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A new mode for the diagnosis of angioimmunoblastic T-cell lymphoma

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Abstract

In order to explore a new mode for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL), 31 cases of AITL and 28 cases of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) were used as the study subjects. Identifying T follicular helper (TFH) cells with CD4, CD10, Bcl-6, and PD-1, identifying proliferative B cells with CD20 and EZH2, identifying proliferative follicular dendritic cells (FDCs) with CD21 and CD23, and analyzing the value of TFH/B/FDC proliferation and immunolocalization in the diagnosis of AITL. (1) Outside the inherent lymphoid follicles, simultaneous proliferation of TFH/B/FDC (a new diagnostic mode) were observed in AITL [83.87%; 26/31], with their immunolocalizations in the same site [83.87%; 26/31], while this phenomenon was not observed in 28 cases of PTCL-NOS ($P<0.05$). (2) The sensitivity and specificity of using this new mode to diagnose AITL were both high (83.87%, 100%), which was superior to CD2 (100%, 0%), CD3 (100%, 0%), CD4 (100%, 32.14%), CD5 (100%, 25%), CD10 (61.9%, 100%), Bcl-6 (42.86%, 100%), PD-1 (83.87%, 96.43%), and its Youden Index (0.84) was the highest. The areas under the curve (AUC) of CD10, Bcl-6, PD-1, and new mode to diagnosis AITL were 0.81, 0.71, 0.90, and 0.92, respectively, while the new mode had the highest AUC. The simultaneous proliferation of TFH/B/FDC cells outside the inherent lymphoid follicles can be used to assist in the diagnosis of AITL, and the simultaneous spatiotemporal proliferation of TFH/B/FDC cells is a specific immunomorphology of AITL.

Keywords: Angioimmunoblastic T-cell lymphoma; Peripheral T-cell lymphoma, Not otherwise specified; Immunolocalization; Diagnosis

1. Introduction

Angioimmunoblastic T cell lymphoma (AITL) originates from follicular helper T cells (TFH), accounting for 1% to 2% of non-Hodgkin's lymphoma (NHL) and 13.8% to 36% of peripheral T cell lymphoma (PTCL) [1-4]. Approximately 85% to 95% of AITL can be detected with EBV infection [5]. In the case of immune disorder or immunosuppression, virus infection (such as EBV) occurs and induces polyclonal proliferation of B cells, which transmits viral protein as an activation signal to follicular T helper cell (TFH) to promote its malignant proliferation. AITL tumor cells retain a certain degree of TFH function, because tumor TFH and recruitment of proliferative B cells are tightly wrapped in the proliferative FDC network, similar to the arrangement of germinal center [6].

AITL tends to occur in the elderly, and the median age of onset was 65 years old. There was no significant gender difference in AITL. The clinical manifestations of patients often consist of multiple lymphadenopathy, hepatosplenomegaly, B symptoms, rash, skin itching, etc.; some patients exhibit inflammatory symptoms such as serous effusion and arthritis, as well as autoimmune tendencies such as autoimmune hemolytic anemia and immune thrombocytopenia. The patients may have abnormal laboratory test results such as increased eosinophil, increased polyclonal immunoglobulin, increased lactate dehydrogenase, positive anti-human globulin test, and increased rheumatoid factor titer [7-9]. AITL has a poor prognosis and the 5-year median survival rate was only 32% [10-12]. The complete or partial disappearance of lymph node structure and significant enlargement of the subcortical area were common in AITL. In most cases, the germinal center was atrophied or disappeared while some follicles were hyperplasia. Tufted T cells with transparent cytoplasm are scattered or infiltrated around blood vessels in lymph nodes. Polymorphic cell infiltration can be seen in the background, including scattered B lymphocytes, B immunoblasts, plasma cells (mainly polyclonal, rarely monoclonal), eosinophil, histiocytes and other inflammatory cell infiltration, most of which are accompanied by EBV-positive B cell infiltration. Background interstitial hyperplasia is accompanied by significant proliferation of branching blood vessels

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and irregular follicular dendritic cell(FDC) proliferative foci which often surround high endothelial blood vessels. However, FDC proliferative foci are difficult to identify under light microscopy and require immunohistochemical labeling of CD21 to identify proliferative follicular dendritic cells [6,13].

