Cancer Association of South Africa (CANSA)

Fact Sheet
on
Angioimmunoblastic
T-Cell Lymphoma

Introduction

Lymphoma is a type of cancer involving cells of the immune system, called lymphocytes. Just as cancer represents many different diseases, lymphoma represents many different cancers of lymphocytes -- about 35 different subtypes, Lymphoma is a group of cancers that affect the cells that play a role in the immune system and primarily represents cells involved in the lymphatic system of the body.

[Picture Credit: Lymphatic System]

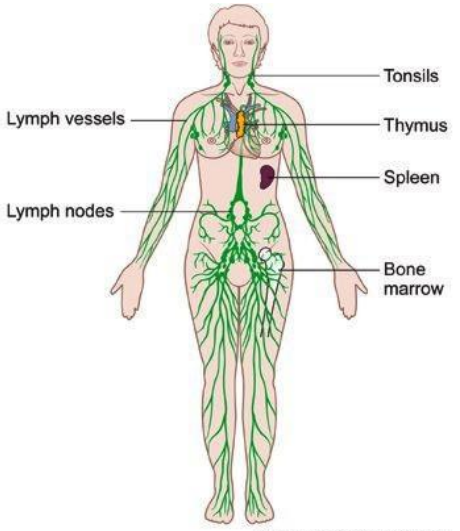

Diagram of the lymphatic system
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Types of Lymphoma

Lymphomas fall into one of two major categories:

- Hodgkin's lymphoma (HL, previously called Hodgkin's disease)
- Non-Hodgkin's Lymphoma (NHL, all other lymphomas)

These two types occur in the same places, may be associated with the same symptoms, and often have similar appearance on physical examination. However, they are readily distinguishable via microscopic examination.

Angioimmunoblastic T-Cell Lymphoma (AITL)

Angioimmunoblastic T-cell lymphoma (AITL) is a rare, aggressive (fast-growing) T-cell lymphoma that accounts for approximately one to two percent of all non-Hodgkin's Lymphoma cases. Elderly patients are more likely to have AITL, and it occurs more often in men than women. The majority of patients with AITL are diagnosed with advanced-stage disease.

Chiba, S. & Sakata-Yanagimoto, M. 2020.

"It has been nearly half a century since angioimmunoblastic T-cell lymphoma (AITL) was characterized in the early 1970's. Our understanding of the disease has dramatically changed due to

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

multiple discoveries and insights. One of the key features of AITL is aberrant immune activity. Although AITL is now understood to be a neoplastic disease, pathologists appreciated that it was an inflammatory condition. The more we understand AITL at cellular and genetic levels, the more we view it as both a neoplastic and an inflammatory disease. Here, we review recent progress in our understanding of AITL, focusing on as yet unsolved questions."

Conflict of interest statement

The authors are conducting a phase II clinical trial of dasatinib in AITL and other Tfh lymphoma patients with a drug supply from Bristol-Meyer Squibb that sells dasatinib.

Yao, W.Q., Wu, F., Zhang, W., Chuang, S.S., Thompson, J.S., Chen, Z., Zhang, S.W., Clipson, A., Wang, M., Liu, H., Bibawi, H., Huang, Y., Campos, L., Grant, J.W., Wright, P., Ei-Daly, H., Rásó-Barnett, L., Farkas, L., Follows, G.A., Gao, Z., Attygalle, A.D., Ashton-Key, M., Liu, W. & Du, M.Q. 2020.

