

# Therapeutic effect of chidamide on relapsed refractory angioimmunoblastic T-cell lymphoma

## A case report and literature review

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### Abstract

**Introduction:** Angioimmunoblastic T-cell lymphoma (AITL) is a kind of rare peripheral T cell lymphoma, which usually has acute onset at old age.

**Materials and methods:** Here we report a case of relapsed refractory AITL, which has achieved obvious curative effect after treatment with chidamide.

**Results:** Initially, the patient received 7 courses of treatment with recombinant human endostatin (endostar)+CHOP. The patient achieved complete remission, but suffered from recurrence later. After changing chemotherapy regimens, the outcome was still not satisfactory, and the patient developed systemic skin infiltration and rashes. After 2 courses of chemotherapy with chidamide (30 mg) twice a week + intravenous injections with cyclophosphamide (0.1 g) twice every other day + thalidomide (50 mg) every night, the patient began with the oral intake of chidamide, and the therapeutic effect was satisfactory, with diminishing systemic rashes and shrunken lymph nodes.

**Discussion and conclusions:** Chidamide has good therapeutic effect in the treatment of AITL, which provides a novel therapeutic strategy for relapsed refractory AITL. However, more cases are still needed to further validate its efficacy.

**Abbreviations:** AITL = angioimmunoblastic T-cell lymphoma, CR = complete remission, CT = computed tomography, DFS = disease-free survival, EBV = Epstein-Barr virus, ORR = objective response rate, OS = overall survival, PET = positron emission tomography, PFS = progression-free survival.

**Keywords:** chemotherapy, chidamide, relapsed refractory angioimmunoblastic T-cell lymphoma

## 1. Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a kind of rare peripheral T cell lymphoma, which accounts for 2% of non-Hodgkin lymphoma,<sup>[1]</sup> and 15%–20% of T-cell lymphoma. AITL usually has acute onset at old age, and the incidence of AITL in males is close to females.<sup>[2,3]</sup> The median age of onset for AITL is 65 years. It usually has aggressive progression and poor prognosis. The main manifestations of AITL include systemic lymphadenopathy, fever, hepatosplenomegaly, and rash.<sup>[2,4–6]</sup> AITL is pathologically characterized by the abnormal clonal proliferation of T cells, accompanied by significant vascular

hyperplasia and follicular dendritic cell proliferation. The immunophenotypic characteristics of AITL represent the increased number of interfollicular CD3+T cells (mostly CD3+CD4+ cells). The immunophenotypes of large lymphoblasts among follicles are CD20 and CD79 positive. Immunophenotypes of follicular dendritic cells with typical features of AITL are CD21, CD23, or CD35 positive.<sup>[4]</sup> At present, the treatment for AITL is the same with that for aggressive lymphoma. Chemotherapy for AITL usually uses CHOP, ECHOP, hyper-CAVD, or MINE. However, their therapeutic effects are not satisfactory, with the 5-year progression-free survival rate of 13%–23%, and the 5-year survival rate of 30%. After complete remission (CR), high-dose chemotherapy combined with autologous hematopoietic stem cell transplantation can improve the overall survival (OS) rate and disease-free survival (DFS) rate. Up to now, there has been no standard treatment plan for AITL, and large-scale prospective studies on the treatment of AITL are also rarely seen. Chidamide, a selective oral inhibitor for histone deacetylase, is the first new drug approved for the treatment of relapsed or refractory peripheral T cell lymphoma in China. Herein, we report a case of refractory AITL admitted at our hospital, which has achieved obvious curative effect after treatment with chidamide.

