SciMedCentral

Journal of Cancer Biology & Research

Case Report

Breast Cancer Complicated With Hemophagocytic Lymphohistiocytosis: A Case Report and Literature Review

Han Xiaomin[2], Sun Lichun[2]*, and Zhao Wendong[1]

[1]*Resident Physician, Harbin Medical University Affiliated Cancer Hospital, China*

[2]*Department of Oncology, Harbin Medical University, China*

***Corresponding author**

Han Xiaomin, Resident Physician, Harbin Medical University Affiliated Cancer Hospital, Nangang District, Harbin City, Heilongjiang Province, China, Tel: 15804624787

Submitted: 24 April 2023

Accepted: 19 May 2023

Published: 21 May 2023

ISSN: 2373-9436

OPEN ACCESS

Keywords

- Malignant tumor
- Breast cancer
- Hemophagocytic lymphohistiocytosis
- Anemia

Abstract

Malignant tumor complicated with hemophagocytic lymphohistiocytosis (HLH) is a rare disease that seriously endangers life and health in the oncology department. The treatment and diagnosis of adults remain unclear. In this paper, the patient progressed to advanced breast cancer, secondary anemia, and fever of unknown origin. Due to the rapid aggravation of anemia, the symptoms of anemia improved slightly after symptomatic treatment, such as erythropoietin, blood transfusion, and fever reduction, but there was still repeated high fever. After laboratory examination and bone marrow puncture, breast cancer with HLH was diagnosed, and symptomatic treatment such as chemotherapy and hormone was given. Later, the patient died of a terminal malignant tumor. This paper introduced the clinical features, pathogenesis, diagnostic criteria, treatment methods, and prognosis of solid tumor complicated with HLH by reporting the diagnosis and treatment of this patient and reviewing relevant literature to improve the understanding of clinicians for this disease, broaden diagnosis and treatment ideas, and reduce missed diagnosis and misdiagnosis.

INTRODUCTION

Hemophagocytic syndrome (hemophagocytic lymphohistiocytosis, HLH) is a macrophage proliferative disease with multi-organ and multi-system involvement and immune dysfunction. HLH is usually divided into two categories, primary hemophagocytic lymphohistiocytosis (pHLH) associated with genetic factors, primarily seen in childhood [1], and secondaryhemophagocyticlymphohistiocytosis (sHLH) induced by infections (viral, bacterial, fungal, etc.), autoimmune diseases, malignancies, drugs, etc. [2-4]. To enhance the knowledge and study of HLH, summarize the clinical experience, improve the understanding of the disease, and find the clinical features of the early manifestations of the disease at an early stage, this paper reviews the diagnosis and treatment of a patient with advanced breast cancer combined with HLH who was admitted to the Cancer Hospital of Harbin Medical University on February 10, 2022.

MEDICAL RECORD INFORMATION

Female, 57 years old, on 2019-7-22 in our hospital, right mastectomy + right modified radical mastectomy; postoperative pathology showed: right breast invasive ductal carcinoma grade 3, mass tough area:1.6cm, axillary lymph nodes 5/15. ER(+, 40%); PR(+40%); Her-2(+); Ki67 index hot spot area about 30%; P53(3+). CK5/6 (focal +); microscopic CD31, D2-40 vascular staining visible as vascular aneurysm plugs. Negative for FISH. From 2019-8-22 to 2019-11-04, the patient was treated with EC-T (epirubicin 75mg/m^2 body surface area, cyclophosphamide 600mg/m^2 body surface area), which was stopped after four cycles of EC chemotherapy. In June 2021, the patient visited our hospital for "right chest wall swelling for more than two months".2021-6-2 Ultrasound of the breast showed: right chest wall with a preexisting occupancy (M possible); multiple lymph nodes in the right subclavian lateral side (M?). IHC: ER (-); PR (-); Her-2(2+); Ki67 index about 50%; P53 (3+). negative for FISH. Diagnosis: recurrence of breast cancer after surgery, chemotherapy with TX (docetaxel 75mg/m2 body surface area combined with capecitabine 1000mg/m^2 body surface area) regimen. 2021-7-6 First cycle of TX regimen chemotherapy. The patient could not tolerate oral capecitabine after one week due to adverse drug reactions and discontinued the drug on his own. The patient refused to continue oral capecitabine. 2021-7-27 to 2021-9-14 Single agent docetaxel (75mg/m2 body surface area ivgtt) chemotherapy was administered for three cycles and then evaluated for efficacy: SD. 2021-October The patient had an enlarged right chest wall mass. 2021-10-08 cervicothoracic abdominopelvic CT showed: right chest wall occupancy, recurrence considered. Efficacy assessment: PD. 2021-10-13 patient's right chest wall puncture pathology return in our

