and decreased fibrinogen (1.32 g/L) (Fig. 2 and Supplementary Fig. 2). Blood cultures were positive for *Bacteroides fragilis*. The Epstein-Barr virus DNA copy number was 2.61 × 10^10^3 copies/mL in peripheral plasma. Blood tests for coronavirus disease 2019, respiratory viruses, and Cytomegalovirus yielded negative results. The level of interleukin (IL)-6 was 57.72 pg/mL, that of IL-10 was 181.34 pg/mL, and that of interferon-γ was 262.66 pg/mL in the peripheral blood plasma. The soluble CD25 level was 8633 U/mL. NK cell activity decreased by 7.87 % (Tables 2–3). Hemophagocytosis (0.5 %) was observed in bone marrow aspirates (Fig. 3). Abdominal ultrasonography revealed splenomegaly. No abnormal findings were observed in the cytogenetic analysis.

2.4. Diagnostic assessment

After consultation for multidisciplinary treatment (MDT), the patient was diagnosed with ICI-associated HLH, meeting seven of the eight diagnostic criteria of the HLH-2004 (Table 2), with an HScore of 289 (HLH is confirmed when HScore≥169) [11,12].

2.5. Therapeutic intervention

After 5 days of sulperazone combined with 2 days of levofloxacin, the patient's fever persisted, reaching a maximum of 40.9 °C. Blood culture results were positive for anaerobic bacteria and *B. fragilis*. Consequently, the anti-infection regimen was adjusted to include tienam. However, even after 2 days of tienam treatment, vancomycin was initiated. Despite a course of 10 days of tienam and 7 days of vancomycin, the fever remained uncontrollable. The medical team considered the possibility of HLH and recommended further diagnostic examinations to confirm the diagnosis. Therefore, methylprednisolone was introduced alongside the ongoing combination therapy of tinenam, vancomycin, and caspofungin to treat suspected HLH and combat persistent infection. Given the poor physical status after cisplatin-based CCRT and ICI therapy as triggering factors, the patient was administered only methylprednisolone. During hospitalization, the patient was administered intravenous methylprednisolone 40 mg twice daily, concurrently with imipenem, vancomycin, and caspofungin. After 1 week, the patient's abdominal distension symptoms and general condition improved. The body temperature and blood count recovered, and blood pressure increased. Given the recovery of the patient's symptoms, there is currently no evidence of infection. Long-term use of antibiotics can cause complications such as secondary infection and bacterial dysbiosis. Anti-infection treatment was discontinued, and methylprednisolone was continued for immune checkpoint inhibitor-induced

Table 2
HLH-2004 diagnostic criteria[a] and the results of the patients.

Syndrome/Laboratory tests	Diagnostic Values	The patient	Reference range
Fever (°C)	≥38·5 °C	Tmax: 40.6	<37.3
Splenomegaly	Yes	Yes	No
Cytopenias (at least 2 of 3 cell lineages):	–	3	–
Hemoglobin (g/L)	<90	56	130–175
Platelets (10^9/L)	<100	35	125–350
Neutrophils (10^9/L)	<1.0	0.44	1.8–6.3
Hypertriglyceridemia and/or hypofibrinogenemia:			
Fasting triglycerides (mmol/L)	≥3.0	3.63	1.7
Fibrinogen (g/L)	≤1.5	1.32	2–4
Hemophagocytosis[b]	Bone marrow, or spleen, or lymph nodes, or liver.	Bone marrow	No
New diagnostic criteria			
Low or absent NK-cell activity		Reduced 7.87 %	
Ferritin (mg/L)	≥500	161.347	0.012–0.150
Soluble CD25 (i.e., soluble IL-2 receptor) (U/mL)	≥2400	8633	≤1033
Other parameters			
ALT (U/L)	Elevated	67	9–50
AST (U/L)	Elevated	81	15–40
HScore	≥169	289	

Note.
[a] . HLH could be diagnosed when fulfilled 5 out of the 8 criteria.
[b] . Hemophagocytosis could be present in bone marrow, spleen, or lymph node.

Table 3
The results of serum cytokines.

