Chidamide in combination with azacitidine for an elderly patient with peripheral T cell lymphoma-not otherwise specified: A case report

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Abstract. Peripheral T cell lymphoma (PTCL) is a type of aggressive non-Hodgkin's lymphoma with poor prognosis. PTCL-not otherwise specified (PTCL-NOS) is one of its most common pathological types. PTCL is not sensitive to conventional chemotherapy regimens and treatment is particularly limited in elderly patients due to their poor tolerance to chemotherapy. The present report shares the treatment experience of one elderly PTCL-NOS case, which achieved complete remission by reduced-intensity chemotherapy with chidamide in combination with azacitidine following the onset of organ failure and chemotherapy insensitivity. The 9-month follow-up showed sustained remission and the long-term efficacy of this regimen is also promising.

Introduction

Peripheral T cell lymphoma (PTCL) is a malignant tumor of the lymphatic system originating from mature natural killer or T cells, and is a type of aggressive non-Hodgkin's lymphoma with poor prognosis (1). It accounts for ~10% of all lymphomas in western countries and 20% in Asian populations (1). Different pathological types of PTCL have distinct immunophenotypes, molecular characteristics and clinical manifestations but all show low sensitivity to chemotherapy. PTCL-not otherwise specified (NOS) is the most common pathological subtype of PTCL, accounting for 21-27% of PTCL cases. PTCL-NOS predominantly occurs in middle-aged and elderly individuals and is more aggressive than B cell lymphoma with a 5-year overall survival (OS) rate of 20-30% (2). Even with intensive treatment, 5-year progression-free survival (PFS) rate is ~20% (3). Moreover, due to the prevalence of underlying disease and weakened organ functions in elderly patients, they are often unable to tolerate standard doses of chemotherapy, which further decreases the treatment effect. Our center, (The 940th Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army; Lanzhou, China), successfully treated an elderly patient with PTCL-NOS with Tet methylcytosine dioxygenase 2 (TET2) and DNA methyltransferase 3α (DNMT3A) gene mutations which were the two causative genes of PCTL. The patient achieved complete remission after combined chemotherapy with azacitidine and chidamide.

Case report

A 71-year-old male patient visited The 940th Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army in February 2023 due to enlargement of lymph nodes in multiple parts of the body. There was no history of diabetes, hypertension or heart disease. He had no symptoms such as fatigue, fever or night sweats, but showed a weight loss >5 kg over the past 6 months. Hematological results were as follows: White blood cell count, $13.42x10^9$/l (reference range, 3.5-$9.5x10^9$/l); lymphocyte count, $1.08x10^9$/l (reference range, 0.8-$4.0x10^9$/l); neutrophil count, $9.98x10^9$/l (reference range, 2.0-$7.0x10^9$/l); red blood cell count, $5.34x10^{12}$/l (reference range, 4.09-$5.74x10^{12}$/l); hemoglobin, 165 g/l (reference range, 131-172 g/l); platelet count, $97x10^9$/l (reference range, 85-$303x10^9$/l); β2-microglobulin (β2-MG), 4.47 mg/l (reference range, 0.97-2.64 mg/l) and lactate dehydrogenase (LDH), 586 IU/l (reference range, 120-250 IU/l); hepatitis series tests were normal (Table I). Superficial lymph node ultrasound revealed multiple enlarged lymph nodes in bilateral neck, axillary and inguinal areas with the largest measuring 3.1x1.6, 2.8x1.9 and 3.3x1.6 cm at each location, respectively, with unclear lymph node hilum structure, suggestive of lymphoma. A neck lymph node biopsy was performed. Briefly, tissue was fixed with 4% paraformaldehyde overnight at room

