Preoperative pembrolizumab-induced hemophagocytic lymphohistiocytosis in a patient with breast cancer: A case report

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Abstract. Recently, the anti-programmed cell death protein 1 antibody pembrolizumab, a type of immune checkpoint inhibitor (ICI), has been used in preoperative systemic chemotherapy for hormone receptor and human epidermal growth factor 2-negative breast cancer, also known as triple-negative breast cancer (TNBC). Chemotherapy with pembrolizumab has demonstrated clinical activity in terms of pathologic complete response and event-free survival. Despite their efficacy, the current understanding of the full spectrum of side effects associated with relatively new ICIs remains incomplete. The present study describes a case of severe pembrolizumab-induced hemophagocytic lymphohistiocytosis in a patient with early-stage TNBC, and the strategies used to manage the patient in light of their pathophysiology.

Introduction

High-risk early-stage triple-negative breast cancer (TNBC) is often associated with early recurrence and high mortality rates (1). In addition to potentially increasing the likelihood of tumor resectability and breast conservation rate, patients who achieve pathologic complete response (pCR) after preoperative chemotherapy have longer event-free and overall survival (2). The recent KEYNOTE-522 trial (3) demonstrated a significantly higher pCR rate in patients who received pembrolizumab plus preoperative chemotherapy (64.8%) compared to that in those who received placebo plus preoperative chemotherapy (51.2%). However, the follow-up period for clinical trials of preoperative chemotherapy, including immune checkpoint inhibitor (ICI), is still short, and little is known about the overall picture of immune-related adverse events (irAEs).

In a randomized phase III trial of pembrolizumab or placebo as preoperative systemic chemotherapy (PST) in patients with stage II or III TNBC, grade 3 or higher irAEs occurred in 12.9% of patients in the pembrolizumab chemotherapy group (4). The most frequent irAEs were hypothyroidism (15.7%), severe skin reactions (5.7%), hyperthyroidism (5.2%), and adrenal insufficiency (2.6%), with no hemophagocytic lymphohistiocytosis (HLH) reported. Fatal irAEs occur in a small number of patients, ranging from 0.36% in patients receiving anti-PD-1 monotherapy to 1.23% in those receiving combination therapy (5).

Hematological irAEs (hemirAEs) are difficult to treat and have a high mortality rate. In a retrospective study, the incidence of hemirAEs was reported to be 0.6%, with higher frequencies of anemia, neutropenia, and thrombocytopenia (6). Among the hemophagocytic irAEs, hemophagocytic syndrome is relatively rare, with only a few case reports of hemophagocytic syndrome with ICIs; however, it can be a life-threatening complication. Here, we report a case of pembrolizumab-induced HLH in a patient with locally advanced TNBC.

Case report

A 38-year-old woman presented to National Center for Global Health and Medicine (Tokyo, Japan) in November 2022 with locally advanced left breast cancer, cT1N3M0, cStage IIIC, which was HR-negative- and HER2-negative (Fig. 1). The patient had no relevant medical history. The patient exhibited a pathogenic mutation in the germline BRCA1 (breast cancer susceptibility gene) as identified by the BRACAnalysis CDx® (Germline Companion Diagnostic Test). PST with pembrolizumab was considered appropriate for this young patient, who had a poor prognosis based on the clinical stage and biomarkers.

The patient was initially treated with carboplatin, paclitaxel, and pembrolizumab without severe adverse events until

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the third course, at which point the mass became non-palpable (cT0). On day 8 of the third course (day 62 from the onset of chemotherapy), she experienced persistent grade 1 diarrhea without infection symptoms for two weeks, raising concerns for immune-related colitis, prompting a colonoscopy. Owing to mild mucosal inflammation and localized sigmoid edema observed on CT, a 5-ASA preparation was administered, improving her colitis to grade 0 within two weeks. However, diarrhea recurred on day 96, 19 days post-colonoscopy, escalating to grade 2. Consequently, steroids (PSL; prednisone) were initiated at a dosage of 0.5 mg/kg/day (30 mg/day), following the guidelines of the Japanese Society of Clinical Oncology. The introduction of PSL led to an improvement in diarrhea to grade 0, and the steroid dosage was subsequently tapered by 5 mg per week.

