Annals of Hematology & Oncology

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Case Report

Diffuse Large B-Cell Lymphoma with Cryagglutininemia: A Case Report

Jiang N[#]; Liu CY[#]; Fu R[*]

Department of Hematology, Tianjin Medical University General Hospital, 154 Anshan Street, Heping District, Tianjin, China

***Corresponding author:** **Fu R**

Department of Hematology, Tianjin Medical University General Hospital, 154 Anshan Street, Tianjin 300052, People's Republic of China.

Email: furong8369@tmu.edu.cn

[#]These author have contributed equally to this article.

Received: June 05, 2023

Accepted: June 30, 2023

Published: July 07, 2023

Abstract

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma in the world. Cryoagglutininemia is an autoimmune disease caused by cold inducing factors and characterized by chronic hemolytic anemia and microcirculation embolism, and it mainly involves IgM antibody and may be secondary to lymphoma, and other diseases. We reported 1 case of DLBCL with cryoagglutininemia. The patient was 39 years old, female, diagnosed as DLBCL stage IVB with aaIPI score = 2 at moderate/high risk. She presented the onset symptoms of generalized skin petechiae and ecchymosis. The physical examination showed a 2×2cm lump at the right 3rd rib on the midclavicular line. The patient was diagnosed as cryoagglutininemia. After admission to our hospital, she was diagnosed as DLBCL by transcostal lump puncture biopsy and then treated with the chemotherapy of Zanubrutinib + CHOPE regimen for 4 cycles. Thereafter, PET-CT reexamination indicated that Deauville score was 2, the treatment was effective, and the disease was relieved.

Keywords: Diffuse large B-cell lymphoma (DLBCL); Cryoagglutininemia; Treatment; Bruton tyrosine kinase (BTK); Zanubrutinib; Case report

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common invasive malignant lymphoma and accounts for 30%-40% of all cases in different regions [1]. We present a 39-year-old female patient with DLBCL and cryoagglutininemia the patient was treated with the chemotherapy of Zanubrutinib + CHOPE regimen for 4 cycles. Thereafter, PET-CT reexamination indicated that the disease was relieved. The treatment process is reported below.

Results

Investigations

There was a 39-years-old female patient. Over half a month ago, the patient repeatedly presented bright red petechiae and ecchymosis on legs and popliteal fossae, as well as urticarioid plaques on the abdomen and axillary fossae without reasons, accompanied by fever. The physical examination showed a 1×1cm lump on the left oral mucosa nearby the gingiva with palpable pain and a 2×2cm lump at the right 3rd rib on the midclavicular line with palpable pain. The patient sought for medical care successively in the First Affiliated Hospital of Zhengzhou University and Peking Union Medical College Hospital.

Diagnosis

The relevant examinations were completed. The results showed: serum protein electrophoresis: M-protein 1.9%, cryoglobulin (+); cold agglutinin test: 4℃ 1:512 (+), 37℃ rewarming (-); Coombs (+); IgM Kappa type; M-protein (-). Cryoagglutininemia was diagnosed. On October 12, 2021, the patient was firstly hospitalized in our department for treatment. After admission, PET-CT examination showed multiple bone destructions in the scanning range and abnormally increased metabolism, thus malignancy was considered. The bone marrow puncture indicated a myelogram of granulocyte, erythrocyte and megakaryocyte hyperplasia and an increased proportion of erythrocytes. The bone marrow biopsy showed: active myeloproliferation, a slightly decreased proportion of granulocytes and erythrocytes, visible cells in various phases dominated by mature cells (CD34 (+, occasional), CD117 (-), Lysozyme (+, sparse), MPO (+, occasional)), an increased number of B lymphocytes in diffuse, sparse and multi-focal distribution (CD20, CD19, Bcl-2: +, multi-focal; CD10: +, occasional; CD21, CD23, CD5, Bcl-6, SOX-11, CycinD1: -; CD3, CD138: +, sparse), normal morphology of megakaryocytes (CD61 (+)); MM phenotype: the abnormal plasmocytes accounted for 0.085% of karyocytes, expressing CD38, CD138, CD56 and kappa, and partially express-

Citation: Jiang N, Liu CY, Fu R. Diffuse Large B-Cell Lymphoma with Cryagglutininemia: A Case Report. Ann Hematol Onco. 2023; 10(4): 1429.

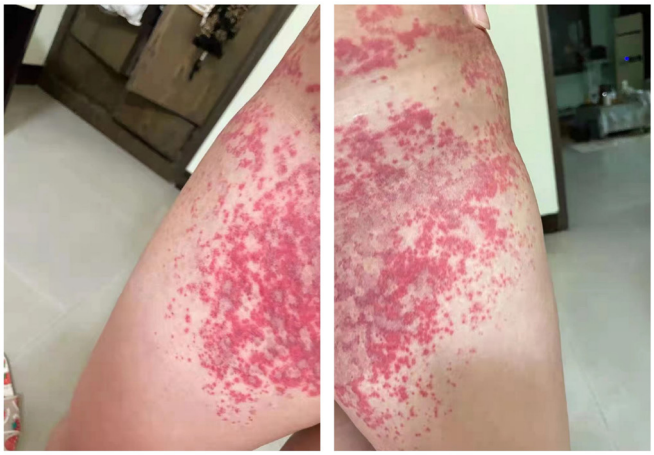

Figure 1: The bright red petechiae and ecchymosis on legs and popliteal fossae.

