Relapsed Angioimmunoblastic T Cell Lymphoma with Fulminant Leukemic Involvement

BCEF 1,2 Rahaf Altahan
CDF 2 Areej AlMugairi
BCF 3 Muhamed Hitham Almahayni
BCDF 3-6 Moussab Damlaj
CD 7 Ahmad Al-Zghoul

Corresponding Author: Rahaf Altahan, e-mail: mt.rahaf@gmail.com
Financial support: None declared
Conflict of interest: None declared

Patient: Female, 45-year-old
Final Diagnosis: Angioimmunoblastic T-cell lymphoma
Symptoms: Fever • general malaise • weight loss
Medication: —
Clinical Procedure: Bone marrow biopsy • CT-scan • excision biopsy • PET-CT • splenectomy
Specialty: Hematology • Oncology

Objective: Rare disease
Background: Angioimmunoblastic T cell lymphoma (AITL) is an aggressive and rare entity that comprises about 1-2% of all non-Hodgkin lymphomas. This entity carries many challenges that start at the diagnosis, as most patients present with non-specific symptoms affecting different systems. As a result, the optimal approach, reaching the accurate diagnosis, and delivering needed treatment are delayed. Furthermore, it is not surprising that the initial set of biopsies are non-diagnostic given the heavy inflammatory background and scarcity of malignant cells in the early course of the disease. Other challenges include delivering the optimal curative therapy, as there is no such therapeutic option available yet. Although stem cell transplantation (SCT) can be considered a curative option, some patients have comorbidities and are not eligible for this option, and some other patients have relapse despite this aggressive approach, as was seen in our case.

Case Report: We present an interesting case of AITL with florid leukemic infiltration at the time of relapse. We included a description of the patient's symptoms, diagnostic challenges, and clinical course, and provided therapy with demonstrative peripheral blood and flow cytometry images. Interestingly, there are very few reports in the literature that described leukemic infiltration of this entity.

Conclusions: Acknowledging the rarity of this aggressive lymphoma combined with all the challenges that face the involved health care workers, publishing this elaborate case report adds some insight and knowledge and helps improve our understanding of this entity.

Keywords: Lymphoma • Lymphoma, Non-Hodgkin • Recurrence • Stem Cell Transplantation

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/936448

1 Hematology Section, Pathology and Clinical Laboratory Medicine Administration, King Fahad Medical City, Riyadh, Saudi Arabia
2 Division of Hematopathology, Department of Pathology and Laboratory Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia
3 Division of Hematology and HSCT, Department of Oncology, King Abdulaziz Medical City, Riyadh, Saudi Arabia
4 King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
5 King Abdullah International Medical Research Center, Riyadh, Saudi Arabia
6 Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates
7 Flow cytometry Lab, Department of Pathology and Laboratory Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia
Background

Angioimmunoblastic T cell lymphoma (AITL) is a rare and aggressive lymphoma, with most patients presenting at an advanced stage of the disease. The diagnosis can be challenging and difficult to reach, as in some patients, the initial histology shows extensive reactive features with no definite malignant pathology [1]. This results in diagnostic challenges and delays in accurate diagnosis and delivering appropriate treatment [2]. We present an interesting case of AITL with florid leukemic infiltration at the time of disease relapse that was not evident at the time of diagnosis. Description of the patient's symptoms, diagnostic approaches, clinical course and provided therapeutic modalities are included, with the corresponding peripheral blood and flow cytometry results. Interestingly, leukemia infiltration of this entity has rarely been reported with certainty. Furthermore, according to the World Health Organization (WHO), there is no mention of a leukemic phase. To the best of our knowledge, this is the first reported case with leukemic infiltration at the time of relapse.