"Angioimmunoblastic T-cell lymphoma (AITL) is a neoplastic proliferation of T follicular helper cells with clinical and histological presentations suggesting a role of antigenic drive in its development. Genetically, it is characterized by a stepwise acquisition of somatic mutations, with early mutations involving epigenetic regulators (TET2, DNMT3A) and occurring in haematopoietic stem cells, with subsequent changes involving signaling molecules (RHOA, VAV1, PLCG1, CD28) critical for T-cell biology. To search for evidence of potential oncogenic cooperation between genetic changes and intrinsic T cell receptor (TCR) signaling, we investigated somatic mutations and T-cell receptor β (TRB) rearrangement in 119 AITL, 11 peripheral T-cell lymphomas with T follicular helper phenotype (PTCL-TFH), and 25 PTCL-NOS using Fluidigm polymerase chain reaction (PCR) and Illumina MiSeq sequencing. We confirmed frequent TET2, DNMT3A, and RHOA mutations in AITL (72%, 34%, 61%) and PTCL-TFH (73%, 36%, 45%) and showed multiple TET2 mutations (2 or 3) in 57% of the involved AITL and PTCL-TFH. Clonal TRB rearrangement was seen in 76 cases with multiple functional rearrangements (2-4) in 18 cases (24%). In selected cases, we confirmed bi-clonal T-cell populations and further demonstrated that these independent T-cell populations harboured identical TET2 mutations by using BaseScope in situ hybridization, suggesting their derivation from a common TET2 mutant progenitor cell population. Furthermore, both T-cell populations expressed CD4. Finally, in comparison with tonsillar TFH cells, both AITL and PTCL-TFH showed a significant overrepresentation of several TRB variable family members, particularly TRBV19*01. Our findings suggest the presence of parallel neoplastic evolutions from a common TET2 mutant haematopoietic progenitor pool in AITL and PTCL-TFH, albeit to be confirmed in a large series of cases. The biased TRBV usage in these lymphomas suggests that antigenic stimulation may play an important role in predilection of T cells to clonal expansion and malignant transformation. "

Incidence of Angioimmunoblastic T-Cell Lymphoma in South Africa (AITL)

The outdated National Cancer Registry (2017), known for under reporting, does not provide information regarding the incidence of Angioimmunoblastic T-Cell Lymphoma.

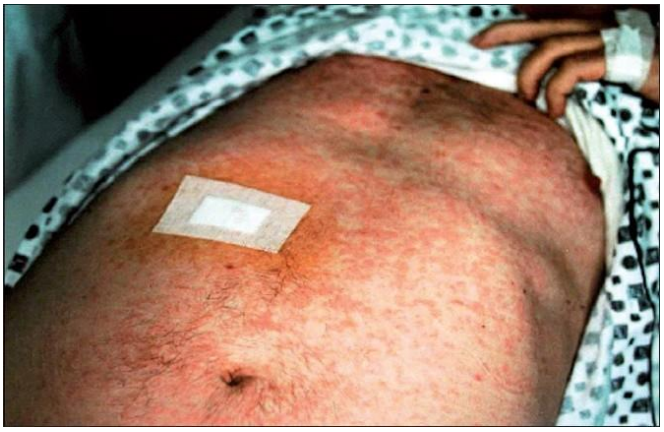
Causes of Angioimmunoblastic T-Cell Lymphoma (AITL)

It has been noticed that many people with this lymphoma show signs of having had an infection with a virus called the Epstein–Barr virus (EBV). It is not clear, however, whether this virus is causing the genetic changes in the lymphocytes – which then grow out of control to form a lymphoma – or

whether an EBV infection has just been reawakened in the body because the immune system is not working as well as it should because of the lymphoma.

Signs and Symptoms of Angioimmunoblastic T-Cell Lymphoma (AITL)
Angioimmunoblastic T-Cell Lymphoma (AITL) causes a wide range of possible symptoms:

- Lumps, which are swollen lymph nodes (glands) found in the groin, armpits and neck
- Feeling generally unwell
- Unexplained fever
- Weight loss without trying to lose weight
- Night sweats
- Itching
- Lymph nodes that are abnormal in size, number or consistency
- Oedema
- Abdominal discomfort and sometimes distension (swelling) caused by cancerous lymphocytes in the spleen and/or the liver or by a collection of fluid in the abdomen (this is called 'ascites')
- Difficulty with breathing due to collection of fluid around the lungs (a pleural effusion)
- Maculopapular rashes (these can resemble a viral rash)



[Picture Credit:
Typical Rash Associated with AITL]

- Joint pains
- Tiredness or shortness of breath due to a type of anaemia called 'haemolytic anaemia', which is caused by an autoimmune reaction against red blood cells
- Symptoms of infections – infections are more likely to occur and to be more severe if there is AITL in the bone marrow.

