ORIGINAL ARTICLE

Angioimmunoblastic T-Cell lymphoma: A critical analysis of clinical, morphologic and immunophenotypic features

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ABSTRACT

Background: Angioimmunoblastic T–cell lymphoma (AITL), a subtype of peripheral T-cell lymphoma (PTCL), is characterized by unique clinical and biological features. Its diagnosis remains a challenge as clinical presentation as well as pathologic findings are frequently misleading. **Material and Methods:** We retrospectively analyzed the clinical, morphological and immunophenotypic spectrum of 17 cases of histologically proven AITL. **Result:** The mean age was 54 years and male to female ratio was 2.4. Common clinical features included generalized lymphadenopathy (60%), hepatomegaly (70%), splenomegaly (50%), anemia (80%) and polyclonal hypergammaglobulinemia (100%). Microscopically, three architectural patterns; pattern I (6%), pattern II (41%) and pattern III (53%) were observed. Bone marrow infiltration was seen in 60% cases and 30% cases revealed plasmacytosis. Absence of follicles, polymorphous infiltrate, extra-follicular follicular dendritic cell (FDC) proliferation, high endothelial venules (HEV) prominence and neoplastic T-cells were the diagnostic features of AITL. CD10 positivity (47%), clear cells in the background (59%) admixture with large size CD20+ B-immunoblasts (35%) and bone marrow plasmacytosis (50%) were common observations. **Conclusion:** Awareness of various morphological and immunophenotypic complexities of AITL and distinction from reactive adenopathies and other types of lymphomas that mimic AITL is underscored in this study.

KEY WORDS: Angioimmunoblastic T-cell lymphoma, immunohistochemistry, morphology

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INTRODUCTION

Angioimmunoblastic T–cell lymphoma (AITL) is an enigmatic clinicopathological entity that is characterized by unique clinical and biological features and has enamored hematopathologists since decades. Current WHO classification recognizes AITL as a distinct entity and a subtype of peripheral T-cell lymphoma (PTCL). It accounts for 1-2% of all non-Hodgkin lymphomas (NHL) and forms approximately 15-20% of PTCLs.[1] AITL is a systemic disease clinically characterized by lymphadenopathy, hepatosplenomegaly, skin rash, constitutional symptoms and often bone marrow infiltration. Polyclonal hypergammaglobulinemia as well as hematological abnormalities such as Coombs-positive hemolytic anemia are common accompaniments.

Morphologically, AITL is characterized by a polymorphous infiltrate, clear cells, prominent vascularity and extra-follicular proliferation of follicular dendritic cells. As these morphologic features can be seen in diverse conditions, both reactive and neoplastic, diagnosis in many instances becomes challenging. [2] At times, the neoplastic T-cells may exhibit minimal cytological atypia or are quantitatively too few to be morphologically identifiable. To add to the histopathologist's woes, admixture of the neoplastic cells with numerous large B-cells is a frequent feature mimicking a T-cell rich B-cell lymphoma (TCRBCL) or even a Hodgkin's lymphoma (HL). Making a distinction from a reactive or atypical lymphoproliferative disorder may be extremely difficult not only on morphologic grounds but also on immunohistochemistry (IHC) causing an erroneous or delayed diagnosis in some cases. The literature on AITL is growing and that has raised awareness of the complexity of this entity. From a pathologists' perspective, there is a pressing need to be aware of the varied morphologic patterns, unique immunophenotypic characteristics, treacherous mimics and the evolving knowledge of the biologic course of this entity.

There are only a few studies in published literature which focus on the histopathologic features of AITL. [3-5] We undertook this retrospective study to analyze the spectrum of clinical, morphologic and immunophenotypic characteristics of our cases of AITL.

MATERIALS AND METHODS

Patients

We retrieved all cases of AITL, diagnosed in the period from January 1, 2006 to December 31, 2008, from the computer records and surgical pathology files of our department and reviewed them. The

cases were diagnosed on lymph node biopsy specimens based on clinical details, morphology and immunophenotypic criteria, in accordance with the WHO classification. Cases which did not fulfill the WHO criteria were excluded. Diagnostic work-up included history, physical examination and parameters such as age, gender, clinical details including "B" symptoms, site of involvement (nodal or extra nodal) and staging at presentation. Laboratory parameters, such as complete blood cell counts, lactate dehydrogenase (LDH), beta-2 microglobulin and serum proteins were recorded. Serological markers for human immunodeficiency virus, hepatitis C virus and hepatitis B virus were also noted. Radiological investigations included chest X-ray, computed tomography scan and magnetic resonance imaging of the chest, the abdomen and the pelvis. Bone marrow (BM) aspirate and biopsy were performed for staging purpose. Clinical stage was evaluated in accordance with conventional Ann Arbor criteria.

