Renamed, not tamed: angioimmunoblastic T-cell lymphoma, a diagnostic troublemaker

Rebecca N Young

Rashmi Lahiri

This Short Case is brought to you in association with the Pathological Society of Great Britain and Ireland. Each month we feature a Short Case written by a member of the Trainees' Subcommittee of the Pathological Society of Great Britain and Ireland. This case, including its scanned slides, is published on the Pathological Society's website www.pathsoc.org/index.php/trainees/case-of-the-month (previous cases can be accessed by members via the education portal login). The Short Case includes a series of Test Yourself Questions at the end to check your understanding of the case. We hope you enjoy reading it.

Pathological Society
Understanding Disease — Guiding Therapy

Abstract

Angioimmunoblastic T-cell lymphoma was reclassified a subtype of nodal T-follicular helper cell lymphoma (nTFHL-AI) in the 5th Edition of the World Health Organization Classification of Haematolymphoid Tumours. It is now grouped with related entities upon recent discovery of a shared T-follicular helper (TFH) cell origin. Numerous studies attest to the many peculiar presentations that impede recognition of the disease. Surgical biopsy is often required to secure a diagnosis though is rarely the first-line intervention. Delayed or missed diagnosis has a high price. Advanced stage of disease at presentation is common and rates of relapse are high. There is an unmet need for earlier detection and improved outcomes. Here we present a case which showed some quintessential clinicopathologic features of nTFHL-AI, and an approach to discerning these is discussed.

Keywords B-symptoms; Hodgkin lymphoma; Lugano classification; lymphadenopathy; nodal TFH cell lymphoma; reactive follicular hyperplasia; T-cell receptor; T-follicular helper cell

Case report

A 55-year-old male presented to his GP with cough and was treated with antibiotics for presumed chest infection. His condition deteriorated over 6 weeks and culminated in admission to hospital for treatment of severe hypoxia. On examination he was found to have cervical lymphadenopathy. Investigations ensued for suspected lymphoproliferative disorder.

Serum LDH was elevated. CT imaging detected generalized lymphadenopathy, pleural effusions and bilateral pulmonary nodules. Initial lymph node core biopsy was non-diagnostic. Subsequent surgical biopsy was required to confirm the diagnosis.

Microscopy showed effacement of nodal architecture by a diffuse infiltrate of lymphoid cells, plasma cells, histiocytes, and fibroblast-like cells. Prominent high endothelial venules were noted. The subcapsular sinus was partly preserved with spillage of the infiltrate into perinodal fat.

Immunohistochemical staining identified a population of CD20+ cells, a subset of which were large, atypical cells also shown to express CD30. The large cells were also EBV-positive. CD21 highlighted follicular dendritic cells encircling high endothelial venules. There was a prominent T-cell infiltrate that showed immunopositivity for CD2, CD3, CD5, and CD7. The T-cells were also convincingly positive for TFH markers PD1, ICOS and CXCL13. Together the morphologic and immunophenotypic features were characteristic of nTFHL-AI.

Staging CT detected supra- and infra-diaphragmatic in addition to bilateral pulmonary involvement by lymphoma, confirming Lugano Classification Stage IV disease. The patient was referred to the Haemato-Oncology Multidisciplinary Team. He commenced oral dexamethasone with a plan for multiagent CHOP chemotherapy and consideration of autologous stem cell transplant.

Discussion

Revised taxonomy in the 5th Edition of the WHO Classification of Haematolymphoid Tumours acknowledges the shared TFH-cell derivation of a subset of mature T-cell lymphomas (Table 1).

Although it comprises only 1%–2% of all non-Hodgkin lymphomas, more than one third of patients with a non-cutaneous T-cell lymphoma receive a diagnosis of angioimmunoblastic T-cell lymphoma. Seventy per cent of patients have bone marrow involvement at presentation, corresponding to Stage IV disease (Lugano classification).[1] Tokunaga et al. reported a series of 207 cases of AITL in which overall survival at 3 years was 54%.[2] By comparison overall survival at 3 years in diffuse large B-cell lymphoma ranges from 59% (high risk group) to 91% (low risk group).[3] Peripheral lymphadenopathy and 'B' symptoms are common presentations but non-specific symptoms are often reported. One retrospective study found one third of patients experienced atypical symptoms.[4]

Despite advances in understanding their pathogenesis, inter-observer variability in classification of nodal TFH-cell lymphomas persists. It is recognized that tumour morphology changes with disease evolution, progression and relapse. Different morphologic patterns imitate multiple alternative conditions: reactive and neoplastic, benign and malignant.[5]

