# Angioimmunoblastic T Cell lymphoma with a secondary clonal Nodal Marginal Zone Lymphoma-like proliferation

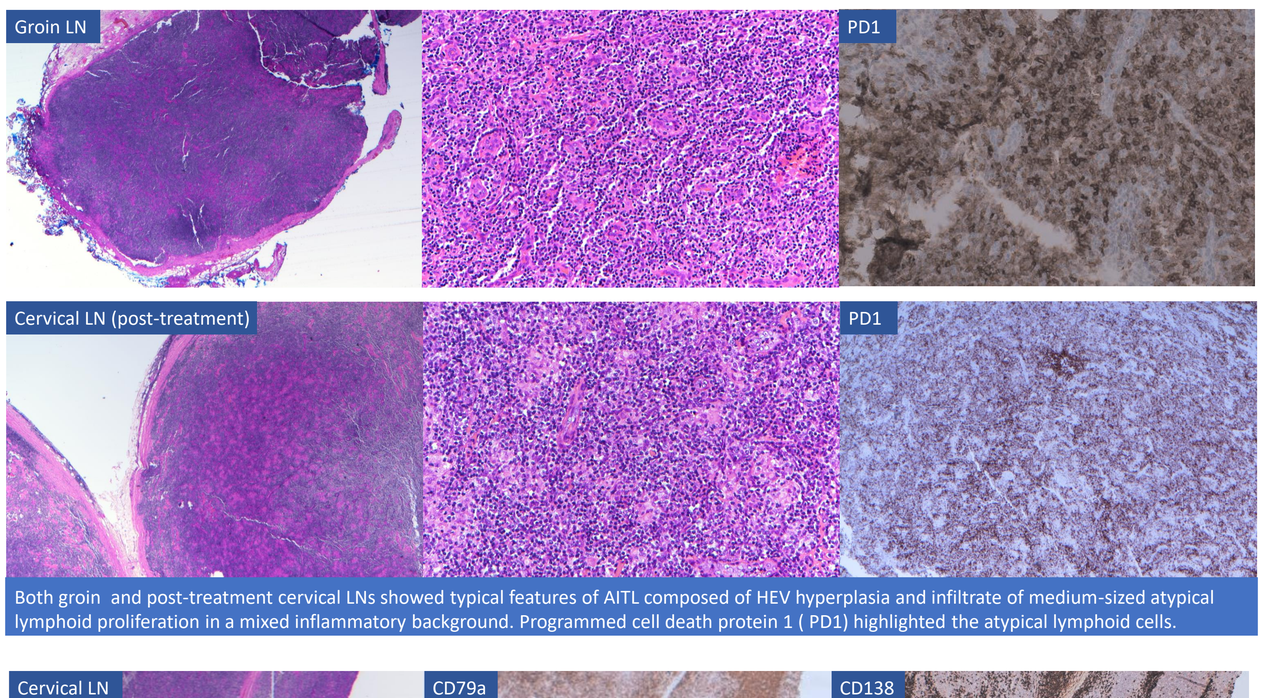
Howard Ho Wai Leung, Betty Pui Kwan Chak
Department of Anatomical and Cellular Pathology, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

## Introduction

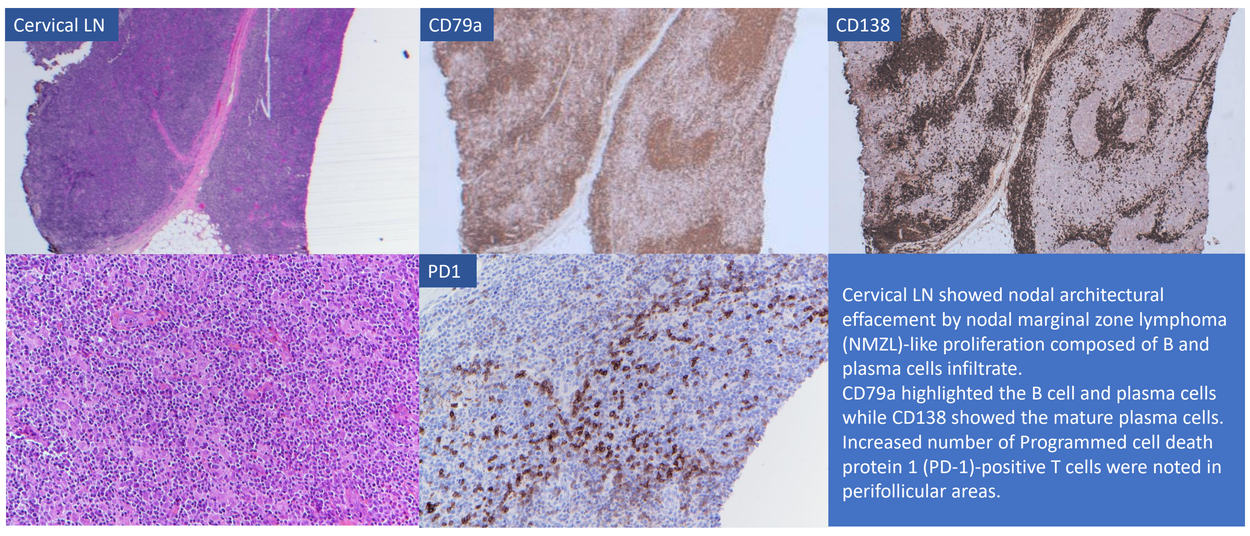
Angioimmunoblastic T Cell lymphoma (AITL) is a subtype of peripheral T-cell lymphoma with distinct clinicopathologic and genetic features, including early mutations in TET2 and DNMT3A occurring in hematopoietic stem cells and late changes (e.g. RHOA G17V mutation). [1] We report a case of angioimmunoblastic T Cell lymphoma with a secondary clonal nodal marginal zone lymphoma (NMZL)-like proliferation showing a parallel evolution of two distinct neoplastic lymphoid proliferations from a common mutated haematopoietic progenitor cell population.