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temperature, embedded in paraffin and sliced into 5-μm sections. The sections were stained by hematoxylin and eosin staining. For immunohistochemistry, the sections were then dewaxed by heating to 65˚C followed by three washes with xylene, and rehydrated via an ethanol series. The sections were treated with 3% H_2O_2 for 10 min to block endogenous peroxidase activity and then blocked with 5% bovine serum albumin for 10 min at 37˚C. Afterwards, sections were incubated with primary antibodies for 1 h at 25˚C and with the secondary antibody at room temperature for 30 min at 25˚C. Observation of sections at x400 and x200 was carried out by a BX53 biological light microscope (Olympus Corporation).Pathology showed lymph node structure damage with diffuse distribution of medium-sized atypical cells and eosinophil infiltration. The tumor cells were characterized by irregular nuclei, prominent nucleoli and scant cytoplasm (Fig. 1A). Tumor cells were negative for EBV-encoded RNA, as well as CD10, 15, 20, 30 and 56, Multiple Myeloma Oncogene 1 and granzyme B (Fig. 1B-P). Tumor cells were positive for CD3-5 and 8, CD21 follicular reticulum and CD38 plasma cells. Ki67 index was ~40%. These results were suggestive of PTCL-NOS. Positron emission tomography/computed tomography (PET-CT; Siemens Biograph 64 True Point; Siemens AG; CT scan parameters were as follows: Tube voltage, 120 kV; automatic tube current; layer thickness, 3 mm and layer spacing, 0.8 mm; Fig. 2A-C) revealed abnormally increased fluorodeoxyglucose (FDG) uptake in multiregional lymph nodes [maximum standard uptake value (SUV) in the neck lymph nodes, 7.79; maximum SUV in the inguinal lymph nodes, 6.88], consistent with stage III lymphocytoma [5-point scale (5-PS) score, 5]. FDG is a glucose analog used to evaluate glucose metabolism by measuring uptake. The PET/CT results were assessed according to the Deauville 5-PS criteria. The 5-PS scoring system was used to qualitatively evaluate the treatment response as follows: i) No uptake; ii) uptake ≤ mediastinal blood pool; iii) uptake > mediastinal blood pool; iv) uptake moderately increased compared with the liver uptake at any site; and v) uptake markedly increased compared with the liver. The 5-PS scoring system was used to qualitatively evaluate the treatment response as follows: i) no uptake; ii) uptake ≤ mediastinal blood pool; iii) uptake > mediastinal blood pool, but ≤ liver; iv) uptake moderately increased compared with the liver uptake at any site; and v) uptake markedly increased compared with the liver at any site. Scores of 4-5 were considered positive, while scores of 1-3 were considered negative (4). The bone marrow cell morphology examination included posterior iliac crest bone marrow aspirate smears were that stained with Wright-Giemsa for 2 min and then rinsed with phosphate buffer (pH 7.0) for another 10 min at room temperature. The image was collected by a light microscope (Olympus BX-53; Olympus Corporation; magnification, x1,000.) and showed no abnormality. Next generation sequencing on a targeted panel of 15 genes was performed by Suzhou Youqin Medical Laboratory on formalin-fixed, paraffin-embedded tumor tissue. Sequencing analyses revealed DNMT3A and TET2 mutations (Table II). There were no mutations in Ras Homolog Family Member A (RHOA) or Isocitrate Dehydrogenase 2 (IDH2) genes. The patient was diagnosed with PTCL-NOS, stage IIIB, (5) International Prognostic Index (IPI) score of 4. CHOEP chemotherapy regimen was administered [cyclophosphamide, 1 g, intravenous (IV) drip, D1; liposomal doxorubicin, 20 mg, IV drip, D1; vincristine, 2 mg, IV drip, D1; etoposide injection, 0.1 g, IV drip, D1-3; prednisone tablets 60 mg/day, D1-5]. The chemotherapy process went smoothly, and no other serious adverse reactions or suspected unexpected adverse reactions occurred. The patient was discharged after treatment in February 2023. In March 2023, CHOEP chemotherapy regimen was continued as a second-course treatment, but the patient had poor tolerance and developed acute renal failure and cardiac insufficiency. The condition gradually stabilized following dialysis treatment. In May 2023, a follow-up ultrasound of superficial lymph nodes showed a slight decrease in size (largest neck lymph node, 2.1x1.3; largest axillary lymph node, 3.0x1.4 and largest inguinal lymph node, 2.3x1.2 cm). The patient was treated with the COEP regimen combined with chidamide [cyclophosphamide, 1 g, IV drip, D1; vincristine, 2 mg, IV drip, D1; etoposide injection, 0.1 g, IV drip, D1-3; prednisone tablets 50 mg/day, D1-5; chidamide, 20 mg, PO orally, twice weekly (biw)]. The treatment proceeded smoothly, and no serious adverse reactions occurred during the treatment. In June 2023, follow-up ultrasound revealed an increase in lymph node size (largest neck lymph node, 2.71.4; largest axillary lymph node, 3.6x1.5; largest inguinal lymph node, 4.5x1.8 cm), suggesting progression of the primary disease. The patient received combined treatment with chidamide + azacitidine + COP (chidamide, 20 mg, PO biw; azacitidine, 100 mg, subcutaneous injection (SC), D1-7; cyclophosphamide, 1 g, IV drip, D1; vincristine, 2 mg, IV drip, D1; prednisone tablets, 50 mg PO, D1-5). After 4 weeks, follow-up ultrasound of the lymph nodes showed notably decreased size (largest neck lymph node, 1.4x0.6; largest axillary lymph node, 1.9x0.7; largest inguinal lymph node, 1.7x0.5 cm). PET-CT (Fig. 2D-F) scan revealed a mild increase in FDG metabolism in multiregional lymph nodes (maximum SUV in the neck lymph nodes, 2.65; metabolic activity in the inguinal lymph nodes disappeared), consistent with complete remission (CR) phase metabolic changes