In the background of pleomorphic cell infiltration, tumor T cells are not dominant in quantity, and TFH markers (including CD10, Bcl-6, and PD-1) often show a low number of positive cells and weak expression intensity. Furthermore, AITL should be differentiated from PTCL, NOS, anaplastic large cell lymphoma, reactive hyperplasia of lymph nodes, etc. The diagnosis of AITL is challenging, so it is important to find new diagnostic modes.

In the clinical-pathological diagnosis, we observed a new mode of diagnosing AITL, that is, when the three conditions of extrafollicular TFH cell proliferation, reactive B cell proliferation and FDC proliferation are met simultaneously, the sensitivity and specificity of diagnosing AITL are high.

2. Materials and methods

2.1. Patients and samples

We reviewed 31 cases of AITL archived in the Department of Pathology, Jiading District Central Hospital, Shanghai University of Medicine & Health Sciences, between January 1, 2009, and October 31, 2021. There were 18 males and 13 females, ranging in age from 47 to 84 years, with a median age of 66 years. 28 cases of PTCL-NOS were collected as the control group. There were 19 males and 9 females, ranging in age from 36 to 83 years, with a median age of 60.5 years. Pathological diagnosis and reevaluation were performed in accordance with the criteria of the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues (2017 version).

2.2. Immunohistochemical staining

The specimens were routinely handled from dehydration, embedding, slicing, and dewaxing to rehydration. Immunohistochemical staining was performed using the EnVision two-step method. All antibodies except EZH2 in this study were purchased from Guangzhou Anbiping Pharmaceutical Technology Co., Ltd. EZH2 antibody was purchased from proteintech company. Cells were considered positive for CD2, CD3, CD4, CD5, CD10, PD1 and CD20 when there were brown granules in the cytoplasm; cells were interpreted positive for CD21 and CD23 when the cell membrane and cell protrusions were brownish yellow, and cells were considered positive for PAX-5 and BCL-6 and EZH2 when there were brown granules in the nucleus. The results were interpreted using the semiquantitative integration method, i.e., (-), (1+), (2+), and (3+).

2.3. Statistical analysis

Statistic Package for Social Science (SPSS) 17.0 statistical software (IBM, Armonk, NY, USA) was used for analyses. Pearson's chi-square test, the continuous calibration test and Fisher's exact probability method were used to compare the positive rates between the two groups. The differences in area under the curve (AUC) were analyzed with the receiver operating curve (ROC). The receiver operating curve (ROC) was performed to analyze the differences in area under the curve (AUC). P-values <0.05 indicate a statistically significant difference (two-sided).

3. Results

3.1. The expression of T-cell immune markers in patients with AITL and PTCL-NOS

The positive rates of CD2, CD3, CD4, CD5, CD10, Bcl-6 and PD-1 expression in patients with AITL were 100% (31, 3+), 100% (31, 3+), 100% (22, 3+ and 9, 2+), 100% (25, 3+ and 6, 2+), 61.29% (19, 1+), 41.94% (13, 1+), and 83.87% (26,1+), respectively. CD10, Bcl-6 and PD-1 were all (1+), and the number of positive cells was low. The positive rates of CD2, CD3, CD4, CD5, CD10, Bcl-6 and PD-1 expression in patients with PTCL-NOS were 100% (3+), 100% (3+), 67.86% (19, 3+), 75% (21, 3+), 0%, 0% and 3.57% (1, 1+), respectively. There were statistically significant differences between the positive rates of CD4, CD5, CD10, Bcl-6 and PD-1expression in AITL and PTCL-NOS ($P < 0.05$) (Table 1, Figure 1).

3.2. Immunohistochemistry expressions of TFH/B/FDCs in patients with AITL and PTCL-NOS

3.2.1. A new mode for diagnosis of AITL:if the following three criteria are met simultaneously, it can be diagnosed as AITL (83.87%, 26/31)

Criteria (1) Extrafollicular TFH cell proliferation: In this study, CD4, CD10, Bcl-6, and PD-1 were all immune markers for TFH cells. If two or more extrafollicular tumor cells were positive among the four antibodies mentioned above, it was determined that TFH cells were positive. The positive rate in this study was 83.87% (26/31). (2) B cells

Table 1. Expressions of immunological markers in AITL and PTCL-NOS.