Cytokines	Results (pg/mL)	Reference ranges (pg/mL)
IL-6	57.72	2.15–12.75
IL-10	181.34	1.48–2.16
IFN-γ	262.66	2.55–4.37

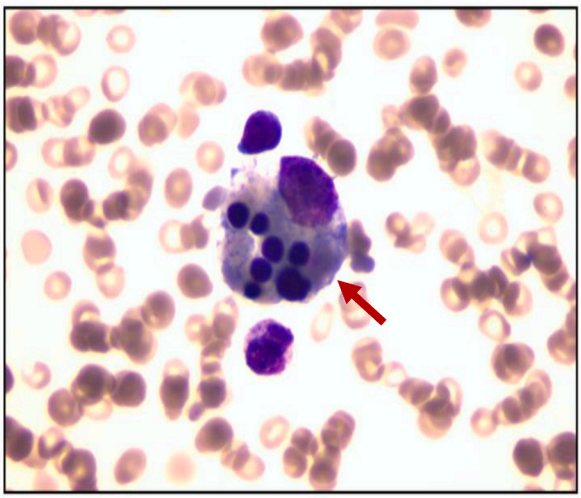

Fig. 3. Morphologic pictures of bone marrow cells. The proliferation of nucleated cells in the bone marrow was reduced (less myeloid granules), and 0.5 % of hemophagocytes were observed (Wright-Giemsa stain, × 500, red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

hemophagocytic syndrome. The entire glucocorticoid therapy process included intravenous injection of methylprednisolone for 1 week, 40 mg, twice a day; after discharge, the patient was switched to oral methylprednisolone 40 mg once a day for 2 weeks, 20 mg once a day for 2 weeks, 10 mg once a day for 2 weeks, and 5 mg once a day for 1 week [13]. The entire treatment process lasted for 8 weeks, during which prophylactic antifungal medications were administered (Supplementary Fig. 3).

2.6. Follow-up and outcomes

During the course of treatment, grade 3 or worse adverse events primarily included hematological toxicity and hypokalemia. In addition to hemoglobin and serum ferritin levels, all symptoms and laboratory test results recovered when the patient was discharged 1 month after the initiation of methylprednisolone (Table 4). At the time of submission of this manuscript, the patient was alive and well for 18.6 months after treatment with a complete tumor response (Supplementary Fig. 1) and no progressive disease, according to the Response Evaluation Criteria in Solid Tumors (Version 1.1) [14].

3. Discussion

ICI-HLH arises from the removal of the immunosuppressive effect of T cells by immune checkpoint inhibitors, which leads to T cell hyperactivation and triggers the release of numerous inflammatory factors, culminating in multiple organ dysfunction, failure, and potentially fatal outcomes [7]. The WHO database has recorded 3106 cases of HLH, with 177 cases attributed to ICI-HLH. Despite constituting only 5.7 % of reported cases, the high fatality rate of ICI-HLH (15.3 %) remains a concern. Notably, the fatality rate of ICI-HLH (40 %) was lower than that of other types of HLH. Moreover, ICI therapy is three times more likely to induce HLH than other antineoplastic agents [15]. However, despite its significance, the Society for Immunotherapy of Cancer has not provided clear treatment guidelines for ICI-HLH [16]. Therefore, early diagnosis and intervention are pivotal to preventing adverse outcomes. Current research on ICI-HLH primarily focuses on identifying risk factors and exploring treatment modalities [16]. Here, when our patient presented with uncontrollable fever, pancytopenia, and splenomegaly, our MDT quickly clarified the differential diagnosis and decisively took treatment measures. Notably, this patient is still alive well with 18.6 months of the follow-up, and the tumor has achieved complete remission, with no progressive disease to date.

Generally, the diagnosis of HLH is based on the fulfillment of five of the eight HLH-2004 criteria and, alternatively, an HScore ≥169 [11]. The challenge in diagnosing HLH, which is a diagnosis of exclusion, lies not in strictly matching the diagnostic criteria but in promptly considering it in the differential diagnosis. The high morbidity and mortality rates associated with HLH are primarily due to

Table 4
The treatment-related adverse events of the patient based on CTCAE 5.0.