Table I. Laboratory data at the time of the initial visit.

Parameter	Result
White blood cell count	13.32x10^9/l
Hemoglobin	165.00 g/l
Platelet count	97.00x10^9/l
Lymphocyte count	1.08 x10^9/l
Lactate dehydrogenase	586.00 IU/l
β2-microglobulin	4.47 mg/l
Creatinine	68.00 μmol/l
Uric acid	305.00 μmol/l
Hepatitis B virus	Negative
Hepatitis C virus	Negative
Globulin	38.80 g/l

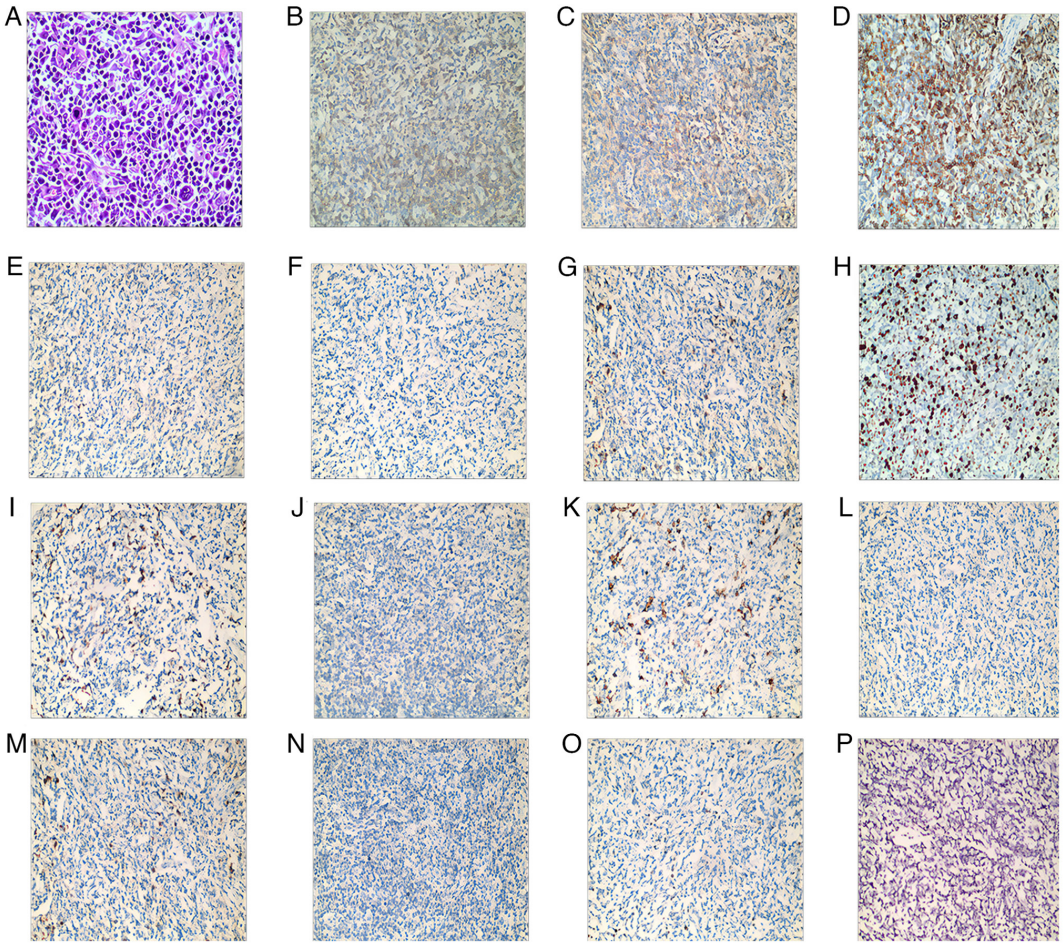

Figure 1. Histological morphology and immunohistochemical staining of the tumor. (A) Diffuse distribution of medium-sized atypical cells (magnification, x400). The tumor cells were positive for (B) CD3 (magnification, x200), (C) CD4 (magnification, x200), (D) CD5 (magnification, x200), (E) CD8 (magnification, x200), (F) CD21 (magnification, x200) and (G) CD38 (magnification, x200). (H) Ki67 index was ~40% (magnification, x200). Tumor cells were negative for (I) CD10 (magnification, x200), (J) CD15 (magnification, x200), (K) CD20 (magnification, x200), (L) CD30 (magnification, x200), (M) CD56 (magnification, x200), (N) granzyme B (magnification, x200), (O) multiple myeloma oncogene 1 (magnification, x200) and (P) EBV-encoded RNA (magnification, x200).

following lymphoma treatment (5-PS score, 2). After starting treatment, β2-MG and LDH levels showed a downward trend with the patient achieving remission (Fig. 3). Considering the patient's advanced age and poor tolerance to conventional chemotherapy, treatment with azacitidine in combination with chidamide was continued (azacitidine, 100 mg, SC, D1-7, every four weeks + chidamide, 20 mg, PO biw). Follow-up was performed once a month and the patient's condition remained stable until final follow-up in December 2023.

Discussion