Owing to immune-related adverse events (irAEs) manifesting as colitis, pembrolizumab was discontinued on day 70, and the patient continued chemotherapy with carboplatin and paclitaxel. On day 114, liver function deteriorated to grade 2, despite treatment with 20 mg/day of steroids. IrAE hepatitis was suspected, leading to hospitalization. A high fever was also observed during this period. The steroid dosage was increased to 30 mg/day (0.5 mg/kg) on day 118, five days following the onset of fever and liver dysfunction, and on the fifth-day post-hospitalization. Liver function temporarily improved but deteriorated again to grade 3, five days after the dosage increase (day 122; post-hospitalization day 9). Consequently, the steroid dosage was elevated to 60 mg/day (1 mg/kg). Although liver function showed slight improvement, it worsened to grade 4 on day 127 (post-hospitalization day 14). The patient then commenced treatment with mycophenol mofetil (MMF) at 2,000 mg/day, as per the Japanese guidelines for irAEs.

A hepatologist performed a liver biopsy on day 126 for further assessment. The subsequent day, continuous bleeding from the biopsy site was noted, with unmeasurably high fibrinogen/fibrin degradation products (FDP) and D-dimer levels. No hematopenia was observed. Given the persistent fever, coagulation abnormalities, liver damage, elevated lactate dehydrogenase (LDH) levels, hyperferritinemia, and the hemophagocytic profile observed in the liver biopsy pathology (Fig. 2), a comprehensive diagnosis of secondary HLH was made. The diagnostic score for reactive hemophagocytic syndrome in adult HLH [HScore (7)] is shown in Table I. Levels of interleukin-6 (IL-6) and soluble IL-2 receptor (sIL2R) were elevated to 325.0 pg/ml and 2180 U/ml, respectively. She was diagnosed with disseminated intravascular coagulation (DIC) with a predominantly fibrinolytic system, and treatment with nafamostat and fresh frozen plasma (FFP) was initiated. The day after MMF management began, liver function and coagulation abnormalities deteriorated. Methylprednisolone (1 g/day) was administered as a steroid pulse for three days (day 128, post-hospitalization day 15). The course of the patient's symptoms, liver function, and medications administered are detailed in Fig. 3.

Liver function and coagulation abnormalities improved after the completion of steroid pulse therapy, and gradual tapering was planned. Given the onset of HLH, whereas she was on 60 mg PSL, we considered the need for further correction of hypercytokinemia before tapering the steroids

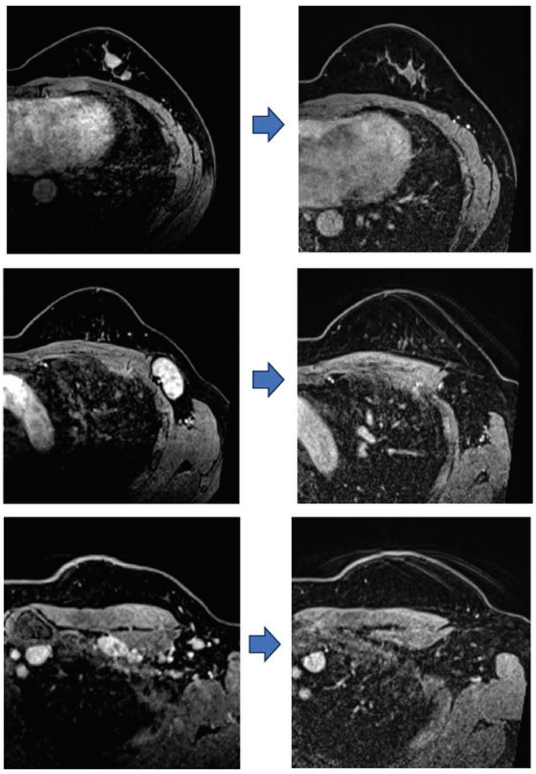

Figure 1. MRI images of breast cancer before and after the start of chemotherapy. The image on the left depicts the patient's condition prior to the initiation of treatment, whereas the image on the right shows the patient's condition after ceasing immune checkpoint inhibitor therapy The tumor has become undetectable on MRI.