## Case report

A 67-years-old female presented with generalized lymphadenopathy and bilateral pleural effusions. Positron emission tomography (PET)-computed tomography (CT) revealed multiple hypermetabolic lymph nodes on both sides of the diaphragm. An excisional biopsy of groin lymph node (LN) was performed and was reported as lymphoid proliferation. No clonal rearrangement of TCR gene was detected. Further investigation was suggested. Bone marrow showed focal atypical lymphoid infiltrates. Subsequently, an excisional biopsy of right neck lymph node was carried out. The cervical lymph node showed an interfollicular expansion of small lymphocytes with scattered intermediate to large cells and plasma cells partially effacing the architecture. The small lymphocytes were mainly B cells. Both the small B cells and plasma cells showed Kappa light chain restriction. EBV-encoded small RNA (EBER) was negative. An increase in number of small to medium sized T-follicular helper (TFH) cells was identified. Mild high endothelial venule (HEV) hyperplasia was also noted. IgH gene rearrangement was detected while T cell receptor gene rearrangement was not found. A provisional diagnosis of nodal marginal zone lymphoma (NMZL) was suggested in view of the relatively indolent clinical presentation and the biopsy findings. Considering the suspicious of underlying AITL/ nodal TFH cell lymphoma, next generation sequencing (NGS) for a lymphoma panel was performed. Two TET2 variants, one DNMT3A variant, RHOA variant and BRAF variant were detected. (see table 2 for detailed mutation profile)
The previous groin lymph node biopsy was then reviewed. Features of AITL, including extrafollicular follicular dendritic cell hyperplasia and small to medium sized TFH cells concentrated around hyperplastic HEVs were noted. The previous failed clonality analyses were found attributed to the poor DNA quality while further target sequencing detected the corresponding TET2 and DNMT3A mutations. The diagnoses were revised as AITL while the NMZL-like proliferation found in cervical LN was interpreted as a synchronous event.
To explore whether the NMZL-like B cells proliferation in the cervical LN carried the mutations detected which are frequently present in AITL, Sanger sequencing on microdissected B cell rich tissue were conducted. TET2, DNMT3A and BRAF mutations were identified. The strong mutant sequence trace signified NMZL-like B cells contained the mutations. The presence of overlapping mutations in both the AITL and the NMZL-like proliferation may suggest a common progenitor.
The patient was treated with six cycles of rituximab, cyclophosphamide, vincristine, doxorubicin and prednisolone (R-CHOP) followed by rituximab maintenance therapy. The PET-CT at 8 months post chemotherapy showed stable disease. However, at 20 months post chemotherapy, enlargement of neck lymph nodes was found. An excisional neck lymph node at level III was performed. The clonal B-cell proliferation was not observed while features of angioimmunoblastic T cell lymphoma had revealed itself. The abovementioned TET2 variants and DNMT3A were also detected.




Both groin and post-treatment cervical LNs showed typical features of AITL composed of HEV hyperplasia and infiltrate of medium-sized atypical lymphoid proliferation in a mixed inflammatory background. Programmed cell death protein 1 ( PD1) highlighted the atypical lymphoid cells.




Cervical LN showed nodal architectural effacement by nodal marginal zone lymphoma (NMZL)-like proliferation composed of B and plasma cells infiltrate.
CD79a highlighted the B cell and plasma cells while CD138 showed the mature plasma cells. Increased number of Programmed cell death protein 1 (PD-1)-positive T cells were noted in perifollicular areas.

