Case Report

Nasal type extranodal natural killer/T-cell lymphoma-associated hemophagocytic lymphohistiocytosis: a case report and literature review

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**Abstract:** Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome in which a large number of inflammatory cytokines are produced due to cytotoxic killing cells and natural killer (NK) cell dysfunction. This syndrome is usually of fatal condition with poor prognosis. Nasal type extranodal natural killer/T-cell lymphoma (ENKTCL) is an aggressive non-Hodgkin lymphoma closely related to Epstein-Barr virus, which can be complicated by HLH at initial diagnosis and recurrence. We report a case of ENKTCL -associated HLH to improve the ability of recognition, diagnosis and treatment of lymphoma-associated HLH.

**Keywords: H**emophagocytic lymphohistiocytosis; Extranodal natural killer/T-cell lymphoma; Etoposide; Prognosis; Tislelizumab

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a kind of histiocytosis caused by reactive hyperplasia of mononuclear macrophage system, mainly due to cytotoxic lymphocyte (CTL) and natural killer (NK) cells function defects, which lead to antigen clearance disorder. HLH is a heterogeneous clinical syndrome. During HLH, the monocyte macrophage system constantly receives antigen stimulation and results in hyperactive proliferation. Then, large inflammatory cytokines are produced. The main manifestations include fever, splenomegaly, thrombocytopenia, hypertriglyceridemia, hypofibrinogenemia and increased serum ferritin, and hemophagocyte can be found in bone marrow, spleen or lymph node biopsy [1]. HLH can be divided into primary HLH and secondary HLH. The former is usually caused by related gene abnormalities and often occurs in children without underlying diseases. The latter is often secondary to diseases such as severe infection, advanced malignancies, serious autoimmune diseases. It has been reported that in 2197 adult HLH patients, the most common primary diseases that induced HLH were T cell or NK cell lymphomas (16.8%), B cell lymphomas (15.2%), Epstein-Barr virus infection (15.0%), HIV infection (7.9%), systemic lupus erythematosus (6.1%), mycobacterium tuberculosis infection (3.6%) [2].

Nasal type extranodal natural killer/T-cell lymphoma (ENKTCL) is one of aggressive non-Hodgkin lymphoma closely associated with Epstein-Barr virus, with approximately 90% of primary lesions in nasal cavity. HLH can be complicated at initial diagnosis, recurrence and progression, usually with low response rate to treatment and poor prognosis. In order to improve the ability to recognition, diagnosis and management of lymphoma-associated HLH, here, we report a case of ENKTCL -associated HLH and summarize its clinical characteristics and treatment, as well as review the literature.