hospital showed: ER(-); PR(-); Her-2(-); Ki67(+ about 80%); P53(3+). 2021-10-14 to 2021-12-09 performed albumin Three cycles of paclitaxel (260mg/ivgtt) combined with capecitabine (1000mg PO bid) chemotherapy with PR. Self-discontinued chemotherapy. The patient had a routine blood test on 2022-02-03 at Harbin Daoli District People's Hospital: hemoglobin 58 g/L. The patient had a daily fever for the past week, with no trigger or regularity. The highest temperature was 38.3°C. The temperature decreased to normal after oral administration of ibuprofen. The patient was admitted to the hospital on 2022-2-10.

The patient had no history of hypertension or diabetes mellitus and had been taking oral hypothyroidism for more than ten years. The patient was admitted to the hospital for physical examination: anemic appearance, clear speech, asymmetric bilateral breasts, right breast is absent, and a surgical scar of about 15 cm in length is visible on the right chest wall, which is healing well. The respiratory sounds in both lungs were clear, no dry rales were heard, respiration was 24/min, heart rate was 123/min, blood pressure was 134/94 mmHg, body temperature was 37.8℃, no pathological murmur was heard in each valve auscultation area, the abdomen was flat and soft without pressure pain, no edema in both lower limbs and no pathological murmur was palpated.

Diagnosis and treatment: admitted to the hospital to improve the relevant examination, 2022-02-10 urine analysis 8 - 11: leukocytes 32.9 (/ul), leukocytes (high magnification field) 6.58/HP; 2022-02-10 blood cell analysis (five classification + complete blood count): leukocyte count 20.59 (10^9/L), hemoglobin 58.0 (g/L), platelet count 955(10^9/L), absolute neutrophil value 15.57(10^9/L), total monocyte value 1.62(10^9/L), 2022-02-10 liver function measurement: alanine aminotransferase 31U/L, aspartate aminotransferase 15U/L. 2022-02-10 Breast ultrasound in our hospital: multiple solid occupations in the right chest wall (consider M); nodular trades in the left breast (BI-RADS category 4a) right breast agenesis, incomplete degeneration of the left breast; multiple lymph nodes in the right supraclavicular and right sub clavicular lateralities double axillary, no enlarged lymph nodes in the left supraclavicular. 2022-02-11 at our hospital, enhanced CT of neck, chest, abdomen, and pelvis: 1. postoperative right breast, suitable chest wall occupancy, considered recurrent, more prominent than before; 2. bilateral lung nodules, as before, please follow up; 3. multiple hepatic occupancies; 4. left adrenal area occupancy; 5. small hepatic cysts; 6. no abnormalities on CT scan of neck and pelvis. Efficacy assessment: PD. 2022-02-11 rechecked patient's coagulation five: activated partial thromboplastin time measured 40.50 (sec). Preliminary diagnosis: 1. suitable chest wall recurrence after right breast cancer surgery; 2. right subclavian and right subclavian lymph node metastasis; 3. severe anemia; 4. hypothyroidism; 5. liver metastasis. Definitive diagnosis: 1. suitable chest wall recurrence after right breast cancer surgery; 2. right subclavian and right subclavian lymph node metastasis; 3. severe anemia; 4. hypothyroidism; 5. liver metastasis; 6. left adrenal metastasis. In this patient, the coagulation abnormalities may be tumor-related or pre-thrombotic. According to the NCCN Clinical Practice Guidelines in Oncology, the Khorana predictive model risk score for chemotherapy-related venous thromboembolism was 3, a high-risk category with a 6.7-12.9% probability of developing symptoms [1]. The patient was given rivaroxaban 20 mg once a day orally. The patient was also given a recombinant human erythropoietin injection of 0.1 ml subcutaneously every other day. Because the patient was severely anemic (Figure 1), bone marrow aspiration was performed to clarify the cause of anemia. 2022-02-14 bone marrow cytology report suggested: increased phagocytosis; 271 megakaryocytes in the whole film, platelets were scattered and clustered, and the morphology was generally normal (Figure 2,3). The author gave the patient 2U of de-leukocyte erythrocyte suspension. After transfusion 2022-02-15, blood cell analysis (five classifications + complete blood count) leukocyte count 19.11 (10^9/L), hemoglobin 62.0 (g/L), platelet count 790 (10^9/L), according to the patient's bone marrow cell analysis report, the author suspected that the patient might have phagocytosis syndrome, to To clarify the diagnosis further, the author gave the patient ferritin, lymphocyte subpopulation monitoring, β2 microglobulin, and hematocrit antigen monitoring, 2022-02-16 the patient ferritin: 1583.00ng/ml; 2022-02-18 hematocrit analysis (five categories