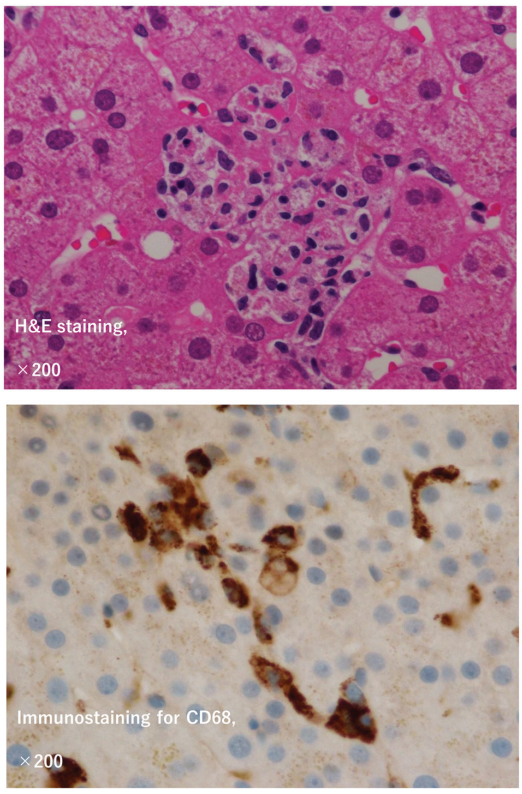

Figure 2. Pathology of liver biopsy. Necrosis and loss of hepatocyte layers were observed in multiple liver lobule units. Additionally, hemophagocytosis was noted, with the phagocytes staining positive for CD68. H&E, hematoxylin and eosin.

Table I. HScore.

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression[a]	0 (no) or **18** (yes)
Temperature, ˚C	0 (<38.4), **33** (38.4-39.4), or 49 (>39.4)
Organomegaly	**0** (no), 23 (hepatomegaly or splenomegaly) or 38 (hepatomegaly and splenomegaly)
No. of cytopenias[b]	**0** (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin, ng/ml	0 (<2,000), 35 (2,000-6,000), or **50** (>6,000)
Triglyceride, mmol/l	0 (<1.5), **44** (1.5-4), or 64 (>4)
Fibrinogen, g/l	**0** (<2.5) or 30 (>2.5)
Serum glutamic oxaloacetic transaminase, IU/l	0 (<30) or **19** (>30)
Hemophagocytosis features on bone marrow aspirate	0 (no) or **35** (yes)

The table presents the definition of Hscore and indicates the patient's position within the Hscore criteria, as delineated by the use of bold text. In a previous study (7), the median HScore was reported to be 230 (IQR, 203-257) for patients with a positive diagnosis of reactive hemophagocytic syndrome and 125 (IQR, 91-150) for patients with a negative diagnosis The probability of having hemophagocytic syndrome ranged from <1% with an HScore of <90 to >99% with an HScore of >250. [a]Human immunodeficiency virus positive or receiving long-term immunosuppressive therapy (glucocorticoids, cyclosporine, azathioprine). [b]Defined as a hemoglobin level <9.2 gm/dl and/or a leukocyte count <5,000/mm^3 and/or a platelet count <110,000/mm^3. IQR, interquartile range.

with tocilizumab, an anti-interleukin (IL)-6 antibody, 8 mg/kg once on the third day after the end of the pulse (day 133, post-hospitalization day 20). The levels of IL-6 decreased to 1.8 pg/ml after the steroid pulse. We also administered cyclosporine after the pulse steroid therapy. The doses of MMF and cyclosporine were tapered, as with the steroids.

The differential diagnoses included coronavirus disease 2019 (COVID-19), tuberculosis, bacterial pneumonia, viral hepatitis, adrenal insufficiency, and irAEs such as CRS and HLH. The patient tested negative for COVID-19. Extensive tests for infectious diseases, including interferon (IFN)-gamma release assay, human immunodeficiency virus, Aspergillus antigen, and urine/sputum/blood cultures on multiple occasions, were unrevealed. The respiratory viral panel was negative (for influenza A/B, parainfluenza 1/2/3/4, adenovirus, coronavirus [not COVID-19], and rhinovirus/enterovirus) before hospitalization. Before the initiation of PST, Epstein-Barr virus (EBV) demonstrated a pre-existing infection pattern (EBV-EBNA 40, EBV-VCA IgG 160, VCA-IgM <10), and an EBV DNA level of $4.0x10^4$ copies/ml on day 127 (the day before the steroid pulse) indicated either reactivation of EBV owing to ICI use or potential EBV hepatitis. Upon detailed analysis, the EBV DNA level decreased during steroid tapering, and liver function consistently improved. Therefore, whereas EBV may influence pathogenesis, its precise role remains unclear. The patients were discharged on post-hospitalization day 69 with a PSL dosage of 25 mg/day and attended weekly outpatient follow-ups. The PSL dose was reduced to 2 mg/day (with MMF completed and cyclosporine at 100 mg/day) by the day of breast cancer surgery (day 209). In the surgical specimen, a pCR was confirmed (pathological stage ypT0ypN0). PSL was discontinued 130 days post-initiation of steroid therapy (post-hospitalization day 108). The patient was monitored without additional cancer-directed treatments and remained recurrence-free.