Case

A 36-year-old woman presented with a one-month history of mass on her left eyelid with fever (Figure 1A). On April 20, 2021, she developed redness and swelling of the left palpebra inferior accompanied by intermittent fever with the maximum temperature of 39.5℃. She was admitted to a nearby hospital where she received topical treatment with antibiotics and glucocorticoids. However, no significant improvement was observed. Gradually, the mass on the left palpebrae inferior enlarged with diminution of vision. Meanwhile, multiple nodules were found in both breasts. Orbital magnetic resonance imaging (MRI) showed left palpebrae inferior incrassation, lacrimal gland enlargement with abnormal signal in right orbit, which was considered as lymphoproliferative lesion. Positron emission tomography/computed tomography (PET/CT) showed multiple systemic lymphadenopathy and multi-organ space-occupying lesions with significantly increasement of metabolic activity, which suggesting a high possibility of lymphoma (Figure 2a). She was admitted to our department on May 21, 2021. Physical examination was as follows. Eastern Cooperative Oncology Group performance status (ECOG-PS) was 2 score. The body temperature was 38.8℃. Multiple enlarged superficial lymph nodes could be palpable. Severe redness and swelling of the left palpebrae inferior with ulcer on the surface, which was about 0.5cm×0.3cm. A 1.5cm×1.0cm mass was palpable. Purulent secretions could be found in the conjunctiva of the right eye. Multiple nodules could be palpated on both breasts. The largest one was located on the left outer lower quadrant, with a diameter of 2.0cm, hard with pressing pain, and erythema could be seen on the surface of the breasts. Liver was palpable under the costa and the distance between the liver and costal margin was 8cm. Spleen was also palpated under the costa and the distance between the spleen and costal margin was 8cm. Complete blood count (CBC): White blood cell 4.3×109/L，neutrohil 2.54×109/L，hemaglobulin 98g/L，platelet 176×109/L. Biochemical results: LDH 504U/L. Other hepatic or nephritic function was basically normal. Tumor markers: CA125 38.9U/ml，CA153 4.3U/ml. Serum ferritin increased to 1570ng/ml. Bone marrow flow cytometry showed that suspected abnormal NK cells accounted for 15.58%, which had immunophenotype of CD3-, CD16- and CD56+. Bone marrow pathology examination did not found definite tumor cells. NK cell activity was decreased to 14.94%. Soluble CD25 was more than 44000pg/ml. Quantitative detection of EBV-DNA was of 1.412×105 copies/mL. Based on continued fever, hepatosplenomegaly, elevated serum ferritin, decreased NK cell activity and elevated sCD25, HLH was diagnosed and lymphoma-associated HLH was probable. After biopsy of an enlarged lymph node on the right neck, DEP regimen (liposomal doxorubicin 40mg on day 1, etoposide 150mg on day 1, methylprednisolone 900mg from day 1 to 3, 40mg from day 4 to 7, and 15mg from day 8 to 10) was administered on May 30, 2021. On June 1, 2021, pathology examination of right neck lymph node confirmed the diagnosis of nasal type extranodal NK/T cell lymphoma [the immunophenotype of lymphoma cells were CD3(+), CD20(-), CD43(+), Ki-67(index85%), C-myc(+), CD56(+), TIA-1(+), GrB(+), CD30(-), ALK(-), CD38(-); ISH: EBER is positive by in situ hybridization]. The patient was definitively diagnosed as ENKTCL with stage IVEB and ENKTCL-associated HLH. PINK-E score was 4 (high risk group) and NRI score was 5 (very high risk group). Thus, a dose of 3750U pegaspargase was added to DEP regimen (the so-called DEPL regimen) on the fourth day to enhance the anti-lymphoma effectiveness. On June 7,2021, lumbar puncture was completed. Although no obvious abnormality was found in cerebrospinal fluid examination, cytarabine 50mg, dexamethasone 5mg and methotrexate 10mg were injected intrathecally for central nervous system lymphoma prophylaxis. After chemotherapy, her body temperature returned to normal, the mass on the eyelid shrank, edema of limbs, lower back and perineum subsided significantly, breast nodules almost disappeared, the pain in lower limbs was relieved, and pericardial effusion gradually decreased. All above suggested response to the treatment. On June 18, 2021, the second cycle of DEPL regimen was administered. Then quantitative detection of EBV-DNA decreased to 3.669×10E4 copies/ml. sCD25 was 12672pg/ml and NK cell activity was 14.84%. The treatment was effective because the lymphoma lesions was smaller than before. However, in consideration of extensive lesions at the diagnosis, large tumor load and lymphoma-associated HLH and several high risk factors above, Tislelizumab (PD-1 monoclonal antibody) 200mg (once every three weeks) was administered on July 9, 2021. The third and fourth chemotherapy regimens were GPED (gemcitabine 1.5g on day 1, pegaspargase 3750U on day 2, etoposide 100mg from day 2 to 4, dexamethasone 20mg from day 1 to 4), which were administrated on July 13, 2021 and August 9, 2021. At the meantime, we completed twice lumbar puncture and intrathecal injection with same medicine and dose as the first time. Routine test, biochemical and flow cytometry of cerebrospinal fluid showed no obvious abnormality. After four cycles of chemotherapy, ferritin decreased to 997.3ng/mL, quantitative detection of EBV-DNA was less than 500 copies/mL, sCD25 was 7916pg/ml and NK cell activity was 13.17%. The mass on the eyelid disappeared. PET-CT was performed on August 27, 2021, which showed that compared to PET-CT on May 20, 2021, lymphoma lesions were significantly reduced and metabolic activity decreased or returned to normal (Figure 2b). The patient reached partial response. As of this writing, the patient is still receiving further treatment and the process is going well.

Discussion

Malignancy is one of the main causes of secondary HLH. The mechanism of HLH induced by malignancy is not fully understood, and maybe cytokines secreted by malignant tumor cells (including interferon γ and interleukin-6) lead to excessive inflammatory response. The most common malignancies that induce HLH are T cell and NK cell lymphoma or leukemia, diffuse large B cell lymphoma, Hodgkin's lymphoma, etc. HLH can occur at any stage of the disease, especially in newly diagnosed advanced patients and patients with relapsed or refractory diseases. Elevated sCD25 is considered to be a marker of T cell activation in HLH and an indicator associated with tumor load of non-Hodgkin's lymphoma. Among HLH induced by malignancies, viral infection may be a side-by-side trigger, such as EBV-associated lymphoma [4]. When this patient was diagnosed with ENKTCL, extensive lesions were found and the clinical stage was IV, and the copy of EBV-DNA significantly increased. So we considered that ENKTCL and EBV infection jointly induced HLH.