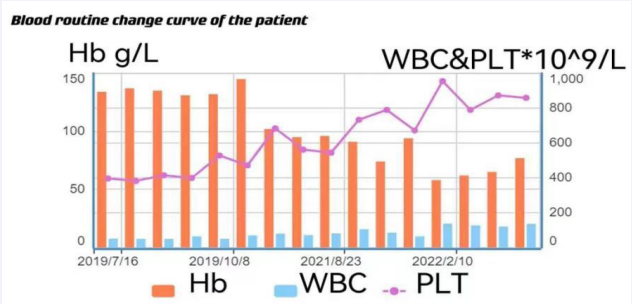

Figure 1 Broken line diagram of the patient's blood routine examination indicators.

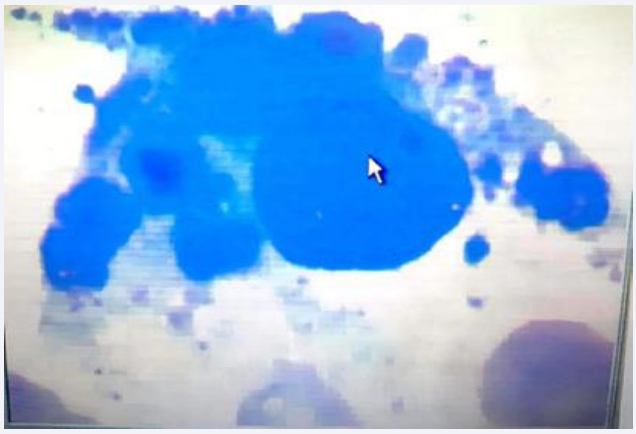

Figure 2 Bone marrow smear showed that various cells such as red blood cells, neutrophils and platelets were phagocytosed by macrophages. This examination did not reveal hematological malignancy (Rehschner staining, original magnification 40x). The white arrow indicates phagocytes.

Figure 3 Morphological characteristics of hemostasis were observed on a bone marrow aspiration smear Rehschner staining, original magnification 100x.

+ complete blood count): white blood cell count 18.06 (10^9/L); hemoglobin 65.0 (g/L), platelet count 873(10^9/L). The patient was continued to be given a de-leukocyte erythrocyte suspension 2U after transfusion 2022-02-22 β2 microglobulin 4.37 (mg/L), lymphocyte subpopulation monitoring CD8+ T lymphocyte subpopulation 11.67% CD4+ T lymphocyte subpopulation 64.9% blood cell cluster differentiation antigen IL-10 211.85 pg/mL, the patient's family was informed of the patient's condition, the patient and family Asked for active treatment, 2022-02-22 performed albumin paclitaxel (260mg/ivgtt) chemotherapy, 10mg/m2 dexamethasone, oral at 8:00 daily, halved after two weeks. After treatment, the patient showed no significant discomfort. 2022-02-24 Blood cell analysis (five categories + complete blood count): white blood cell count 20.35 (10^9/L), hemoglobin 77 (g/L), platelet count 859 (10^9/L). 2022-02-25 The patient was discharged from the hospital. The patient then came to the hospital for future treatment. 2022-05-06 The patient died due to an end-stage tumor.