Case Report

A 45-year-old woman sought medical care at our center in 2017 with a 1-month history of fever, loss of appetite, weight loss, and general malaise. At that time, a physical examination showed multiple enlarged non-tender cervical lymph nodes (bilateral, the largest measured 2×3 cm on the left side). Her initial complete blood count (CBC) showed a white blood cell count (WBC) of 13.7×10^9/L with a normal differential, hemoglobin of 81 g/L with microcytic hypochromic red blood cells (RBCs), and platelets count of 186×10^9/L. These findings warranted further evaluation that included a computed tomography (CT) scan, which revealed generalized lymphadenopathy that extended above and below the diaphragm, in addition to an enlarged spleen. Furthermore, a positron emission tomography (PET) scan was done that demonstrated hyperactivity of the lymph nodes and spleen. Accordingly, the patient underwent multiple excisional lymph node biopsies, in addition to a bone marrow biopsy and splenectomy, in search of the underlying pathology. Unfortunately, none of these biopsies showed any clonal/malignant process and were inconclusive at that time. As a result, the patient was followed closely at the Hematology Clinic at our center. Around 2 months later, in September 2017, the patient started to report more weight loss and fever. Repeated physical examination revealed enlarged tonsils with exudative discharge, along with her previously documented enlarged cervical lymph nodes. Consequently, the team's decision was to repeat evaluation of the lymph nodes by performing new excisional biopsies, which now showed morphological and immunophenotypic features compatible with AITL. As a result, the patient was started on CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) regimen in November 2017. By January 2018, she had received a total of 4 cycles of that regimen. Unfortunately, a reassessment CT scan showed progressive disease. The patient decided to seek further medical care abroad, where she received 2 cycles of salvage therapy; ICE (ifosfamide, carboplatin, and etoposide), as per her medical file. Despite this intensive regimen, she did not respond. Therefore, she was given GDP (gemcitabine, dexamethasone, and cisplatin) as a second salvage therapy, followed by autologous stem cell transplantation (ASCT) in August 2018. After recovery, the patient came back and was seen as an outpatient at our center.

Two months later, she started to have progressively enlarged inguinal lymph nodes, along with new skin lesions on her trunk and upper limbs. Cutaneous and nodal biopsies confirmed a relapsed AITL. At the time of her relapse, her CBC showed a high WBC count (75.9×10^9/L) with a predominance of lymphocytes with an absolute count of 56.17×10^9/L (Figure 1), hemoglobin of 93 g/L, and platelets count of 128×10^9/L. Multiparameter flow cytometry was performed on her peripheral blood and detected a clonal T lymphocytes population (Figure 2) with a positive T cell receptor (TCR) gene rearrangement that was confirmed by molecular studies. It was such a challenging case with a poor prognosis, presenting with a disease relapse despite several courses of chemotherapy in addition to an ASCT. After discussing available options in a multidisciplinary team and with the patient, we planned to administer brentuximab and nivolumab as salvage chemotherapy. Although the lymphocytes count dropped initially, it showed a rebound before her next scheduled cycle. Unfortunately, shortly after the second cycle, her disease progressed and she died.

Discussion

Angioimmunoblastic T cell lymphoma (AITL) is a distinct and generally aggressive lymphoma that arises from mature T follicular helper cells (TFH) [3]. It constitutes 1-2% of all non-Hodgkin lymphomas and about 15-30% of peripheral T cell lymphomas (PTCL) [1,4]. Most patients present at an advanced stage with acute onset of various symptoms. Symptoms are usually non-specific and include generalized lymphadenopathy, hepatosplenomegaly, pruritic skin rash, serositis, and constitutional symptoms. Usual laboratory findings include presence of a polyclonal hypergammaglobulinemia and circulating immune complexes (eg, cold agglutinins, rheumatoid factor, and anti-smooth muscle antibodies) [5,6]. The diagnosis is usually confirmed by morphological assessment of an excisional lymph node biopsy with further immunophenotyping. Morphological assessment of tissue sections shows effacement of the normal architecture by a rich background of reactive cells that in
most cases include Epstein-Barr virus (EBV)-positive B immunoblasts and other inflammatory cells with prominent endothelial venules that are best demonstrated with special stains for follicular dendritic cells. Large atypical lymphoma cells are seen intermixed with the reactive cells and are usually positive for CD3, CD4, and other normally expressed TFH cell antigens like CD10. These malignant cells can further express aberrant markers or lose antigens that are typically expressed on normal T cells; CD7 is an example, and its loss indicates an aberrancy (as was seen in our presented case). Of note, reaching the diagnosis can be very challenging, especially early in the disease course, when the prominent features are mainly heavy inflammatory elements. Additional molecular testing to detect the presence of TCR gene rearrangement can assist in reaching the diagnosis by confirming the clonal nature of the T cells, especially in challenging cases [7].