Histomorphological Features

Primary diagnoses based on Hematoxylin and Eosin (H and E) sections and IHC were reviewed independently by two pathologists (MB and SG). Additional IHC was performed, wherever indicated. Diagnostic criteria for AITL included atypical neoplastic T-cells, polymorphous infiltrate, presence of high endothelial venules (HEV) and extra-follicular proliferation of follicular dendritic cellular (FDC) meshwork.[1] Other morphologic features included architectural effacement (diffuse or partial), growth pattern (classified as I, II, III) based on the presence of hyperplastic, regressed or absent follicles, respectively,[6] presence of obliterated or patent sinuses, nature of background infiltrate, monomorphic or polymorphous size of atypical lymphoid cells, small or intermediate or large, clear cells (present or absent), percentage of LCA+, CD20+ large sized B-cells (extra-follicular), high endothelial venules, semi-quantitatively scored as 1-3 based on mild, moderate and marked prominence of vascularity.

Immunohistochemistry

IHC was performed on formalin-fixed paraffin-embedded sections using standard avidin-biotin complex peroxidase (ABCP) method (Vector peroxidase ABC kit, PK4001 and PK4002; Vector Laboratories, Burlingame, CA, USA). Pre-treatment was done by heating in a microwave oven in 0.01 M citrate buffer (pH 6.0) EDTA buffer (pH 8.0) or using pepsin. The panel of antibodies (Dako) used for IHC included LCA, CD20, CD3, CD43, CD15, CD30, EMA, ALK-1, anti-kappa, anti-lambda, CD10, CD21, CD23 and Mib-1. Antibodies for CD3 was polyclonal and for the others monoclonal. The number of antibodies used varied from case to case based on morphologic evaluation.

RESULTS

Patients

Two thousand and eighteen cases of NHL were diagnosed during this three-year period and it included 20 cases of AITL. On review, two of these cases were re-classified as PTCL unspecified (PTCLu) and one as TCRBCL. Thus, a total of 17 cases of AITL were studied. Ten of these were in-patients and received treatment at our center while the remaining seven referral cases with availability of paraffin blocks had sketchy clinical details.

Clinical Features

Clinical findings are depicted in Table 1. Age ranged from 28-82 years (Mean 54 years, median 57 years). Male to female ratio was 2.4:1. Detailed clinical information was available in ten in-patients only. Six of these ten patients had generalized while four had localized lymphadenopathy (axillary - 2, cervical – 1, paraaortic – 1). Seven patients had B-symptoms; two had only splenomegaly while five had hepatosplenomegaly. Eight patients were anemic (Hemoglobin ranged from 6.3 to 12.4 g/dL), and thrombocytopenia was seen in three patients (Platelet count range, 70-503 X 10^9/L). Erythrocyte sedimentation rate (ESR ranged from 8 to 90 mm fall in first hour), Beta-2 microglobulin (range, 1.1 to 12.1 mg/L) and LDH (range, 236-608 U/L) were raised in nine patients. All 10 patients showed polyclonal hypergammaglobulinemia (range 4.5-11.2 g/dL). Serology for HIV, HCV and HBV was negative in all 10 cases. All the seventeen patients had nodal disease. Out of total 10 cases, six showed classical bone marrow infiltration inform of lymphoid aggregates, while another three revealed plasmacytosis. Bone marrow aspirate in five patients revealed polyclonal plasmacytosis (range, 25-37%), including two cases with infiltration by AITL. In one case with 37% plasma cells in the bone marrow aspirate, patient was initially investigated for myeloma before a diagnosis of AITL was established. None of the cases showed any spill-over of tumor cells into the peripheral blood.