Adverse events	Grade
Leukopenia	IV
Anemia	III
Nausea	I
Thrombocytopenia	III
Hyponatremia	III
Neutropenia	III
Lymphopenia	III
Fatigue	I
Decreased appetite	I
Diarrhea	I
Hypokalemia	IV
Vomiting	II
Pyrexia	II
Infection	II
Hypoalbuminemia	II
Radiation proctitis	I
Hypochloremia	Yes
Radiation cystitis	No
Vagina hemorrhage	No
Chromatosis	No
Hypomagnesemia	I
Thrombosis	No
Radiation dermatitis	II
ALT increased	I
AST increased	I
Abdominal distension	No
Mucous membrane reaction	No
Hypocalcemia	II
Hypothyroidism	No
Adrenal Insufficiency	No
Rash	No
Abdominal pain	No
Constipation	I
Pruritus	No
Musculoskeletal pain	No
Peripheral sensory neuropathy	No

delays in diagnosis rather than diagnostic difficulties. HLH typically manifests with fever, cytopenia, splenomegaly, and hyperinflammation following cancer immunotherapy. In recent years, HLH has been reported in patients with various tumors treated with other immune checkpoint inhibitors, including pembrolizumab and ipilimumab [5]. Our patient presented with continuous pyrexia (>38.5 °C), sepsis, hypotension, and hyperlactatemia, but without a defined exact infection lesion. To prevent septic shock, imipenem, vancomycin, and caspofungin are administered to treat as many potential bacterial or fungal infections as possible. However, the symptoms were not relieved after the administration of broad-spectrum antibiotics. Furthermore, she had absolute neutropenia, thrombocytopenia, and anemia but no evidence of hypotension or multi-organ failure. The likelihood of severe myelosuppression due to concurrent chemoradiotherapy is relatively low. To exclude the differential diagnosis of immune-related cytokine release syndrome, macrophage activation syndrome reported in previous studies [17], and other immune-associated hematological diseases, including autoimmune hemolytic anemia, idiopathic thrombocytopenia, and aplastic anemia, our MDT proposed conducting bone marrow aspiration, cytogenetic analysis, and testing ferritin and soluble CD25 levels to further confirm the possibility of acquired HLH. Taken together, her clinical presentation and inspection reports met seven of the eight diagnostic criteria for HLH-2004, with an HScore of 289, and she was diagnosed with acquired HLH.

The treatment of acquired HLH depends on the underlying triggers, clinical conditions, and concomitant therapy. As mentioned above, our patient was already heavily treated with concurrent chemoradiotherapy and toripalimab when she developed severe cytopenia and continuous fever and was unable to tolerate subsequent intensive therapies such as etoposide and R-DED regimens (ruxolitinib, doxorubicin, etoposide, and dexamethasone) [18]. Furthermore, the current practice of treating malignancy-associated HLH, according to HLH-1994, is guided by the assumption that the tumor itself is the main trigger of HLH [19]. However, in our patient, MR evaluation during EBRT showed a 64 % shrinkage of the tumor, indicating that our case was not associated with progressive malignancy. Cytogenetic analysis was conducted to exclude the possibility of genetic HLH. As previous studies have reported HLH after the incorporation of ICIs, we considered toripalimab as the driving factor in our patients [5]. Therefore, we chose corticosteroids as an anti-inflammatory therapy against the hyperinflammatory conditions in our patient. EBV infection was a predisposing factor for HLH, as the EBV DNA copy number was abnormal in our case [20]. Importantly, corticosteroid treatment administered as an initial strategy can mask new or transformed lymphoma diagnoses such as EBV-associated lymphoma [21]. However, several studies have reported successful treatment of EBV-associated HLH with PD-1 blockade, suggesting that blocking the interaction between PD-1

and PD-L1 can restore imbalanced immunological function and control cytokine storms in EBV-associated HLH [22–25]. Therefore, we speculate that it is unlikely that EBV drives HLH, and this strategy for treating EBV-associated HLH requires further investigation.

Given the current advances in ICI-HLH, we propose the following questions.