PTCL-NOS is the most common type of T cell tumor and is characterized by high heterogeneity and aggressiveness. PTCL-NOS can involve any site but typically occurs within lymph nodes. A total of ~85% of patients present with stage III-IV disease, accompanied by involvement of the bone marrow, spleen and other extranodal sites (2,6). B symptoms including unexplained fever, drenching night sweats and ≥10% weight loss over the previous 6 months are common, and some patients may exhibit increased eosinophil and hemophagocyte counts. The cytological features are highly variable, often exhibiting a mixture of medium and small cells with irregular nuclear shapes (2,6). One of the primary characteristics of the immunophenotype is the absence of one or more T cell markers, most commonly the loss of CD5 and CD7 expression (7). Furthermore, in ~40% of cases, there is a presence of CD4 and CD8 double negativity or co-expression (7).

With the development of gene sequencing technology, genetic analysis of PTCL has improved, and the molecular pathogenesis is being increasingly uncovered. Epigenetic mechanisms serve a crucial role in the development of many tumors, including PTCL. Abnormal DNA methylation and histone acetylation can activate oncogenes, promoting the progression of PTCL (8,9). Several mutations in epigenetic modifier genes have been reported in PTCL, such as TET2, IDH2-R172, RHOA, IDH2 and DNMT3A (10,11). Among these, DNMT3A, IDH2, and TET2 mutations are the most common in angioimmunoblastic T cell lymphoma (AITL) and PTCL-NOS. These mutations are associated with disease progression (10,11). TET2 mutation is a common driving factor in myeloid and lymphoid system tumors, which can cause malignant lymphoma by disrupting the conversion of 5-methylcytosine to 5-hydroxymethylcytosine (12). Mice with TET2 mutation are prone to T cell diseases, such as

Table II. Test results of lymphoma-associated gene mutations in the patient.

Gene	Mutation site	Nucleotide change	Variant allele frequency, %
DNMT3A	Exon 20	c.2408G>A	3.40
	Exon 23	c.2645G>T	31.70
TET2	Exon 3	c.2725C>T	22.10
		c.1337delT	22.70
	Exon 5	c.3594G>A	2.50
	Exon 9	c.4045A>T	4.50

DNMT3A, DNA methyltransferase 3α; TET2, Tet methylcytosine dioxygenase 2.