ing CD45, of which 0.018% plasmocytes did not express CD56; lymphocyte phenotype: the abnormal cell clusters accounted for 19.15%, expressing CD19, CD20 and Kappa, and partially expressing CD5, thus they were considered as monoclonal B lymphocytes; chromosome: 45, XX [11]; LPL/WM gene test: MYD88 (primary variation), BCL2 (tertiary variation); DLBCL hotspot gene screening: MYD88 (primary variation); bone marrow lymphoma FISH test: IGH rearrangement (+); in-situ lymphoma cell leukemia FISH test: negative. On October 22, 2021, a CT-guided right rib lump puncture was performed. The findings showed: B cell lymphoma, probable DLBCL, non-GCB-derived; immunohistochemistry: positive CD20, CD19, Mum-1 and CyclinD1, sparsely weak positive Bcl-6, negative CD10, CD3, CD5, SOX-11, TdT, CD56, CD38, CD138, CD235a, CD34, CD117 and CD61, and partially positive Kappa and Lambda in tumor cells. Combining the clinical manifestations and examination results, DLBCL stage IVB with aaIPI score =2 at moderate/high risk accompanied by cryoagglutininemia were definitely diagnosed.

Treatment

From October to December 2021, the chemotherapy of Zanubrutinib + R-CHOPE regimen (Zanubrutinib 80mg BID po + cyclophosphamide 1g d1 + vindesine 4mg d1 + liposome doxorubicin 40mg d1 + prednisone 60mg d1-5) was administrated for 4 cycles.

Follow-up and outcomes

After treatment, the PET-CT indicated: 1. Post lymphoma treatment; 2. Multiple bone destructions and no abnormal hyperplasia in the scanning range, conforming to the imaging characteristics after lymphoma treatment. Combining the medical history, it was considered that the treatment was effective and the disease was relieved, with Deauville score = 2.

Discussion

DLBCL is the most common non-Hodgkin's lymphoma in the world, and is usually manifested as rapidly growing lumps at single or multiple lymph nodes or extra-nodular sites [1]. Autoimmune Hemolytic Anemia (AIHA) is a highly heterogeneous disease mainly caused by increased damage of red blood cells from several immune mechanisms. Furthermore, AIHA is a common complication of lymphoproliferative disease in adult cases. Based on the homotype and thermal characteristics of auto antibodies, AIHA is conventionally classified into warm type, Cold Agglutinin Disease (CAD), and more rare types. CAD is more common; in CAD patients, the best reaction temperature of IgM autoantibody is 4°C at which the complements are strongly activated, DAT test is positive, and there is high-titer cold agglutinin in the serum. Some studies have revealed that CAD is closely related with the cloning of CD5+CD20+B cells [2,3].

So far, there are few reports about Malignant Lymphoma (ML) with AIHA. Secondary AIHA is consistent with primary AIHA in severity, and can be relieved with the improvement of lymphoma, thus the treatment of primary AIHA is still dominant. In patients with B-cell Non-Hodgkin's Lymphoma (B-NHL) and AIHA, rituximab plays a double role of anti-tumor and immune clearance by rapidly eliminating CD20-positive B lymphocytes in the body, and can increase the remission rate of ML with AIHA by combined chemotherapy. Therefore, rituximab becomes a first-line therapy for ML with AIHA and for Autoimmune Cholangitis (AIC) induced by ITP and other antibodies. A previous case report showed that R-CHOP chemotherapy had good efficacy in treating DLBCL patients with cryoagglutininemia [15]. In addition, Alemtuzumab and Bortezomib are also the optional therapies for ML with AIHA [4]. The combined chemotherapy of Fludarabine + CHOP regimen was administrated in the investigational group, with the overall response rate of 90.0% and the incidence rate of adverse reactions being 13.33% [5].

Bruton tyrosine kinase (BTK) is a non-receptor kinase and one of five TEC family members [6]. BTK is a downstream regulator of B-cell receptor signaling pathway and expressed on the surface of B cells, has the capability of specifically recognizing antigens, and plays a critical role in the development and maturation of B cells and a key role in the transduction of oncogenic signals. BTK deficiency is proved to be present in primary immunodeficiency X-Linked Agammaglobulinemia (XLA), and BTK is very important for the proliferation and survival of tumor cells in many B-cell malignancies. Recently, small molecular inhibitors of BTK demonstrate their excellent antitumor activities, and they are usually used to treat Waldenstrom macroglobulinemia and chronic lymphocytic leukemia [7]. BTK inhibitors also can be used for the treatment of autoimmune diseases. A retrospective study indicates that ibrutinib is an optional drug for patients with cAIHA (CAD/CAS) [8]. Zanubrutinib is a new, effective, specific BTK inhibitor and can irreversibly inactivate BTK through covalent binding with cysteine residue at BTK active site [9], and it is used to treat mantle cell lymphoma in adult patients who previously received one therapy [10]. Compared with the first-generation BTK inhibitor ibrutinib, Zanubrutinib has higher specificity, fewer side effects, a higher target occupying rate, and a longer inhibiting effect, and can be used in combination with other therapies, which provides more possible treatment options for patients with leukemia and lymphoma [11-13]. In addition, another study has shown that Zanubrutinib can be used for the prevention and treatment of autoimmune diseases [14].

However, the application of Zanubrutinib in patients with lymphoma and cryoagglutininemia is still rare.

Conclusion

In our reported case, the patient was diagnosed as DLBCL with cryoagglutininemia by transcostal lump puncture. After 4-cycle chemotherapy of Zanubrutinib + R-CHOP, PET-CT reexamination showed that the treatment was effective, and the disease was relieved. This can provide a new idea and clinical evidence for the application of Zanubrutinib in treating the patients with malignant lymphoma and cryoagglutininemia.

Author Statements

Author Contributions

All authors contributed eqally to this article.

Funding

This present work was supported by the National Natural Science Foundation of China (81870101, 81970115).

Conflict of Interest

The authors declare no conflict of interest.

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