Table 1. A summary of the Immunohistochemistry results

| Site | Cell type | Positive markers | Negative markers |
|---|---|---|---|
| Groin LN | Small B cells | CD20, CD79a, PAX5 | EBER |
| | T follicular helper cells | CD2, CD3, CD5, CD7, CD4, PD1, CD10, ICOS, CXCL13 | CD8 |
| | Follicular dendritic cells (FDC) | Extrafollicular expansion (CD21+) | |
| Cervical LN | Small B cells | CD20, CD79a, PAX5, Kappa light chain restriction | CD10, bcl-6, cyclin D1, IgD, CD5, CD23 |
| | Plasma cells | CD138, CD79a, Kappa light chain restriction | CD20, PAX5, cyclin D1, CD56, EBER-ISH |
| | T follicular helper cells | CD2, CD3, CD5, CD7, CD4, PD1, CD10, ICOS, CXCL13 | CD8 |
| | Follicular dendritic cells | | No expansion |
| Cervical LN (Post-treatment) | Small B cells | CD20, CD79a, PAX5 | EBER |
| | T follicular helper cells | CD2, CD3, CD5, CD7, CD4, PD1, CD10, ICOS, CXCL13 | CD8 |
| | Follicular dendritic cells (FDC) | Extrafollicular expansion (CD21+) | |

Table 2. A summary of the molecular results

| Gene | Variants | Groin LN | Cervical LN | | Cervical LN (post treatment) |
|---|---|---|---|---|---|
| | | | Whole section | Microdissected NMZL-like proliferation | |
| TET2 | c.1815C>G p.Tyr605Ter | + | + | + | + |
| | c.2083dup p.Met695AsnfsTer17 | + | + | + | + |
| DNMT3A | c.1074_1075del p.Tyr395GlnfsTer33 | + | + | + | + |
| RHOA | c.50G>T p.Gly17Val | + | + | + | – |
| BRAF | c.1405G>A Gly469Arg | – | + | + | – |
| **Clonal analyses** | | | | | |
| B cell | – | IgH gene rearrangement | IgH gene rearrangement | | - |
| T cell | – | - | - | | T cell receptor Beta gene rearrangement |

## Discussion

AITL is a subtype of peripheral T-cell lymphoma with distinct clinicopathologic and genetic features. The tumor cells in AITL are perceived to originate from TFH cells based on the characteristic gene expression profile. Recurrent mutations, including genes encoding the epigenetic regulators, TET2, DNMT3A and IDH2, the small GTPase, RHOA, and the components of the TCR signaling pathways, PLCG1, CD28, FYN, and VAV1, are identified. AITL 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 T cells signaling molecules (RHOA, VAV1, PLCG1, CD28).[2] The RHOA mutations detected in groin and cervical LNs are present in up to 70% of AITLs. It is seldom detected in other cancers except in other TFH lymphoma. Therefore, its detection helps the diagnosis of TFH lymphoma, including AITL.
It is not uncommon for AITL to have B cell proliferations, consisting commonly of variable numbers of immunoblasts and plasma cells.[3] Cases of AITL with diffuse large B cell lymphoma and rarely clonal B-cell proliferation resembling nodal marginal zone lymphoma, have been reported. The demonstration of similar but distinct mutations in this case study of AITL and NMZL-like proliferations suggest a parallel progression from a common hematopoietic progenitor cell population carrying TET2 and DNMT3A mutations to 2 neoplastic lymphoid proliferations. Studies have identified shared somatic mutations within the B cells and T cells in some cases of AITL through microdissection of individual samples.[4] Mutations including TET2, DNMT3A and other genes were found in both populations. The findings are consistent with TET2 and DNMT3A occurring early in haematopoietic stem cells. It also raises the possibility that AITL and the B cell proliferations are arising in a pluripotential stem cell. These observations are further supported by common TET2 and DNMT3A mutations in cases with metachronous myeloid neoplasms and AITL, suggesting a divergent evolution of a common clonal hematopoiesis clone.
Other than TET2 and DNMT3A mutations, the B cells in AITL lymph nodes can acquire additional B-cell–specific mutations in NOTCH1 and other genes, which may account for the frequent occurrence of clonal B-cell expansion in AITL. In this case, BRAF mutation was detected in the microdissected NMZL like proliferation of cervical LN. It was not detected in the groin and subsequent cervical LN in which lack of NMZL like proliferation. The detection of BRAF may share some similarity with NMZL and compatible with previous finding of recurrent hotspot BRAF mutations demonstrated in de-novo NMZL.[5]

Reference
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