Annals of Clinical Case Reports

Case Report
Published: 01 Feb, 2023

Hemophagocytic Lymphohistiocytosis (HLH) due to EBV Reactivation on Durvalumab: A Case Report

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Abstract

Background: Hemophagocytic lymphohistiocytosis is a serious life-threatening event. It is therefore essential to know how to recognize it and treat it quickly in order to reduce mortality.

Methods: This study present a case of a 60-year-old female patient followed in oncology for a recurrent ovarian cancer. She was undergoing a treatment with Durvalumab Bevacizumab, Olaparib and Durvalumab. She subsequently developed fever, dyspnea, anemia and thrombocytopenia, syndrome that was quickly diagnosed as Hemophagocytic Lymphohistiocytosis (HLH). The rapid initiation of treatment with etoposide, dexamethasone and Type G immunoglobulin allowed a normalization of the patient's clinical condition.

Discussion: We postulate two causes that could have led to this syndrome: First, the infectious origin by EBV, but also the immunological origin by durvalumab. The rapid initiation of treatment with etoposide, dexamethasone and Type G immunoglobulin allowed a normalization of the patient's clinical condition. It is essential to make people aware of HLH and its causes in order to introduce a curative treatment as soon as possible; our objective being the reduction of its mortality.

Keywords: Hemophagocytic lymphohistiocytosis; Pancytopenia; Etoposide; Dexamethasone; Immunotherapy; Viral infection

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Received Date: *09 Jan 2023*
Accepted Date: *24 Jan 2023*
Published Date: *01 Feb 2023*

Citation:
Maury A, Corbaux P, Reverdy T, Tartas S, Bonin N, You B, et al. Hemophagocytic Lymphohistiocytosis (HLH) due to EBV Reactivation on Durvalumab: A Case Report. Ann Clin Case Rep. 2023; 8: 2387.
ISSN: 2474-1655.

Introduction

Immunotherapies are now recognized treatments in the fight against cancer. They are innovative therapies that have revolutionized the established prognosis of many types of cancer. However, some information is lacking, particularly concerning their adverse effects, which can be life-threatening. The latter are on the rise due to the increase in the number of indications for immunotherapies. It therefore seems essential to identify them in order to prevent them. One of the adverse effects of immunotherapy that can be life-threatening is Hemophagocytic Lymphohistiocytosis (HLH) [1-4], which is difficult to diagnose because of its non-specific symptoms. In our article, we report our experience with HLH during the management of metastatic ovarian cancer with a BOLD (Bevacizumab, Olaparib, Durvalumab) combination therapy. Currently, this is the only existing report of HLH under immunotherapy but also with EBV reactivation. We can thus ask ourselves the question of what is the influence of EBV on the pathogenesis of this HLH and what practical therapeutic consequence it can generate.

Case Presentation

We present the case of a 60-year-old female patient followed in oncology for a recurrent ovarian cancer. She had already received several lines of treatment and was in relapse (lymph node metastases and peritoneal carcinosis). She was then included in a protocol called BOLD (ClinicalTrials.gov Identifier: NCT04015739). It is a trial evaluating the safety and efficacy of the combination of bevacizumab, Olaparib and Durvalumab (MEDI 4736) in patients with high-grade serous or endometrioid ovarian tumor or other high-grade non-mucinous epithelial tumor, who have received at least one prior platinum-taxane-based chemotherapy regimen, and who have Platinum-Resistant Disease (PRR) or Platinum-Sensitive Relapse (PSR), regardless of the line of chemotherapy administered at the time of relapse. The patient received a first course of BOLD but presented 6 weeks later (fifth course) a poor clinical tolerance with the appearance of a fever of 39° and dyspnea at the slightest effort. Cardiopulmonary auscultations did not reveal any abnormality. On

palpation we found splenomegaly with a known left supra-clavicular adenopathy of tumoral origin. Biologically, we found pancytopenia (hemoglobin 6.7 g/L, leukocytes 1.26 G/L including neutrophils 0.66 G/L, platelets 12 G/L) with a CRP 174 mg/L. The blood smear did not show any Schistocytes but the haptoglobin was collapsed with LDH at 1440). The liver workup is altered (AST 219, ALT 183, GGT, 709, PAL 384, total bilirubin 26). Serum ferritin was measured at 28 g/L. Imaging (CT scan) and bacteriological examinations (blood cultures + urinary cytobacteriological examination) were negative. Given this clinical and biological picture, the diagnosis of HLH was evoked. The patient's poor clinical tolerance led to the suspension of immunotherapy and platelet and blood transfusions.