Histologic Features

Histomorphological features [Figures 1 and 2] are summarized in Table 2. Diffuse replacement of normal nodal architecture

Table 1: Clinical characteristics of patients of AITL

Clinical features	*Seen in*	*Total number of cases*	*Percentages*
Age 54 (Mean)		17	
Sex (M:F) 2.4:1		17	
B-symptoms	6	10	60
Lymphadenopathy	10	10	100
Hepatomegaly	5	10	50
Splenomegaly	7	10	70
Laboratory investigations			
Anemia	8	10	80
Leucopenia	1	10	10
Thrombocytopenia	3	10	30
Raised ESR	9	10	90
Raised beta 2 microglobulinemia	9	10	90
Raised LDH	9	10	90
Polyclonal hypergammaglobulinemia	10	10	100
Bone marrow involvement	6	10	60
Bone marrow plasmacytosis	5	10	50

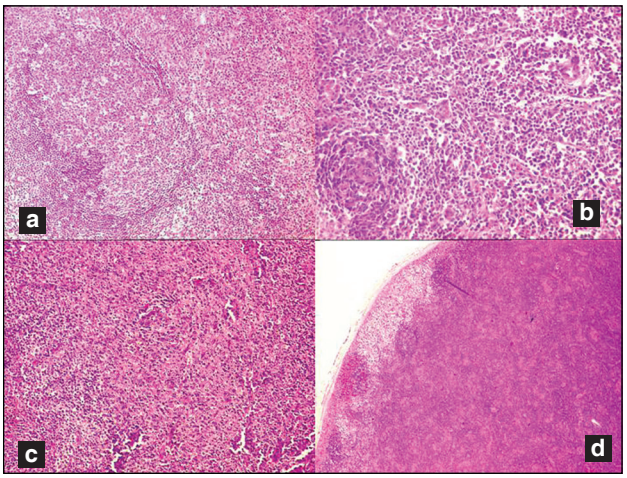

Figure 1: Different architectural patterns in AITL: (a) Pattern I containing hyperplastic follicles (H and E, ×100); (b) Pattern II containing abortive burnt-out follicles (H and E, ×200); (c) Pattern III showing diffuse nodal effacement (H and E, ×100); (d) patent peripheral sinuses in a case of AITL (H and E, ×40)

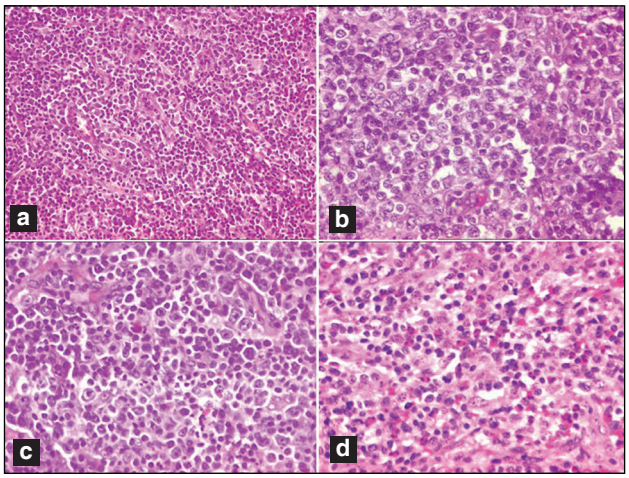

Figure 2: Morphological features of AITL. (a) Diffuse and prominent HEV proliferation (H and E, ×100); (b) clusters of clear neoplastic cells (H and E, ×400); (c) conspicous immunoblast rich infiltrate (H and E, ×400); (d) scanty neoplastic cells masked by a dominant polymorphous infiltrate in a case of AITL (H and E, ×400)