DISCUSSION

Secondary hemophagocytic lymphohistiocytosis (sHLH) is a rare and fatal disorder that can lead to cytokine storms, with uncontrolled immune cell activation being the main feature of the disease [5]. Malignancy-associated HLH (M-HLH) frequently occurs in 1% of patients with hematologic malignancies. Its pathogenesis may include severe inflammation, sustained antigenic stimulation of tumor cells, and loss of immune homeostasis due to chemotherapy, hematopoietic stem cell transplantation, or infection. M-HLH is most often seen in pediatric patients, is rare in solid adult tumors, and is frequently underdiagnosed. Because of the rapid progression of secondary phagocytic syndrome, the median survival is less than two months [6]. By the time patients are diagnosed, most of their disease has reached an advanced stage, and the best time for further treatment is lost. Therefore, there has been a clinical search for a method to diagnose secondary phagocytic syndrome early.

There are no uniform diagnostic criteria for adults, and the HLH-2004[7], guidelines for children are mostly used. The original 1991 HLH guidelines for diagnosis included five features: 1. fever; 2. splenomegaly; 3. cytopenias affecting at least 2 or 3 spectrums in the peripheral blood; 4. hypertriglyceridemia and/or hypofibrinogenemia; and 5. Phagocytosis in the bone marrow, spleen, or lymph nodes. The 2004 guidelines added three additional criteria: 6. low or no NK cell activity; 7. hypergammaglobulinemia; and 8. high levels of s-IL2ra [8-10]. Five of the eight criteria must be met to diagnose secondary HLH. Two (sIL2ra and NK cell activity) require sending specialized laboratory tests, which are difficult to obtain promptly in small institutions or community hospitals. Even in large institutions, these tests take 5 to 8 days to complete. The non-availability or delayed availability of these tests delays the diagnosis of adult HLH, which may further worsen the poor prognosis of adult HLH and M-HLH [17-20]. In a recent consensus review of adult malignancy-associated phagocytic lymphohistiocytosis, the consensus diagnosis was that patients who meet any 5 of the 18 criteria might be diagnosed with M-HLH, including 1. erythrophagocytosis; 2. compliance with HLH-2004; 3. thrombocytopenia; 4. anemia; 5. hepatosplenomegaly; 6. neutropenia mononucleosis; 7 . coagulation disorders; 8. transaminases elevated more than 2.5 times the normal value online; 9. renal failure; 10. hypoferritinemia; 11. LDL elevation; 12. hypertriglyceridemia; 13. elevated β2 microglobulin; 14. elevated soluble IL-2R; 15. previous HLH treatment; 16. survival; 17. fever; 18. positive hematologic malignancies exceeding certain values [8-11]. Among these, the finding of phagocytes in bone marrow on bone marrow biopsy is a key criterion to confirm the diagnosis of HLH. Still, early in the disease, bone marrow biopsy may not show phagocytosis [2,12], or phagocytes may be present in other tissues outside the bone marrow, so when HLH is highly suspected but bone marrow biopsy does not confirm the diagnosis, repeat biopsy is recommended, or biopsy of other tissues may be performed [2,13].

This patient did not develop anemia after adjuvant chemotherapy for surgery. On 2021-6-2, the patient had a recurrence of the chest wall for two months before he came to our hospital with mild anemia, which was considered to be tumor-related. The patient was given recombinant human erythropoietin injection, blood-generating granules, and ferrous fumarate to correct the anemia and stopped the treatment on his own after PR. 2022-02-10, the patient had severe anemia (Figure 1 for details) with a fever when he was admitted to our hospital again with a recurrent high fever after admission. After active symptomatic blood transfusion treatment, the body temperature did not drop significantly, and the blood routine showed no significant improvement in RBC and Hb. Phagocytosis was seen on bone marrow aspiration. The patient met five of the 18 criteria: fever, phagocytes found in the bone marrow, elevated serum ferritin, elevated β2 microglobulin, and coagulation disorder, confirming the diagnosis of breast cancer in combination with HLH. The goal of HLH treatment is to suppress the overactive immune system. In most patients with primary

HLH, induction therapy is usually followed by allogeneic stem cell transplantation if a suitable donor is available, in addition to which pharmacological treatment can be administered under appropriate conditions, with most centers using steroids and initial treatment regimens based on etoposide or adriamycin (CHOP)-based [16]. However, patients with M-HLH have a high mortality rate [6]. This patient was treated with albumin paclitaxel and dexamethasone for one cycle, and the patient's fever and general status improved. The family was informed of the patient's poor prognosis and subsequently abandoned the treatment. The patient has discharged on 2022-02-25, and on 2022-05-06, the patient died of a terminal tumor.

