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Original Article

Clinical analysis of prolymphoblastic leukemia: the rare hematological malignancy in the elderly

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Abstract: Objective: To discuss and analyze the clinical and prognostic characteristics of rare prolymphocytic leukemia (PLL), in order to provide new references for the clinical diagnosis and treatment and basic research of PLL. Methods: The clinical data of 8 patients with PLL admitted to the Department of Hematology in Fujian Medical University Union Hospital from January 1, 2011 to May 31, 2023 were collected and retrospectively studied, and the clinical treatment and prognosis were analyzed. Meanwhile, the latest literature from PubMed was retrieved to systematically discuss the research progress in the diagnosis and treatment of PLL. Results: In this study, of the 8 patients with PLL, 6 were males and 2 were females; the ages ranged from 52 to 80 years, with a median age of 70.5 years. The immunophenotypes were divided into B-PLL (7 cases) and T-PLL (1 case). Morphological, flow cytometric, cytogenetic and molecular biological tests of bone marrow cells were performed in all patients. Among them, 1 case refused chemotherapy after diagnosis and died in a short time, the other 7 cases received standard chemotherapy. Among the 7 patients, one patient died of severe infection caused by myelosuppression after chemotherapy, one patient died within 3 months after chemotherapy; two patients died of progression at 4 and 7 months after chemotherapy. A total of 3 patients achieved complete remission (CR) after chemotherapy, and 1 patient underwent allogeneic hematopoietic stem cell transplantation without disease progression or recurrence. Conclusion: PLL is a rare lymphoid malignancy with an extremely poor prognosis, which tends to occur in the elderly, and the clinical manifestations of PLL lack specificity. Chemotherapy combined with targeted drugs or epigenetic drugs may benefit PLL patients. Hematopoietic stem cell transplantation should be performed after CR is obtained to improve the prognosis to the greatest extent.

Keywords: Prolymphocytic leukemia, diagnosis, differential diagnosis, treatment, prognosis

Introduction

Prolymphocytic leukemia (PLL) is an extremely rare malignant clonal tumor of mature lymphocytes, which can be divided into B-PLL and T-PLL according to immunophenotype. Due to its high aggressiveness and heterogeneity, PLL has poor response to conventional chemotherapy, poor prognosis and easy recurrence, which is generally found in elderly male patients, accounting for less than 1% of lymphocytic leukemia [1, 2]. Considering that PLL usually invades bone marrow, peripheral blood and spleen, the clinical manifestations, symptoms and signs lack specificity, and it usually needs to be clearly diagnosed by bone marrow morphology, flow immunotyping and pathology. In view of the low incidence of PLL, at present, there are few clinical studies on PLL at home and abroad, and most of them are reported in single-center cases. The studies on the pathogenesis, differentiation and diagnosis, treatment and prognosis of PLL are relatively simple and limited. To this end, the clinical data of 8 patients with PLL admitted to the Fujian Medical University Union Hospital over the past 12 years were retrospectively studied in this paper, and the clinical diagnosis, treatment and prognosis

of PLL were analyzed and discussed, aiming to improve the understanding of rare PLL in the field of hematology and oncology, and provide new ideas for the basic research and clinical diagnosis and treatment of PLL.

Materials and methods

Clinical data

The clinical data of 8 patients with PLL admitted to the Department of Hematology, Fujian Medical University Union Hospital from January 1, 2011 to May 31, 2023 were retrospectively analyzed and collated. Among them, 6 were male and 2 was female. Age ranged from 52 to 80 years, with a median age of 70.5 years. Diagnostic criteria refer to the World Health Organization (WHO) classification criteria for lymphopoietic and hematopoietic tumors. Inclusion criteria: (1) Initial treatment of PLL, that is, did not receive any clinical intervention treatment in other hospitals; (2) The diagnosis was confirmed by peripheral blood smear, bone marrow routine (cytochemical staining), bone marrow pathological biopsy, flow immunotyping, cytogenetic detection and molecular biological examination. Exclusion criteria: (1) PLL transformed from other hematologic malignancies; (2) Recurrent PLL; (3) Treatment-related (post-chemotherapy or post-transplant) PLL; (4) A history of other malignant tumors (complex or multiple cancers).

Collected clinical data of 8 patients with PLL (such as age, gender, and whether associated with anemia, bleeding, infection and clinical manifestations of liver, spleen, lymph node enlargement, etc.), laboratory results (such as routine blood routine, blood biochemistry, bone marrow and pathological results, flow cytometry immune classification and cytogenetics, molecular biology test results), imaging examination results (such as CT, PET-CT, ultrasound, etc.) and related materials such as treatment plans. This study was approved by the Ethics Committee of Fujian Medical University Union Hospital (Grant number: 2019KY097) with the knowledge and consent of patients or their families. The baseline data of patients included in this study are detailed in **Table 1**.

