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CASE SERIES

PD-1 Blockade-Induced Hemophagocytic Lymphohistiocytosis, a Dilemma Therapeutic Outcome in 2 Patients with CAEBV: A Case Series

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Abstract: Hemophagocytic lymphohistiocytosis (HLH), whether primary or secondary, is a rare and fatal clinical syndrome of uncontrolled immune activation and inflammatory cascade. Immune checkpoint inhibitors (ICIs) induced HLH has no standard diagnostic and treatment guidelines. Early diagnosis and appropriate treatment according to different disease backgrounds are crucial. Herein, we first report 2 cases of patients with chronic active Epstein-Barr virus infection (CAEBV) who developed HLH after the use of sintilimab, a monoclonal antibody against programmed cell death protein 1 (PD-1), and the DEP (liposomal doxorubicin, etoposide, methylprednisolone) chemotherapy regimen in combination with ruxolitinib were used to successfully control the disease.

Keywords: PD-1 blockade, hemophagocytic lymphohistiocytosis, CAEBV, case report case series

Introduction

Hemophagocytic lymphohistiocytosis is a syndrome of excessive inflammation and tissue destruction due to abnormal immune activation. The immunological abnormalities are thought to result from the absence of normal downregulation driven by activated macrophages and lymphocytes. In HLH, natural killer cells and cytotoxic lymphocytes fail to eliminate activated macrophages. This lack of normal feedback regulation results in activation of CD8+ T cells and macrophages activation with highly elevated levels of interferon gamma (IFN-γ) and other cytokines that drive the pathology of HLH. HLH occurs either as primary HLH or as acquired HLH. Both terms can be triggered by infection or other immune-activating events.[1,2]

Currently, programmed cell death receptor 1 (PD-1) blockade has been widely used in numerous solid tumors and refractory/relapsed Hodgkin lymphoma, and has expanded the treatment landscape of these tumors due to its efficacy. There are now several reports of CAEBV being successfully treated with PD-1 blockade.[3,4] PD-1 blockade can bind to PD-1, preventing it from binding to programmed death ligands 1 (PD-L1) and 2 (PD-L2), and restoring CD8+ T cells function.[5] However, persistent off-target activation of CD8+ T cells can lead to multi-organ failure as immune-related adverse events (irAEs) or ultimately induce HLH.[6] Nevertheless, cases of immunotherapy-induced HLH triggered by immunotherapy in CAEBV patients are rarely reported. In this report, we present 2 cases of CAEBV patients diagnosed with HLH induced by sintilimab during immunotherapy. The disease was completely controlled by initiation of DEP chemotherapy regimen combined with ruxolitinib after appropriate and timely diagnosis.

Case Presentation

Patient 1

A 35-year-old man with a 1-year history of intermittent fever was admitted to our center on 19 January 2021. Approximately 1 year before, the patient was admitted to a local hospital for intermittent fever. Abdominal ultrasound