Q1. Is ICI-HLH associated with specific cancer types? According to data from the WHO VigiBase and literature on ICI-HLH, lung cancer and melanoma predominantly appear to be associated with ICI-HLH. However, it is not feasible to conclude that the occurrence of ICI-HLH is specific to these cancers alone, given that immunotherapy initially targeted melanoma before being applied to other tumor types [26]. With the broader application of ICI across various cancer types, the incidence of HLH is also increasing. Recently, the KEYNOTE-A18 study reported promising outcomes from combining pembrolizumab with CCRT in LACC, marking an expansion of ICI-HLH beyond melanoma and lung cancer [8]. Although one study reported the occurrence of ICI-HLH in a patient with metastatic cervical cancer during the same period after receiving paclitaxel, cisplatin, pembrolizumab, and bevacizumab [16], our study represents the first case of HLH in a patient with LACC following CCRT and ICI therapy.

Q2. Is the occurrence of ICI-HLH associated with immunotherapy targets? The study summarized HLH induced by ICIs targeting various molecules such as PD-1, PD-L1, and CTLA-4 [15]. Although there are currently more reported events associated with drugs such as pembrolizumab and nivolumab, this could be attributed to the sequencing of studies and their widespread application [16]. Toripalimab, used in this study, is a humanized IgG4 anti-PD-1 monoclonal antibody, with several randomized controlled trials demonstrating its promising prognosis in nasopharyngeal cancer [27], esophageal squamous cell carcinoma [28], lung cancer [29], and gastric cancer [30]. However, its potential for inducing HLH and its application in cervical cancer are yet to be reported. By blocking the PD-1/PD-L1 and CTLA4 signaling pathways, these drugs alleviate the immunosuppressive effects exerted by tumor and myeloid cells on T and NK cells, leading to T-cell hyperactivation and an excessive inflammatory response [31]. Consequently, the extent to which this is linked to the specific targets of these inhibitors warrants further elucidation in future studies. In addition, this issue should be considered in the development of new targeted drugs. Particularly for multitarget immunotherapy drugs, greater attention should be devoted to the monitoring and management of adverse reactions.

Q3. Is ICI-HLH associated with a combinatorial regimen? For example, does combining multiple ICIs with other targeted agents increase the risk of ICI-HLH? A recent study documented HLH development in patients with metastatic cervical cancer following treatment with anti-PD-1 and anti-VEGF agents, which suggested that anti-angiogenic drugs might exacerbate T cell overactivation by abolishing the suppressive effects of VEGF on T cells [16]. However, this hypothesis requires further investigation.

Q4. Is ICI-HLH associated with infection? Previous studies have confirmed the relationship between infection and HLH, predominantly viral infections, although cases triggered by bacterial infections have also been reported [11]. However, the WHO VigiBase lacks information on whether patients with ICI-HLH have concurrent sepsis [15]. In this study, the patient had EBV infection and sepsis. Nonetheless, the role of EBV infection in the induction of HLH remains controversial. Interestingly, some studies have indicated that ICI can lead to EBV reactivation [32], but there are also conflicting studies suggesting that ICI can effectively treat EBV-related HLH [23,32,33]. Thus, further investigation is necessary to determine whether concomitant infections exacerbate ICI-HLH. Given that EBV infection is a predisposing factor for HLH, the implementation of a viral infection screening program as a routine examination before initiating immunotherapy to increase vigilance and attention to HLH warrants further research. Therefore, identifying potential markers to predict populations vulnerable to HLH is essential.

Q5. Is ICI-HLH associated with an autoimmune disease? Preexisting autoimmune diseases may pose a significant risk of developing ICI-HLH [31]. Several deaths associated with ICI-HLH have been linked to autoimmune encephalitis, indicating an increased risk of disease progression and mortality in patients with autoimmune conditions [16]. Autoimmune diseases are crucial risk factors requiring close monitoring and vigilance. Notably, a recently published study reported that patients who developed HLH after receiving chemotherapy combined with immunotherapy had a history of psoriasis [16]. However, in the present study, the patient had no history of autoimmune disease or other underlying conditions. Nevertheless, continuous monitoring of the thyroid function and cortisol, lipase, and amylase levels is necessary during ICI treatment. Early screening for autoimmune disease markers and other indicators is imperative to identify and mitigate the potential risks associated with autoimmune diseases.