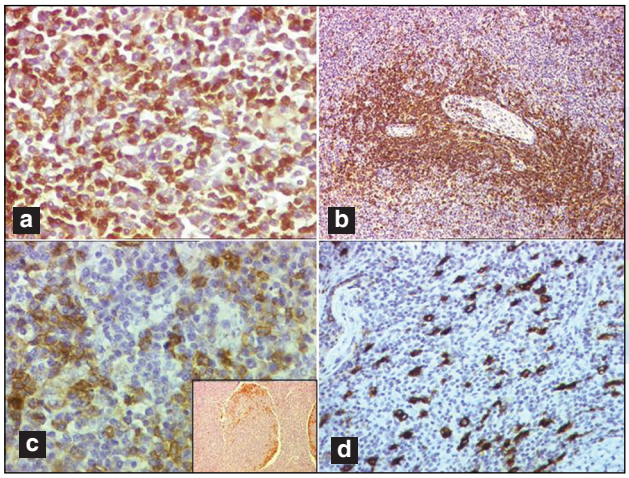

Figure 3: Immunohistochemical features in AITL cases. (a) T-cell marker (CD3) expression in neoplastic cells (IHC, ×400); (b) FDC marker CD21 expression in expanded extra follicular and perivascular FDC meshwork (IHC, ×400); (c) Extra-follicular large CD20+B-cells in AITL (IHC, ×400); (d) Germinal center marker CD10 expression in AITL (IHC, ×400)

Table 2: Pathologic and immunophenotypic features of AITL cases

Pathologic features	*Number of cases n = 17*	*Percentages*
Patent sinuses	6	35.3
Pattern		
I	1	5.9
II	7	41.2
III	9	52.9
Extra follicular FDC	17	100
HEV		
I	0	0
II	5	29.4
III	12	70.6
Clear cells	10	58.9
Tumor cell size		
Small	6	35.3
Intermediate	6	35.3
Large	5	29.4
Large size B-cells (immunoblasts) >25%	6	35.3
CD10 positive	8	47.1
CD3 positive	17	100
CD43 positive	17	100
CD5 positive	17	100
CD30 positive	0	0
CD15 positive	0	0
Alk-1 positive	0	0
Mib-1 labeling	25-55%	

(Pattern III) was present in 9 (53%) cases while 7 (41%) harbored burnt-out abortive follicles (Pattern II). Hyperplastic follicles with expanded paracortex was present in one case (6%) (Pattern I). Six cases showed peripheral patent sinuses. All 17 cases showed HEV proliferation in an arborizing pattern (moderate to marked) and extra-follicular proliferation of FDC meshwork. The latter were seen as fusiform to ovoid cells with pale, eosinophilic cytoplasm, elongated bland nuclei with fine chromatin and discernible nucleoli. These FDC networks could be identified as pale pink areas at low magnification, mostly encroaching blood vessels. FDC proliferations were subtle and IHC with FDC markers (CD21, CD23 and CD35) substantiated the morphological findings. Clusters of neoplastic cells showing cytoplasmic clearing were observed in 10 cases (58%). Tumor cells were innocuous looking small to intermediate in size (71% cases) while were large, nucleolated in remaining 29% cases. Percentage of tumor cells ranged from 20-75% of the total cellular infiltrate. Background revealed a polymorphous population in all cases comprising of varying proportions of eosinophils, plasma cells, lymphocytes, histiocytes (microgranulomas in 1

case) and a prominence of immunoblasts. Neoplastic lymphoid cells were immunoreactive with various T-cell markers, CD3, CD43 and CD5 in all the cases [Figure 3]. CD10 positivity, both cytoplasmic and membranous mixed, was observed in 47% cases. The percentage of CD10+ tumor cells ranged from 10-85% while staining intensity was weak in two, moderate in six and strong in two cases. Variable numbers of B-cells were seen admixed with the neoplastic T-cells. In 6 cases (35%), large sized immunoblasts-like B-cells (LCA and CD20 +) formed more than 1/4th (>25% of) the total cellular population. In two of these cases, these cells expressed CD30 positivity also. These large B-cells were seen in the extra-follicular areas admixed with the background reactive cells. In one case, peculiar peripheralized marginalization of large B-cells surrounding expanded T-cell zones was observed. Neoplastic T-cells were negative for CD30, CD15 or Alk-1. Mib-1 proliferation index ranged from 25-55%.