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showed splenomegaly. Laboratory tests showed an EBV-DNA loads of 1.0E+06 copies/mL in peripheral blood mononuclear cells (PBMC). He was treated with dexamethasone at the local hospital without improvement. On admission, his vital signs were normal with an unremarkable physical examination except for inguinal lymphadenoma and splenomegaly. Initial workup revealed the EBV-DNA loads in plasma and PBMC of 1.9E+04 copies/mL and 3.3E+06 copies/mL, respectively. Lymphocyte subgroups of EBV infection showed CD3+CD4+ cells 3.6E+04 copies/mL, CD3+CD8+ cells 0, CD3-CD19+ cells 0, CD56+ cells 7.4E+05 copies/mL. Histopathological examination of the left inguinal lymph nodes revealed EBV-positive T cell proliferation disease (stage 1) (EBV^+ T-LPD 1). An initial complete blood count revealed a white blood cell (WBC) count of $2.99*10^9$/L, a neutrophil granulocyte (GR) count of $1.96*10^9$/L, a hemoglobin (Hb) count of 120 g/L, and a platelet (PLT) count of $149*10^9$/L. The results of the biochemical tests were as follows; alanine aminotransferase (ALT) 37 U/L (normal; 9–50 U/L), aspartate aminotransferase (AST) 36 U/L (normal; 58–40 U/L), total bilirubin (TBIL) 13.9 umol/L (normal; 3.4–17.1 umol/L), and lactate dehydrogenase (LDH) 248 U/L (normal; 120–250 U/L). Whole exome sequencing (WES) revealed no immunodeficiency mutations, and positron emission tomography/computed tomography (PET/CT) showed no enlarged and hypermetabolic lesions except for inguinal lymph nodes, and the bone marrow biopsy showed no evidence of lymphoma. This patient was diagnosed with CAEBV based on the history of fever, lymphadenoma, splenomegaly, laboratory findings and lymph nodes biopsy pathology. He was registered to receive sintilimab (Suchow Xinda Biotechnology Co.; Ltd., Suchow, China) and lenalidomide at a dose of 200 mg via IV infusion every 2 to 3 weeks for induction therapy in the context of a clinical trial (NCT04518982). Fever occurred when he received the first dose of sintilimab and was controlled by 10 mg of ruxolitinib orally twice a day, which was used continuously throughout the entire treatment. After the first dose of sintilimab, the EBV-DNA loads in plasma and PBMC decreased to 1.0E+04 copies/mL and 1.4E+04 copies/mL, respectively. On the same day as he received the second dose of sintilimab, he developed a high-grade fever (39.1°C) with no obvious accompanying symptoms. A full blood count and contrast-enhanced computed tomography (CT) scan of the neck, chest, abdomen and pelvic cavity were performed to evaluate the cause of fever. On day 2 of the fever, laboratory tests revealed bi-lineage cytopenia (WBC $2.84*10^9$/L, GR $0.97*10^9$/L, Hb 104 g/L, PLT $48*10^9$/L), hypertriglyceridemia (3.2 mmol/L) and hyperferritinemia (1197 ng/mL) (24–336 ng/mL), high level of ALT (347 U/L) and AST (245 U/L), high levels of soluble CD25 (sCD25) (9495 pg/mL) (<6400 pg/mL) and low NK cell activity (12.04%) (>15.11%); bone marrow aspiration showed hemophagocytosis. The EBV-DNA loads had no significant change in plasma or PBMC. No evidence of infection was found in laboratory or radiological tests. Seven out of eight criteria for HLH with hepatic impairment were met: fever, cytopenia in 2 lines, hypertriglyceridemia, hyperferritinemia, bone marrow hemophagocytosis, high sCD25 levels and low NK cell activity. The diagnosis of sintilimab-related hemophagocytic lymphohistiocytosis (HLH) was made based on the HLH-2004 guideline. Therefore, sintilimab was permanently discontinued, and the HLH-directed therapeutic DEP regimen (liposomal doxorubicin 25 mg/m2/day, day 1; etoposide 100 mg/m2/day, day 1; and methylprednisolone 1.5 mg/kg/day for days 1 to 3, which was then sharply reduced to 8 mg/day for the remaining days until the next therapy session) was initiated to control the activation of the cytokine storm. As soon as the DEP regimen was applied, the patient's temperature returned to normal. On the 7th day of DEP, the patient's liver function improved significantly, platelets returned to $140*10^9$/L, ferritin decreased to 408ng/mL, and sCD25 decreased to 3200pg/mL. The EBV-DNA loads in plasma and PBMC was 3.3E+04 copies/mL and 2.4E+04 copies/mL, respectively. Unfortunately, this patient refused allogeneic hematopoietic stem cell transplantation (allo-HSCT) for economic reasons. Therefore, an additional 5 courses of DEP chemotherapy were given to control the HLH. After 3 months of chemotherapy, he was given 8 mg of methylprednisolone orally twice a day and 10 mg of ruxolitinib twice a day for 3 months. He eventually died from the progression of the disease.

Patient 2

A 20-year-old man was admitted to our hospital on 24 May 2021 because of intermittent high-grade fever and hepatic insufficiency for 9 months. Before being admitted to our hospital, he had been on methylprednisolone for 9 months at the local hospital. Diagnostic tests performed at the local hospital were as follows; EBV-DNA loads in plasma and PBMC were 4.9E+03 copies/mL and 4.2E+05 copies/mL, respectively; EBV-infected lymphocyte subgroups showed CD56+ cells 3.0E+06 copies/mL; abdominal ultrasound showed hepatosplenomegaly; pathological examination of liver, cervical