When HLH is secondary to advanced tumors, there is a lot of overlap between HLH and tumor presentations, making it very difficult to identify HLH. Therefore, the diagnosis of HLH is based on a series of clinical manifestations and laboratory tests. According to HLH-2004 criterion, altogether five of the eight criteria must be fulfilled if HLH is diagnosed[5]: ① fever: constant fever longer than 7 days, body temperature higher than 38.5℃; ② splenomegaly(longer than or equal to 3cm subcostal); ③ cytopenias, affecting at least two of three lineages in the peripheral blood(Hemoglobin < 90g/L, platelet < 100×109/L, neutrophil < 1.0×109/L), and it is not caused by bone marrow hematopoietic dysfunction; ④ hypertriglyceridemia and/or hypofibrinogenemia: triglyceridemia > 3mmol/L or are higher than 3 standard deviations for the same age; fibrinogenemia < 1.5g/L or are lower than 3 standard deviations for the same age. ⑤ hemophagocytosis in bone marrow, spleen, or lymph nodes; ⑥ low or absent NK-cell activity; ⑦ ferritin ≥500μg/L; ⑧ high levels of sIL-2r(sCD25). This patient had fever, splenomegaly, and increased ferritin, decreased NK cell activity and increased sCD25. The diagnosis of HLH was made without controversy. For any patient who has been diagnosed as HLH, primary or underline diseases inducing HLH should be investigated [4]. Young patients should receive the tests for HLH related genes to determine whether it is primary HLH. This patient was diagnosed as ENKTCL and EBV infections, so HLH related gene tests were not performed.

 The treatment principle of secondary HLH is to control the primary disease as soon as possible while actively treating HLH. Primary HLH is intended for allogeneic hematopoietic stem cell transplantation as soon as possible after control of HLH. Etoposide combined with dexamethasone was recommended as induction therapy in HLH 1994 and 2004 guidelines. Before treatment, patients' primary diseases, physical status and vital organ functions should be fully considered for individualized therapy [4]. This patient with ENKTCL was a newly diagnosed and advanced disease with extensive lesions. Considering etoposide combined with dexamethasone is difficult to simultaneously control HLH and ENKTL, we chose DEP±L regimen (liposomal doxorubicin, etoposide, methylprednisolone ± l-asparaginase/pegasparagase). In a multicenter study of combination DEP regimen as therapy for adult refractory HLH, etoposide and corticosteroids were used as core agents, increasing the dosage of corticosteroids for pulse therapy during initial induction period, and using liposomal doxorubicin as an important induction therapy. First, glucocorticoids have strong inhibitory effects in the activation of immune system and immunoreaction. Second, doxorubicin, a broad-spectrum cell toxic drug, has strong cell toxicity for a variety of tumor cells. Liposomes can promote drug accumulation in capillary permeability-increased sites and enrichment in the lymphatic system, prevent the drug from being engulfed by macrophages and monocytes, and prolong the drug half-life to ultimately increase the therapeutic effect [6]. Third, etoposide inhibits topoisomerase II, leading to dsDNA breaks, suppresses the production of inflammatory cytokine, selectively depletes of activated T cells in HLH mice models and improve survival rate. Therefore, etoposide is considered to be a key drug in the HLH-94 and HLH-2004 guidelines. In cases of lymphoma-associated HLH, treatment of HLH and lymphoma are needed simultaneously. Several experts suggested that this kind of patients should be treated with an etoposide-containing chemotherapy as quickly as possible. Therefore, for this patient with ENKTCL-associated HLH, we adopted the salvage treatment regimen of DEPL for recurrent/refractory HLH, in which pegasparagase is the key drug to ENKTCL [7]. After two cycles of chemotherapy, HLH reached partial response. So we quickly switched to the treatment of primary ENKTCL, using GPED regimen that takes both ENKTL and HLH into account, and added PD-1 monoclonal antibody, which has a good effect on ENKTCL. After another two cycles of chemotherapy, PET-CT showed that the overall tumor load was reduced by more than 80%. The patient achieved partial response (Figure 2B). No standard treatment has been recommended for consolidation therapy of advanced ENKTCL-associated HLH. Previous studies have reported that autologous hematopoietic stem cell transplantation cannot significantly reduce the recurrence rate of advanced ENKTCL [12]. If complete response can be achieved, allogeneic HSCT can be attempted for consolidation therapy in young patients with lymphoma-associated HLH. The patient is undergoing further treatment, and if a complete response is achieved, allogeneic HSCT will be considered for subsequent treatment.

 HLH is of high mortality rate. For newly diagnosed HLH patients, we must exclude or confirm the underlying causes, especially malignancies and infection, and timely treat the primary disease after confirmation. For lymphoma-associated HLH, a combination chemotherapy regimen containing etoposide and glucocorticoid can be selected to take both HLH and lymphoma into account, which can play the role of "killing two birds with one stone". However, the overall cure rate of lymphoma-associated HLH is still low and the prognosis is extremely poor. Therefore, new strategies should be actively explored. Whether immunochemotherapy regimens including immune checkpoint inhibitors can improve the prognosis of ENKTCL patients with HLH needs to be confirmed in prospective studies with larger sample sizes.

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| (**a**) | (**b**) |

**Figure 1.** Signs of left palpebra inferior before and after treatment: (**a**) Severe swelling of the left palpebrae inferior with ulcer and purulent secretions before treatment; (**b**) Normal left palpebrae inferior after two cycles of treatment.

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**Figure 2.** Results of PET-CT before and after treatment: (**a**) Multiple hypermetabolic lesions were observed in PET/CT before treatment; (**b**) After two cycyles of threapy, PET-CT showed that most of the lesions disappeared or shrank, which metabolic activity returned to normal or decreased, and the curative effect achieved partial remission.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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