DISCUSSION

AITL is a complex lymphoproliferative disorder that is characterized by unique clinical and biological features. Long considered a pre-neoplastic disorder (known as angioimmunoblastic lymphadenopathy with dysproteinemia), it has finally made its way into the WHO classification as a distinct subtype of PTCL. [1] Patients are usually elderly, with B-symptoms, skin rash, generalized lymphadenopathy and hepatosplenomegaly. Clinical characteristics of our patients were similar as reported, with the exception of skin involvement. Only one patient had skin rash at presentation. However, the skin lesion was not biopsied in that case. All patients had nodal diseases. Myriad clinical presentations in AITL such as glomerulonephritis, rheumatoid arthritis, pleural effusions, and polyneuropathy involving almost any organ-system can clinically mislead the diagnosis to a non-lymphomatous process. Similarly, almost any laboratory value can be abnormal in AITL, most characteristic being anemia (autoimmune type) and polyclonal hypergammaglobulinemia. Anemia was present in 80%, thrombocytopenia in 30%, raised ESR in 90% and polyclonal hypergammaglobulinemia in 100% of our in-patients. Bone marrow was infiltrated in 60% cases while another 30 cases revealed polyclonal plasmacytosis. Bone marrow plasmacytosis is a common accompaniment (seen in 50% of cases) in AITL, with or without lymphoma infiltration.

Though the clinical significance is unknown, morphologically all three patterns based on the presence of hyperplastic, abortive or absent lymphoid follicles were observed, as defined elsewhere.[6] However, awareness of these patterns is relevant as they can be observed in a diverse numbers of morphological mimics of AITL. Pattern III (diffuse with absent follicles) was the commonest pattern observed in our series, followed by pattern II. Pattern II with burnt-out follicles mimics the abortive follicles of Castleman's disease. Only one of our cases had hyperplastic follicles with expanded paracortex (Pattern I). This case with pattern I morphology was initially misdiagnosed as a reactive lymphadenopathy. The sinuses may remain patent is AITL, a feature pathognomic of reactive adenopathies.[7] This was noted in 6 of our cases. A pathologic feature unique to AITL is an exuberant proliferation of HEV and the presence of extra-follicular FDC meshwork. HEV prominence is a feature common to all T-zone proliferations, both reactive as well as neoplastic. However, in AITL, HEV proliferation is quantitatively much more than any other T-cell lymphoma [4] and is usually a striking feature on a scanner view. Similarly, a low power examination may pick-up FDC networks impinging upon blood vessels as pale pink spindly areas.

These areas bear a superficial resemblance to the regressive 'lollipop' germinal centers of Castleman's disease. FDC markers (CD21, CD23 and CD35) are essential to highlight and confirm the presence of these expanded FDC networks in the extra-follicular areas for a diagnosis of AITL. A particularly challenging aspect of AITL is that the neoplastic cells account for a small fraction of the infiltrate, varying from 5 to 30%.[7] Neoplastic cells formed 20 to 70% of the infiltrate in our series and were small to intermediate in size in the majority (71%). Clear cell clusters of tumor cells, previously considered pathognomic of AITL, were seen in 59% cases. Moreover, of all the T-cell lymphomas, AITL shows the maximum variability in the density of non-neoplastic cells, that include CD4+ or CD8+ non-neoplastic T cells, B cells, dendritic cells, histiocytes, immunoblasts and plasma cells. Any of these background cellular components can predominate to an extent to completely mask and conceal the true neoplastic cells. In this regard, a prominent admixture of large B-cells, which is a frequent finding in AITL, may mislead to a diagnosis of a TCRBCL. By using 25% large B-cells as a criterion for this phenomenon, a French study found an incidence of 18% in AITL.[8] Outcome of these patients did not differ significantly from those with less than 25% of B-cells.[8] Large B-cells (immunoblasts) were seen in 35% of our cases. These were usually intermixed with the polymorphous infiltrate diffusely, or in the paracortical areas. In one case, a peculiar marginal distribution of large B-cells surrounding tumor nodules (T-cell) was noted, a finding not reported and the significance of which is uncertain at present.

A similar observation of 'peripheralized' distribution of CD20+ B-cells exists.[5] Limited literature on this finding reveals that approximately 70% of the B-cell proliferations in the setting of AITL are positive for EBV, usually shown by *in situ* hybridization for EBV small-encoded RNA (EBER).[8-11] Tumor cells marked with CD45 and T-cell markers (CD3, CD5, and CD43) in all cases. Recent reports, including data from gene profiling, have indicated a germinal center follicular T-helper cell (FT_h) origin of the neoplastic cell in AITL.[12] This has been reinforced further by recent demonstration of immunoreactivity for germinal centre FT_h markers CD10, PD-1, Bcl-6 and a chemokine CXCL13 in various studies.[13-15] In a recently reported large retrospective series, CD10 immunoreactivity was detected in 39% of AITL cases, suggesting that this marker is a useful but not absolute diagnostic tool in AITL.[16] CD10 positivity (membranous and cytoplasmic mixed) was observed in 8 (47.1%) cases. The percentage of tumor cell immunoreactivity ranged from 10-80% while staining intensity