Discussion

HLH is a rare and severe disease characterized by the hyperactivation of immune cells (such as T lymphocytes, monocytes, and macrophages). They can be of primary or secondary origin, mainly owing to infection, cancer, or autoimmune diseases (Table II). Primary HLH is most frequently observed in infants and children. The diagnosis of secondary hemophagocytic HLH is based on exclusion rather than direct evidence of specific triggers and is associated with aberrant immunomodulatory mechanisms such as hypercytokinemia. Consequently, once HLH pathogenesis is established, it is essential to confirm the presence of potential underlying factors, including infections, malignancies, and autoimmune diseases. In this case, a genetic predisposition seemed unlikely, given the absence of family history or immunodeficiency. Moreover, considering the observed reduction in breast cancer size following chemotherapy, the likelihood of secondary HLH resulting from the tumor was also deemed unlikely. Importantly, no evidence of rheumatic disease, such as arthralgia or skin rash, was observed, and antinuclear antibodies were negative prior to the initiation of PST. Thus, considering the exclusion of infectious diseases, a diagnosis of secondary HLH resulting from ICI was considered. Although not previously conceptualized, knowledge of ICI-related HLH is essential for oncologists treating patients with ICI. HLH is generally life-threatening, with a mortality rate of up to 66% (3). In clinical practice, the rapid progression of HLH often leads to multiple organ failure and death, which are difficult to treat. Therefore, accurate diagnosis and early intervention are critical to improve the prognosis of HLH.

Patients with HLH typically present with recurrent high fever and pancytopenia. Blood tests reveal hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia. Features of hemophagocytosis may be observed in a bone marrow smear

Table II. Classification of HLH.

Primary (inherited) HLH	Secondary (reactive) HLH
•FHL	•Infection-associated hemophagocytic syndrome Virus-associated hemophagocytic syndrome Bacteria-associated hemophagocytic syndrome Fungus-associated hemophagocytic syndrome Parasite-associated hemophagocytic syndrome
•Immune deficiency syndrome Griscelli syndrome Chedial-Higashi syndrome, etc.	•Malignancy-associated hemophagocytic syndrome •Lymphoma-associated hemophagocytic syndrome
	•Autoimmune-associated hemophagocytic syndrome •Immune checkpoint inhibitors-associated hemophagocytic syndrome •Other (transplanting-associated hemophagocytic syndrome, etc.)

FHL, familial hemophagocytic lymphohistiocytosis.