## 2. Case report

A 60-year old married female, with more than 1 year of cough, pharyngalgia, and systemic lymphadenopathy and 1 week of rash, was admitted at our hospital on March 9th 2016. Prior written and informed consent was obtained from the patient, and the study was approved by the local ethics review board. On admission, physical

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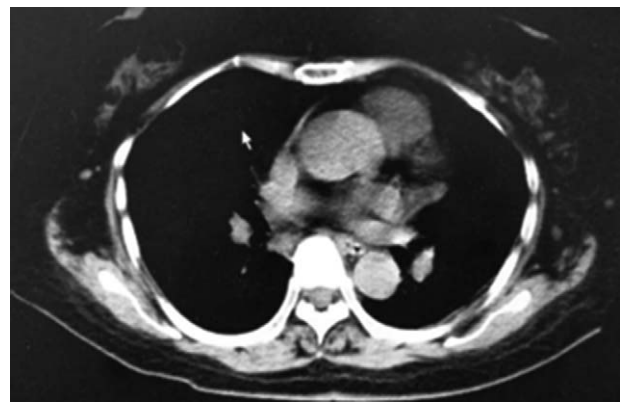
examination showed pharyngeal hyperemia, lymph node enlargement at neck, double oxter, and inguen with press pain (1–2 cm in diameter), and rashes at trunk and limbs. Heart and lung functions were normal. Lymph node biopsy showed lymph node hyperplastic lesions, which met the diagnostic standards for AITL. Results from immunohistochemistry showed that, M15-0453: Bcl-6 (partially+) CD10 (partially+) CD20 (partially+) CD21 (partially+) CD3 (partially+) CD5 (majorly+) CD79a (majorly+); Ki-67 (30%–40%), TIA 1 (scattered minority+). M15-0453: EBER (very few+). Bone marrow examination showed bone marrow hyperplasia, and active proliferation of granulocytes and erythrocytes. Epstein–Barr virus (EBV) quantification was  $9.8E+5$  copies/mL. Examination of EBV-IgM antibody showed weak positive results. Abdominal computed tomography (CT) showed splenomegaly, multiple infarct foci in spleen, and multiple lymph node enlargement at abdominal cavity, retroperitoneum, and bilateral inguens. Positron emission tomography (PET)-CT showed: (i) systemic multiple lymph node enlargement, abnormal increase of fluorodeoxyglucose metabolism, and spleen infiltration; (ii) nasopharyngeal and oropharyngeal infiltration were not excluded. The patient was clinically diagnosed as IVB stage of AITL.

Immediately after diagnosis, the patient received 7 courses of chemotherapy using recombinant human endostatin (endostar) +CHOP. In each course of chemotherapy, the patient received 15 mg endostar on day 1; injection of 870 mg cyclophosphamide, 4 mg vindesine; and 72 mg pirarubicin on day 2; and 50 mg prednisone tablets twice a day on days 2 to 6. Re-examination by PET-CT showed no systemic swelling or abnormal increase of fluorodeoxyglucose metabolism. Therapeutic efficacy evaluation showed CR, and chemotherapy was then terminated.

About 1 month after the termination of chemotherapy, pharyngalgia reoccurred, and right lymph node was significantly enlarged. Ultrasonography of lymph node showed lymphadenectasis at bilateral neck (maximum on the left, 26 mm × 9 mm; maximum on the right, 35 mm × 11 mm), supraclavicle (maximum, 6 mm × 3 mm), oxter (maximum on the left, 55 mm × 11 mm; maximum on the right, 34 mm × 10 mm), and inguens (maximum on the left, 26 mm × 8 mm; maximum on the right, 28 mm × 6 mm). Abdominal CT showed multiple lymphadenectasis at abdominal cavity, retroperitoneum, and bilateral inguens (Fig. 1). Chest CT displayed multiple lymphadenectasis at mediastinum and bilateral axillas (Fig. 2). The patient was



**Figure 1.** Abdominal computed tomography showing multiple lymphadenectasis at abdominal cavity, retroperitoneum, and bilateral inguens before chemotherapy with chidamide.