Diagnostic method

The following conditions were met for the diagnosis of PLL [3]: (1) B-PLL (B-cell prolymphocytic leukemia) usually presents with giant spleen without obvious enlargement of lymph nodes, while T-PLL (T-cell prolymphocytic leukemia) mostly has enlargement of liver, spleen and lymph nodes; (2) The white blood cell (WBC) count in peripheral blood was increased, usually > 100×10^9/L, and the proportion of naive lymphocytes in lymphocytes was ≥ 55%; (3) PLL naive lymphocytes are morphologically large, basophilic in cytoplasm, with round nuclei, clearly visible nucleolus, dense chromatin and karyoplasmic ratio is low; (4) In immunotyping, sIgM and sIgD of B-PLL were highly expressed, and CD19+, CD20+, CD22+, CD79a+, FMC7+, CD23- and CD5 could be positive. T-PLL usually showes CD2+, sCD3+/-, cCD3+/-, CD5+, CD7+, TdT-, CD1a-, and some patients may have CD4+CD8- or CD4+CD8+ or CD4-CD8+.

All patients included in this study underwent bone marrow puncture biopsy after admission, bone marrow smear was stained by morphology and cytochemistry, and bone marrow biopsy was stained by immunohistochemistry. At the same time, the corresponding bone marrow samples were collected to improve the detection of immune typing (flow cytometry), genetics (chromosome) and molecular biology (fusion and mutated genes). Comprehensive diagnosis of PLL was performed after the above medical detection results were reported.

Therapeutic schedule (regimen)

Since there is no international consensus protocol for the treatment of PLL in the field of hematology, and the eight patients with PLL included in this study were admitted between 2011 and 2023, after the diagnosis of PLL patients, the induction remission chemotherapy regimen was formulated by integrating the academic literature at that time and the well-known hematologists in our hospital. So in this study, 8 patients with PLL were included, 7 with B-PLL and 1 with T-PLL. Except for 1 patient with B-PLL who refused chemotherapy after diagnosis and received symptomatic supportive treatment (hydroxyurea for leukocyte reduction, alkalization, hydration, etc.), the other 7 patients were treated with chemotherapy. Among the 7 PLL patients, two patients with B-PLL were treated with FC regimen and mini-CHOP regimen for 2 courses each. One B-PLL patient received one course of R-CP regimen and one course of R-COP regimen. One B-PLL

Table 1. Clinical features and laboratory indicators of 8 patients with PLL

Number	Gender	Age (years)	Initial symptom	Clinical hematological symptoms					Peripheral blood index				
				Anaemia	Hemorrhage	Fever	Hepatosplenomegaly	Enlargement of the lymph nodes	WBC ($\times10^9$/L)	HGB (g/L)	PLT ($\times10^9$/L)	LDH (IU/L)	Proportion of peripheral blood lymphocytes (%)
1	Male	74	None (only found during physical examination)	Positive	Negative	Negative	Positive	Positive	132.6	94	130	468	56.9
2	Female	69	General pain and discomfort	Positive	Negative	Positive	Giant splenomegaly	Positive	196.1	91	75	487	87.5
3	Male	71	Fatigue	Positive	Negative	Negative	Negative	Positive	71.45	106	485	312	83.1
4	Male	65	Abdominal bloating	Positive	Negative	Positive	Giant splenomegaly	Positive	116.79	99	94	443	52.1
5	Male	76	Dizziness and fatigue	Positive	Negative	Negative	Giant splenomegaly	Positive	125.7	81	73	563	66.6
6	Male	70	Dizziness and fatigue	Positive	Negative	Negative	Giant splenomegaly	Positive	376.1	74	99	884	72.8
7	Male	80	Recurrent cough	Positive	Negative	Negative	Positive	Negative	74.55	95	98	504	63.7
8	Female	52	Abdominal bloating	Positive	Negative	Negative	Giant splenomegaly	Negative	92.36	74	94	258	58.3

Note: PLL: prolymphocytic leukemia; WBC: White blood cell count; HGB: Hemoglobin; PLT: Platelet count; LDH: lactate dehydrogenase.