Concerning the etiological work-up, two attempts at myelograms were made but were inconclusive, eliminating however a leukemia or myelodysplasia. The various serologies (Hepatitis B, Hepatitis C, CMV, PVB19 and HHV6) were negative except for an old serology against EBV (identified with positive anti-VCA IgG antibodies but negative anti-VCA IgM) and an EBV viral load was detectable at 4.7 log. Macrophagic activation syndrome under immunotherapy is retained in this patient with EBV viral reactivation as a favoring factor. A single course of Etoposide was given with 20 mg of dexamethasone and a dose of 0.4 mg/kg of type G immunoglobulin. The patient's clinical condition was normalized within 48 h after initiation of treatment. Her only symptom was dyspnea for several weeks and she finally returned home with biweekly biological monitoring. At the 30th day follow-up, the patient was symptom free (except for the persistence of the left supra-clavicular lymph node) and her biological check-up was normalized (notably Hb 11.1 and CRP 7 mg/L).

Discussion

Among the many etiologies of HLH, immunotherapy [4] and viral infection [3-6] are important to know because they are preventable. Moreover, they have a good prognosis when managed in time. In our case, the onset of immuno-induced HLH was concomitant with EBV infection. This article is the first to report a HLH on durvalumab. The prognosis of EBV-HLH was until recently appalling because no antiviral treatment had been shown to be effective. The use of high-dose dexamethasone [2] and etoposide (VP-16) [3] has finally proven to be effective, regardless of the origin of the HLH (immuno- or virus-induced). The estimated survival rate was 59% to 75%. The main predictive factor of response was administration within 2 days of the highest ferritin concentrations. The majority of case reports published to date concerning immuno-induced HLH confirm a clinical and biological normalization a few weeks after initiation of treatment [1-12]. However, the risk of Etoposide-induced acute myeloid leukemia remains significant. Some protocols offer the option of cyclosporine as a treatment, but no clear benefit has been demonstrated. It avoids exposure to chemotherapy and the risk of bone marrow aplasia associated with etoposide. Etoposide avoids the risk of severe reactions that can be associated with cyclosporine, and may be less immunosuppressive to T cells [8]. Rituximab [7] suppresses B cells (which are a reservoir for EBV), whereas Etoposide and Dexamethasone target T and NK cells (and thus promote EBV clearance and elimination [9]). One study concluded that Rituximab was very effective in patients whose B cells were affected by EBV. It is therefore not effective in patients whose EBV virus affects T and NK5 cells. Some studies have shown the therapeutic role of molecules such as Emapalumab or Ruxolitinib in the management of HLH. Their mechanism of action is not cellular but rather against cytokines. It would therefore be useful in future studies to determine whether these latter molecules are sufficiently effective to suppress Etoposide in the management of HLH.

In addition, one study has monitored the efficacy of Nivolumab in the treatment of HLH. Nivolumab was found to be effective against all subtypes of cells affected by the virus (T, B, NK). These results suggest the importance of anti-PD1 molecules in the treatment of MAS [10]. A retrospective study [4] identified certain factors that increase the risk of immuno-induced HLH. These are mainly age over 60 years, male gender, and the length of time since the start of immunotherapy. Genetics (in particular the PRF1A91V3 gene polymorphism) also plays a role in the development of HLH. The risk of immunotherapy in the occurrence of HLH being established, the knowledge of additional factors is important in order to recognize the clinical warning signs as soon as possible. Cancer itself is a cause of HLH, in this case called paraneoplastic HLH [11]. The latter remains a rare complication but has a survival rate of <25% at one year [5]. The delay in diagnosis is long because this pathology is rare and with a broad and non-specific clinic. Its recognition is a priority in order to initiate adequate treatment as early as possible.

In this case, the basis of treatment of HLH is etiological treatment: A study [11] reporting MAS in a patient with ovarian cancer. Complete symptom resolution resulted from tumor resection and medical treatment. Unfortunately, malignancy-triggered HLH is associated with increased mortality. A study [13] present a series of nine pediatric and young adult patients in whom an initial diagnosis of HLH delayed the discovery of underlying malignancy and frequently delayed truly curative therapy. All of these patients ultimately died from multiorgan failure with active malignancy present. Both patients who received full-dose chemotherapy are still alive with no evidence of disease. These cases highlight the importance of distinguishing malignancy-associated HLH in order to limit morbidity and mortality. One pediatric series [14] describing a 6-month overall survival of 67% and median overall survival of 1.2 years, with the majority of deceased patients having active malignancy at the time of death [15].

Conclusion

In this article, we report our experience in the management of immuno- and virus-induced HLH in stage 3B ovarian cancer with Etoposide, Dexamethasone and Immunoglobulin G. New molecular targets appear to offer a therapeutic solution with fewer complications than Etoposide but need to be further investigated. It is important to initiate treatment as soon as possible, especially when the origin of HLH is curable. In other cases, it is necessary to know how to recognize and manage it early because its prognosis remains poor with a low survival rate at 1 year.

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