CONCLUSION

In conclusion, clinicians should consider the possibility of M-HLH when encountering patients with solid tumors who present with persistent or intermittent hyperthermia and progressive decline in peripheral blood cells. Laboratory tests such as bone marrow picture examination, blood cell examination, serum ferritin examination, lipid examination, and plasma fibrinogen examination should be performed on them as soon as possible to avoid missing the best time for treatment.

REFERENCE

1. Goggins, M Daly MB, Pal T, Berry MP, Buys SS, Dickson P, et al. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021; 19: 77-102.
2. Lu Xiaoshan, Xin Jiachun, Li Li, Wang Hailin. A case of pregnancy complicated with hemophagocytic syndrome and literature review[J]. Chinese Medicine Herald. 2022; 19: 184-187.
3. Takahashi M, Makino S, Iizuka H. Chronic active Epstein-Barr virus -associated secondary hemophagocytic lymphohistiocytosis in pregnancy a case report [J]. BMC Pregnancy Childbirth. 2021; 21: 681
4. Lemiale V, Valade S, Calvet L. Management of Hemophagocytic Lympho-Histiocytosis in Critically Ill Patients [J]. J Intensive Care Med. 2020; 35: 118-127.
5. Takahashi M, Makino S, Iizuka H, Noguchi M, Yoshida K. Chronic active Epstein-Barr virus-associated secondary hemophagocytic lymphohistiocytosis in pregnancy: a case report. BMC Pregnancy Childbirth. 2021; 21: 681.
6. Daver N, McClain K, Allen CE, Parikh SA, Otrock Z, Rojas-Hernandez C, et al. A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. Cancer. 2017; 123: 3229-3240.
7. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S. HLH-2004. Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007; 48: 124-131.
8. Henter JI, Horne A, Arico M. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007; 48: 124-131.
9. Henter JI, Arico M, Egeler RM. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. HLH Study Group of the Histiocyte Society. Med Pediatr Oncol. 1997; 28: 342-347.
10. Henter JI, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. Semin Oncol. 1991; 18: 29-33.
11. Tamamyan GN, Kantarjian HM, Ning J. Malignancy-associated hemophagocytic lymphohistiocytosis in adults: relation to hemophagocytosis, characteristics, and outcomes. Cancer. 2016; 122: 2857-2866.
12. Rosado FG, Kim AS. Hemophagocytic lymphohistiocytosis an update on diagnosis and pathogenesis [J]. Am J Clin Pathol. 2013; 139: 713-727.
13. Nasser MF, Sharma S, Albers E. Pregnancy-related Hemophagocytic Lymphohistiocytosis Associated with Herpes Simplex Virus -2 Infection. A Diagnostic Dilemma [J]. Cureus. 2018; 10: e2352.
14. Zhang HQ, Yang SW, Fu YC, Chen MC, Yang CH, Yang MH, et al. Cytokine storm and targeted therapy in hemophagocytic lymphohistiocytosis. Immunol Res. 2022; 70: 566-577.
15. Setiadi A, Zoref-Lorenz A, Lee CY, Jordan MB, Chen LYC. Malignancy-associated haemophagocytic lymphohistiocytosis. Lancet Haematol. 2022; 9: e217-e227.
16. Hayden A, Park S, Giustini D, Lee AY, Chen LY. Hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) in adults: A systematic scoping review. Blood Rev. 2016; 30: 411-420.
17. Lemiale V, Valade S, Calvet L. Management of Hemophagocytic Lympho-Histiocytosis in Critically Ill Patients [J]. J Intensive Care Med. 2020; 35: 118-127.
18. Otrock ZK, Daver N, Kantarjian HM, Eby CS. Diagnostic challenges of hemophagocytic lymphohistiocytosis. Clin Lymphoma Myeloma Leuk. 2017; 17: S105-S110.
19. Jordan MB, Allen CE, Greenberg J. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: ecommendations from the North American Consortium for Histiocytosis (NACHO). Pediat Blood Cancer. 2019; 66: e27929.
20. Li Wencong, Zhang Xiaoxiao, Nan Yuemin. Advances in diagnosis and treatment of hemophagocytic syndrome [J]. Journal of Practical Hepatology. 2022; 25: 612-615.