Despite the fact that most patients present with an advanced-stage disease with multisystem involvement, spread to the peripheral blood has rarely been reported with certainty. Furthermore, the WHO classification of lymphoid malignancies does not include a leukemic phase of AITL [8]. In 1983, Pangalis et al examined peripheral blood smears and bone marrow of a case series that included 38 patients; they detected atypical lymphocytes in 12 patients and described them as “immunocytes”, but immunophenotyping confirmation was not yet available [9]. In 2006, Bassiggo et al were the first group to detect and report circulating neoplastic CD10 positive T cells in patients diagnosed with AITL. They examined 6 peripheral blood smears of 12 patients diagnosed with AITL. Interestingly, all the smears showed atypical lymphoid cells by morphological inspection and a subset of CD10-positive T cells using a 4-color flow cytometry analysis [10]. On the other hand, Mourad et al reported a large case series that included 157 patients diagnosed with AITL treated within the GELA trials in 2008. They found that 60% of patients with anemia had bone marrow involvement. However, peripheral blood examination and description (ie, presence of lymphoma cells in the peripheral blood) was not included [11]. In 2014, Lin et al reported a patient who was diagnosed with AITL with florid blood dissemination but CD10 was negative on the lymphoma cells (the same finding was noted in the present case) [12].
Due to the previously reported primary progression and/or short duration of remission (DOR), [13,14] and because the current evidence is based on descriptive reports and limited comparison studies to other PTCL subtypes, the latter being due to the low incidence [14], there is no standard therapeutic regimen for this entity. Adopting a risk-based approach is proposed until we have a recommended regimen based on clinical trials and good-quality evidence [2].

The CHOP regimen remains the most-used intensive regimen in PTCL [15]. With a reported 53% complete response (CR) when used as a first-line therapy for AITL [16], the addition of etoposide to CHOP (CHOEP) shows an overall response rate (ORR) of 82% and a CR of 51% in the management of PTCL [16] and better progression-free survival (PFS) in young and fit patients when compared to CHOP alone. However, it has higher toxicity in patients older than 60 years [17]. Based on the available evidence, CHOEP was given to our patient as a first-line therapy.

Management of patients with relapse/refractory (R/R) disease should include careful assessment of the patient’s eligibility for autologous stem cell transplantation (ASCT) [18], although this can be very challenging given the disease-related symptoms and comorbidities that most patients have [14,19]. Delivery of high-dose therapy (HDT) followed by ASCT (HDT-ASCT) is considered the standard of care for R/R lymphomas, including PTCL. However, results are dismal in PTCL patients, with a relapse rate over 80% [18,20]. A multicenter study that evaluated long-term disease-free survival in 29 patients with AITL after HDT-ASCT found that 5-year overall and event-free survival were 44% and 37%, respectively [21].

There is no standard salvage therapy to be delivered before SCT in this setting [22]. GDP (gemcitabine, dexamethasone, and cisplatin) showed a similar overall response rate compared to DHAP (dexamethasone, high-dose cytarabine, and cisplatin) (DHAP 33% and GDP 38%), with a 1-year event-free survival of 16% and a 1-year overall survival of 28%. Furthermore, in patients who received ASCT, the 2-year EFS and OS were 21% and 42%, respectively [23]. Other regimens, such as ICE (ifosfamide, carboplatin, and etoposide), have been investigated and showed similar results [22,24].