Diagnosis of Angioimmunoblastic T-Cell Lymphoma (AITL)
The patient will have a physical examination and may have some or all of the following tests:

- blood tests – to measure the numbers of different blood cells in the sample (the blood counts
- bone marrow biopsy, a test in which a small sample is taken from the bone marrow in the hip bone to see if the lymphoma is affecting the bone marrow
- scans – computed tomography (a CT scan) of the chest, abdomen and
- positron-emission tomography (a PET scan)

Gerlach, M.M., Juskeyicius, D., Vela, Dirnhofer, S. & Tzankoy, A. 2020.

Context.—: Angioimmunoblastic T-cell lymphomas originate from T follicular helper cells and express respective markers (BCL6, CD10, CXCL13, ICOS, and PD-1). Although commonly present, bone marrow involvement by angioimmunoblastic T-cell lymphoma can be diagnostically challenging. Additionally, only little is known about the distribution of T follicular helper cells in healthy and reactively changed bone marrows or in samples affected by other lymphomas.

Objective.—: To establish a diagnostic approach to reliably identify bone marrow infiltration of angioimmunoblastic T-cell lymphoma.

Design.—: We analyzed the morphologic infiltration pattern and the expression of T follicular helper-cell markers in 42 matched paired lymph node and bone marrow samples and applied comparative clonality testing. Furthermore, we studied the expression of BCL6 and PD-1 in a control cohort of healthy, reactively changed, and otherwise affected bone marrows.

Results.—: We identified 3 different bone marrow infiltration patterns correlating with overall survival (interstitial/micronodular infiltration with or without eosinophilia and diffuse infiltration with eosinophilia). The matched pairs showed a consistent (co)expression of PD-1 and BCL6 with a generally weaker expression in the bone marrow than in the lymph nodes. Comparative clonality testing was helpful in only a minority of cases. Infiltrates of the most important differential diagnoses contained either PD-1- or BCL6-positive tumor-infiltrating cells, but no coexpressing cells.

Conclusions.—: Bone marrow infiltration by angioimmunoblastic T-cell lymphoma displays 3 different patterns that correlate with prognosis. BCL6 and PD-1 can be reliably used to identify lymphoma infiltrates and to help rule out several differential diagnoses. Comparative clonality testing rarely provides additional value and cannot replace morphologic and phenotypic analyses.

Szablewski V, Dereure O, René C, Tempier A, Durand L, Alame M, Cacheux V, Costes-Martineau V. 2019.

BACKGROUND: We report the cases of three patients presenting skin lesions whose biopsies showed nodular polymorphic infiltrates consisting of lymphocytes, plasma cells, histiocytes, eosinophils, B blasts, and Hodgkin Reed-Sternberg (HRS)-like cells. Two of them were initially diagnosed as classical Hodgkin lymphoma (cHL), on the other hand, the last one as a B-cell lymphoma. All patients have been treated for angioimmunoblastic T-cell lymphoma (AITL).

METHODS: We performed a second review of the skin biopsies with further immunophenotypic molecular analyses. Scrupulous observation revealed, in the background of the three cases, atypical small to medium-sized lymphocytes carrying a CD3+, CD4+ T-cell phenotype and expressing PD1 and CXCL13 follicular helper T-cell markers. The two lesions initially diagnosed as cHL showed scattered HRS-like cells with CD30+, CD15+, PAX5+, CD20-, Epstein Barr Virus (EBV) + classical phenotype. The case initially diagnosed as B-cell lymphoma showed a diffuse B-cell proliferation associated with small B-cell and medium to large-sized B blasts that were positive for EBV.

CONCLUSION: Those cases highlighted that atypical T-cells may be obscured by B-cell proliferation mimicking cHL or B-cell lymphoma in cutaneous localization of AITL and confirmed the requirement of collecting clinical information before performing a diagnosis.

Staging of Angioimmunoblastic T-Cell Lymphoma (AITL)

Once the test results of all the tests are back the medical team will be able to tell what stage the lymphoma is at.