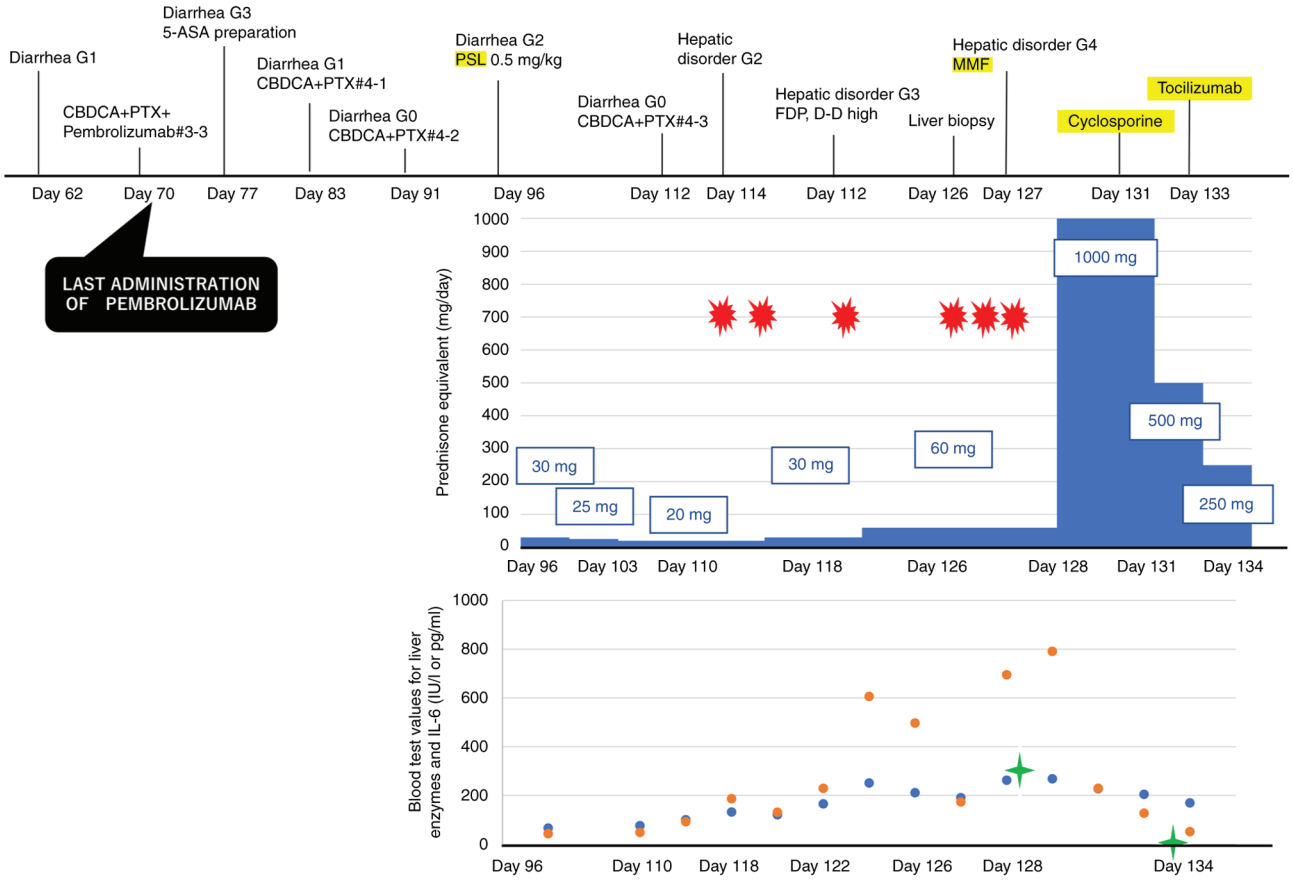

Figure 3. Clinical course following pembrolizumab administration. Yellow background: Drugs used in hemophagocytic lymphohistiocytosis treatment. Red circles with jagged edges indicate fever ≥39˚C. Green diamonds: IL-6 (pg/ml); orange circles: AST (IU/l); blue circles: ALT (IU/l). AST, aspartate aminotransferase; ALT, alanine aminotransferase; CBDCA, carboplatin; PTX, paclitaxel; 5-ASA, 5-aminosalicylic acid; PSL, prednisolone; FDP, fibrinogen/fibrin degradation products; D-D, D dimer; MMF, Mycophenolate Mofetil.

examination. Diagnostic criteria for children are well established (HLH-2004) (8), and a probability score (HScore) for adults has recently been proposed (Table I) (7). The onset of HLH can range from 5 days to 1 year following the initial dose of ICI (9), with a median time of 6 weeks (10). Although rare, HPS should be suspected when persistent high fever and blood cell loss in two or more systems are observed, with or without associated hypertriglyceridemia, hyperferritinemia, hypofibrinogenemia, and elevated sIL2R levels. In this instance, the HScore was 199 (90-250), and establishing a diagnosis was challenging owing to the absence of clear thrombocytopenia evidence.

Table III. List of prior cases of HLH secondary to ICI therapy.