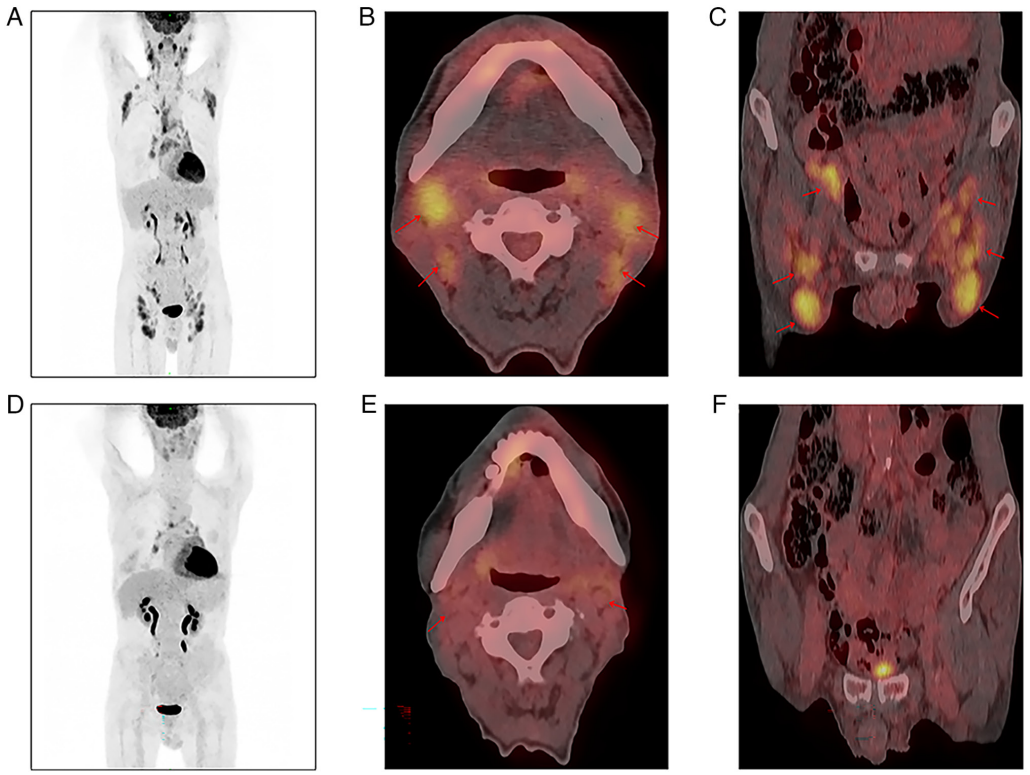

Figure 2. Initial PET-CT showing increased FDG metabolism in multiregional lymph nodes. (A) Whole body PET-CT. (B) Neck and (C) inguinal lymph nodes. Mildly increased FDG metabolism in multiregional lymph nodes was observed following treatment, assessed as CR. (D) Whole body PET-CT. (E) Neck and (F) Inguinal lymph nodes. The arrows point to the areas of increased FDG uptake. PET-CT, positron emission tomography/computed tomography; FDG, fluorodeoxyglucose.

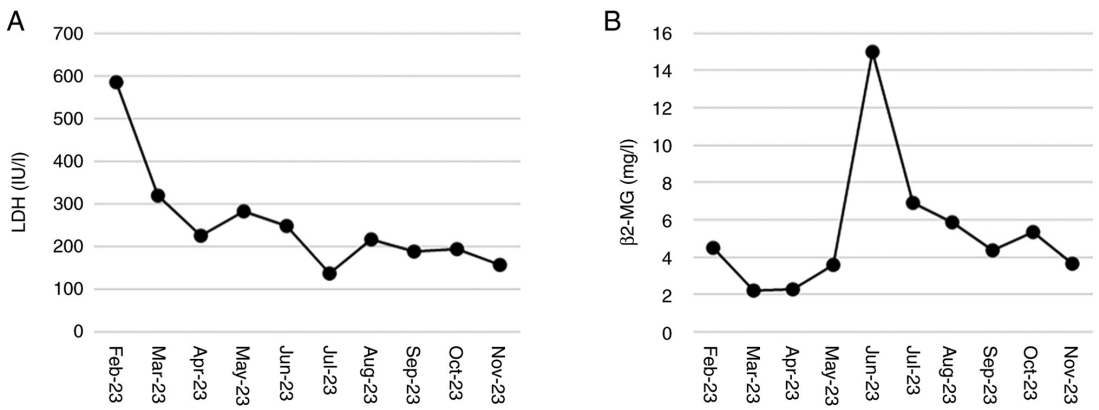

Figure 3. Serum biochemical indicators levels from initial diagnosis to last follow-up. (A) LDH and (B) β2-MG. LDH, lactate dehydrogenase; β2-MG, β2-microglobulin.