The addition of monoclonal antibodies directed against some of the antigens expressed by neoplastic lymphoma cells showed an impressive improvement in B cell lymphoma [18]. Brentuximab vedotin (BV) is an anti-CD30 monoclonal antibody-drug conjugate, and since CD30 is expressed in most AITL [25], BV has been investigated as a promising agent [18,26]. A significant improvement in PFS (48.2 months) was seen in patients treated with BV combined with CHP compared to CHOP for CD30-positive PTCL in the ECHELON-2 study [18,27].

Preclinical data shows that programmed death ligand 1 (PD-L1) is overexpressed in neoplastic cells in PTCL. It interacts with the programmed death receptor-1 (PD-1) that is expressed on activated T lymphocytes, thus provides suppressive antitumor immunity [28]. Although the use of anti-PD-1-blocking monoclonal antibodies has shown impressive results, especially in the treatment of relapsed Hodgkin lymphoma, early results in PTCL were not as impressive. A recent phase 2 prospective study that evaluated the effect of nivolumab (a PD-1-blocking antibody) as a single agent for patients with relapse/refractory PTCL was halted due to the short duration of response and the moderate activity of the drug, and half of their patient cohort had AITL (6/12 patients). The role of this agent should be explored in future studies but as a combination regimen rather than a single agent [29].
Conclusions

The challenges described in this case, starting early at the time of presentation with deceiving initial morphological features that not surprisingly caused a delay in reaching the accurate diagnosis, to delivering optimal front-line therapy, to finally dealing with a disease relapse after many courses of intensive therapies, demonstrate the difficulties facing health care practitioners around the world. To the best of our knowledge, this is the first reported case of AITL that shows an overt leukemic phase at the time of relapse that was not documented at the initial presentation. Adding this elaborative case to the literature confirms the challenging nature and improves our overall understanding of the characteristics of this aggressive and rare entity.

References:

