Contents lists available at ScienceDirect

Acta Haematologica Polonica

journal homepage: www.elsevier.com/locate/achaem

Case report/Kazuistyka

Recurrent diffuse large B-cell lymphoma presenting initially as hemophagocytic syndrome

Zhenyu Lin, Yinchao Zhao, Gang Wu, Xiaorong Dong *

Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

ARTICLE INFO

Article history:
Received: 28.06.2013
Accepted: 03.01.2014
Available online: 15.01.2014

Keywords:
- Hemophagocytic syndrome
- Diffuse large B-cell lymphoma
- Thrombocytopenia

ABSTRACT

Hemophagocytic syndrome (HPS) is an extremely rare and life-threatening abnormality, and the cases secondary to B cell lymphoma are rare. We report a case of relapsed diffuse large B-cell lymphoma initially presenting with hemophagocytic syndrome. The patient developed multiple erythematous macules and progressive thrombocytopenia during the treatment, and died two weeks after admission. The HPS presented as an initial manifestation of the relapsed diffuse B-cell lymphoma and the maculea that appeared during the treatment might be a strong predictor of unfavorable outcome.

Introduction

Hemophagocytic syndrome (HPS) is a rare disorder characterized by persistent fever without clear cause, hepatosplenomegaly, cytopenia, deranged liver function, hypertriglyceridemia, hyperferritinemia and hemophagocytosis in bone marrow [1]. Acquired HPS in adults is associated with various causes including infections, connective tissue diseases, and malignancies, especially non-Hodgkin's lymphoma [2]. In contrast to T or NK/T cell lymphoma, B-cell lymphoma associated with HPS is extremely rare [3, 4]. And hemophagocytic syndrome secondary to the relapsed B-cell lymphoma has never been reported before. We herein reported an unusual and life-threatening presentation of hemophagocytic syndrome in a patient with relapsed diffuse large B-cell lymphoma.

Case presentation

An 81-year-old man was admitted to our hospital presenting with a 4-week history of fever of exceeding 38 °C and weakness of the lower limbs. Two years before this episode, he had developed diffuse large B-cell lymphoma of the tongue, and had been successfully treated with wide excision of the lesion followed by chemotherapy and radiotherapy. On examination, the abdomen showed hepatosplenomegaly and there was no superficial lymphadenopathy. Laboratory examination showed normal white blood cell, thrombocytopenia with a platelet count of 77×10^9/L and hemoglobin level of 77 g/L. Negative results of coagulation testing including activated partial thromboplastin time (aPTT), prothrombin time (PT), antithrombin III (AT) activity, fibrinogen concentration, fibrin–fibrinogen degradation product

* *Corresponding author at*: Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1277 Jiefang Road, Wuhan, Hubei, China. Tel.: +86 27 85726196; fax: +86 27 85755457.
E-mail address: tojilzy@gmail.com (X. Dong).

0001-5814/$ – see front matter © 2014 Polskie Towarzystwo Hematologów i Transfuzjologów, Instytut Hematologii i Transfuzjologii. Published by Elsevier Urban & Partner Sp. z o.o. All rights reserved.
http://dx.doi.org/10.1016/j.achaem.2014.01.001

(FDP) concentration, and D-dimer assays excluded the diagnosis of disseminated intravascular coagulation (DIC). He was also noted to have elevated levels of aspartate aminotransferase (105 U/L), alanine aminotransferase (112 U/L), lactate dehydrogenase (1257 U/L) and ferritin (10 414.56 pmol/L). Serological tests for virus infection including Epstein–Barr virus, cytomegalovirus, human immunodeficiency virus, hepatitis B and C virus were all negative. The bone marrow aspiration revealed macrophages distributed throughout the bone marrow. Computed tomographic (CT) scan revealed lesions of lungs suggesting localization of lymphoma and magnetic resonance imaging (MRI) showed multiple epidural mass lesions at T4, L2 and L4 with compression of the spinal cord (Fig. 1). The result of CT-guided percutaneous lung biopsy was consistent with diffuse large B cell lymphoma. These findings together fulfilled the HLH-2004 criteria (fever, splenomegaly, cytopenias, hyperferritinaemia and hemophagocytosis in the bone marrow). Thus, a diagnosis of hemophagocytic syndrome secondary to the relapsed diffuse large B-cell lymphoma was finally made. Immediately after initiation of treatment with a 1000-mg methylprednisolone pulse for 3 days and intravenous immunoglobulin (0.4 g/kg/day for 5 days), the fever stopped and the platelet count returned to 101×10^9/L. However, on the 3rd day of the treatment, the patient suddenly developed various-sized, tender and slightly infiltrated erythematous macules on the face and trunk (Fig. 2). A careful review of the patient's medication lists ruled out the possibility of drug-induced rash. Meanwhile, the platelet count decreased rapidly to 59×10^9/L on the 5th day of treatment and even to 7×10^9/L on the 9th day of treatment. In addition, the hemoglobin level also decreased to 57 g/L on the 5th day of treatment. During this period, the patient had been dependent on platelet transfusions, which became gradually more frequent. He got worse around the 12th day after admission. The family decided to discontinue further therapies, and the patient died of circulatory and respiratory distresses due to HPS about two weeks after admission.