Q6. Is there an association between higher-grade immune-related adverse reactions (irAEs) and improved tumor outcomes? An initial correlation was observed between ICI-HLH and rapid tumor regression [33]. Subsequent studies indicated that patients experiencing grade 3–4 irAEs tend to have better tumor prognoses compared to those with grade 1–2 irAEs [34–36]. A recent systematic review, which summarizes data from the WHO database and previous case studies, also supports this statement, suggesting that patients with HLH experience approximately 80 % tumor regression. Additionally, a small proportion of patients exhibit persistent antitumor effects after the cessation of antitumor therapy [16]. Consistently, in this study, our patients experienced 64 % tumor regression upon cessation of treatment and maintained a complete tumor response from 2 months post-treatment until the present. However, the underlying mechanism remains unclear. It is plausible that heightened inflammatory conditions contribute to a more robust antitumor immune response, which requires further investigation to elucidate this phenomenon.

Q7. How can ICI-HLH be diagnosed at an early stage? According to the WHO VigiBase and previous studies, the most common symptoms observed in patients with ICI-HLH are fever and hepatosplenomegaly, accompanied by laboratory findings such as pancytopenia and hyperferritinemia [15]. In this study, the initial symptom of the patient was an uncontrollable fever treated with antibiotics. Therefore, there is an urgent need to enhance education and awareness among oncologists regarding secondary HLH. Guidelines should emphasize the rarity and severity of HLH. Oncologists should maintain a high index of suspicion for HLH when patients present with unexplained fever, cytopenia, or splenomegaly, which prompts MDT involvement.

Q8. What is the standard care for patients with ICI-HLH? Currently, there is no recommended treatment for ICI-HLH, and most interventions rely on glucocorticoids. Although the HLH-1994 regimen is the conventional approach for HLH, the incorporation of intensive chemotherapy in patients following ICIs combined with CCRT might exacerbate their physical condition [31]. For hormone-refractory HLH, chemotherapy and monoclonal antibodies should be considered in the HLH-1994 regimen [15,16,31]. The identification of more effective treatment strategies requires further investigation.

This study has several limitations. First, the single-case design: The case report describes a single patient with a rare condition, limiting the ability to draw causal inferences and generalize findings to other populations or settings. Moreover, the absence of a control group means the report lacks a comparative basis to evaluate the treatment's effectiveness and safety or to discount alternative explanations for the outcomes observed. Additionally, the retrospective nature of the study introduces potential biases, as it relies on data from medical records and laboratory tests, which may be prone to errors, missing values, or incomplete records. Finally, it fails to consider potential confounding factors that could affect the development and resolution of HLH, such as genetic predispositions, comorbidities, concurrent medications, or environmental exposures.

Given that immune-related HLH is a rare complication, conducting a large-scale randomized controlled trial is relatively difficult, and the occurrence of this complication is not anticipated in clinical settings. Therefore, for ongoing and upcoming clinical trials concerning immunotherapy, it is imperative to establish an international HLH collaborative group. This group should promptly report adverse events, facilitating the creation of an international multicenter cohort and exploring the optimal treatment modality for acquired HLH. Importantly, the education of young physicians is also crucial to advance precision and avoid delays in the diagnosis of HLH.

Ethics statement

The study protocol was approved by the institutional review board (IRB) of Peking University Third Hospital (M2019482) and was registered with ClinicalTrials.gov, NCT04368273. The patient provided written informed consent before enrollment All procedures in this study were performed according to the Declaration of Helsinki and Good Clinical Practice guidelines.

Consent for publication

Yes.

Availability of data and materials

All data are available in this manuscript.

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CRediT authorship contribution statement

Shuhua Wei: Writing – original draft, Resources, Funding acquisition, Formal analysis, Data curation. **Hongbo Chen:** Formal analysis, Data curation. **Xiuwen Deng:** Data curation. **Ping Jiang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Junjie Wang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33816.