Table 2. Chemotherapy regimens and usage in 8 patients with PLL

Chemotherapy regimen	Specific types and usage of chemotherapy drugs
FC regimen	Fludarabine 25 mg/m^2, intravenous d1-3; Cyclophosphamide 250 mg/m^2, intravenous d1-3
mini-CHOP regimen	Vindesine 3 mg/m^2, intravenous d1; Cyclophosphamide 400 mg/m^2, intravenous d1; Liposomal Doxorubicin 30 mg/m^2, intravenous d1; Dexamethasone 6 mg/m^2, intravenous d1-5
R-CP regimen	Rituximab 375 mg/m^2, intravenous d0; Cyclophosphamide 750 mg/m^2, intravenous d1; Prednisone 60 mg/m^2, orally d1-5
R-COP regimen	Rituximab 500 mg, intravenous d0; Cyclophosphamide 600 mg, intravenous d1; Liposomal doxorubicin 20 mg, intravenous d1; Dexamethasone 10 mg, intravenous d1-5
VFD regimen	Vindesine 3 mg/m^2, intravenous d1; Fludarabine 25 mg/m^2, intravenous d1-3; Dexamethasone 6 mg/m^2, intravenous d1-5
CP regimen combined with R-FC regimen	CP regimen (Cyclophosphamide 750 mg/m^2, intravenous d1; Prednisone 60 mg/m^2, orally d1-5) combined with R-FC regimen (Cyclophosphamide 750 mg/m^2, intravenous d1; Prednisone 60 mg/m^2, orally d1-5; Rituximab 375 mg/m^2, intravenous d0; Fludarabine 25 mg/m^2, intravenous d1-3; Cyclophosphamide 250 mg/m^2, intravenous d1-3)
Chidamide combined with P-Gemox regimen	Chidamide combined with P-Gemox regimen (Chidamide 30 mg/time, 2 times/week, continuous medication; Gemcitabine 800~1000 mg/m^2, intravenous d1, d8; Oxaliplatin 130 mg/m^2, intravenous d1; Pegaspargase 2500 IU/m^2, intravenous d2)

patient received 2 courses of VFD. Two B-PLL patients received CP regimen combined with R-FC regimen for 1 course of treatment. One patient with T-PLL was treated with Chidamide combined with P-Gemox for 1 course of chemotherapy. Details of specific chemotherapy regimen and usage of chemotherapy drugs are shown in **Table 2**.

Curative effect evaluation

To evaluate the efficacy of patients we conducted bone marrow puncture between 21 and 28 days after the completion of the full course of chemotherapy, and the evaluation and judgment of the efficacy were made by referring to the diagnosis and efficacy criteria of blood diseases. Firstly, complete remission (CR): (1) Symptoms disappeared and signs completely returned to normal; (2) The three blood lines returned to normal, with hemoglobin ≥ 120 g/L, platelets ≥ 100×10^9/L, absolute lymphocyte count (ALC) ≥ 1.5×10^9/L, and no naive lymphocytes in blood smears; (3) The bone marrow image returned to normal, the naive lymphocytes were small, and the lymphocyte value was in the normal range. Secondly, partial remission (PR): liver and spleen shrinkage > 50%, more than two samples of peripheral blood were recovered or nearly normal, and the reduction of naive lymphocytes in blood smear was > 50%. Thirdly, progress: the physical signs were improved, the blood signs were improved in the peripheral blood, and the naive lymphocytes in the blood and bone marrow were reduced. Finally, invalid: The above indicators are not met.

Efficacy evaluation and follow-up

The follow-up method adopted in this study was telephone and electronic inpatient record system was used to follow up the indicators of the patients' recent return to the hospital for re-examination and hospitalization status. The follow-up period was up to May 31, 2023, and the follow-up frequency was to follow up the latest survival situation of patients once a month. For patients who had already reached endpoint events (such as death), the time and cause of death were recorded in detail, and other patients would continue to be followed up. Disease free survival (DFS) is the period from CR to disease recurrence, and overall survival (OS) is the period from diagnosis to death.

Statistical analysis

Statistical analysis and plotting were performed by GraphPad Prism 7 software, and SPSS 20.0 software was used for data processing. Measurement data are expressed as median (range), and counting data are expressed as cases and percentages. The survival curve was plotted by Kaplan-Meier method.

Result

Morphological and cytochemical staining of bone marrow cells of PLL

In the bone marrow of PLL patients, there is active proliferation of nuclear cells, and diffuse infiltration of prolymphocytic cells can be seen, and the proliferation of other cells is suppressed. The volume of the prolymphocytic cells is slightly larger than that of the lymphocyte, about 12-14 μm in diameter, the cytoplasm is rich, basophilic, light blue, no particles, low nuclear/plasma ratio, round or oval nuclei, and some incisors may be serrated or irregular. The nuclear chromatin is slightly coarser than that of the proto-lymphocyte, but slightly finer than that of the mature lymphocyte. It is granular or massive. There is relatively more chromatin around the nuclear membrane, and the nucleolus is large, prominent, and mostly single. Peroxidase stain (POX) and naphthol-AS-D chloracetateesterase stain (AS-DCE) were negative. While periodic acid-Schiff reaction (PAS) was positive, and the positive particles were massive and distributed in the cytoplasm with different sizes. Some of α-naphthol acetate esterace (α-NAE) showed a weak brown-black positive reaction, which was not inhibited by sodium fluoride (NaF). As shown in **Figure 1**.

