

## CASE REPORT

# Cyclosporine A therapy of chronic lymphoblastic leukemia-related pancytopenia: A case report

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## Abstract

To explore the clinical characteristics, diagnosis, and treatment of chronic lymphocytic leukemia with secondary pancytopenia. Here, a case of pancytopenia secondary to chronic lymphocytic leukemia is reported. Additionally, a review of relevant chronic lymphocytic leukemia literature was conducted to summarize its diagnosis, clinical characteristics, treatment history, and experience. After treatment with cyclosporine A, the patient's chronic lymphocytic leukemia continued to resolve, and hematopoiesis returned to normal. Cyclosporine A therapy resulted in improved patient outcomes. However, the mechanism by which cyclosporine A rebuilds the immune microenvironment and its antileukemia effect in the body remains to be studied.

## KEYWORDS

case report, chronic lymphoblastic leukemia, cyclosporine A, immune microenvironment

## 1 | INTRODUCTION

Chronic lymphoblastic leukemia (CLL) is a chronic B-cell proliferative disorder. The median age of patients suffering from CLL is 67–72 years, and the incidence rate is higher in men than in women (2:1).<sup>1</sup> Although autoimmune cytopenia (AIC) frequently cooccurs with chronic CLL, its relationship to pancytopenia is rarely reported and its pathogenesis remains unknown. Recently, the treatment of CLL-related pancytopenia using cyclosporine A (CsA) induced a prolonged remission of CLL. We hypothesize that CsA treatment may have the dual effect of acting as an immunosuppressant while simultaneously inducing immune microenvironment reconstruction, which, together with its immunosuppressive role, may facilitate its

antileukemia potential; however, this needs to be verified. In the current case study, a CLL patient presented with secondary pancytopenia, did not respond adequately to treatment using stimulating factors, and was reliant on blood transfusion. After CsA treatment, routine blood indices rose to the normal range indicating that the patient's CLL was remitted.

## 2 | CASE PRESENTATION

In March 2016, a 63-year-old female patient was admitted to the Affiliated Hospital of Qingdao University due to the enlargement of the bilateral cervical lymph nodes. The patient had no obvious medical history; however, upon

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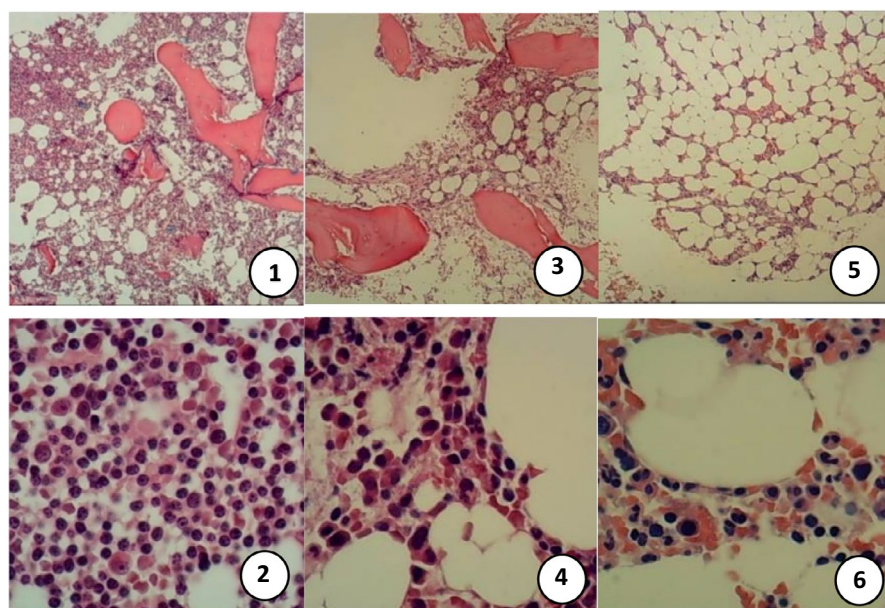
systemic examination, several enlarged lymph nodes were detected in both the cervical and inguinal locations. The diameter of the largest cervical lymph node was approximately 3 cm; however, no tenderness or adhesion was detected. Furthermore, the spleen was enlarged with Line I, Line II, and Line III measuring 6, 7, and 2 cm, respectively. No tenderness was noted. Hematological examination revealed the following results: WBC  $87.40 \times 10^9/L$ , NEU  $4.95 \times 10^9/L$ , RBC  $3.43 \times 10^{12}/L$ , HGB 94 g/L, PLT  $86 \times 10^9/L$ , and LYM  $81.03 \times 10^9/L$ .

