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Case Report

Chronic Natural Killer Cell Lymphoproliferative Disorders Treated with Interferon-A: A Case Report

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2. Key words

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1. Abstract

Chronic natural killer cell lymphoproliferative disorders are a hematological disorder which is characterized by the proliferation of CD3- cytotoxic natural killer cells. So far, the pathogenesis of CLPD-NK is still unclear, and there is no consensus on the effectiveness of drug therapy. Here, we report a case of a 52-year-old female who presented with asymptomatic and was initially diagnosed with chronic natural killer cell lymphoproliferative disorders after examining the clinical features, the morphology and immunophenotype of neoplastic cells. Because of the high state of lymphocytes,the patient was treated with interferon-α (3 MU/m2 daily) for a year but she didn't achieve a complete remission. Meanwhile, there was no progression of the disease. Therefore, the effectiveness of interferon-α in CLPD-NK is still unclear.

3. Abbreviations: ASO: Anti-Streptolysin O; BM: Bone Marrow; CLPD-NK: Chronic Natural Killer Cell Lymphoproliferative Disorders; CRP: C-Reactive Protein; CyA: Cyclosporin A; EBV: Epstein-Barr Virus; ESR: Erythrocyte Sedimentation Rate; G-CSF: Granulocyte Colony-Stimulating Factor; IFNs: Interferons; MTX: Methotrexate; NK: Natural Killer; PB: Peripheral Blood; PCR: Polymerase Chain Reaction; SH2: Src homology 2; STAT3: signal transducers and activators of transcription 3; WBC: white blood cells

4. Introduction

Chronic natural killer (NK) cell lymphoproliferative disorders (CLPD-NK) is an uncommon but probably underestimated disease caused by clonal proliferation of CD3- cytotoxic NK cells [1]. Diagnosis is typically based on the high number of morphologically characteristic lymphoid cells and finding of an abnormal immunopheno type by flow cytometry. Because of its relatively indolent clinical behavior, observation is often an appropriate therapy. However, there is still no standard regimen for drug treatment. This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University and was performed according to the Declaration of Helsinki. Patient has provided informed consent for publication of the case.

5. Case report

Our patient, a 52-year-old woman, was admitted to our hospital with complaints of lymphocytosis with asymptomatic of a year's duration in October 2017. The complete blood count in a physical examination a year ago revealed atypical lymphocytes that constituted 72.74% of the white blood cell population. During the course of the disease, a high proportion of lymphocytes was indicated in peripheral blood (PB) smears without treatment. The patient was hospitalized for further diagnosis and treatment for this reason. No abnormality was found in the patient's past history and family history. Her physical examination revealed a well-developed female with normal temperature, hemodynamics and respirations. She had no palpable peripheral lymphadenopathy, splenomegaly or hepatomegaly. Her peripheral blood smear displayed a white blood cells (WBC) of 15.74×109/L, with 78.5% atypical lymphocytes, 15.8% neutrophils, 4.4% monocytes, hemoglobin of 12g/dl, and a platelet count of 189×10^9/L. Bone marrow (BM) smear indicated that abnormal lymphocyte was 30%. Large granular lymphocyte could be seen in the peripheral blood (Figure 1a) and bone marrow (Figure 1b), which were characterized by an eccentric nucleus and a slightly basophilic cytoplasm containing azurophilic granules. Lymphocyte subtype analysis by flow cytometry showed prominently exceptional elevated ratio of the total lympocytes with 72.76%, increased number of CD2+CD56+CD94+ cells with 53.91%, and slightly elevated proportion of CD7+CD8+CD16+CD57+CD161+ cells. Besides, a few cells expressed specific markers, such as Ki-67, CD158a/h, CD158b and CD 158e (Figure 2). Cytogenetic studies using GTG banding revealed a normal karyotype, 46 XX (Figure 3). No clonal T-cell receptor gene rearrangements

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were detected by polymerase chain reaction (PCR) studies. No activating somatic signal transducers and activators of transcription 3 (STAT3) mutation were detected by next-generation sequencing. The EBV-DNA and CMV-DNA examined by PCR were both negative. What's more, Coombs test, immunoglobulin, complement, autoantibodies, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Anti-Streptolysin O (ASO), rheumatoid factor, serum virus signs of viral hepatitis, tumor markers etc. were all negative.