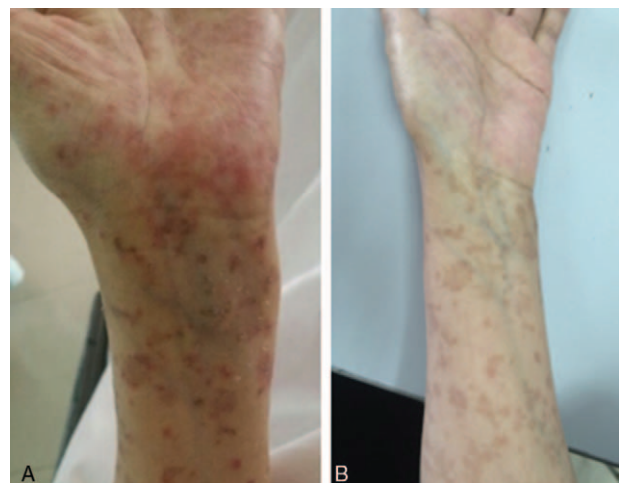


**Figure 2.** Chest computed tomography showing multiple lymphadenectasis at mediastinum and bilateral axillas before chemotherapy with chidamide.

considered to have recurrent lymphoma, and then given another 2 courses of chemotherapy. During the chemotherapy, the patient received dexamethasone (20 mg) injection on days 1 to 8, vindesine (4 mg) injection on day 1, VP-16 (70 mg) on days 3–6, cisplatin (30 mg) injection on days 3 to 6, cytosine arabinoside (3g) on day 8, and endostar (15 mg) on days 1 and 2.

After changing chemotherapy regimen, the therapeutic effect was poor. In addition, the patient was not tolerant for the chemotherapy and had severe bone marrow transplantation. Efficacy evaluation result was disease progression. Later, the patient developed systemic rashes at face, trunk, and limbs, with no obvious causes (Fig. 3). In addition, the patient had pruritus, fever (body temperature, 38–39°C), and pharyngalgia, and was considered to have recurrence of lymphoma with skin infiltration.

On March 11, 2016, the patient started to receive chemotherapy with chidamide (30 mg) twice a week + intravenous injections with cyclophosphamide (0.1g) twice every other day + thalidomide (50 mg) every night. One week later, systemic rashes began to disappear, and nausea, vomiting, and other side effects occurred during oral administration. After 2 courses, the patient began with the oral intake of only chidamide (30 mg) twice a



**Figure 3.** Rashes on the patient with angioimmunoblastic T-cell lymphoma. (A) Rashes of the patient after 9 courses of chemotherapy and before chemotherapy with chidamide. (B) Subsided rashes one month after the patient begins oral intake of chidamide.

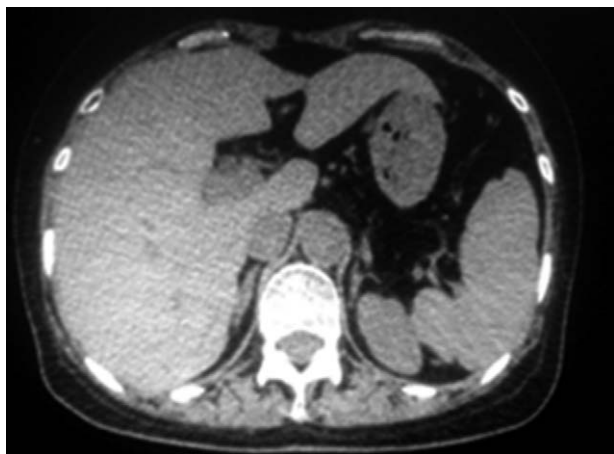


**Figure 4.** Chest computed tomography showing shrunken lymph nodes 6 months after the patient began oral intake of chidamide.

week. Afterward, the patient was followed-up until the writing-up of the report. The condition of the patient was stable, and rashes disappeared, but pigmentation of skin remained (Fig. 3B). In addition, the patient had no pharyngalgia, chills, fever, cough, or expectoration, and the sizes of lymph nodes were significantly reduced. Re-examination by ultrasonography of lymph nodes showed multiple elliptical low echoes at right supraclavicle (maximum of 8 mm × 5 mm), bilateral axillae (maximum of 16 mm × 3 mm), and bilateral inguens (maximum of 6 mm × 3 mm). On August 31st, chest CT showed multiple small lymph nodes at mediastinum and axillae (Fig. 4). Abdominal CT showed no lymphadenectasis (Fig. 5).