An examination of the patient's bone marrow revealed that the proliferation of granulocytes was inhibited and the proliferation of erythrocytes was normal. Furthermore, erythroblasts of slightly different sizes were noted. Lymphatic hyperplasia was significant (88.5%) with most cells being abnormal, small lymphocytes. Morphologically, the lymphocytes were small, round, and possessed large round nuclei, dense chromatin, and little sky-blue cytoplasm (Figure 1①②). Together, these observations are indicative of lymphoproliferative disease (LDP). Mature lymphocytes and abnormal cell populations expressing CD19, CD5, CD43, CD23, CD200, and weakly expressing of CD20, CD79b, CD38, CD81, CD22, Kappa, and SigD accounted for 93.2% and 91.78% of the nuclear cells, respectively. Together, these lines of evidence are typical of a CLL/SLL phenotype. Fluorescence in situ hybridization (FISH) analysis highlighted that the patients' samples were positive for the rearrangement of IGH and IGK. Furthermore, the patient was negative for the ATM, CCND1/IGH, CEP12, P53, and RB-1 genes. Based on these data, the patient was diagnosed with CLL (Rai stage IV; Binet stage C; and high-risk group).

From the March 28, 2016, a 5-course fludarabine and cyclophosphamide (FC) chemotherapy regimen (on days

1–3, fludarabine 50 mg and cyclophosphamide 0.4 g) were initiated following symptomatic supportive treatment. Bone marrow suppression was observed after each course of chemotherapy, and hematopoiesis returned to normal after symptomatic supportive treatment, for example, stimulating the hematopoiesis. From the examination of the bone marrow, the patient was determined to be in complete remission (CR). On the September 22, 2016, the 6th course of FC chemotherapy was started, and the patient was discharged after the bone marrow hematopoiesis was recovered. No additional chemotherapy was carried out.

On the November 3, 2016, the patient was readmitted to the hospital. Hematological examination revealed the following: WBC ( $2.18 \times 10^9/L$ ), NEU ( $1.41 \times 10^9/L$ ), RBC ( $2.33 \times 10^{12}/L$ ), HGB (64 g/L), PLT ( $15 \times 10^9/L$ ), and LYM ( $1.29 \times 10^9/L$ ). Furthermore, the absolute number of reticulocytes was decreased. Additionally, there was no evidence of viral infection or hemolysis. Symptomatic supportive treatment to stimulate hematopoiesis was administered; however, these treatments were not effective and additional blood transfusions were necessary. On the November 15, 2016, the re-examination of bone marrow morphology found that the proliferation of bone marrow cells was less active. Cells at each stage were rare, and the size and morphology of the erythroblasts were good. Furthermore, 18% were mature lymphocytes and an occasional 1% were prolymphocytes. On the whole film, no megakaryocytes were observed and platelets were rare, which is indicative of a poor proliferation of bone marrow cells (Figure 1③④). No clonal abnormality on the chromosome was observed. The patient refused a multisite bone marrow biopsy for personal reasons. On the November 24, 2016, after relevant disease progression



**FIGURE 1** Bone marrow biopsy (①②) Bone marrow pathology at initial diagnosis: hyperactive myelodysplasia (~90%), lymphocytosis (March 16, 2016). (③④) Bone marrow pathology: poor myelodysplasia, rare megakaryocytes (November 15, 2016). (⑤⑥) Bone marrow pathology after treatment showed low myelodysplasia (~30%) and rare megakaryocytes (January 12, 2018)

was excluded, additional CsA (100 mg) was supplemented empirically, twice a day. At the same time, hematopoiesis stimulation and intermittent transfusion of blood components were administered. The patient's platelet level gradually increased, and the hemoglobin count also increased to 70 g/L where it stabilized. The patient was successfully weaned off the blood transfusions and did not receive FC chemotherapy; however, oral CsA treatment was continued at home. On the January 12, 2018, a follow-up bone marrow biopsy revealed that no clonal abnormalities were observed in the B lymphocytes and that there was a low proliferation of bone marrow cells (~30%) (Figure 1ⓈⓈ). FISH analysis was negative. To date, the patient has remained in remission of CLL 5 years and 3 months as confirmed by routine assessments.

### 3 | DISCUSSION

The typical manifestations of CLL are excessive proliferation and aggregation of clonal B lymphocytes in peripheral blood, bone marrow, lymphaden, and spleen. Clonal B lymphocytes are similar to mature lymphocytes in morphology; however, these cells possess abnormal immune expression and dysregulated cell functioning. Furthermore, despite having the typical immunophenotypes of clonal B lymphocytes (CD5<sup>+</sup>, CD10<sup>-</sup>, CD19<sup>+</sup>, FMC7<sup>-</sup>, CD23<sup>+</sup>, CD43<sup>+/-</sup>, and CCND1<sup>-</sup>), the cells are considered abnormal. In the 1980s, the ability to assess genomic sequences for markers of disease facilitated a significant breakthrough in CLL diagnosis and therapy. Combination treatment using FC has become the basic recommendation, which is stated in the NCCN guidelines.<sup>2,3</sup> However, the main complication of the FC regimen is myelosuppression, especially fludarabine-induced cytopenia caused by treatment-related immunosuppression that can last for months. Cytopenia can be relieved with the gradual attenuation of drug toxicity and the clinical response to administered stimulating factors.