Immune markers	AITL No. (%)		PTCL-NOS No. (%)		$\chi 2$ values	P-values
	+	-	+	-		
CD2 expression	31(100%)	0(0%)	28(100%)	0(0%)	—	—
CD3 expression	31(100%)	0(0%)	28(100%)	0(0%)	—	—
CD4 expression	31(100%)	0(0%)	19(67.85%)	9(32.14%)	9.40	0.00
CD5 expression	31(100%)	0(0%)	21(75.0%)	7(25.0%)	6.57	0.01
CD10 expression	19(61.29%)	12(38.71%)	0(0%)	28(100%)	25.31	0.00
BCL-6 expression	13(41.94%)	18(58.06%)	0(0%)	28(100%)	15.06	0.00
PD-1 expression	26(83.87%)	5(16.13%)	1(3.57%)	27(96.43%)	38.22	0.00
New mode(TFH cells+B cells+FDCs)	26(83.87%)	5(16.13%)	0(0%)	28(100%)	41.97	0.00

AITL, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; TFH cells, t follicular helper cells; FDCs, follicular dendritic cells; P-values were obtained by chi-square test.

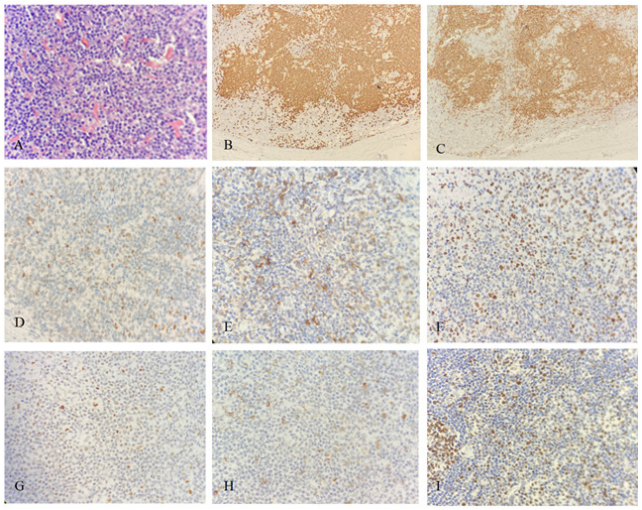

Fig. 1. Representative histologic findings of the entities of AITL. (A) Lymph node architecture shows effacement with prominent high endothelial venules (400×). (B) CD20+ B cells (100×). (C) CD21+ FDCs (100×). (D) Bcl-6+ TFH cells (400×). (E) PD-1+ TFH cells (400×). (F) Small lymphocytes of EZH2- (400×). (G) Bcl-6+ TFH cells (400×). (H) PD-1+ TFH cells (400×). (I) Small lymphocytes of EZH2- (400×). D, E, and F show the same patient. G, H and I show another patient.

with reactive proliferation outside lymphoid follicles: this study used CD20+and EZH2- to identify reactive proliferation B cells.EZH2 is usually expressed in the follicle centre B cells and the immunoblasts in the interfollicular zone [14]. Among the 31 cases, 30 cases showed proliferation of B lymphocytes recruited outside the lymphoid follicles (96.77%), with an immunophenotype of CD20+/EZH2- (Figure 2). (3) The proliferation of FDCs outside lymphoid follicles was studied using CD21 and CD23. Among the 31 cases, 30 showed FDCs proliferation with positive CD21 and CD23 (96.77%) (Figure 2-3).