In normality TFH cells are distributed across secondary lymphoid organs. They localize to B-cell zones and stimulate B-cell proliferation and maturation within germinal centres. Without TFH cells, germinal centre formation fails and antibody production by B-cells falters. TFH-cell lymphoproliferative

Rebecca N Young *MBChB MA(Res) Trainee Histopathologist, Department of Histopathology, Western General Hospital, Edinburgh, UK. Conflicts of interest: none declared.*

Rashmi Lahiri *MBBS FRCPath Consultant Histopathologist, NHS Lothian, Edinburgh, UK. Conflicts of interest: none declared.*

Changes in nomenclature in the current 5th Edition of the WHO Classification of Haematolymphoid Tumours

Current 5th Edition WHO Classification	4th Edition WHO Classification
Nodal TFH cell lymphomas:	
Angioimmunoblastic-type (nTFHL-AI)	Angioimmunoblastic T-cell lymphoma
Follicular-type (nTFHL-F)	Follicular T-cell lymphoma
Not otherwise specified (nTFHL-NOS)	Nodal peripheral T-cell lymphoma with TFH phenotype

Table 1

disease causes immune dysregulation with diverse clinical manifestations. Atypical B cell and plasma cell populations can arise as secondary phenomena. Epstein—Barr virus is recognized as a driver of tumorigenesis and active EBV infection is invariably detected in B-cells which form part of the tumour microenvironment.

Detection of clonal T-cell receptor rearrangement, or of mutations in RHOA and IDH2 genes are important diagnostic tools in challenging cases. But an approach based on interpretation of morphologic and immunophenotypic features is required in routine clinical practice.

During assessment of this case, one appreciates the effacement of nodal architecture by a diffuse and polymorphous infiltrate. The infiltrate spills over into perinodal fat, and despite fragmentation of the biopsy, one can observe focal preservation of the subcapsular sinus.

A panel of immunohistochemical stains helps to discern several compelling features which render the diagnosis. CD21 highlights follicular dendritic cells with envelopment of high endothelial venules. There are aggregates of small CD20+ cells, in addition to scattered large CD20+ cells with enlarged nuclei and prominent nucleoli, including occasional binucleate forms. The large cells are also shown to express CD30 and a proportion is positive for EBER on in situ hybridization. These are outnumbered by a dense population of small CD3+ lymphoid cells, which are somewhat obscured on the H&E sections by the heterogeneous milieu and eye-catching large cells (Figure 1).

The features resemble Hodgkin lymphoma in some respects, and it is a key differential in this presentation of lymphoproliferative disorder. Genuine Reed-Sternberg cells should have more eosinophilic nuclei than the large cells present in this case and, importantly, they suppress rather than retain markers of B-cell lineage, including CD20.

A prior core biopsy of the same nodal lesion also demonstrates a dense T-cell population with a high proliferation rate and, whilst insufficient for definitive diagnosis, it is highly suspicious for a T-cell neoplastic process. The inclusion of multiple TFH-cell markers in the immunohistochemistry panel on the surgical biopsy confirms the TFH phenotype of the tumour cells.

WHO diagnostic criteria for the angioimmunoblastic subtype of nodal TFH-cell lymphoma includes strong expression of at least two TFH markers. PD1 and ICOS show greatest sensitivity and CD10 and CXCL13 are more specific.[6] Staining intensity varies and a degree of positive staining is expected in normal follicles. High staining intensity with PD1 is most diagnostically useful. In the case presented here PD1, ICOS and CXCL13 showed varying degrees of positive staining (Figure 2).

The case presented in this report studies the dominant morphologic pattern of nodal TFH-cell lymphoma, one which