### 3. Discussion

AITL is a highly heterogeneous malignant disease that has rapid clinical progress and strong invasiveness. The occurrence of AITL may be related with infections, inherent causes, or immunodeficiency. About 70%–100% of the AITL patients have EBV infection.<sup>[7,8]</sup> The mechanism of EBV may be related with abnormal immune functions caused by EBV infection. In the



**Figure 5.** Abdominal computed tomography showing shrunken lymph nodes 6 months after the patient began oral intake of chidamide.

hosts, EBV infects immunocytes such as B cells, T cells, and natural killer cells, and impairs immune functions that can clear neoplastic cells in the body. As a result, neoplastic cells proliferate, leading to the occurrence of tumors. Systemic symptoms of AITL include systemic lymphadenectasis, fever, and rashes.<sup>[2,4–6,9]</sup> The case reported herein had shown rashes, lymphadenectasis, hepatosplenomegaly, and EBV infection. The chemotherapy regimens for AITL were CHOP, CVP, or VAP, but their complete remission rates are lower than 50%.<sup>[10]</sup> It is reported that chemotherapy of AITL with endostar combined with CHOPT results in 7 cases of complete remission (50%) and 4 cases of progressive disease (28.6%).<sup>[11]</sup> The symptoms of the AITL patient in the present case report had been quickly alleviated after administering endostar+CHOP regimen, but the duration of remission was very short, with recurrence and progression, in line with previous reports.<sup>[12,13]</sup> Early hematopoietic stem cell transplantation can prolong the patients' survival time.<sup>[14]</sup> A multicenter retrospective study shows that high-dose chemotherapy combined with autologous stem cell transplantation on 146 AITL patients result in 1- and 2-year survival rates of 67% and 59%, respectively, and 1- and 2-year disease-free survival rates of 70% and 56%, respectively, for CR patients.<sup>[15]</sup>

The patient in the present report had AITL for 1 year. After 7 courses of chemotherapy with endostar and CHOP, the patient had CR, but later reported recurrence. After changing chemotherapy regimens, the therapeutic efficacy was not satisfactory, and the patient had developed systemic skin infiltration. Then, the patient was classified to have relapsed refractory PTCL with poor prognosis.<sup>[12,13]</sup> After trying a variety of chemotherapy regimens, chidamide achieved significant efficacy in the treatment of AITL.

Chidamide is the first original patent drug in China that is authorized to be sold in developed countries,<sup>[16]</sup> and it has good effects for the treatment of relapsed refractory AITL.<sup>[17,18]</sup> Chidamide inhibits activities of HDAC1, 2, 3, 10 in lymphoma cells,<sup>[19,20]</sup> interferes with the binding between histone and DNA, suppresses T lymphoma cell growth, and promotes the apoptosis of T lymphoma cells.<sup>[21,22]</sup>

A phase II clinical trial by Shi et al<sup>[23]</sup> shows that chidamide has therapeutic effect on peripheral T lymphoma. Another clinical trial on 83 refractory PTCL patients who are orally given 30 mg chidamide twice a week shows that 79 cases can be used for statistical analysis. Among the 79 cases, 28% (22/79) cases have objective response rate (ORR), including 14% cases of CR (11/79). The progression-free survival (PFS) and overall survival (OS) are 2.1 and 21.4 months, respectively. Notably, the effective rate for AITL cases has achieved 50% (5/10), CR accounts for 40% (4/10), and median OS is 21.4 months. Based on this trial, chidamide has been approved by China Food and Drug Administration for the treatment of relapsed refractory PTCL.<sup>[16]</sup> In conclusion, the present case report showed that the AITL patient had received unsatisfactory therapeutic efficacy even after 9 courses of chemotherapy. After additional chemotherapy with chidamide combined with cyclophosphamide, the symptoms were alleviated. By the time of manuscript preparation, it has been 9 months since the patient begins to receive oral intake of chidamide. Rashes have subsided, and the sizes of lymph nodes have been significantly reduced, suggesting that chidamide has satisfactory therapeutic efficacy in the treatment of AITL, which provides a novel therapeutic strategy for relapsed refractory AITL. However, more cases are still needed to further validate its efficacy.

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