Flow immunotyping, cytogenetics and molecular biology detection

In this study, all patients with PLL have had flow immunotyping and cytogenetic detection. As shown in **Table 3**.

Prognostic follow-up and outcome

Among the 8 patients with PLL included in this study, 1 patient refused chemotherapy after diagnosis and received symptomatic supportive treatment such as hydroxyurea for leukocyte reduction, alkalization, hydration, and anti-

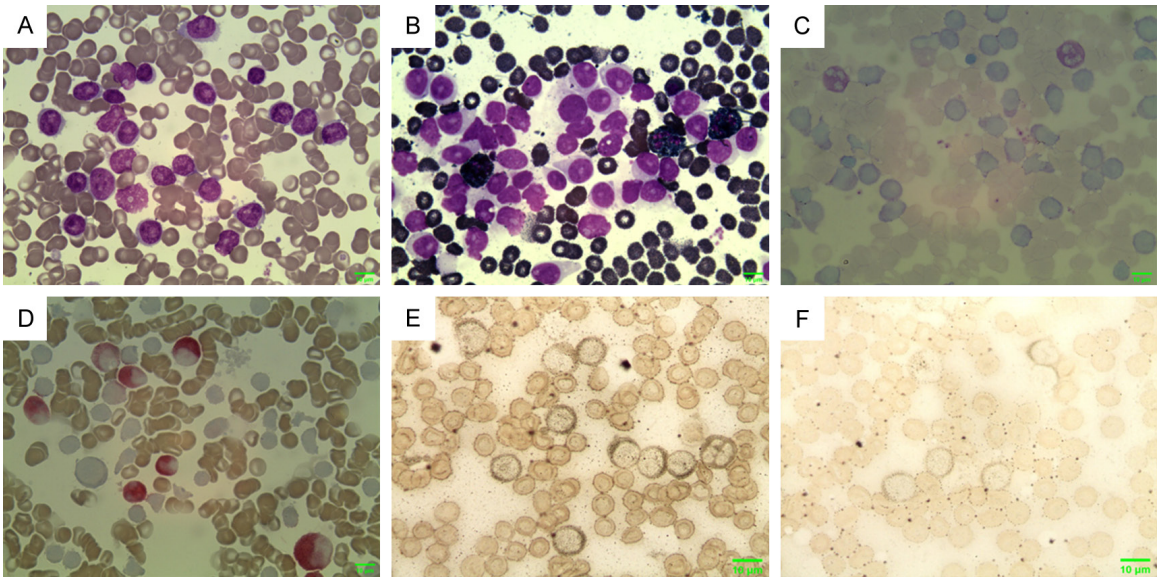

Figure 1. Cytochemical staining of bone marrow in PLL patients (all ×400). Note: A. Wright-Giemsa staining showed diffuse infiltration of nematocytic cells and inhibited proliferation of other cells. B. POX staining was negative. C. PAS staining showed that the original cells were block-positive. D. AS-DCE staining was negative. E. α-NAE staining showed weak brown-black positive. F. Sodium fluoride inhibition test (NAF) showed that primitive naive cells were not inhibited.

Table 3. Flow cytometry typing and cytogenetic and molecular biological detection results of PLL patients

Case number	Flow immunotyping antigen expression types	Genetic karyotype test results	Molecular biology test results
1	87.1% cells (all nucleated cells) expressed CD19, CD20, CD22, CD5, HLA-DR, CyCD79a, CD38, Kappa and IgM	Normal karyotype	Negative
2	97.3% cells (all nucleated cells) expressed CD19, CD20, CD22, HLA-DR, FMC7, CD23, CD79b, CyCD79a, CD38, Lambda, IgM	t(8; 14)	Fusion gene IGH rearrangement, TP53 mutation
3	79.3% of cells (all nucleated cells) expressed CD2, CD7, CD5, CD4 and CyCD3	Normal karyotype	JAK3, EZH2 mutations
4	84.3% cells (all nucleated cells) expressed CD22, CD20, cCD79a, FMC7, CD79b, IgM, Kappa, and did not express CD5, CD10, CD200, CD23, and Lambda	del 17p	MYC, TP53 mutations
5	79.4% cells (all nucleated cells) expressed CD19, CD20, CD22, CD5, FMC7, CD23, CD79b, cCD79a and Kappa/Lambda	Normal karyotype	Fusion gene IGK, IGL rearrangement
6	96.3% cells (all nucleated cells) expressed CD19, CD20, CD22, FMC7, CD23, CD24, cCD79a, CD25 and SmIg	del (17)(p12)	MYC, TP53 mutations
7	89.6% of cells (all nucleated cells) expressed CD19, CD20, CD22, CD5, HLA-DR, CD25, CD23, cCD79a	Normal karyotype	Negative
8	79.8% cells (all nucleated cells) expressed CD20, CD22, CD19, HLA-DR, CD11c dim, CD38 dim, Kappa	46,X,add(X)(p22),?add(14)(q32),add(19)(p13),inc[cp6]/46,XX [5]	Negative