3.2.2. Relationships between TFH/B/FDCs immunolocalization and AITL clinical parameters

In this study, it was observed that TFH/B/FDCs immunolocalization had special commonality in AITL cases meeting the diagnostic requirements of the new mode. Outside the inherent lymphoid follicles, 26 out of 31 cases of AITL were observed significant TFH/B/FDCs in the same place (under a 40-fold field of view) (83.87%), and none were observed in 28 cases of PTCL-NOS cases (0%). There was statistical difference in the positive rate comparison of this phenomenon ($P<0.05$). No differences were observed in the positive rates between the two groups with regard to sex, age, Eastern Cooperative Oncology Group (ECOG) score, Ann Abor stage, number of extranodal lesions, lactate dehydrogenase (LDH) level, international Prognostic Index (IPI) score, and sampling site ($P > 0.05$) (Table 2, Figure 3).

3.2.3. Sensitivity, specificity, Youden Index and Receiver operating characteristic analysis of the new mode and T cell immune markers in the diagnosis of AITL

Those that meet the three criteria of the new mode are considered to be positive for diagnosing AITL. The sensitivity and specificity of using this mode to diagnose AITL are high (83.87%, 100%), which is superior to CD2 (100%, 0%), CD3 (100%, 0%), CD4 (100%, 32.14%), CD5 (100%, 25%), CD10 (61.9%, 100%), Bcl-6 (42.86%, 100%), and PD-1 (83.87%, 96.43%). The Youden Index (0.84) of AITL diagnosed by this mode is the highest, and which of CD2, CD3, CD4, CD5, CD10, Bcl-6 and PD-1 is 0, 0, 0.32, 0.25, 0.62, 0.43 and 0.80, respectively. The ROC was used to compare the AUC of AITL diagnosed by CD10, Bcl-6, PD-1 and the new mode, and significant differences were shown ($P<0.05$). The AUC of CD10 is 0.81 (95% CI: 0.69~0.92), the AUC of Bcl-6 is 0.71 (95% CI: 0.58~0.84), the AUC of PD-1 is 0.90 (95% CI: 0.81~0.99), and the AUC of the new mode is 0.92 (95% CI: 0.84~1). The AUC area of the new mode is the largest (Table 3).

4. Discussion

The immunophenotypes of AITL neoplastic T cells mainly contain two categories: pan-T-cell markers and TFH cell markers. Germinal TFH cell markers include CD4, CD10, Bcl-6, CXCL-13, PD-1, ICOS, etc. Rodriguez-Justo et al. [15] found that in 10 patients with AITL, tumorous T cells weakly expressed CD10 and which can identify only 5-10% of the tumor cell. In a prospective cohort study, AITL and PTCL-NOS had different positive expression rates of CXCL13 and PD-1. The positive rates of CXCL13 in AITL and PTCL-NOS were 95% and 17%, respectively. The positive rates of PD-1 in AITL and PTCL-NOS were 84% and 3%, respectively [16]. In this study, the diagnostic sensitivity and specificity of TFH

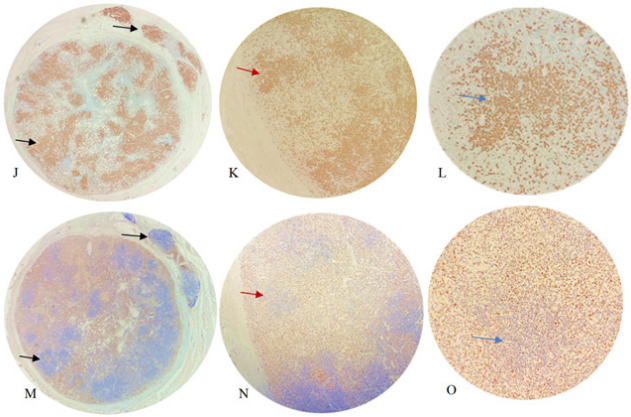

Fig. 2. CD20+/EZH2- reactive proliferative B cells with the same color arrow. (J) CD20+ B cells (20×). (K) CD20+ B cells (100×). (L) CD20+ B cells (200×). (M) EZH2(-) B cells (20×). (N) EZH2(-) B cells (100×). (O) EZH2(-) B cells (200×).