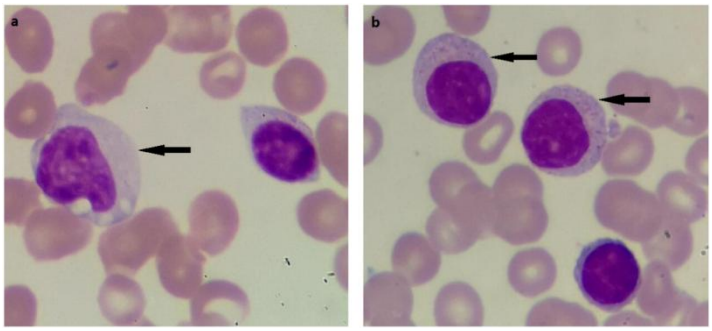

Figure 1: (a) Large granular lymphocyte (arrow) in the peripheral blood (Magnification, x1000);
(b) Large granular lymphocyte (arrow) in the bone marrow (Magnification, x1000)

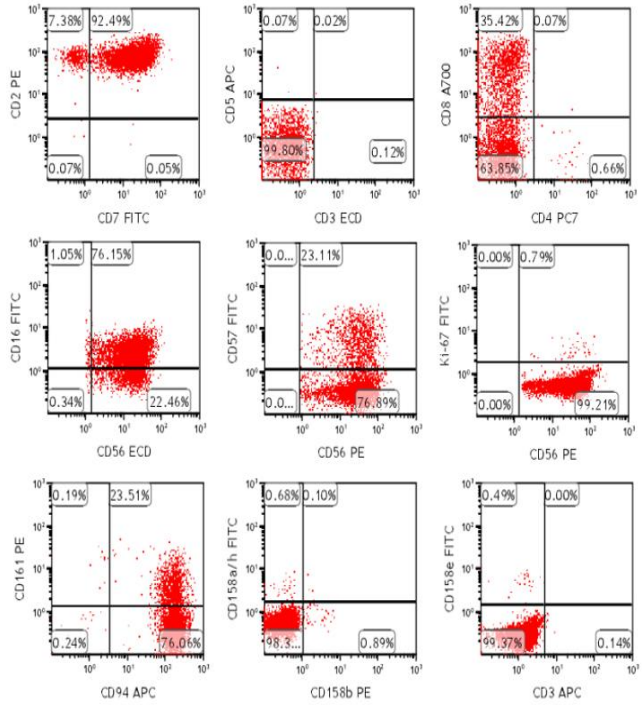

Figure 2: Flow cytometric analysis clarified that bone-marrow lymphocytes were CD2+CD3-CD56+CD94+.

This patient was diagnosed with chronic NK cell proliferative disease. Interferon-α therapy was given because the patient was in a high lymphocyte state for 1 year. Following up regularly after discharge, blood routine examination showed no significant decrease in white blood cells and lymphocytes. Epstein-Barr virus (EBV) was always negative, and there was no abnormality in immune indexes. A total of 1 year of interferon-α treatment(3 MU/m2 daily) was given. Because the re-examination index had no significant changes compared with 1 year ago, and the patient had no neutropenia, anemia, autoimmune disorder related diseases, she was not treated with interferon-α again. Up to now, the patients still had no discomfort.

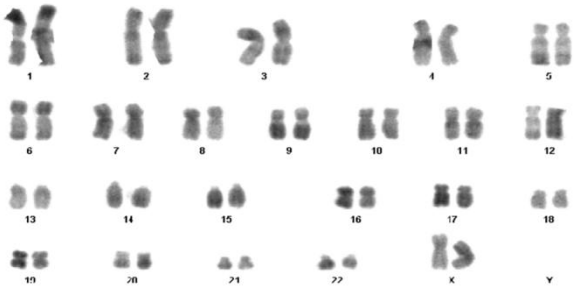

Figure 3: Cytogenetic studies using GTG banding revealed a normal karyotype, 46 XX.