Note: CD: Leukocyte differentiation antigen; CD19, CD20, CD5, CD22, CD23, CD24, CD79, CD25, FMC7, CD200 and SmIg are B-cell antigens. CD2, CD4, CD3, CD7 are T cell antigens; Kappa: Kappa type (κ) light chain antigen; Lambda: Lambda type (λ) light chain antigen; CD38: Plasma cell antigen; IgM: Immunoglobulin M (B-PLL specific high expression); HLA-DR: hematopoietic progenitor cell antigen; IGH: Immunoglobulin heavy chain gene; IGK: Light chain (κ) chain gene; IGL: Light chain (λ) chain gene.

infection, and died after discharge (specific details are unknown). The other 7 patients were treated with chemotherapy, except for 1 patient who died of severe infection caused by bone marrow suppression after chemotherapy, 1 patient died within 3 months after chemotherapy, 2 patients died of disease progression within 4 months and 7 months after chemotherapy. Three patients reached CR after chemotherapy, and 1 patient underwent allogeneic hematopoietic stem cell transplantation and is still alive, no progression or recurrence occurred. The survival curve of all PLL patients in this study is shown in **Figure 2**.

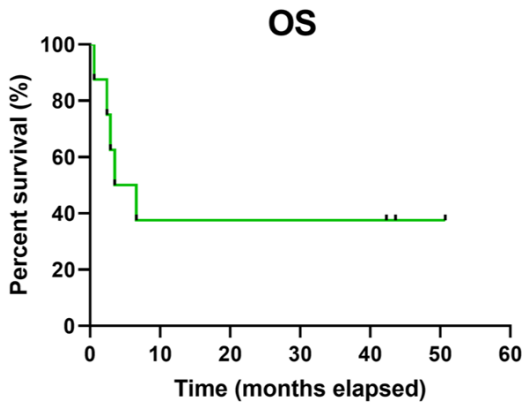

Figure 2. Survival curve of 8 PLL patients in this study.

Discussion

PLL is an extremely rare malignant proliferative tumor of mature lymphocytes, it is highly heterogeneous and invasive, and is more common in elderly men and has poor prognosis [1, 2]. PLL originates from B or T lymphocytes and can be divided into B-PLL and T-PLL according to their immunophenotype, of which B-PLL accounts for about 4/5 cases and T-PLL accounts for 1/5 [3]. The clinical manifestations of PLL are varied and lack specificity. Fatigue, spleen enlargement, or abdominal discomfort are usually the characteristics of PLL. About 60% of patients may have a large spleen or liver enlargement. Generally speaking, B-PLL may not have lymph node enlargement, while T-PLL often has multiple lymph node enlargement, and about 30% of T-PLL patients may have nodular rash on the trunk, upper limb or face, indicating skin infiltration [4]. In addition, due to the older age of PLL patients when they first visited the hospital, the routine blood indicates high white blood cells, and the symptoms or signs of correspondingly high tumor load may appear. Flow immunotyping is an effective method to distinguish PLL phenotypes. B-PLL often expresses SmIg, and CD19, CD20, CD22, CD79b, CD7 and FMC7 are positive, while CD5, CD23, CD11c, CD25 and CD103 are negative. T-PLL is positive for CD2, CD3, CD5, CD52, CD7 and cyTCL1, while TdT, CD1a, CD16, CD30 and CD20 are negative [5, 6]. As shown in **Tables 1** and **2** of this study, among the included patients, 6 cases were B-PLL and 1 case was T-PLL, all of whom were > 65 years old in terms of age of onset, 6 cases were male and 1 case was female. Routine blood examination after admission of all patients indicated high white blood cells and heavy tumor load, which was consistent with the characteristics of onset of PLL.