First author, year	Type of ICI	Timing/cycles of therapy	Primary malignancy	Method of diagnosis	BM biopsy/pathology	Treatment	Clinical outcome	(Refs.)
Present case	Pembrolizumab	3 doses	Breast cancer	Liver biopsy, fever, coagulation abnormality, elevation of ferritin, LDH, iver enzyme levels l and IL-6	Liver biopsy for HLH	Steroids, mycophenolate mofetil, tocilizumab, cyclosporine	Improvement	-
Kurozumi, 2021 (case 1)	Pembrolizumab	1 dose	NSCLC	BM biopsy, fever, cytopenia, coagulation abnormality, elevation of ferritin and liver enzyme levels	N/A	Steroids	Improvement	(15)
Kurozumi, 2021 (case 2)	Pembrolizumab	16 cycles of durvalumab, 2 of doses pemetrexed + pembrolizumab	NSCLC	Cytopenia, coagulation abnormalities, and elevation of ferritin, liver enzyme levels	N/A	Steroids	Improvement	(15)
Sackstein, 2021	Pembrolizumab	3 doses	NSCLC	Fever, cytopenia, elevation of ferritin, soluble IL-2R, LDH and liver enzyme levels	N/A	Steroids, tocilizumab	Improvement	(16)
Okawa, 2019	Pembrolizumab	1 dose	NSCLC	BM biopsy, liver biopsy, soluble IL-2R, ferritin elevation, cytopenias	BM biopsy for HLH	Steroids	Improvement	(17)
Laderian, 2019	Pembrolizumab	12 months	Thymic cancer	BM biopsy, liver biopsy, soluble IL-2R, ferritin elevation, cytopenias	BM biopsy for HLH	Steroids, IVIG, anakinra[a]	Death	(18)
Honjo, 2019	Nivolumab	4 doses	NSCLC	Ferritin, soluble IL-2R, triglyceride elevation	N/A	Steroids, mycophenolate mofetil	Improvement	(19)
Hantel, 2018	Ipilimumab and nivolumab	4 doses of ipilimumab, 1 dose of ipilimumab and nivolumab	Melanoma	BM biopsy, soluble IL-2R elevation	BM biopsy for HLH	Steroids	Improvement	(20)
Satzger, 2018	Ipilimumab and nivolumab	4 doses	Melanoma	Liver biopsy, ferritin, triglyceride, soluble IL-2 elevation, cytopenias	N/A	Steroids, mycophenolate mofetil	Improvement	(21)
Sadaat, 2018	Pembrolizumab	6 doses	Melanoma	NK cell functional assay, soluble CD163 elevation	N/A	Steroids	Improvement	(22)
Takeshita, 2017	Nivolumab	2 doses	NSCLC	BM biopsy	BM biopsy for HLH	Steroids	Improvement	(23)

Table III. Continued.

First author, year	Type of ICI	Timing/cycles of therapy	Primary malignancy	Method of diagnosis	BM biopsy/pathology	Treatment	Clinical outcome	(Refs.)
Malissen, 2017 (case 1)	Nivolumab	17 months	Melanoma	BM biopsy	BM biopsy for HLH	Steroids	Death	(24)
Shah, 2017	Pembrolizumab	9 months	Bladder cancer	BM biopsy, NK cell functional assay, soluble IL-2R elevation	BM biopsy for HLH	Steroids and etoposide (HLH 2004)	Unknown	(25)
Malissen, 2017 (case 2)	Ipilimumab	1 dose of ipilimumab; prior history of 9 months of nivolumab	Melanoma	Ferritin, triglyceride elevation, cytopenias	BM biopsy negative for HLH	Steroids	Improvement	(24)
Malissen, 2017 (case 3)	Avelumab	1 dose	Merkel cell carcinoma	Ferritin, triglyceride elevation, cytopenias	N/A	Steroids	Death	(24)

[a]Anakinra; IL-1 receptor antagonists. N/A, not applicable.

Case reports of HLH during ICI treatment for solid tumors are summarized in Table III. The mean time to symptom onset was after eight doses. Bone biopsies were conducted in approximately half of the patients and were not universally performed despite numerous reports where HLH was clinically diagnosed. We performed a liver biopsy, although it was not obligatory. However, the phagocytic images provided sufficient evidence to suggest that HLH developed in these patients. Steroids were administered in all cases, and nonsteroidal immunosuppressive therapies (NSIT) were used in four cases, as in the current case. Of the 14 patients, 11 showed improvement, three (one of whom was receiving nonsteroidal immunosuppressive therapy) died, and the outcome of one patient was not documented.

HLH is an umbrella term for hyperinflammatory conditions that involve supramaximal activation of the immune system. The overproduction of inflammatory cytokines by abnormally activated T lymphocytes and macrophages is one of the main factors in disease pathogenesis (11). There are many reports of increased blood levels of inflammatory cytokines such as tumor necrosis factor α, IFN-γ, IL-1, IL-6, IL-12, IL-18, sIL-2R, and FasL in patients with HLH. It is also widely known that such hypercytokinemia is accompanied by abnormal activation of the blood coagulation system/fibrinolytic system (fibrinolytic system), a condition known as DIC. Therefore, the prognosis of HLH can be improved by suppressing inflammatory cytokine expression.