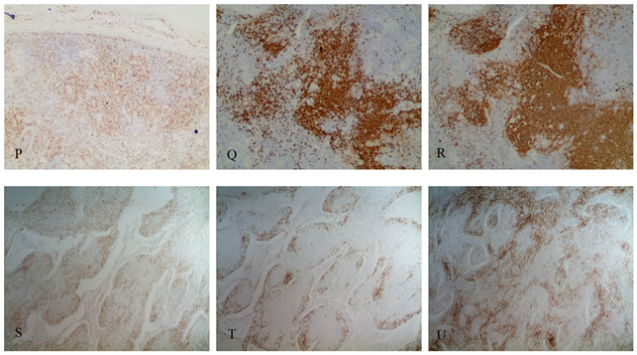

Fig. 3. Immunolocalization of TFH/B/FDCs in patients with AITL. (P) CD10+ TFH cells (40×). (Q) CD20+ B cells (40×). (R) CD21+ FDCs (40×). P,Q and R show the same patient. (S) CD10+ TFH cells (40×). (T) CD20+ B cells (40×). (U) CD21+ FDCs (40×). S,T and U show another patient.

Table 2. Relationships between TFH/B/FDC immunolocalization and clinical parameters in AITL.

Immunolocalization		n (case)	Immunolocalization of TFH/B/FDCs		P-values
			Same location	Different locations	
Clinical parameters					
Gender	Male	18	14	4	> 0.05
	Female	13	12	1	
Age	≥ 60	25	22	3	> 0.05
	< 60	6	4	2	
ECOG score	0-1	19	15	4	> 0.05
	2-4	12	11	1	
Ann Arbor staging	I~II	5	4	1	> 0.05
	III~IV	26	22	4	
Number of extranodal lesions	< 2	19	16	3	> 0.05
	≥ 2	12	10	2	
LDH level	Normal	13	11	2	> 0.05
	Elevated	18	15	3	
IPI score	≤ 2	10	8	2	> 0.05
	> 2	21	18	3	
Sampling site	Lymph nodes	30	26	4	> 0.05
	Extranodal	1	0	1	

AITL, angioimmunoblastic T-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; IPI, international prognostic index; p-values were obtained by chi-square test.

Table 3. Diagnostic efficacy of CD10, Bcl-6, PD-1, and new mode in AITL.

Index	Youden Index	Sensitivity (%)	Specificity (%)	AUC	95%*CI*
CD10	0.62	61.9	100	0.81	0.69~0.92
Bcl-6	0.43	42.86	100	0.71	0.58~0.84
PD-1	0.80	83.87	96.43	0.90	0.81~0.99
New mode	0.84	83.87	100	0.92	0.84~1

cell markers were CD4 (100%, 32.14%), CD10 (61.9%, 100%), Bcl-6 (42.86%, 100%), and PD-1 (83.87%, 96.43%), respectively. CD4 had high sensitivity and low specificity in the diagnosis of AITL, CD10 and Bcl-6 had low sensitivity and high specificity, and PD-1 had both good sensitivity and specificity, but the quantity of CD10, Bcl-6 and PD-1 positive tumor cells was small.

The tumor T cells of AITL do not have an advantage in quantity. In the context of pleomorphic cell infiltration, TFH markers CD10, Bcl-6, and PD-1 often show a low number of positive cells and weak or moderate expression intensity. Pathologists often face challenges in the diagnosis of AITL, and it is important to find new diagnostic modes for AITL. Similar expression patterns of PD-1 and CXCL13 were found in AITL: the expanded CD21-positive FDC networks surrounded PD-1-positive and CXCL13-positive tumor cells [17]. It has been reported that CD21, CD23, and CD35 positive FDC expansion networks usually appear in the neoplastic T cell region of AITL [18], moreover, neoplastic T cells and recruited reactive proliferative B cells were closely connected in the FDC network rich in CXCL13+ cells [6]. Therefore, the author speculated that TFH/B/FDC cells may be located in the same reaction site, and the TFH cells and recruited B cells are closely wrapped in the FDC network by imitating the function of the germinal center. Based on the above mechanism hypothesis, we speculate that simultaneous proliferation of TFH cells, B cells and FDC cells (even the same spatiotemporal proliferation) can be seen in AITL, excluding lymphoid follicles. Therefore, a new diagnostic mode is proposed, and those who meet the following three criteria can be diagnosed as AITL. Criteria (1) If two or more TFH cell immune markers outside the lymphoid follicles are positive, it is judged as TFH cell proliferation;(2) reactive hyperplasia B cells are found outside lymphoid follicles, which can be identified by CD20+ and EZH2-;(3)FDC proliferation appears outside the lymphoid follicles, and FDCs are labeled with CD21 and CD23.