According to the 2017 WHO classification, T-PLL is defined as aggressive T-cell leukemia, which is a small T-lymphocytic proliferative tumor with both retrothymus origin T cells and mature T cell phenotypes [3], accounting for about 2% of adult CLL [7]. As early as the 1990s, Matutes et al. [8] found that the clinical manifestations of T-PLL patients included B symptoms, peripheral blood WBC > 100×10^9/L and abnormal increase of lymphocytes, often accompanied by lymph node enlargement or extranodal infiltration, about 1/4 of patients showed effusion in the skin or serous space, and a few patients were accompanied by central nervous system involvement. Since T-PLL is a highly heterogeneous malignant hematologic disease, bone marrow morphologic examination is usually the first step in the diagnosis of T-PLL, and flow cytometry and pathology examination should be actively improved. In addition, it is necessary to improve cytogenetic tests (chromosome karyotype analysis) and molecular biological tests (polymerase chain reaction detection, high-throughput second-generation sequencing) to make a definitive diagnosis. Clonal T cell receptor gene detection is a necessary condition for initial evaluation, and the detection of T-cell leukemia/lymphoma 1A (TCL1) protein using flow cytometry or immunohistochemistry is considered to be more sensitive than cytogenetics [5, 8].

Among the patients included in this study, only 1 patient was diagnosed with T-PLL. The patient had palpable swelling of superficial lymph nodes in multiple places throughout the body, and flow cytometry typing indicated abnormal T cells expressing CD7, CD2, CD5, CD4, and CyCD3. The biopsy pathology of cervical lymph nodes also indicated T-cell tumors and the molecular biological examination indicated abnormalities. In line with the characteristics of T-PLL, it was finally diagnosed as “T cell lymphocytic leukemia”. The common genetic abnormalities of T-PLL were inv(14) (q11q32) and t(14; 14) (q11; q32), the above genetic changes lead to overexpression of the proto-oncogenes TCL-1 and MTCP1, which in turn

lead to the aberrant activation of protein kinase B (PKB/Akt) and extracellular signal-regulated kinase (ERK) pathway promotes malignant proliferation of T-PLL cells [5, 9]. In addition, abnormal regulation of Janus activated kinase (JAK)/signal transducer and activator of transcription (STAT) pathway also plays an important role in the occurrence and development of T-PLL. Since there was only one T-PLL patient in this study, the genetic detection of this patient showed no abnormality, but the molecular biological detection found that this patient had Janus kinase 3 (JAK3) and enhancer of zeste homolog 2 (EZH2) mutation, suggesting that genetic and molecular abnormalities may play a key role in the pathogenesis of T-PLL. In conclusion, T-PLL, as an aggressive hematologic tumor, has a short median survival, and poor prognostic factors such as age > 65 years, presence of serous lumen effusion and extramedullary infiltration, abnormal peripheral blood lymphocyte count, elevated lactate dehydrogenase (LDH), elevated β2-microegg are adverse prognostic factors. Moreover, high expression of TCL1, AKT serine/threonine kinase 1 (AKT1) and JAK3 mutation in T-PLL also suggest poor prognosis [9].

Since T-PLL is a highly heterogeneous malignant hematologic disease, the differential diagnosis of T-PLL and indolent lymphocytic tumors should be clinically combined, diseases such as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Sézary syndrome, T cell large granular lymphocytic leukemia (LGL), adult T cell lymphoma/leukemia (ATLL), and hair cell leukemia (HCL) need to be distinguished from T-PLL [9]. (1) CLL/SLL cells may be positive for CD5 and CD23 to varying degrees, and weakly positive for CD22 and CD79b, but CD10 is usually negative, and genetic analysis often suggests 13q del, 11q del, 17p del, or trisomy 12. (2) Sézary syndrome cells were positive for CD2, CD3, CD4, and CD25, while negative for TCL1, CD7, and CD26. About 20% of patients were accompanied by skin lesions, which could be definitively diagnosed by skin biopsy. (3) LGL cells were negative for TCL1, but positive for CD2, CD3, CD8, CD16 and CD57, and expressed CD7 to varying degrees, and rarely expressed CD4. The median survival of LGL patients is > 10 years, and neutropenia is common in clinical practice. LGL patients may be accompanied by hepatosplenomegaly and myofibrosis, but there is rarely lymph node enlargement. Cytological examination often shows large lymphocytes containing cyanophil granules. (4) ATLL patients are often accompanied by human T-cell leukemia virus I (HTLV-1) infection, TCL1 and CD7 were negative, CD3, CD4 and CD25 were positive, ATLL patients are prone to hypercalcemia and skin damage, and ATLL cells have unique petaloid or polymorphonuclear lymphocytes, that is, “flower cells” morphological manifestations. (5) HCL, as a rare hematologic tumor with low grade mature B cells in clinic, is often accompanied by a giant spleen. HCL can be divided into classic HCL (HCLc) and variant HCL (HCLv). The immunophenotypes of HCLc cells often expressed CD19, CD20, CD11c, CD25, CD103, CD123 and CD200, while CD27 was negative. For HCL that does not express CD5, CD10, CD25, CD123 and Annexin A1, it is HCLv. B-Raf proto-oncogene serine/threonine protein kinase V600E mutant ($BRAF^{V600E}$) mutation is a specific molecular biological abnormality of HCL. In addition, HCL cells have characteristic serrated cytoplasmic boundaries, with typical “hair-like” bulges in cell morphology.

