Case Report

CLINICAL INVESTIGATION

# A case report of Hemophagocytic Lymphohistiocytosis (HLH) brought on by EBV reactivation on durvalumab

## Abstract

**Background:** The condition known as hemophagocytic lymphohistiocytosis poses a major threat to life. So, in order to decrease mortality, it is crucial to understand how to identify it and treat it swiftly.

**Methods:** In this paper, a case of a 60-year-old female patient with recurrent ovarian cancer is presented. Durvalumab, Bevacizumab, Olaparib, and Durvalumab were all used in her treatment. Her syndrome, which was promptly identified as Hemophagocytic Lymphohistiocytosis (HLH), included fever, dyspnea, anaemia, and thrombocytopenia. The patient's clinical condition was able to normalise thanks to the quick start of the Etoposide, Dexamethasone, and Type G Immunoglobulin treatments.

**Results:** We propose two potential origins for this syndrome: first, an infectious origin caused by EBV, as well as an immunological origin caused by durvalumab. The patient's clinical condition was able to normalise thanks to the quick start of the Etoposide, Dexamethasone, and Type G Immunoglobulin treatments. To implement a curative treatment as soon as feasible with a reduction in its mortality as our goal, it is crucial to raise awareness about HLH and its causes.

**Keyword: Haemophagocytic lymphohistiocytosis • Pancytopenia • Etoposide • Dexamethasone • Immunotherapy • Viral infection**

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## Introduction

Today, immunotherapies are accepted cancer therapy options. These are cutting-edge treatments that have completely altered the conventional prognosis for many different forms of cancer. Unfortunately, there is some information that is inadequate, especially in regards to their harmful effects, which can be fatal. Due to the surge of immunotherapy indications, the latter are becoming more prevalent. So, it would appear crucial to recognise them in order to stop them. Haemophagocytic Lymphohistiocytosis (HLH), one of the potentially fatal side effects of immunotherapy, is challenging to identify due to its vague symptoms. In our publication, we discuss our experiences using HLH in the context of BOLD (Bevacizumab, Olaparib, Durvalumab) combination therapy for the treatment of metastatic ovarian cancer. As of right now, this is the only report of HLH while receiving immunotherapy and EBV reactivation. So, we can consider what effect EBV may have on the pathophysiology of this HLH and what potential therapeutic benefits it may have [1-4].

## Case Presentation

We describe a 60-year-old woman who was treated for ovarian cancer that had returned. She was in relapse after receiving multiple lines of therapy (lymph node metastases and peritoneal carcinosis). She was then included to the BOLD protocol (ClinicalTrials.gov Identifier: NCT04015739). Patients with high-grade serous or endometrioid ovarian tumours or other high-grade non-mucinous epithelial tumours who have received at least one prior platinum-taxane-based chemotherapy regimen and who have platinum-resistant disease are being studied to determine the safety and effectiveness of the combination of bevacizumab, olaparib, and durvalumab (MEDI 4736). (PRR) or Platinum-Sensitive Relapse (PSR), regardless of the line of chemotherapy administered at the time of relapse.

The patient was given a first course of BOLD, but six weeks later (the fifth course), he showed signs of poor clinical tolerance, including a 39°C fever and dyspnea with the slightest exertion. Cardiopulmonary auscultations did not find anything out of the ordinary. During probing, we

discovered splenomegaly along with a known tumor-related left supra-clavicular adenopathy.

With a CRP of 174 mg/L, we discovered pancytopenia (haemoglobin 6.7 g/L, leukocytes 1.26 G/L, including neutrophils 0.66 G/L, and platelets 12 G/L) biologically. Schizocytes were not visible on the blood smear, however the haptoglobin was compressed with LDH at 1440. The liver workup has been changed (AST 219, ALT 183, GGT, 709, PAL 384, total bilirubin 26). 28 g/L of serum ferritin was recorded.

Blood cultures plus a urinary cytobacteriological examination and imaging (CT scan) tests for bacteria were negative. This biochemical and clinical picture led to the diagnosis of HLH. Immunotherapy, platelet transfusions, and blood transfusions have to be stopped because of the patient's low clinical tolerance.

Two attempts at myelograms were undertaken as part of the etiological work-up, but they proved inconclusive, ruling out either myelodysplasia or leukaemia. Apart for an ancient serology against EBV (recognised by positive anti-VCA IgG antibodies but negative anti-VCA IgM), all of the different serologies (Hepatitis B, Hepatitis C, CMV, PVB19, and HHV6) were negative. An EBV viral load was evident at 4.7 log. This patient still has macrophagic activation syndrome while receiving immunotherapy, and EBV virus reactivation is a contributing reason.