was weak in two, moderate in six and strong in two cases. Due to overlapping histologic features, diverse differential diagnoses needed to be considered in most of our cases. Phenytoin-associated and viral-induced adenopathy, PTCLu and TCRBCL were common differentials. However, distinction was possible on clinical, histologic and immunophenotypic characteristics. Prominence of immunoblasts and atypical T-zone proliferation, a feature shared by viral-induced (especially EBV-driven) and drug-induced (notably, phenytoin-induced) T-zone proliferations, can completely simulate AITL morphologically. A careful history, patient's general condition and temporal resolution of symptoms following infection control or drug withdrawal can be important leads to a non-neoplastic condition. Resemblance to hyaline vascular type Castleman's disease is superficial as it lacks the neoplastic T-cells, extra follicular FDC meshworks and HEV proliferations. Distinction from other lymphomas, i.e. PTCLu, TCRBCL, diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma is important. There is a tremendous overlap in the morphological features of PTCLu and AITL, namely, the polymorphous background, T-zone expansion, HEV proliferation, and variable accompaniment of EBV-positive large B-cells. However, distinguishing features exist. The quantum of HEV proliferation is much more in AITL than PTCLu. Also, clear cells, EBV infection and CD10 positivity favor AITL. [4] Extra-follicular FDC proliferations and germinal-center marker positivity in the neoplastic cells are the defining features of AITL and are absent in PTCLu. The presence of substantial numbers of large B-cells can bring TCRBCL and DLBCL into the picture. T-cell component is neoplastic in AITL while it is reactive in TCRBCL with scant clonal neoplastic B-cells (forming less than 10% of the cells). Bone marrow plasmacytosis was a remarkable feature noted in 50% cases. One case with 38% plasma cells was initially mislabeled as plasma cell dyscrasia. Serum electrophoresis revealed a polyclonal hypergammaglobulinemia.

To provide support for a presumptive diagnosis of lymphoma, many cases of AITL require gene rearrangement studies. However, only 75-80% cases show TCR gene rearrangement and as many as 1/4th cases did not show a T-cell clone when studied by DNA-based polymerase chain reaction primers on paraffin-embedded tissue samples.[17] In addition, about a third of cases will manifest clonal immunoglobulin gene rearrangement compounding the enigma of this entity. Some, but not all, of these cases with clonal immunoglobulin gene rearrangements have an associated EBV+ve or EBV–ve B-cell proliferation.[17] In contrast with the consistent cytogenetic abnormalities seen in other subtypes of NHL, AITL shows a high frequency of unrelated clones and single cell aberrations with completely different karyotypes. Trisomy 3 and 5 and an additional X chromosome are the most frequent cytogenetic abnormalities detected in AITL.[7] Nevertheless, the constellation of clinical, histologic, immunophenotypic, and molecular findings generally allows a firm diagnosis of AITL. Etiology and pathogenesis of AITL are unknown. While Epstein Barr virus (EBV) and B-cell dysregulation are clearly implicated in the pathogenesis of this disease, their exact mechanistic roles are still not fully understood. While it was originally believed that reduced immune surveillance in AITL led to EBV reactivation, EBV positive B cells detected very early in AITL suggest a role in the early pathogenesis by activating FT_h cells. [18] AITL usually presents as a high stage disease, follows an aggressive clinical course with median survivals of only 36 months and five-year survival rates of between 30 and 35%.[18]

The focus of the present study has been the morphologic and immunohistochemical complexities of this poorly understood lymphoma. IHC for the newer markers like CXCL-13 and molecular techniques for clonal studies and EBV co-infection were not performed. To conclude, although understanding of this mystical entity is evolving, much remains to be unraveled in terms of its pathobiology. For a pathologist, diagnosis of AITL is always a challenge. In our opinion, polyclonal hypergammaglobulinemia, polymorphous infiltrate, extra-follicular FDC proliferation, HEV prominence and neoplastic T-cells are indispensable features while germinal centre marker positivity including CD10 positivity, clear cells, bone marrow plasmacytosis are vital clues towards a diagnosis of AITL. For pathologic diagnosis of AITL, it is essential to be aware of the diverse histologic facets, innumerable morphologic trapdoors and characteristic immunoprofile of this fascinating entity.