CLL can cause various complications, especially infection and autoimmune diseases. Globally, the incidence of autoimmune diseases is approximately 10%–25% and often affects the blood system. The most common autoimmune diseases are autoimmune cytopenias (AICs) that develop in 4%–7% of CLL patients. Among these cases, pure erythrocyte aplastic anemia (PRCA) is a rare disorder that is often observed in fludarabine-treated patients experiencing terminal-stage disease.<sup>4,5</sup> PRCA may be related to immune dysfunction induced by immune inhibitors, but this remains to be elucidated. Immune-mediated hypocytosis occurs frequently in CLL, but only two cases have reported CLL with secondary pancytopenia.<sup>6,7</sup> The pathogenesis of CLL-related AIC is associated

with T-lymphocyte dysfunction, clonally proliferating B-lymphocyte antigen presentation, and autoantibody production by normal residual B lymphocytes.<sup>8,9</sup> Previous studies have shown that these antibodies directly inhibited erythropoiesis and thrombocytopoiesis.<sup>10,11</sup> Additionally, CLL-related AIC can easily be confused with CLL progression, chemotherapy-related marrow suppression, myelodysplastic syndrome, and acute arrest of hemopoiesis. Previous work has shown that pancytopenia caused by chemotherapy-related myelosuppression gradually recovers within 1 month. Immunohistochemical analyses and the assessment of the recovery period after treatment provide key strategies to differentiate and diagnose these diseases.

Lad et al.<sup>12</sup> reported that dysfunctional T lymphocytes in CLL, especially at the late stage of disease, may explain the pathogenesis of CLL-associated AIC. Therefore, while no direct evidence has shown that CLL patients have a significant tendency to develop autoimmune disorders, the correlation between CLL and nonhematological autoimmunity should not be ignored. In the current case report, the increased frequency of inhibitory T lymphocytes was indicative of immunologic derangement in the patient. Furthermore, these data suggest that the induction of autoantibodies and T-lymphocyte dysfunction may play important roles in our case. Here, the patient presented with cytopenia for as long as 2 months after withdrawal from a six course FC regimen. Additionally, the patient was not responsive to stimulating factors and was diagnosed with transfusion dependence and low bone marrow hyperplasia. Cytopenia was corrected with CsA treatment, and CLL was relieved. It was unclear whether cytopenia was caused by CLL or fludarabine-induced immune responses. This observation should be clarified in future studies using a sufficiently large sample size with the correct biological controls in place. Notably within the current case report, after the discontinuation of FC therapy, the treatment of immune cytopenia using CsA resulted in long-term remission of CLL that was maintained throughout the follow-up period. CsA, an immunomodulator, can regulate T-lymphocyte function and suppress the release of lymphokines such as IL-2, IL-4, and TNF from antigen-activated T lymphocytes. We further explored how CsA regulates immunologic derangement in CLL patients and whether CsA can facilitate complete remission. Previously, in a study of 31 cases where CsA treatment was used to treat CLL-related AIC, the authors confirmed CsA's effectiveness in alleviating disease. In that study, 19 of 29 (66%) thrombocytopenic patients and 11 of 16 (69%) anemic patients were remitted following treatment. Additionally, a reduction in tumor load and lymph nodes was observed in some patients.<sup>13</sup> Zhao et al.<sup>14</sup> suggested that CsA can regulate the immune micro-environment,

recover T-lymphocyte function, inhibit auto-antibodies, eliminate tumor cells, and reduce tumor cell escape. These mechanisms may be the methods by which CsA sustained remitted CLL and exerted synergistic effects in leukemia therapy. However, the underlying mechanism of CsA in CLL cell lines remains unknown. Furthermore, any evidence for the treatment of CLL-related autoimmune disease using CsA treatment is mostly found in cases reports. Together, data in the literature highlight the urgent need for the assessment of CsA in a large-scale, sufficiently powered experimental setting. Additionally, after the reduction in tumor load in CLL, the ability of CsA to regulate marrow immune-environment and exert synergistic antitumor effects need to be further explored.

In the current report, we present a CLL patient with pancytopenia who developed unexplained immune cytopenia following FC treatment and achieved long-term complete remission of CLL after CsA treatment. Currently, FC treatment is limited to early-stage and young patients. Elderly patients can be treated with lower doses of FC or can be prescribed new drugs. The question of whether immune cytopenia in CLL patients after treatment can be corrected by the action of immunomodulators like CsA regulating the immune microenvironment, and their potential synergistic antitumor effects need to be further validated using a sufficiently large sample size. These findings provide new insights into CLL treatment and help to inform future studies.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHOR CONTRIBUTIONS

Mengying Wang conceived and analyzed the case report. Ruoyu Meng drafted the manuscript. Xianqi Feng drafted and revised the manuscript. Yan Gao, Junxia Huang, Tianlan Li, Chunxia Mao, Shanshan Liu, Yujie Xu, and Han Xu MS collected data and analyzed the case report.

### ETHICAL APPROVAL

This case collection was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University.

### CONSENT

Patient informed consent and signed informed consent form were obtained.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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