Among the 31 AITL cases in this study, 26 cases met the criteria of extrafollicular TFH cell proliferation, with a positive rate of 83.87%. The positive rate of CD10 in AITL was 61.29% (1+, 19 cases), Bcl-6 was 41.94% (1+, 13 cases), and PD-1 was 83.87% (1+, 26 cases), respectively. However, the number of positive TFH cells is small, and pathological diagnosis still faces challenges. The above three TFH markers are strongly expressed in the germinal center. Why is the expression of migration germinal center down-regulated? In describing the differentiation, function and role of TFH cells in diseases, Crotty et al. [19] mentioned that the maturation and differentiation of follicle centre B cells require the synergistic action of TFH cells and FDC cells. Once the mission is completed, TFH cells can move outside the germinal center. After migrating out of the germinal center, TFH cell had three places to go,

(1) It can be transferred to the adjacent lymphoid follicles, (2) It stay in the adjacent lymphoid follicles temporarily, waiting for the opportunity to enter the same germinal center again, (3) It can develop to memory TFH cell once it go outside the germinal center, and the expression of PD-1 in TFH cells is down-regulated, so is bcl-6 [19]. Alonso et al. [20] showed that the expressions of Bcl-6, ICOS and PD-1 in blood circulation were down-regulated compared with TFH cells in the germinal center, and the former had auxiliary and memory functions. The above studies suggest that AITL tumor cells may have the phenotype of memory TFH after migrating outside the germinal center, and the original immunolabeling expression of TFH cells may be down-regulated. The number of tumor cells in AITL is not dominant, and the expression of TFH immune markers is down-regulated. Is the synergetic proliferative background cells helpful for diagnosis?

Significant proliferation of B cells is one of the histological characteristics of AITL, but B-cell lymphoma needs to be excluded.CXCL13 and IL-4 secreted by TFH cells in AITL promote recruitment and proliferation of B cells in the background [6,21]. In some tumors, the body can recruit B lymphocytes through the CXCL13/CXCR5 axis to form tertiary lymph node structures to fight the tumor [22]. In this study, CD20 and EZH2 were selected to identify proliferative B cells. Undifferentiated stem cells and precursor cells express EZH2, however, this phenomenon was not observed in most somatic cells [23]. EZH2 is expressed in the follicle centre B cells and immune blast cells scattered in the interfollicular area, and the absence of EZH2 can inhibit the formation of follicular germinal centers [14]. EZH2 is overexpressed in hematological tumors such as acute myeloid leukemia, multiple myeloma, and NHL, and can promote the occurrence of cancer [24]. The above researches suggest that EZH2 may be negative in reactive proliferative B cells and positive in tumor B cells. In this study, EZH2 immunostaining showed that focal small lymphocytes in AITL were negative, and the rest cell groups were mottled positive. Based on histological morphology and CD20 immunolocalization, we identified the small lymphocytes of EZH2- as B lymphocytes and the combination of EZH2-/CD20+ can recognize the B cell population recruited in AITL. In this study, 96.77% (30/31) of reactive hyperplasia B cell populations were identified in AITL with this method. The proliferation of FDCs is easy to identify by CD21 and CD23, which often forms a "blow-like" histological morphology. In this study, 30 out of 31 cases were found to have FDC proliferation, and only 1 extranodal case did not show FDC proliferation.