References

[1] P. Sharma, S. Goswami, D. Raychaudhuri, et al., Immune checkpoint therapy-current perspectives and future directions, Cell 186 (8) (2023) 1652–1669.
[2] K.R. McCarter, T. Wolfgang, S. Arabelovic, et al., Mortality and immune-related adverse events after immune checkpoint inhibitor initiation for cancer among patients with pre-existing rheumatoid arthritis: a retrospective, comparative, cohort study, Lancet Rheumatol 5 (5) (2023) e274–e283.
[3] C. Sung, J. An, S. Lee, et al., Integrative analysis of risk factors for immune-related adverse events of checkpoint blockade therapy in cancer, Nat Cancer 4 (6) (2023) 844–859.
[4] S.E. Yoon, Y. Eun, K. Huh, et al., A comprehensive analysis of adult patients with secondary hemophagocytic lymphohistiocytosis: a prospective cohort study, Ann. Hematol. 99 (9) (2020) 2095–2104.
[5] R. Noseda, R. Bertoli, L. Müller, et al., Haemophagocytic lymphohistiocytosis in patients treated with immune checkpoint inhibitors: analysis of WHO global database of individual case safety reports, J Immunother Cancer 7 (1) (2019) 117.
[6] A. Dupré, J.M. Michot, A. Schoeffler, et al., Haemophagocytic lymphohistiocytosis associated with immune checkpoint inhibitors: a descriptive case study and literature review, Br. J. Haematol. 189 (5) (2020) 985–992.
[7] G.N. Tamamyan, H.M. Kantarjian, J. Ning, et al., Malignancy-associated hemophagocytic lymphohistiocytosis in adults: relation to hemophagocytosis, characteristics, and outcomes, Cancer 122 (18) (2016) 2857–2866.
[8] D Lorusso, Y Xiang, K Hasegawa, et al., Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial, Lancet 403 (10434) (2024) 1341–1350.
[9] B.J. Monk, T. Toita, X. Wu, et al., Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial, Lancet Oncol. 24 (12) (2023) 1334–1348.
[10] National Cancer Institute, National Institutes of Health, US Department of Health and Human Services, Common Terminology Criteria for Adverse Events (CTCAE), 2018, Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Published November 7, 2017. Accessed March 09, 2018.
[11] M. Ramos-Casals, P. Brito-Zerón, A. López-Guillermo, et al., Adult haemophagocytic syndrome, Lancet 383 (9927) (2014) 1503–1516.
[12] F. Debaugnies, B. Mahadeb, A. Ferster, et al., Performances of the H-score for diagnosis of hemophagocytic lymphohistiocytosis in adult and pediatric patients, Am. J. Clin. Pathol. 145 (6) (2016) 862–870.
[13] P. La Rosée, A. Horne, M. Hines, et al., Recommendations for the management of hemophagocytic lymphohistiocytosis in adults, Blood 133 (23) (2019) 2465–2477.
[14] L.H. Schwartz, S. Litière, E. de Vries, et al., RECIST 1.1-Update and clarification: from the RECIST committee, Eur. J. Cancer 62 (2016) 132–137.
[15] L. Diaz, B. Jauzelon, A.C. Dillies, et al., Hemophagocytic lymphohistiocytosis associated with immunological checkpoint inhibitors: a pharmacovigilance study, J. Clin. Med. 12 (5) (2023).
[16] C. Zhai, X. Jin, L. You, et al., Hemophagocytic lymphohistiocytosis following pembrolizumab and bevacizumab combination therapy for cervical cancer: a case report and systematic review, BMC Geriatr. 24 (1) (2024) 32.
[17] L.L. Liu, M. Skribek, U. Harmenberg, et al., Systemic inflammatory syndromes as life-threatening side effects of immune checkpoint inhibitors: case report and systematic review of the literature, J Immunother Cancer 11 (3) (2023).
[18] J. Wang, R. Zhang, X. Wu, et al., Ruxolitinib-combined doxorubicin-etoposide-methylprednisolone regimen as a salvage therapy for refractory/relapsed haemophagocytic lymphohistiocytosis: a single-arm, multicentre, phase 2 trial, Br. J. Haematol. 193 (4) (2021) 761–768.