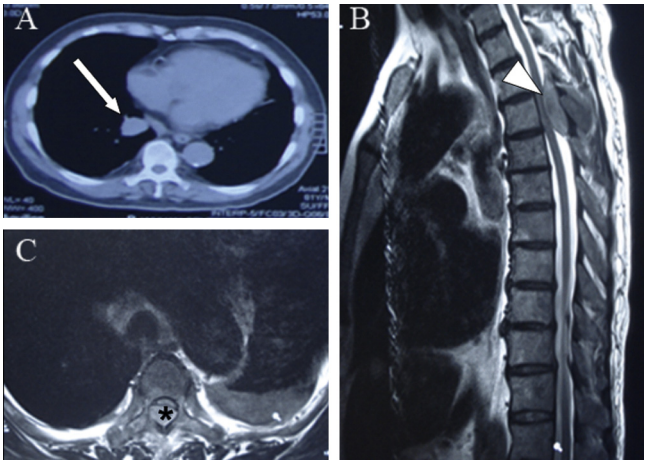

Fig. 1 – (A–C) CT and MRI images of the patient at the diagnosis of HPS. CT image (A) showed a metastatic lesion (arrow) in the right lung on mediastinal window. T2-weighted images (B–C) showed epidural mass lesion (arrow) at T4 level with compression of the spinal cord (asterisk)

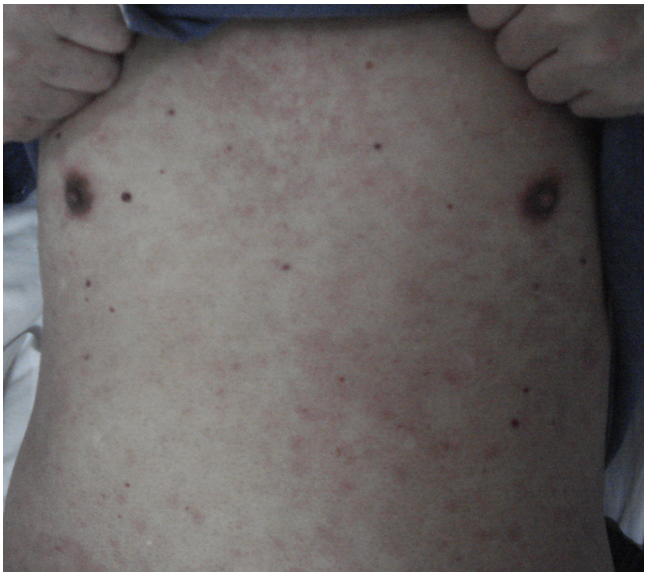

Fig. 2 – Widespread erythematous macules on the trunk

Discussion

The clinical course of HPS may be fulminant with rapid progression of symptoms, and the disease is usually fatal without treatment. The clinical features, proper treatment, and prognostic factors of HPS remain ill-defined because of its rarity, difficulty in diagnosis, and the poor general condition of the patient at the time of diagnosis [5–7]. The Histiocyte Society has established the clinicopathologic criteria for the diagnosis of HPS, which is defined by the presence of at least 5 of the following 8 criteria, including fever, splenomegaly, cytopenia (affecting $\geq$2 cell lines), hypertriglyceridemia, hemophagocytosis in the bone marrow, low or absent NK cell cytotoxicity, hyperferritinemia, and elevated soluble CD25 [8]. However, initial clinical diagnosis is difficult since not all patients meet all of these diagnostic criteria and many patients do so only in the late course of their disease. Early diagnosis and treatment often are essential for survival. In this case, the patient initially presented with only fever and weakness of lower limbs which was quite inconspicuous and easily misdiagnosed. There may also be a long prodromal period of non-specific illness before development of the complete syndrome. Since acquired HPS is usually associated with lymphoma, in those patients who present with manifestation of HPS, the suspicion of tumor regression is often crucial.