The positive rate of the new mode for diagnosing AITL was 83.87% (26/31). Compared with PTCL-NOS, the new diagnostic mode proposed in this study has high sensitivity and specificity in diagnosing AITL (83.87%, 100%), and which were superior to CD2 (100%, 0%), CD3 (100%, 0%), CD4 (100%, 32.14%), CD5 (100%, 25%), CD10 (61.9%, 100%), Bcl-6 (42.86%, 100%) and PD-1 (83.87%, 96.43%). The Youden index of AITL diagnosed by this mode is as high as 0.84 and AUC is 0.92. In addition, we also observed unique commonalities in the immunolocalization of TFH/B/FDCs. Outside the inherent lymphoid follicles, significant TFH/B/FDCs were observed in 26 out of 31 AITLs (83.87%), whereas none were observed in 28 cases of PTCL-NOS (0%). In summary, this study suggests that the "new mode" can assist the diagnosis of AITL effectively, and the phenomenon of TFH/B/FDC cell immune localization in the same place can collaboratively review diagnosis.

5. Conclusion

The number of AITL tumor cells is not dominant, the background is diverse, and there are still some cases of missed diagnosis and misdiagnosis. An effective diagnostic mode has been discovered based on its pathogenesis in this study, and those who meet the following three criteria simultaneously can be diagnosed as AITL: Criteria (1) TFH cell proliferation outside the lymphoid follicles, (2) reactive hyperplasia B cells outside the lymphoid follicles, (3) FDCs proliferation outside the lymphoid follicles. In addition, this study also found that the immune localization of TFH/B/FDC cells in the same location is a unique immune morphological feature possessed by AITL, which also contributes to the differential diagnosis of AITL.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics Approval

This protocol was approved by the Ethics Review Board of Jiading District Central Hospital (Ethics Committee reference number 2020K06).

Informed Consent

Written consent for study participation was received from the patients or their guardians.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

HXW, RY and YJJ designed the study and provided the study material. YHN, CFZ and JL collected and analyzed pathologic data. XHH and YJJ collected clinical data and performed clinical analysis. HXW and RY performed histopathologic review and performed clinicopathologic analysis. YJJ contributed to the statistical analysis. HXW, RY and YJJ wrote the draft of the manuscript and critically revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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References

1. Vose J, Armitage J, Weisenburger D (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26:4124-4130. doi: 10.1200/JCO.2008.16.4558