For the treatment of T-PLL, as there are few clinical trials for T-PLL and CHOP chemotherapy is ineffective, current studies [10] believe that CD52 monoclonal antibody Alemtuzumab is the best first-line therapy for T-PLL to achieve CR, with an overall response rate (ORR) of up to 90%, and progression-free survival (PFS) is 8 to 11 months, but unfortunately, T-PLL is prone to relapse and difficult to treat, therefore, allogeneic stem cell transplantation should be considered as early as possible when CR is achieved, which will be beneficial to improve the survival of T-PLL patients [11]. However, the latest study of Jain et al. [12] found that more than half of T-PLL patients had complex karyotypes and aberrations on chromosome 14, and the median OS of T-PLL patients was 19 months. In addition, the ORR and CR of patients receiving Alemtuzumab alone and Alemtuzumab combined with Penstatin were 83%, 66% and 82%, 73%, respectively. Bone marrow transplantation in patients with initial CR was not associated with long-term PFS and OS. It is noteworthy that Bendamustine, as a conventional alkylating agent for the treatment of CLL and inert lymphoma, can also benefit T-PLL patients who do not respond to first-line

Alemtuzumab monotherapy due to its unique cytotoxicity [13]. In addition, CDK9 inhibitor LDC526 and its derivative Atuveciclib can up-regulate the expression of tumor suppressor FBXW7, down-regulate the expression of MYC and MCL1, and inhibit the activation of JAK-STAT signaling pathway, thus inducing the programmed death of T-PLL cells, and then play an anti-leukemia role. Correspondingly, the combination of Atuvecliclib and the Bcl-2 inhibitor Venetoclax showed good synergistic anti-leukemia activity [14]. At present, epigenetic drugs have become an important and effective therapy for hematologic tumors, and studies have confirmed that Venetoclax alone or in combination with Ruxolitinib is a promising clinical strategy for the treatment of refractory T-PLL patients [15, 16]. At the same time, Toutah et al. [17] found that HDAC6 was highly expressed in T-PLL patients and developed an HDAC6 inhibitor, KT-531, which showed good safety, reliable biological activity and specificity against T-PLL. Equally, KT-531 also has a good synergistic effect when combined with Bendamustine, Idasanutlin and Venetoclax, prolongs the survival of T-PLL patients. However, allogeneic hematopoietic cell transplantation can improve the prognosis of T-PLL patients with stable disease and CR in the short term [18]. In this study, the patient with T-PLL was treated with P-Gemox combined with Chidamide for 1 course after diagnosis, and the effect was satisfactory without adverse reactions. The blood image returned to normal and lymph nodes were smaller than before. After discharge, the patient continued chemotherapy in a local hospital, and the blood image and bone marrow status were regularly reviewed. This patient did not experience disease progression or other adverse events, suggesting that P-Gemox in combination with epigenetic agents such as Chidamide could benefit T-PLL patients.