lymph node and terminal ileum all showed positive EBV-encoded small RNA (EBER). Biochemical test results showed ALT 78.4 U/L, AST 115 U/L, TBIL 66.8 umol/L. Routine blood tests, ferritin and fibrinogen were all within the normal limits. Bone marrow cytology and flow cytometry assays showed that there was no abnormality in the bone marrow. Besides, WES was also done and no immunodeficiency gene was found. Meanwhile, whole-body enhanced CT had been performed and showed no evidence of tumor or lymphoma. Finally, the patient was diagnosed with CAEBV according to the 2017 WHO classification.[7] Therefore, after admission, sintilimab (NCT04518982) was administered at a dose of 200 mg every 2 weeks in combination with lenalidomide 10mg once daily. High fever (41.0°C) occurred immediately after the first infusion of sintilimab. On day 3, tri-lineage cytopenia (WBC $0.89*10^9$/L, GR $0.23*10^9$/L, Hb 86 g/L, PLT $76*10^9$/L), hypofibrinogenemia (fibrinogen 1.13 g/L), hyperferritinemia (ferritin 2315 ng/mL), and sCD25 up to 15,405 pg/mL were observed in line. On day 5, total bilirubin increased from 22.05 umol/L to 89.98 umol/L, with alanine aminotransferase raised from 64.2 U/L to 237 U/L and aspartate aminotransferase from 44.0 U/L to 667.0 U/L. Cytokine expression analysis showed IFN-γ increased to 59.2 pg/mL (3–30.3 pg/mL) and interleukin (IL)-1 RA up to 4476 pg/mL (0–908.3 pg/mL), with high levels of IL-18 1412 pg/mL (0–319 pg/mL). Extensive investigations for autoimmune diseases and infectious diseases were negative. The EBV-DNA loads in plasma and PBMC was 7.2E+03 copies/mL and 8.8E+04 copies/mL, respectively. Given the above changes, the diagnosis of HLH was considered. A bone marrow biopsy was performed and showed hemophagocytosis and atypical lymphocytes. Finally, HLH was confirmed and sintilimab was stopped. After the diagnosis, the DEP regimen combined with ruxolitinib (10mg, twice a day) was administered. After chemotherapy, his temperature returned to normal and his HLH was well controlled. The EBV-DNA loads in plasma and PBMC was 1.3E+04 copies/mL and 3.4E+04 copies/mL, respectively, without significant reduction compared to before. After a further 2 courses of the DEP regimen combined with ruxolitinib, he underwent allo-HSCT and died from uncontrolled gastrointestinal bleeding after 2 months.

Discussion

Acquired HLH is usually caused by a variety of conditions, including bacterial and viral infections, malignancies, and autoimmune diseases.[8] Some other unusual causes can also trigger HLH, such as pregnancy, chemotherapy, and immunotherapy.[9,10] Recently, ICIs-associated HLH has been reported in patients with various solid tumors following administration of ICIs, and there are no standard diagnostic and treatment guidelines. In these 2 cases, we first reported 2 patients with CAEBV who developed HLH after the use of sintilimab, and the DEP chemotherapy regimen combined with ruxolitinib was used to successfully control the life-threatening hyper-inflammatory condition. In these 2 patients, fever was the first symptom, followed by a decrease in WBC and PLT and an increase in ALT and AST. HLH should be suspected when a patient on ICIs develops unexplained fever, cytopenia, and elevated transaminases.

The presentation of HLH is typically defined by hyperactivation of the immune system and hypercytokinemia. The immunological abnormalities are thought to result from the uncontrolled activation of CD8+ T cells and macrophage activation with highly elevated levels of IFN-γ and other cytokines.[11] CAEBV is a prototype of EBV-associated T or NK cell lymphoproliferative diseases (EBV+T/ NK-LPDs) with high mortality, and the only proven effective treatment is allo-HSCT.[12] However, given the high risk and cost, disease relapse after transplantation, donors shortage and other factors associated with allo-HSCT, programmed cell death protein-1 (PD-1) blockade has received attention as an emerging and effective treatment strategy.[4,13] It has been reported that EBV-associated lymphomas have a virally mediated overexpression of PD-1, which making them sensitive to PD-1 blockade.[14] In previous reports of CAEBV patients treated with PD-1-targeted therapy, an apparent recovery in the proportion of CD8+ T cells and a significant decrease in PD-1 expression on CD8+ T cells can be observed. This supports the therapeutic effect of PD-1 blockade by restoring the activation and proliferation of CTLs.[15] However, boosting the immune system is a double-edged sword that can prolong patient survival, while immune activation can cause numerous immune-related adverse events (irAEs), and sustained immune activation eventually induces HLH.[16,17] In addition to this, we compared these 2 patients with the other 32 patients enrolled in this clinical trial but without HLH and found that the EBV-DNA load in plasm of these 2 patients was higher than 1.0E+04 copies/mL. EBV-infected cells that acquire alterations involving PD-1/PD-L1 are thought to effectively evade host immune surveillance,[18] and the administration of PD-1 inhibitor may have removed this