2. de Leval L, Parrens M, Le Bras F, Jais JP, Fataccioli V, Martin A et al (2015) Angioimmunoblastic T-cell lymphoma is the most common T-cell lymphoma in two distinct French information data sets. Haematologica 100:e361-e364. doi: 10.3324/haematol.2015.126300
3. Advani RH, Skrypets T, Civallero M, Spinner MA, Manni M, Kim WS et al (2021) Outcomes and prognostic factors in angioimmunoblastic T-cell lymphoma: final report from the international T-cell Project. Blood 138:213-220. doi: 10.1182/blood.2020010387
4. Liu W, Ji X, Song Y, Wang X, Zheng W, Lin N et al (2020) Improving survival of 3760 patients with lymphoma: Experience of an academic center over two decades. Cancer Med-Us 9:3765-3774. doi: 10.1002/cam4.3037
5. Bahri R, Boyer F, Halabi MA, Chaunavel A, Feuillard J, Jaccard A et al (2022) Epstein-Barr Virus (EBV) Is Mostly Latent and Clonal in Angioimmunoblastic T Cell Lymphoma (AITL). Cancers 14:2899. doi: 10.3390/cancers14122899
6. Ohtani H, Komeno T, Agatsuma Y, Kobayashi M, Noguchi M, Nakamura N (2015) Follicular Dendritic Cell Meshwork in Angioimmunoblastic T-Cell Lymphoma Is Characterized by Accumulation of CXCL13(+) Cells. J Clin Exp Hematop 55:61-69. doi: 10.3960/jslrt.55.61
7. Lunning MA, Vose JM (2017) Angioimmunoblastic T-cell lymphoma: the many-faced lymphoma. Blood 129:1095-1102. doi: 10.1182/blood-2016-09-692541
8. Mourad N, Mounier N, Briere J, Raffoux E, Delmer A, Feller A et al (2008) Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials. Blood 111:4463-4470. doi: 10.1182/blood-2007-08-105759
9. Wei C, Li W, Qin L, Liu S, Xue C, Ren K et al (2023) Clinicopathologic characteristics, outcomes, and prognostic factors of angioimmunoblastic T-cell lymphoma in China. Cancer Med-Us 12:3987-3998. doi: 10.1002/cam4.5248
10. Donner I, Katainen R, Kaasinen E, Aavikko M, Sipila LJ, Pukkala E et al (2019) Candidate susceptibility variants in angioimmunoblastic T-cell lymphoma. Fam Cancer 18:113-119. doi: 10.1007/s10689-018-0099-x
11. Lemonnier F, Gaulard P, de Leval L (2018) New insights in the pathogenesis of T-cell lymphomas. Curr Opin Oncol 30:277-284. doi: 10.1097/CCO.0000000000000474
12. Xu B, Liu P (2014) No survival improvement for patients with angioimmunoblastic T-cell lymphoma over the past two decades: a population-based study of 1207 cases. Plos One 9:e92585. doi: 10.1371/journal.pone.0092585
13. Paik JH, Koh J, Han B, Kim S, Lee KR, Lee S et al (2023) Distinct and overlapping features of nodal peripheral T-cell lymphomas exhibiting a follicular helper T-cell phenotype: a multicenter study emphasizing the clinicopathological significance of follicular helper T-cell marker expression. Hum Pathol 131:47-60. doi: 10.1016/j.humpath.2022.12.003
14. Liu Y, Yu K, Li M, Zeng K, Wei J, Li X et al (2017) EZH2 overexpression in primary gastrointestinal diffuse large B-cell lymphoma and its association with the clinicopathological features. Hum Pathol 64:213-221. doi: 10.1016/j.humpath.2017.04.011
15. Rodriguez-Justo M, Attygalle AD, Munson P, Roncador G, Marafioti T, Piris MA (2009) Angioimmunoblastic T-cell lymphoma with hyperplastic germinal centres: a neoplasia with origin in the outer zone of the germinal centre? Clinicopathological and immunohistochemical study of 10 cases with follicular T-cell markers. Modern Pathol 22:753-761. doi: 10.1038/modpathol.2009.12
16. Hsi ED, Horwitz SM, Carson KR, Pinter-Brown LC, Rosen ST, Pro B et al (2017) Analysis of Peripheral T-cell Lymphoma Diagnostic Workup in the United States. Cl Lymph Myelom Leuk 17:193-200. doi: 10.1016/j.clml.2016.10.001
17. Yu H, Shahsafaei A, Dorfman DM (2009) Germinal-center T-helper-cell markers PD-1 and CXCL13 are both expressed by neoplastic cells in angioimmunoblastic T-cell lymphoma. Am J Clin Pathol 131:33-41. doi: 10.1309/AJCP62WRKERPXDRT
18. de Leval L, Gisselbrecht C, Gaulard P (2010) Advances in the understanding and management of angioimmunoblastic T-cell lymphoma. Brit J Haematol 148:673-689. doi: 10.1111/j.1365-2141.2009.08003.x
19. Crotty S (2014) T follicular helper cell differentiation, function, and roles in disease. Immunity 41:529-542. doi: 10.1016/j.immuni.2014.10.004
20. Alonso GT, Fomin DS, Rizzo LV (2021) Human follicular helper T lymphocytes critical players in antibody responses. Einstein-Sao Paulo 19:eRB6077. doi: 10.31744/einstein_journal/2021RB6077
21. Ren YL, Hong L, Nong L, Zhang S, Li T (2008) [Clinicopathologic, immunohistochemical and molecular analysis in 15 cases of angioimmunoblastic T-cell lymphomas]. Beijing Da Xue Xue Bao Yi Xue Ban 40:352-357.
22. Gao SH, Liu SZ, Wang GZ, Zhou GB (2021) CXCL13 in Cancer and Other Diseases: Biological Functions, Clinical Significance, and Therapeutic Opportunities. Life-Basel 11:1282. doi: 10.3390/life11121282
23. Heyn H, Esteller M (2013) EZH2: an epigenetic gatekeeper promoting lymphomagenesis. Cancer Cell 23:563-565. doi: 10.1016/j.ccr.2013.04.028
24. Nakagawa M, Kitabayashi I (2018) Oncogenic roles of enhancer of zeste homolog 1/2 in hematological malignancies. Cancer Sci 109:2342-2348. doi: 10.1111/cas.13655