B-PLL is also a rare and highly aggressive leukemia, accounting for less than 1% of B-cell leukemia/lymphoma, which is prone to drug resistance and chemotherapy resistance to induction chemotherapy regimen, poor sensitivity and poor efficacy of novel targeted therapy, with a median OS of only 3 years [19]. Previous studies have suggested that B-PLL is a variant or subtype of chronic lymphocytic leukemia (CLL), but according to the 2008 WHO classification and the 2016 WHO Revised Classification of Lymphoma, B-PLL is a special type of mature B-cell proliferative tumor [3]. Patients with B-PLL are often accompanied by B symptoms, while peripheral lymph node enlargement is rare, and peripheral blood WBC > 100×10^9/L is accompanied by splenomegaly and peripheral hypocytosis, and further suggested that anemia and thrombocytopenia is often associated [20]. Moreover, when B-PLL patients relapse after treatment, central nervous system involvement, refractory hypercalcemia, soft tissue mass and other symptoms or signs may occur [21]. Due to B-PLL being similar to other mature B-cell leukemia/lymphoma, and lacking typical immunophenotype or cytogenetic characteristics, B-PLL is difficult to diagnose, resulting in some B-PLL patients being missed or misdiagnosed clinically. From the perspective of morphology, B lymphocytes are slightly larger, round or oval in size, with nuclear chromatin condensation, central nucleolus protrusion, and cytoplasm without hairlike or villous processes [21]. Although cell morphology can assist in the diagnosis of B-PLL, flow immunotyping of bone marrow or peripheral blood cells or improved cytogenetic and molecular biological assaying is needed to make a more accurate diagnosis. In immunophenotypic analysis, B-PLL, as a monoclonal B-cell tumor, usually expresses bright IgM+/-IgD, IGκB, or λ light chains and is positive for CD20, CD19, CD22, CD79a, and FMC7, while CD11c, CD103, CD10, CD25, and CyclinD1 are generally negative, which helps to link B-PLL with other lymphocytic proliferative tumors, such as T lymphoblastic lymphoma/leukemia (T-LBL/ALL), mantle cell lymphoma (MCL), follicular lymphoma (FL), lymphoplasmacytic lymphoma (LPL), splenic marginal zone lymphoma (SMZL) and HCL were differentiated [20]. Some studies [22] have shown that B-PLL can be transformed from CLL, so the neocytes of B-PLL will retain the immunophenotype of CLL. In addition, common cytogenetic abnormalities of B-PLL include MYC rearrangement/overexpression and 17p, 13q14 deletion or TP53 mutation, and B-PLL does not respond to most chemotherapy protocols and novel targeted therapies, and 17p deletion or TP53 mutation suggest poor prognosis of B-PLL [23]. In this study, except for one T-PLL patient, the remaining 7 patients were B-PLL patients, most of whom were accompanied by genetic and molecular biological abnormalities, with strong

clinical heterogeneity, involvement of hematopoietic cells, heavy tumor load, poor response to conventional chemotherapy, short survival, poor prognosis, and death within a short time after diagnosis, which was basically consistent with the conclusions of previous studies.

From the perspective of B-PLL treatment, Hew et al. [24] reported a B-PLL patient who received the combination treatment of Rituximab and Bendamustine with poor effect and whose disease continued to progress, and this B-PLL patient obtain CR after 4 courses of treatment by applying the novel monoclonal antibody Obinutuzumab combined with Chlorambucil. Similarly, Ibrutinib alone or in combination with Venetoclax has a good effect on B-PLL with del17p and TP53 mutations, and negative measurable residual disease (MRD) can be measurable for a long time [25, 26]. Meanwhile, Zanubrutinib, Rituximab, and Lenalidomide induced long-term remission in TP53-mutated B-PLL [27]. Chapiro et al. [28] found that B-PLL patients were often accompanied by MYC and TP53 mutations and genetic abnormalities, and in vitro studies found that MYC-targeting inhibitor OTX015 could significantly reduce the activity of B-PLL cells, indicating that targeting MYC would be a potentially effective treatment for B-PLL. Phenyl ethyl isothiocyanate (PEITC), a natural compound, Nachat et al. [29] reported a case of B-PLL in an elderly male patient transformed from CLL. The patient was treated with PEITC and R-CHOP and initially achieved hematological remission. After 8 consecutive weeks of PEITC combined with Penstatin and 6 cycles of R-CHOP, CR was obtained, and allogeneic hematopoietic stem cell transplantation was performed. The prognosis was satisfactory. It is worth noting that CD52 monoclonal antibody Alemtuzumab and anti-Bruton tyrosine kinase (BTK) inhibitor Ibrutinib have shown considerable efficacy in B-PLL treatment [30]. Although B-PLL is prone to relapse and difficult to treat, current studies have shown that after the use of B cell antigen receptor (BCR) inhibitors, such as Ibrutinib, Idelalisib and Venetoclax, B-PLL patients can achieve long-term clinical remission [31, 32].

In summary, PLL, as a clinically rare lymphocytic tumor, is generally found in the elderly population. Its clinical symptoms and signs lack specificity, and it is easy to be misdiagnosed or missed, thus delaying the treatment opportunity of patients, resulting in low long-term survival rate and poor prognosis of the disease. Due to the lack of treatment guidelines and consensus on PLL diseases in domestic and foreign academia, in addition to conventional chemotherapy regimen, clinical trials can be preferred, and induction remission chemotherapy combined with new targeted drugs or epigenetic drugs may benefit PLL patients. Admittedly, complications should be actively prevented, and hematopoietic stem cell transplantation should be performed as soon as possible after CR to improve the prognosis and outcome of PLL patients to the greatest extent. In the future, we should actively explore the pathogenesis of PLL and the development and exploration of new targeted drugs from the perspectives of genetics, molecular biology or immunology, so as to bring new references for the clinical diagnosis, treatment and basic research of rare elderly hematological malignancies.

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Disclosure of conflict of interest

None.

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