6. Discussion

CLPD-NK used to be called chronic natural killer cell lymphocytosis. It is seldom known because of its low incidence rate. Only a few cases of CLPD-NK have been published at home and abroad since Tefferi et al. first discovered and named in 1994[2]. CLPD-NK has no special clinical manifestations, with a long disease course and a good prognosis. Men are affected more common, and the median age is about 60 years [3-6]. CLPD-NK is characterized by chronic expansion of mature NK cells in peripheral blood [7]. The diagnosis of CLPD-NK needs to combine with peripheral blood smear, immunophenotypes and clinical manifestations.

As to this patient, the most common presentation was persistent lymphocytosis without symptomatic. Besides, the patient did not present with anemia or splenomegaly. Her bone marrow smears were mainly lymphocyte elevation, and the immunophenotype showed CD3-CD56+CD94+. In addition, EBV genome, chromosomal karyotype and other laboratory test results were negative. Consequently, the patient was diagnosed as chronic natural killer cell lymphoproliferative disorders.

CLPD-NK is a clinically indolent disorder. Most patients do not need treatment. Only a few can be transformed into aggressive NK cell leukemia [8]. Patients with moderate to severe cytopenia require therapeutic intervention. Immunosuppressive therapy is the foundation of treatment of chronic NK cell lymphoproliferative disorders. The most frequent therapy relies on the use of single immunosuppressive oral agents such as methotrexate (MTX), cyclophosphamide, or cyclosporin A (CyA)[7, 9]. For patients suffering from anemia or neutropenia, supportive care could be considered, such as using erythropoietin or granulocyte colony-stimulating

factor (G-CSF) [10]. However, there is still no definite criterion for the treatment. The antitumor effects of interferons (IFNs), such as inhibiting proliferation, inducing apoptosis, restraining oncogene expression and immunoregulation, have been well confirmed [11-13]. Interferons are widely used in the treatment of various tumors, including leukemia, lymphoma and other diseases, with a good effectiveness [14]. Nevertheless, no case of interferons therapy for CLPD-NK had been reported so far. So we hypothesized that interferons could be used to treat CLPD-NK. For this reason, interferon-α was treat in this case for 1 year. Her condition was stable, but the hematology did not alleviate. Considering that the patient's disease had not progressed, the drug treatment was discontinued. Thus, it has yet to be concluded that interferon-α can treat CLPD-NK.

The pathogenesis of CLPD-NK is still unclear by now. The recent discovery of STAT3 mutations has shed light on the genetic basis of CLPD-NK pathogenesis. Correlation studies demonstrated that activating STAT3 somatic mutations, primarily within the Src homology 2 (SH2) domain mediated the dimerization and activation of STAT

7. Conclusion

protein, have been identified in 10% to 70% of CLPD-NK. Downstream target genes of STAT3 pathway (eg, IFNGR2, JAK2, and Bcl2L1) are up-regulated in patients with CLPD-NK[5,6][15-17]. Unfortunately, activating STAT3 somatic mutation was negative in our patient. In addition, some studies suggest that STAT3-mutated patients require more frequent treatment and have better overall survival [18]. It is conceivable that STAT3 inhibitors might be ideal targeted therapies for CLPD-NK. It was reported that STA-21, a novel synthetic inhibitor of STAT3 dimerization, DNA binding, and STAT3-dependent luciferase reporter activity, might induce apoptosis of chronic natural killer cell lymphoproliferative disorders' cells [6]. Therefore, although STAT3 mutations are not required for a diagnosis of CLPD-NK, detection of the mutation should prompt additional evaluation for the disease if unsuspected.

Our study presents that whether interferon-α is effective in the treatment of CLPD-NK remains to be further explored. What's more, this highlights the essentiality of sequencing STAT3 gene and raises the necessity of systematic long-term follow-up studies.

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