Pembrolizumab is a monoclonal antibody that inhibits the programmed cell death-1 (PD-1) receptor. PD-1 is expressed by immune cells and plays a role in regulating self-tolerance by downregulating immune responses. The interaction of PD-1 with PD-L1 in the tumor microenvironment compromises normal T cell function and promotes the conversion of cytotoxic T cells into regulatory T cells (12). Inhibition of PD-1 and PD-L1 signaling through checkpoint inhibitors enhances T-cell cytotoxicity and induces tumor regression. However, given the comprehensive nature of these interactions, there are significant implications for both cancer cells and the host's normal tissues. It has been hypothesized that the hyperinflammatory state caused by immunotherapy-induced T-cell activation may lead to HLH. In the absence of definitive physical evidence, it is crucial to exclude other causes of secondary HLH.

In this case, we suspected HLH based on the clinical findings and measured IL-6 levels before administering the steroid pulse, which confirmed that it decreased with treatment. Although IL-6 measurement was not necessary for the diagnosis of HLH, it was helpful in understanding the pathophysiology while awaiting the results of the liver biopsy, allowing us to initiate treatment. Hyperactivation of immune cells by EBV reactivation is also considered to have had an effect.

Although the recent irAE guidelines from the Society of Immunotherapy for Cancer discuss HLH as an irAE with potentially high lethality, no specific treatment recommendations have been made (13). Hence, real-world data and case reports of rare irAEs are needed to understand their frequency and severity and improve clinical management. A review of the management of blood-related irAEs recommends the prompt administration of high-dose corticosteroids (2-5 mg/kg/day, IV) and anti-IL-6 inhibitors such as tocilizumab for cytokine storms associated with hemophagocytic syndrome.

Should corticosteroids fail to elicit an adequate response, the use of cyclosporine or a single dose of etoposide (150 mg/kg, IV) should be considered in collaboration with a hematologist (14). Earlier case reports of ICI-associated HLH have utilized anti-inflammatory cytokines, including tocilizumab, alongside steroids (Table III). Importantly, recent evidence underscores the significance of early intervention with nonsteroidal immunosuppressive therapies over steroids for treating irAEs (15). In this case, the onset of HLH during lymphocyte suppressive therapy involving high-dose steroids (1 mg/kg) and MMF, indicates a cytokine storm. Steroid pulses were administered to inhibit the cytokine cascade, and the anti-IL-6 antibody, tocilizumab, was used during steroid tapering. Additionally, cyclosporine was employed to suppress T cells through a mechanism distinct from that of steroids, contributing to successful treatment.

In conclusion, we encountered cases of HLH and DIC associated with ICI administration during preoperative systemic chemotherapy for breast cancer. HLH is a rare but severe life-threatening complication of checkpoint inhibitor therapy that underscores the need for vigilance and preparedness. Our understanding of the full spectrum of side effects associated with ICIs that have a relatively short history of use is incomplete. Anticipation of the underlying pathophysiology and identification of appropriate treatment strategies are of paramount importance. Prospective data are crucial for assessing the efficacy of nonsteroidal immunosuppressive therapies in conjunction with steroids.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YK wrote the manuscript. YK, AS, TT and HS analyzed and interpreted the patient's clinical data for the manuscript. YK, AS, TT, HH, KH, YH, DK, RN, HS, AH and CS contributed to collecting the relevant literature and to data analysis, and reviewed and critically interpreted the information. AS and CS confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of this case report.

Competing interests

The authors declare that they have no competing interests.