1. Chiba S, Sakata-Yanagimoto M. Advances in understanding of angioimmunoblastic T-cell lymphoma. Leukemia. 2020;34(10):2592-606
2. Mosalpuria K, Bociek RG, Vose JM. Angioimmunoblastic T-cell lymphoma management. Semin Hematol. 2014;51(1):52-58
3. Grogg KL, Artygalle AD, Macon WR, et al. Angioimmunoblastic T-cell lymphoma: A neoplasm of germinal-center T-helper cells? Blood. 2005;106(4):1501-2
4. Nathwani BN, Rappaport H, Moran EM, et al. Malignant lymphoma arising in angioimmunoblastic lymphadenopathy. Cancer. 1978; 41(2):578-606
5. Aber DA, Orazi A, Hasseriyan R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-405
6. Federico M, Rudiger T, Belleti M, et al. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: Analysis of the international peripheral T-cell lymphoma project. J Clin Oncol. 2013;31(2):240-46
7. Loghavi S, Wang SA, Medeiros LJ, et al. Immunophenotypic and diagnosti- tic characterization of angioimmunoblastic T-cell lymphoma by advanced flow cytometric technology. Leuk Lymphoma. 2016;57(12):2804-12
8. Grogg KL, Morice WG, Macon WR. Spectrum of bone marrow findings in patients with angioimmunoblastic T-cell lymphoma. Br J Haematol. 2007;137(5):416-22
9. Pangalis GA, Moran EM, Nathwani BN, et al. Angioimmunoblastic lymphadenopathy: Long-term follow-up study. Cancer. 1983;52(2):318-21
10. Baseggio L, Berger F, Morel D, et al. Identification of circulating CD10 positive T cells in angioimmunoblastic T-cell lymphoma. Leukemia. 2006;20(2):296-303
11. Mourad N, Mounier N, Briere J, et al. Clinical, biologic, and pathologic fea-
tures in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Group e'Tude des Lymphomes de l'Adulte (GELA) trials. Blood. 2008;111(9):4463-70
12. Lin KW, Lee YS, Phipps C. Leukaemic presentation of angioimmunoblastic T-cell lymphoma. Br J Haematol. 2014;166(6):808
13. Siegert W, Agthe A, Gresser H, et al. Treatment of angioimmunoblastic lymphadenopathy (AILD)-type T-cell lymphoma using prednisone with or without the COPBLAM/IMVP-16 regimen. A multicenter study. Kiel Lymphoma Study Group. Ann Intern Med. 1992;117(5):364-70
14. Lunning MA, Vose JM. Angioimmunoblastic T-cell lymphoma: The many-faced lymphoma. Blood. 2017;129(9):1095-102
15. Vose J, Armitage J, Weisenburger D. International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: Pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-30
16. Simon A, Peisch M, Casassus P, et al. Upfront VIP-reinforced-ABVD (VIP-
RABVD) is not superior to CHOP/21 in newly diagnosed peripheral T-cell lymphoma. Results of the randomized phase III trial GELAMS-ITPPS. Br J Haematol. 2010;151(2):159-66
17. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol. 2004; 15(10):1467-75
18. Mohammed Saleh MF, Kotta A, et al. Recent advances in diagnosis and ther-
apy of angioimmunoblastic T cell lymphoma.Curr Oncol. 2021;28(6):5480-98
19. Lunning MA, Moskowitz AJ, Horwitz S. Strategies for relapsed peripheral T-cell lymphoma: the tail that wags the curve. J Clin Oncol. 2013;31(16):1922-27
20. Smith SD, Bolwell BJ, Rybicki LA, et al. Autologous hematopoietic stem cell transplantation in peripheral T-cell lymphoma using a uniform high-dose regimen. Bone Marrow Transplant. 2007;40(3):239-43
21. Schetelig J, Feltcher S, Reichle A, et al. Long-term disease-free surviv-
al in patients with angioimmunoblastic T-cell lymphoma after high-dose chemotherapy and autologous stem cell transplantation. Haematologica. 2003;88(11):1272-78
22. Foster C, Kuruvilla J. Treatment approaches in relapsed or refractory pe-
ripheral T-cell lymphomas. F1000Res. 2020;9:F1000 Faculty Rev-1091
23. Skamene T, Crump M, Savage KJ, et al. Salvage chemotherapy and autol-
ogous stem cell transplantation for peripheral T-cell lymphoma: A subset analysis of the Canadian Cancer Trials Group LY.12 randomized phase 3 study(). Leuk Lymphoma. 2017;58(10):2319-27
24. Zelenetz AD, Hamlin P, Kewalarmani T, et al. Ifoflamide, carboplatin, eto-
poside (ICE)-based second-line chemotherapy for the management of re-
lapsed and refractory aggressive non-H Hodgkin’s lymphoma. Ann Oncol. 2003;14(Suppl.1):i5-10
25. Onaindia A, Martinez N, Montes-Moreno S, et al. CD30 expression by B and T cells: A frequent finding in angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma – not otherwise specified. Am J Surg Pathol. 2016;40(3):378-85
26. Moskowitz AJ. Practical treatment approach for angioimmunoblastic T cell lymphoma. J Oncol Pract. 2019;15(3):137-43
27. Horwitz S, O'Conner OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): A global, double-blind, randomised, phase 3 trial. Lancet. 2019;393(10168):229-40
28. Shi L, Chen S, Yang L, Li Y. The role of PD-1 and PD-L1 in T-cell immune suppression in patients with hematological malignancies. J Hematol Oncol. 2013;6(1):74
29. Bennani NN, Pederson LD, Atherton P, et al. A phase II study of nivolumab in patients with relapsed or refractory peripheral T-cell lymphoma. Blood. 2019;134:467