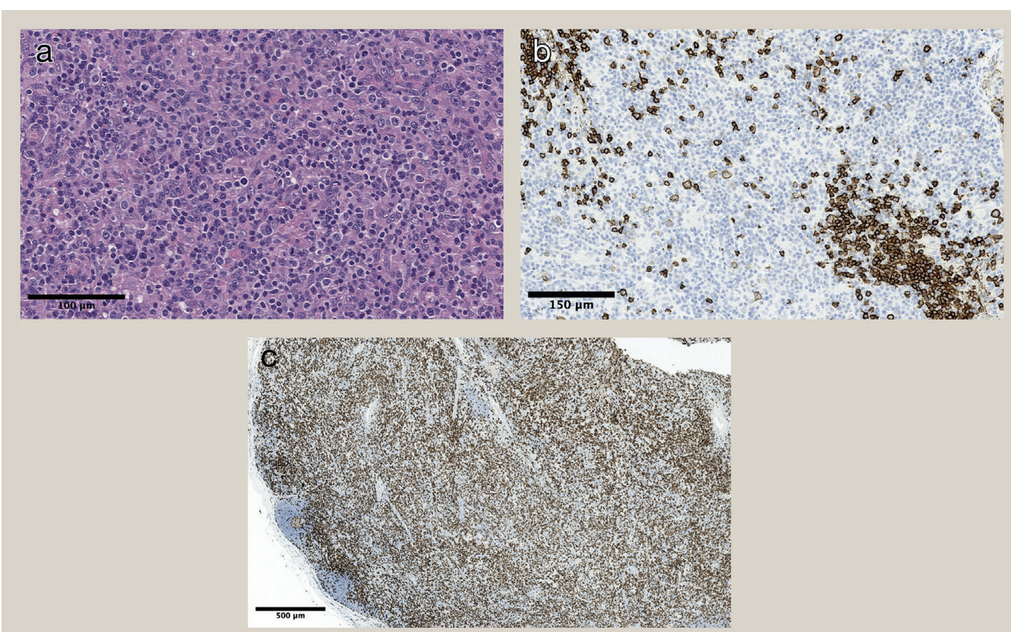

Figure 1 Nodal architecture is effaced by a diffuse and polymorphous infiltrate of small to medium lymphoid cells, large cells with abundant cytoplasm and enlarged nuclei, plasma cells, histiocytes and sparse eosinophils (**a**). Antibody raised against CD20 stains aggregates of small B lymphocytes in addition to dispersed large cells (**b**). The CD20+ population is outnumbered by a diffuse population of CD3+ T-cells (**c**). (**a**) Haematoxylin & eosin stain, 30× magnification. (**b**) Immunohistochemistry, 18× magnification, CD20. (**c**) Immunohistochemistry, 5× magnification, CD3.

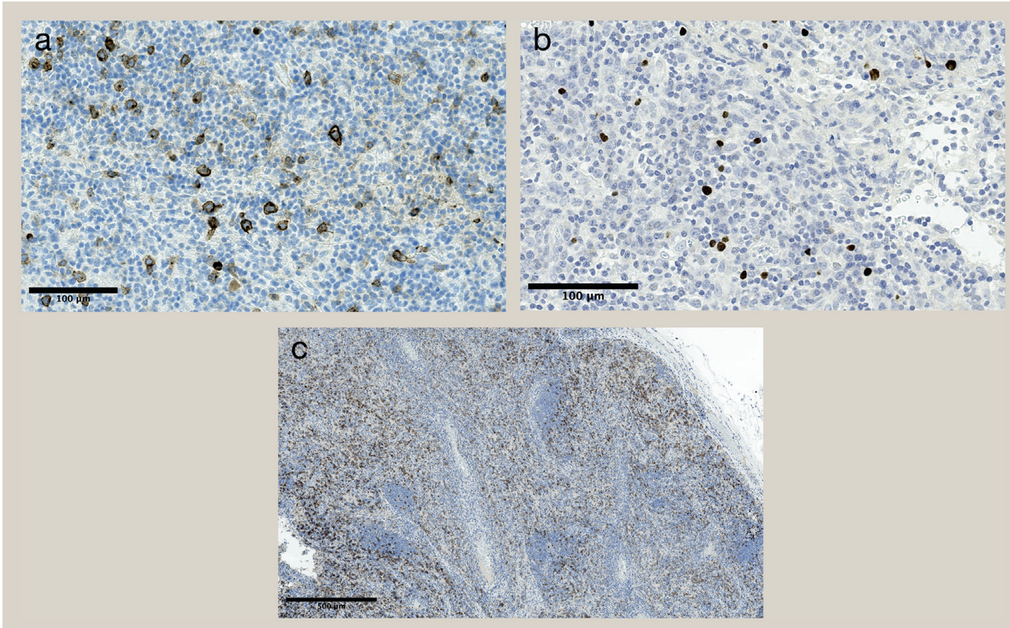

Figure 2 A significant proportion of large CD20+ cells are also shown to express CD30 and are positive for EBER on in situ hybridisation (**a & b**). The CD3+ T cell population is shown to express markers of T-follicular helper cell differentiation, including PD1 (**c**) in addition to ICOS and CXCL13. (**a**) Immunohistochemistry, 30× magnification, CD30. (**b**) Immunohistochemistry, 40× magnification, EBER. (**c**) Immunohistochemistry, 5× magnification, PD1.

can mimic Hodgkin lymphoma. A rarer pattern demonstrates preserved follicular architecture, the follicular subtype. The perifollicular distribution of atypical T-cells with expression of TFH markers helps to distinguish this deceptively banal appearance from reactive follicular hyperplasia, in which TFH cells remain appropriately localized within follicle centres.