Treatment of Angioimmunoblastic T-Cell Lymphoma (AITL)
A few people can be treated with steroid tablets alone, but Angioimmunoblastic T-Cell Lymphoma (AITL) is usually treated with:

- Chemotherapy - chemotherapy is treatment with drugs that kill the lymphoma cells or stop them from dividing.
- Stem cell transplantation

Nguyen, T.B., Sakata-Yanagimoto, M., Fujisawa, M., Nuhat, S.T., Miyoshi, H., Nannya, Y., Hashimoto, K., Fukumoto, K., Bernard, O.A., Kiyoki, Y., Ishitsuka, K., Momose, H., Sukegawa, S., Shinagawa, A., Suyama, T., Sato, Y., Nishikii, H., Obara, N., Kusakabe, M., Yanagimoto, S., Ogawa, S., Ohshima, K. & Chiba, S. 2020.
"Recurrent hotspot (p.Gly17Val) mutations in *RHOA* encoding a small GTPase, together with loss-of-function mutations in *TET2* encoding an epigenetic regulator, are genetic hallmarks of angioimmunoblastic T-cell lymphoma (AITL). Mice expressing the p.Gly17Val RHOA mutant on a *Tet2*-null background succumbed to AITL-like T-cell lymphomas due to deregulated T-cell receptor (TCR) signaling. Using these mice to investigate therapeutics for AITL, we found that dasatinib, a multikinase inhibitor prolonged their survival through inhibition of hyperactivated TCR signaling. A phase I clinical trial study of dasatinib monotherapy in 5 patients with relapsed/refractory AITL was performed. Dasatinib was started at a dose of 100 mg/body once a day and continued until days 10-78 (median day 58). All the evaluable patients achieved partial responses. Our findings suggest that AITL is highly dependent on TCR signaling and that dasatinib could be a promising candidate drug for AITL treatment. SIGNIFICANCE: Deregulated T-cell receptor signaling is a critical molecular event in angioimmunoblastic T-cell lymphoma and can be targeted with dasatinib."

Yamasaki, S., Yoshida, S., Kato, K., Choi, I., Imamura, Y., Kohno, K., Henzan, J., Tanimoto, K., Oqawa, R., Suehiro, Y., Miyamoto, T., Eto, T., Ohshima, K., Iwasaki, H., & Jukuoka Blood and Marrow Transplantation Group. 2020.
"The effects of stem cell transplantation (SCT) in patients with peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) and angioimmunoblastic T-cell lymphoma (AITL) remain controversial. We analyzed the feasibility of SCT and risk factors associated with outcomes of PTCL-NOS and AITL patients to identify the potential clinical efficacy of SCT. We retrospectively analyzed the data of PTCL-NOS (n = 83) and AITL (n = 112) patients who received autologous (n = 10 and 16, respectively) or allogeneic (n = 12 and 4, respectively) SCT, or no SCT (n = 61 and 92, respectively) between 2008 and 2018. All PTCL-NOS and AITL diagnoses were reconfirmed by an experienced hematopathologist. Median age at PTCL-NOS and AITL diagnoses in the SCT group was younger than that in the no SCT group. Significant risk factors for lower overall survival were intermediate-high and high-risk international prognostic indexes in PTCL-NOS patients (P = 0.0052), and a > 2 modified prognostic index for T-cell lymphoma (P = 0.0079) and no SCT (P = 0.028) in AITL patients. Autologous or allogeneic SCT compared with no SCT in AITL patients resulted in 3-year overall survival of 68.6% and 100% vs. 57.2% (P = 0.018). Strategies should be developed to improve selection of PTCL-NOS and AITL patients suitable for SCT and/or additional novel therapies."

Follow-up Care and Support
Once treatment is completed and AITL is in remission, physicians will continue to monitor the health and status of each patient. Patients in remission should have regular visits (at least 6-monthly in the

beginning) with their physician who is familiar with their medical history as well as with the treatments they have received.

Disease relapse and infections are common with this cancer. It is important to seek medical attention for fever or other symptoms related to improper functioning of the immune system.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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