Cutaneous manifestations in HPS are relatively uncommon and detailed descriptions of skin lesions and their histopathologic findings have rarely been reported. It can accompany underlying hemophagocytic syndrome in the form of purpuric, macular, papular, erythrodermic, or morbilliform eruptions [9–11]. Right now it is considered that the pathophysiology of its cutaneous manifestations is

consistent with that of the current understanding of HPS. The latter is associated with a generalized immune activation with release of proinflammatory cytokines, which can cause the vicious circle of inflammatory ''cytokine storm'' of infiltrated organ systems, including skin [12–14]. Thus, the clinical cutaneous presentation in HPS may be an important sign of the judgment of severity, effect of treatment, and prognosis of the disease. The reappearance of cutaneous manifestations in a patient may herald a recurrence of HPS [15]. In our case, the fever stopped during the first few days and the platelet count even returned to the normal range. However, the patient immediately developed widespread macules accompanied with the following progressive thrombocytopenia and paralysis of the lower limbs, and failed to receive further chemotherapy. The macules that appeared during the therapy was quite rare and might serve as a strong predictor of unfavorable outcome.

In summary, hemophagocytic syndrome secondary to the relapse diffuse B cell lymphoma is rare and has a dismal prognosis with a quick disease progression. The cutaneous presentation in the clinical course might be a strong predictor of unfavorable outcome.

Authors' contributions/Wkład autorów

According to order.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES/PIŚMIENNICTWO

[1] Risma K, Jordan MB. Hemophagocytic lymphohistiocytosis: updates and evolving concepts. Curr Opin Pediatr 2012; 24:9–15.
[2] Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med 2012;63:233–246.
[3] Shimazaki C, Inaba T, Nakagawa M. B-cell lymphoma-associated hemophagocytic syndrome. Leuk Lymphoma 2000;38:121–130.
[4] Han AR, Lee HR, Park BB, Hwang IG, Park S, Lee SC, et al. Lymphoma-associated hemophagocytic syndrome: clinical features and treatment outcome. Ann Hematol 2007; 86:493–498.
[5] Aricò M, Danesino C, Pende D, Moretta L. Pathogenesis of haemophagocytic lymphohistiocytosis. Br J Haematol 2001;114:761–769.
[6] Larroche C, Mouthon L. Pathogenesis of hemophagocyticsyndrome (HPS). Autoimmun Rev 2004;3:69–75.
[7] Imashuku S. Advances in the management of hemophagocytic lymphohistiocytosis. Int J Hematol 2000;72:1–11.
[8] 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.
[9] Morrell DS, Pepping MA, Scott JP, Esterly NB, Drolet BA. Cutaneous manifestations of hemophagocytic lymphohistiocytosis. Arch Dermatol 2002;138:1208–1212.
[10] Filipovich AH. Hemophagocytic lymphohistiocytosis and related disorders. Curr Opin Allergy Clin Immunol 2006;6:410–415.
[11] Ghobrial IM, Weenig RH, Pittlekow MR, Qu G, Kurtin PJ, Ristow K, et al. Clinical outcome of patients with subcutaneous panniculitis-like T-cell lymphoma. Leuk Lymphoma 2005;46:703–708.
[12] Tzeng HE, Teng CL, Yang Y, Young JH, Chou G. Occult subcutaneous panniculitis-like T-cell lymphoma with initial presentations of cellulitis-like skin lesion and fulminant hemophagocytosis. J Formos Med Assoc 2007;106:55–59.
[13] Weenig RH, Ng CS, Perniciaro C. Subcutaneous panniculitis-like T-cell lymphoma: an elusive case presenting as lipomembranous panniculitis and a review of 72 cases in the literature. Am J Dermatopathol 2001;23:206–215.
[14] Voelkl A, Then C, Schmidmaier R, Seibold C, Reincke M, Oduncu F. Subcutaneous panniculitis-like T-cell lymphoma-associated hemophagocytic syndrome with fulminant relapse during corticosteroid treatment and fatal outcome. Leuk Res 2011;35:154–156.
[15] Pipkin CA, Lio PA. Cutaneous manifestations of internal malignancies: an overview. Dermatol Clin 2008;26:1–15.