Additional immunohistochemical tests distinguish the various cell types present in the tumour microenvironment. Plasma cells are polytypic. Concurrent clonal populations of small or large B-cells were not identified.

Conclusion

Confirmation of the T-follicular helper cell derivation of nodal T-cell lymphomas improves understanding of the natural history of these malignancies and enhances methods for their detection. Appreciation of the prototypical features of nTFHL-AI and its mimicry of Hodgkin lymphoma and of practical approaches to its recognition are essential to reducing the time interval from initial presentation to definitive treatment for patients. In tumour cell-poor infiltrates, without a high index of suspicion for nTFHL-AI, and without inclusion of at least two TFH markers in an IHC panel, a prompt and accurate diagnosis may be elusive. ◆

REFERENCES

1 Chan J, Attygalle AD, Alaggio R, et al. Nodal T-follicular helper (TFH) cell lymphoma. In: WHO Classification of Tumours Editorial Board. Haematolymphoid tumours [Internet; beta version ahead of print] 2022. Lyon (France): International Agency for Research on Cancer [cited 2024 Feb 11]. (WHO classification of tumours series, 5th ed.; vol. 11). Available from: https://tumourclassification.iarc.who.int/chapters/63.

2 Tokunaga T, Kazuyuki S, Kazuhitu Y, et al. Retrospective analysis of prognostic factors for angioimmunoblastic T-cell lymphoma: a multicenter cooperative study in Japan. *Blood* 2012; **119:** 2837–43.

3 Susanibar-Adaniyar S, Barta SK. 2012 Update on Diffuse Large B cell lymphoma: a review of current data and potential applications on risk stratification and management. *Am J Hematol* 2021; **96:** 617–29.

4 Lachenal F, Berger F, Ghesquières H, et al. Angioimmunoblastic T-cell lymphoma: clinical and laboratory features at diagnosis in 77 patients. *Medicine* 2007; **86:** 282–92.

5 Lunning MA, Vose JM. Angioimmunoblastic T-cell lymphoma: the many-faced lymphoma. *Blood* 2017; **129:** 1095–102.

6 Xie Y, Jaffe ES. How I diagnose angioimmunoblastic T-cell lymphoma. *Am J Clin Pathol* 2021; **156:** 1–14.

Practice points

- Angioimmunoblastic T-cell lymphoma (AITL) has been redesignated nodal T-follicular helper cell lymphoma, angioimmunoblastic-type (nTFHL-AI) to reflect confirmation of its T-follicular helper cell origin
- Multiple overlapping morphologies are recognized and mimic alternative neoplastic and non-neoplastic entities
- In its classical presentation nTFHL-AI can mimic Hodgkin lymphoma with large Hodgkin-like cells, but can be distinguished from the latter by retained B-cell markers, notably CD20
- An immunohistochemical panel that includes at least two, ideally three T-follicular helper cell markers is recommended by the WHO and strong PD1 staining is most diagnostically useful

Self-assessment questions

1. Which of the following statements is true about nodal T-follicular helper cell lymphoma-angioimmiunoblastic type?

a. It is one of the most commonly diagnosed non-Hodgkin lymphomas.
b. Diagnosis requires expression of at least two markers of T-follicular helper cell differentiation.
c. Secondary clonal populations of B-cell linage aid diagnosis.
d. Preservation of follicular architecture is stereotypical of the subtype.
e. Large B-cells in the tumour microenvironment are typically CD20- and CD30+

Correct answer: b

2. Which of the following is not a marker of T-follicular helper cell differentiation?

a. PD1
b. CXCL13
c. ICOS
d. CD10
e. CD3

Correct answer: e

3. In normal lymph node mature T-follicular helper cells tend to localize to:

a. Germinal centres
b. Mantle zones
c. Interfollicular areas
d. Subcapsular sinus
e. Paracortex

Correct answer: a