[19] S. Ehl, I. Astigarraga, T. von Bahr Greenwood, et al., Recommendations for the use of etoposide-based therapy and bone marrow transplantation for the treatment of HLH: consensus statements by the HLH steering committee of the histiocyte society, J. Allergy Clin. Immunol. Pract. 6 (5) (2018) 1508–1517.
[20] C. Bigenwald, L. Fardet, P. Coppo, et al., A comprehensive analysis of Lymphoma-associated haemophagocytic syndrome in a large French multicentre cohort detects some clues to improve prognosis, Br. J. Haematol. 183 (1) (2018) 68–75.
[21] O. Pasvolsky, A. Zoref-Lorenz, U. Abadi, et al., Hemophagocytic lymphohistiocytosis as a harbinger of aggressive lymphoma: a case series, Int. J. Hematol. 109 (5) (2019) 553–562.
[22] L.H. Dong, J. Liu, P. Zu, et al., PD-1 blockade with nivolumab-controlled Epstein-Barr virus infection and associated haemophagocytic lymphohistiocytosis: a case report, Clin. Microbiol. Infect. 25 (11) (2019) 1438–1440.
[23] Y. Song, W. Li, D. Wu, et al., Successful treatment of refractory EBV-associated hemophagocytic lymphohistiocytosis with combined emapalumab and PD-1 blockade, J. Clin. Immunol. 44 (3) (2024) 70.
[24] Y. Xu, W. Li, J. Gan, et al., An analysis of sintilimab combined with ruxolitinib as compassionate therapy for 12 adults with EBV-associated hemophagocytic lymphohistiocytosis, Ann. Hematol. 102 (12) (2023) 3325–3333.
[25] Y. Pi, J. Wang, Z. Wang, Successful treatment of relapsed epstein-barr virus-associated hemophagocytic lymphohistiocytosis after allo-HSCT with PD-1 blockade: a case report, Infect. Drug Resist. 15 (2022) 3751–3756.
[26] C. Robert, A. Ribas, J.D. Wolchok, et al., Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial, Lancet 384 (9948) (2014) 1109–1117.
[27] H.Q. Mai, Q.Y. Chen, D. Chen, et al., Toripalimab plus chemotherapy for recurrent or metastatic nasopharyngeal carcinoma: the JUPITER-02 randomized clinical trial, JAMA 330 (20) (2023) 1961–1970.
[28] X. Xu, Z. Sun, Q. Liu, et al., Neoadjuvant chemoradiotherapy combined with sequential perioperative toripalimab in locally advanced esophageal squamous cell cancer, J Immunother Cancer 12 (3) (2024).
[29] S. Lu, W. Zhang, L. Wu, et al., Perioperative toripalimab plus chemotherapy for patients with resectable non-small cell lung cancer: the neotorch randomized clinical trial, JAMA 331 (3) (2024) 201–211.
[30] S.Q. Yuan, R.C. Nie, Y. Jin, et al., Perioperative toripalimab and chemotherapy in locally advanced gastric or gastro-esophageal junction cancer: a randomized phase 2 trial, Nat. Med. 30 (2) (2024) 552–559.
[31] A. Setiadi, A. Zoref-Lorenz, C.Y. Lee, et al., Malignancy-associated haemophagocytic lymphohistiocytosis, Lancet Haematol 9 (3) (2022) e217–e227.
[32] M.R. Pugh, G.D. Leopold, M. Morgan, et al., Epstein-barr virus-positive mucocutaneous ulcers complicate colitis caused by immune checkpoint regulator therapy and associate with colon perforation, Clin. Gastroenterol. Hepatol. 18 (8) (2020) 1785–1795.e1783.
[33] M. Takeshita, S. Anai, S. Mishima, et al., Coincidence of immunotherapy-associated hemophagocytic syndrome and rapid tumor regression, Ann. Oncol. 28 (1) (2017) 186–189.
[34] Y. Jing, J. Yang, D.B. Johnson, et al., Harnessing big data to characterize immune-related adverse events, Nat. Rev. Clin. Oncol. 19 (4) (2022) 269–280.
[35] T. Fujii, R.R. Colen, M.A. Bilen, et al., Incidence of immune-related adverse events and its association with treatment outcomes: the MD Anderson Cancer Center experience, Invest. N. Drugs 36 (4) (2018) 638–646.
[36] M.A. Socinski, R.M. Jotte, F. Cappuzzo, et al., Association of immune-related adverse events with efficacy of atezolizumab in patients with non-small cell lung cancer: pooled analyses of the phase 3 IMpower130, IMpower132, and IMpower150 randomized clinical trials, JAMA Oncol. 9 (4) (2023) 527–535.