PTCL, predominantly originating from follicular helper T (TFH) cells, which may be associated with the effect of TET2 on T cell polarization (13-15). TET2 loss promotes $CD4^+$ T-cell differentiation manifested by strong skewing towards TFH/Th17 phenotypes (15). DNMT3A mutation is common in myeloid malignancy and can lead to abnormal DNA methylation patterns, thereby altering expression of genes involved in cell differentiation or regulating hematopoietic function. The specific mechanisms of DNMT3A mutation in PTCL are not clear. Experiments have shown that $DNMT3A^{+/-}$ mice have an increased risk of developing CD8-positive lymphomas when p53 expression is downregulated (16). In PTCL, DNMT3A mutation occurs more frequently in AITL compared with other subtypes, with ~30% overlapping with TET2 mutation, while in PTCL-NOS, the incidence of DNMT3A with TET2 mutation is 4-10% (17,18). The patient in the present case had both DNMT3A and TET2 mutations.

Currently, the first-line treatment for PTCL is based on anthracyclines (usually CHOP or CHOEP). However, the outcomes are not satisfactory, as nearly half of patients fail to achieve CR and the efficacy is short-lived and prone to relapse. High-dose chemotherapy followed by autologous stem cell transplantation as consolidation therapy can improve prognosis, with 2-year event-free survival (EFS) rate of 40-50% (19-21). However, this benefit is observed primarily in patients who are tolerant and highly responsive to the treatment. Relapsed/refractory PTCL-NOS has median EFS and OS typically <6 months (22,23). Considering the adverse factors of age and comorbidities, this highlights the importance of developing new therapies, especially for elderly patients who may be intolerant to chemotherapy (24). To address the recurrent epigenetic changes in PTCL, histone deacetylase inhibitor (HDACi) and hypomethylating agents (HMA) are employed in the treatment of PTCL. HDACi has shown significant benefits in 20-25% of PTCL-NOS cases, with chidamide monotherapy for relapsed/refractory PTCL showing an efficacy rate of 28% and a median OS of 21.4 months (25). Moreover, it exhibits synergistic effects with chemotherapy agents, enhancing chemosensitivity, and combination therapy has advantages in response rate and long-term survival (25). The HMA, azacitidine monotherapy (SC) for TET2-mutated relapsed/refractory AITL has an overall response rate (ORR) of 75% and a CR rate of 50% (26). Azacitidine (PO) in combination with CHOP as a first-line treatment for PTCL has a CR rate of up to 75%, and 2-year PFS and OS rates of 65.8 and 68.4%, respectively (27). The dual epigenetic regulating treatment (HDACi + HMA) shows advantages in ORR and CR. In a study of azacitidine (PO) in combination with romidepsin in the treatment of PTCL, among the 25 enrolled patients, 13 were relapsed/refractory PTCL and 17 were AITL or TFH phenotype PTCL. The ORR and CR rates for this regimen were 61 and 48%, respectively. In the AITL and TFH phenotype PTCL subgroups, ORR and CR rates were 80 and 67%, respectively, indicating superior efficacy (28). The regimen of chidamide combined with azacytidine + CHOP has been proved to be feasible and safe in the treatment of PTCL in a phase 2 trial (29). In the present case, the elderly patient was initially treated with first-line CHOEP chemotherapy regimen and did not achieve an ideal effect, with superficial lymph nodes showing enlargement and cardiac and renal function failure occurred due to the toxicity of the chemotherapy. Considering the patient's DNA methylation-associated TET2 and DNMT3A mutations, chidamide in combination with azacitidine was used for the treatment with dose-reduced chemotherapy, without anthracyclines. The outcome was equally encouraging with CR achieved as the dose-reduced chemotherapy regimen was also effective. The patient was subsequently treated with a chemotherapy-free regimen of chidamide + azacitidine. During the follow-up period, the condition remained in a stable state. Therefore, it was hypothesized that chidamide + azacitidine is more effective for patients with PTCL-NOS with associated mutations of epigenetic regulator genes, and these mutations may serve as biomarkers for the treatment of chidamide in combination with azacitidine. However, this should be validated using a large sample size prospective study.

To the best of our knowledge, there are few reports (29) of chidamide in combination with azacitidine in the treatment of PTCL-NOS. The present case demonstrated good short-term treatment effects, and the long-term efficacy of this regimen was also promising. The present case may provide new treatment ideas for elderly patients with PTCL who are intolerant or insensitive to chemotherapy, and also facilitate development of new treatment regimens for PTCL.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

FX, RZ, HT, JM, HL and TW contributed to study conception and design. FX, RZ, HT and JM collected data. HL and TW confirm the authenticity of all the raw data. HL wrote the manuscript. TW edited the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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