REFERENCES

1. Jaffe ES, Harris NL, Stein H, Vardiman J. In: Jaffe ES, Harris H, Stein H, Vardiman JW, editors. World Health Organization Classification: Tumours of Hematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2007.
2. Ferry JA. Angioimmunoblastic T-cell lymphoma. Adv Anat Pathol 2002;9:273-79.
3. Attygalle AD, Kyriakou C, Dupuis J, Grogg KL, Diss TC, Wotherspoon AC, *et al*. Histologic evolution of angioimmunoblastic T-cell lymphoma in consecutive biopsies: clinical correlation and insights into natural history and disease progression. Am J Surg Pathol 2007;31:1077-88.
4. Attygalle AD, Chuang SS, Diss TC, Du MQ, Isaacson PG, Dogan A. Distinguishing angioimmunoblastic T-cell lymphoma from peripheral T-cell lymphoma, unspecified, using morphology, immunophenotype and molecular genetics. Histopathology 2007;50:498-508
5. Merchant SH, Amin MB, Viswanathan DS. Morphologic and immunophenotypic analysis of angioimmunoblastic T-cell lymphoma: Emphasis on phenotypic aberrancies for early diagnosis. Am J Clin Pathol 2006;126:29-38.
6. Dogan A, Attygalle AD, Kyriakou C. Angioimmunoblastic T-cell lymphoma. Br J Haematol 2003;121:681-91.
7. Iannitto E, Ferreri AJ, Minardi V, Tripodo C, Kreipe HH. Angioimmunoblastic T-cell lymphoma. Crit Rev Oncol Hematol 2008;68:264-71.
8. Lome-Maldonado C, Canioni D, Hermine O, Delabesse E, Damotte D, Raffoux E, *et al*. Angio-immunoblastic T-cell lymphoma (AILD-TL) rich in large B cells and associated with Epstein-Barr virus infection: a different subtype of AILD-TL? Leukemia 2002;16:2134-41.
9. Higgins JP, van de Rijn M, Jones CD, Zehnder JL, Warnke RA. Peripheral T-cell lymphoma complicated by a proliferation of large B cells. Am J Clin Pathol 2000;114:236-47.
10. Ohshima K, Takeo H, Kikuchi M, Kozuru M, Uike N, Masuda Y, *et al*. Heterogeneity of Epstein-Barr virus infection in angioimmunoblastic lymphadenopathy type T-cell lymphoma. Histopathology 1994;25: 569-79.
11. Weiss LM, Jaffe ES, Liu XF, Chen YY, Shibata D, Medeiros LJ. Detection

and localization of Epstein-Barr viral genomes in angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy-like lymphoma. Blood 1992;79:1789-95.

12. de Leval L, Rickman DS, Thielen C, Reynies A, Huang YL, Delsol G. The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. Blood 2007;109:4952-63.
13. Yu H, Shahsafaei A, Dorfman DM. 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 2009;131:33-41.
14. Dupuis J, Boye K, Martin N, Copie-Bergman C, Plonquet A, Fabiani B. Expression of CXCL13 by neoplastic cells in angioimmunoblastic T-cell lymphoma (AITL): a new diagnostic marker providing evidence that AITL derives from follicular helper T cells. Am J Surg Pathol 2006;30:490-94.
15. Attygalle A, Al-Jehani R, Diss TC, Munson P, Liu H, Du MQ. Neoplastic T cells in angioimmunoblastic T-cell lymphoma express CD10. Blood 2002;99:627-33.
16. Went P, Agostinelli C, Gallamini A, Piccaluga PP, Ascani S, Sabattini E, *et al*. Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol 2006;24:2472–9.
17. Tan B, Warnke R, Arber D. The frequency of B- and T-cell clones and EBV in T-cell lymphomas: a comparison between AITL and PTCL-NOS. J Mol Diagn 2006;8:466-75.
18. Dunleavy K, Wilson WH, Jaffe ES. Angioimmunoblastic T cell lymphoma: pathobiological insights and clinical implications. Curr Opin Hematol 2007;14:348–53.

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