Etoposide was administered once along with 20 mg of dexamethasone and 0.4 mg/kg of type G immunoglobulin. After starting the medication, the patient's clinical status was normalised after 48 hours. For several weeks, her main symptom was dyspnea; however, she eventually went home with biweekly biological monitoring. At the 30-day checkup, the patient had no symptoms (apart from the continued presence of the left supra-clavicular lymph node) and her biological profile had returned to normal, particularly her haemoglobin level of 11.1 and her CRP level of 7 mg/L.

## Discussion

The fact that immunotherapy and viral infection are two of the numerous aetiologies of HLH is significant because they can be avoided [3-6]. Nevertheless, when treated early, they have a fair prognosis. In our situation, immuno-induced HLH began to manifest together with EBV infection. The first HLH on durvalumab was reported in this publication.

EBV-HLH had a terrible prognosis until recently because no antiviral therapy had been proven to be efficient. Regardless of where the HLH originated, strong doses of dexamethasone and etoposide (VP-16) have now been shown to be effective (immuno- or virus-induced). Estimated survival rates ranged from 59% to 75%. Administration within two days of the peak ferritin level was the main predictor of response.

A few weeks after the start of treatment, the majority of case reports on immuno-induced HLH that have been published to date confirm a return to clinical and biological normality [6-12].

Nonetheless, there is still a considerable chance that Etoposide will cause acute myeloid leukaemia. Cyclosporine is a therapy option that some protocols provide, although no demonstrable benefit has been shown. It prevents exposure to chemotherapy and the danger of Etoposide-related bone marrow aplasia. Etoposide may be less immunosuppressive to T cells and eliminates the possibility of serious responses that can be related to cyclosporine.

Etoposide and Dexamethasone Target T and NK cells, whilst Rituximab inhibits B cells (which serve as a reservoir for EBV) (and thus promote EBV clearance and elimination). According to one study, Rituximab was highly effective in treating patients whose B cells were harmed by EBV. Hence, it is ineffective in patients whose NK and T cells are affected by the EBV virus.

Studies have demonstrated the therapeutic value of drugs like Emapalumab and Ruxolitinib in the treatment of HLH. Their method of action works against cytokines rather than cells. The ability of these latter molecules to suppress Etoposide in the treatment of HLH should therefore be determined in further research.

Also, one research has tracked Nivolumab's effectiveness in the treatment of HLH. Nivolumab was discovered to be efficient against all sorts of virus-affected cells (T, B, NK). The importance of anti-PD compounds in the therapy of MAS is suggested by these findings.

Several factors have been linked to an increased risk of immuno-induced HLH, according to a retrospective study They primarily include being older than 60, being a man, and how long immunotherapy has been used. The PRFAV gene polymorphism, in particular, plays a role in the development of HLH.

In order to identify the clinical warning signals as soon as feasible, it is crucial to be aware of additional considerations, including the immunotherapy risk in the event of HLH that has been demonstrated.

HLH can be brought on by cancer, specifically paraneoplastic HLH. The latter is still an uncommon issue with a one-year survival rate of about 25%. Due to the rarity and non-specific nature of this illness, there is a significant delay in diagnosis. Its identification is crucial for starting appropriate treatment as soon as feasible.

In this instance, etiological treatment is the foundation of HLH treatment: a study describing MAS in an ovarian cancer patient. Tumor excision and medical care led to complete symptom relief. Unfortunately, malignancy-triggered HLH is associated with increased mortality.

An initial diagnosis of HLH in nine paediatric and young adult patients delayed the identification of an underlying cancer and frequently postponed really curative treatment, according to a study. All of these

patients ultimately passed away from aggressive cancer and multiorgan failure. Both full-dose chemotherapy patients are still alive and have no signs of illness. These cases emphasise how crucial it is to distinguish HLH caused by cancer in order to reduce morbidity and mortality [13].

According to one juvenile series, the median overall survival at 6 months was 1.2 years, and the majority of the deceased patients had active cancer at the time of death [14, 15].

## Conclusion

In this article, we discuss our experiences treating st-

-age B ovarian cancer patients with immuno- and virus-induced HLH with etoposide, dexamethasone, and immunoglobulin G. Although more research is required, new molecular targets seem to offer a treatment option with fewer drawbacks than Etoposide.

Since the cause of HLH is treatable, it is crucial to start therapy as soon as possible. In other situations, it's important to understand how to spot and treat it quickly because the prognosis is still bad and the survival percentage is low after a year.

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