control, facilitating cytokine secretion and leading to the development of HLH. Elevated IFN-γ in patient 2 may proves this. Extensive EBV-DNA load in plasma may be more intrinsic to HLH when receiving anti-PD1.

There are currently no standard treatment guidelines for anti-PD1-induced HLH, especially in CAEBV patients. The therapeutic goal in these patients is to rapidly suppress the inflammatory storm to prevent further organ damage. High-dose glucocorticoids, etoposide, and cyclosporine are the core therapeutic drugs of the treatment regimen based on HLH-94 and 2004.[19] However, the HLH-94 and the HLH-2004 are mainly based on pediatric genetic forms of HLH, and the efficacy and outcomes of these regimens in some anti-PD1-induced HLH cases are still questionable.[20] There have also been some reports of patients with ICIs-induced HLH who died despite receiving high-dose steroid therapy.[21] Furthermore, a 36-year-old patient with metastatic right atrial angiosarcoma was progressed to HLH after treatment with the PD-1 blockader toripalimab and pazopanib and was successfully treated with one dose of infliximab and 2 TPE procedures.[20] Therefore, appropriate treatment must be considered based on clinical features and symptoms needs to be taken into account. The DEP regimen is a modified regimen based on the HLH-94 regimen, by using etoposide and corticosteroids as the core treatment, increasing the dose of corticosteroids for pulse therapy, and using liposomal doxorubicin as an important induction therapy, which have a stronger multi-immunosuppression.[22] Etoposide is a widely used chemotherapeutic agent that inhibits topoisomerase II. A study of a murine model of HLH with a perforin deficiency suggested that the therapeutic mechanism of etoposide may involve potent selective deletion of activated T cells and efficient suppression of inflammatory cytokine production.[23] Doxorubicin is a broad-spectrum cytotoxic chemotherapeutic agent that can inhibit lymphocyte production. When liposomal doxorubicin is administered in the body, it can be phagocytized mainly by leukocytes, monocytes, and macrophages in the reticuloendothelial system and bind to cell DNA, destroying the synthesis and division of cell nucleic acids and leading to cell death, thus inhibiting the excessive activation of monocytes and macrophages.[24] Previous studies have confirmed that the DEP regimen is superior to the HLH-1994 regimen as first-line therapy for lymphoma-associated HLH, and has a clear therapeutic effect on CAEBV and EBV-HLH.[25–27] The final common pathway in HLH pathogenesis is characterized by the overproduction of T-cell-derived cytokines, including interferon-γ (IFN-γ), IL-6, and others, as well as the phosphorylation-dependent activation of the Janus family kinases JAK1 and JAK2.[28] Ruxolitinib can block the JAK-STAT pathway and reduce HLH-associated immunopathology by dampening downstream signaling of numerous HLH-associated cytokines. Considering that the 2 patients' disease background is CAEBV, we applied the DEP regimen combined with ruxolitinib instead of the HLH-94/04 regimen with the following considerations: suppression of immune activation and reduction of EBV-DNA concentration. In particular, after the treatment, the duration of HLH remission in 2 patients is 6 months and 2 months, respectively.

In conclusion, in our reports, anti-PD1 therapy may be a double-edged sword in CAEBV patients, and ICIs-induced HLH is a dilemma in terms of therapeutic outcome. For this type of patient with HLH, the DEP regimen combined with ruxolitinib may be a good choice to control the hyper-inflammatory state. Moreover, with the widespread use of anti-PD-1, the patient population may expand, and we need to learn more about its side effects in different patient populations. Meanwhile, systemic treatment strategies for ICIs-induced HLH need to be explored in further prospective trials.

Ethics Approval and Consent to Participates

The research protocol for this study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University. The ethics approval number is 2022-P2-079/DR20220079. 2 patients provided written informed consent for their personal or clinical details along with any identifying images to be published in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest.

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