References

1. Hudis CA and Gianni L: Triple-negative breast cancer: An unmet medical need. Oncologist 16 (Suppl 1): S1-S11, 2011.
2. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, *et al*: Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet 384: 164-172, 2014.
3. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, *et al*: Pembrolizumab for early triple-negative breast cancer. N Engl J Med 382: 810-821, 2020.
4. Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, *et al*: Event-free survival with pembrolizumab in early triple-negative breast cancer. N Engl J Med 386: 556-567, 2022.
5. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, Zhao S, Das S, Beckermann KE, Ha L, *et al*: Fatal toxic effects associated with immune checkpoint inhibitors: A systematic review and meta-analysis. JAMA Oncol 4: 1721-178, 2018.
6. Kramer R, Zaremba A, Moreira A, Ugurel S, Johnson DB, Hassel JC, Salzmann M, Gesierich A, Weppler A, Spain L, *et al*: Hematological immune related adverse events after treatment with immune checkpoint inhibitors. Eur J Cancer 147: 170-181, 2021.
7. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, Coppo P and Hejblum G: Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol 66: 2613-2620, 2014.
8. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J and Janka G: HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 48: 124-131, 2007.
9. Dupré A, Michot JM, Schoeffler A, Frumholtz L, Baroudjian B, Delyon J, Lebbe C and Lambotte O: Haemophagocytic lymphohistiocytosis associated with immune checkpoint inhibitors: A descriptive case study and literature review. Br J Haematol 189: 985-992, 2020.
10. Noseda R, Bertoli R, Müller L and Ceschi A: Haemophagocytic lymphohistiocytosis in patients treated with immune checkpoint inhibitors: Analysis of WHO global database of individual case safety reports. J Immunother Cancer 7: 117, 2019.
11. Planas R, Felber M, Vavassori S and Pachlopnik Schmid J: The hyperinflammatory spectrum: From defects in cytotoxicity to cytokine control. Front Immunol 14: 1163316, 2023.
12. Brahmer JR, Abu-Sbeih H, Ascierto PA, Brufsky J, Cappelli LC, Cortazar FB, Gerber DE, Hamad L, Hansen E, Johnson DB, *et al*: Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 9: e002435, 2021.
13. Michot JM, Lazarovici J, Tieu A, Champiat S, Voisin AL, Ebbo M, Godeau B, Michel M, Ribrag V and Lambotte O: Haematological immune-related adverse events with immune checkpoint inhibitors, how to manage? Eur J Cancer 122: 72-90, 2019.
14. Faleck DM, Dougan M, Tello M, Grossman JE, Moss AC and Postow MA: Accelerating the evolution of immune-related enterocolitis management. J Clin Oncol 41: 3110-3115, 2023.
15. Kurozumi A, Takahashi H, Watanabe T and Iwasaki Y: Two cases of lung cancer with hemophagocytic lymphohistiocytosis caused by immune checkpoint inhibitors. Thorac Cancer 12: 1625-168, 2021.
16. Sackstein P, Zaemes J and Kim C: Pembrolizumab-induced cytokine release syndrome in a patient with metastatic lung adenocarcinoma: A case report. J Immunother Cancer 9: e002855, 2021.
17. Okawa S, Kayatani H, Fujiwara K, Ozeki T, Takada K, Iwamoto Y, Minami D, Sato K and Shibayama T: Pembrolizumab-induced autoimmune hemolytic anemia and hemophagocytic lymphohistiocytosis in non-small cell lung cancer. Intern Med 58: 699-702, 2019.
18. Laderian B, Koehn K, Holman C, Lyckholm L and Furqan M: Association of hemophagocytic lymphohistiocytosis and programmed death 1 checkpoint inhibitors. J Thorac Oncol 14: e77-e78, 2019.

19. Honjo O, Kubo T, Sugaya F, Nishizaka T, Kato K, Hirohashi Y, Takahashi H and Torigoe T: Severe cytokine release syndrome resulting in purpura fulminans despite successful response to nivolumab therapy in a patient with pleomorphic carcinoma of the lung: A case report. J Immunother Cancer 7: 97, 2019.
20. Hantel A, Gabster B, Cheng JX, Golomb H and Gajewski TF: Severe hemophagocytic lymphohistiocytosis in a melanoma patient treated with ipilimumab + nivolumab. J Immunother Cancer 6: 73, 2018.
21. Satzger I, Ivanyi P, Länger F, Kreipe HH, Schaper-Gerhardt K, Beutel G, Cornberg M and Gutzmer R: Treatment-related hemophagocytic lymphohistiocytosis secondary to checkpoint inhibition with nivolumab plus ipilimumab. Eur J Cancer 93: 150-153, 2018.
22. Sadaat M and Jang S: Hemophagocytic lymphohistiocytosis with immunotherapy: Brief review and case report. J Immunother Cancer 6: 49, 2018.
23. Takeshita M, Anai S, Mishima S and Inoue K: Coincidence of immunotherapy-associated hemophagocytic syndrome and rapid tumor regression. Ann Oncol 28: 186-189, 2017.
24. Malissen N, Lacotte J, Du-Thanh A, Gaudy-Marqueste C, Guillot B and Grob JJ: Macrophage activation syndrome: A new complication of checkpoint inhibitors. Eur J Cancer 77: 88-89, 2017.
25. Shah D, Shrestha R, Ramlal R, Hatton J and Saeed H: Pembrolizumab associated hemophagocytic lymphohistiocytosis. Ann Oncol 28: 1403, 2017.