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The T-Cell Predominance: Angioimmunoblastic T-Cell Lymphoma

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ABSTRACT

A lymph node based T cell lymphoma which originates from a T follicular helper cell phenotype may cogitate the angio-immunoblastic T cell lymphoma (AITL) or an angio-immunoblastic lymphadenopathy with dysproteinaemia (AILD). At an estimated 1%-2% of Non-Hodgkin's lymphoma, it may emerge at a median age of 59-65 years with a slight male predominance. Approximately 70% individuals exemplify B symptoms such as fever, weight loss greater than 10% of the body weight, drenching night sweats, lymph node enlargement, hepato-splenomegaly (74%) and skin involvement (50%). The immune hyper-active lymphoma may enunciate an elevation of the erythrocyte sedimentation rate (ESR), reactive autoimmune rheumatoid factor (RF), anti-smooth muscle antibody and coexistent circulating immune complexes or a cold agglutinin reaction. An all prevailing dysregulation of the follicular T helper (TFH) lymphocytes ensues within the disorganized germinal centres with an emerging angio-immunoblastic T cell lymphoma. Immunoblasts, B lymphocytes, plasma cells, eosinophils, histiocytes and epitheloid cells may predominate with diverse immune reactive T cell antigens such as CD3+, CD4+, CD8-, CXCL13+, CD10+, BCL6-, CD19+, C20+, CD1a+, CD21+, CD23+ and TdT. Multiple genetic aberrations such as TET2 (47%-73%), DN MT 3A (33%) and IDH2-R172 (20-40%) may be exemplified. The classic combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) is a gold standard of therapy with AITL. Solitary agents employed in combination with CHOP regimen are romidepsin, belinostat or pralatrexate. Median 5 year survival of the lymphoma (AITL) appears at an estimated (32%).

Keywords: Angio-immunoblastic T cell lymphoma, Immune hyper-activity, Follicular T helper (TFH) lymphocyte malignancy

PREFACE

Angio-immunoblastic T cell lymphoma (AITL) may be designated as a lymph node based T cell lymphoma which originates from a T follicular helper cell phenotype by the world health organization [1]. Angio-immunoblastic T cell lymphoma (AITL) may constitute as a distinct, infrequent subcategory of matures peripheral T cell lymphoma (PTCL). The lymphoma (AITL) presents as an advanced stage disease and demonstrates an anomalous and oligoclonal T cell proliferation. Atypical laboratory findings and co-existent autoimmune disease may obscure initial diagnosis [2]. Angio-immunoblastic T cell lymphoma (AITL) may simultaneously be cogitated as angio-immunoblastic lymphadenopathy with dysproteinaemia (AILD), immunoblastic lymphadenopathy or lymphogranulomatosis X [2,3]. The disorder was labelled as a benign immune activation of B lymphocytes despite the fatal course of disease. Evaluation of clone specific T and B lymphocytes may confirm a malignant and T lymphocytic manifestation of the neoplasm. Hence the current terminology of angio-immunoblastic T cell lymphoma (AITL) may be preferred.

DISEASE CHARACTERISTICS

Angio-immunoblastic T cell lymphoma (AITL) comprises of an estimated 1%-2% of Non-Hodgkin's lymphoma and roughly one fifth (20%) of the annual incidence of peripheral T cell lymphoma (PTCL). Angio-immunoblastic T cell lymphoma (AITL) generally implicates the elderly with a median age of disease emergence at 59-65 years with a slight male predominance [2,3]. The lymphoma (AITL) may be frequent in Europe (28.7%) in contrast to the Asian (17.9%) subcontinent. Angio-immunoblastic T cell lymphoma (AITL) may concur with an Epstein Barr viral (EBV) infection (70% to 100%). The B lymphocytes denominate a perpetual viral infection whereas the malignant

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T lymphocytes may lack the viral trigger [2,3]. The lymphoma (AITL) generally displays an aggressive clinical course with a median survival of below 3 years irrespective of the therapeutic intervention. AITL may progress to a high grade B lymphocyte or T lymphocyte lymphoma or an Epstein Barr virus (EBV+) reactive B cell lymphoma or chronic lymphatic leukaemia (CLL). Mortality may ensue due to infections and immunological compromise [2,3].

CLINICAL ELUCIDATION

The subjects may enunciate non-specific constitutional symptoms, transient physical signs and inconclusive serological or radiographic features, thus detection of the disorder may be delayed by several weeks or months. Individuals incriminated with the Non-Hodgkin's lymphoma (AITL) may exemplify B symptoms(70%) such as fever, weight loss greater than 10% of the body weight, drenching night sweats, lymph node enlargement, hepato-splenomegaly (74%) and skin involvement (50%) [2,3]. Angio-immunoblastic T cell lymphoma (AITL) or previous angio-immunoblastic lymphadenopathy with dysproteinemia (AILD) with clinical features characteristic of a lymphoma may display a maculo-papular rash (simulating a viral rash), poly-arthritis (sero-positive), fever, pruritus, lymph node enlargement, night sweats and weight loss. Additionally edema, acute abdomen, disseminated bacterial infection and herpes virus type 6 or associated viral infections may be demonstrated. Discordant clinical manifestations such as a sick sinus syndrome and collagen vascular disease such as rheumatoid arthritis and dermatomyositis may indicate the presence of an AITL. AITL may simulate an infection by M. tuberculosis with the consequent initiation of anti-tubercular therapy. Proliferative glomerular-nephritis concomitant to the lymphoma (AITL) may be exceptional. Pulmonary involvement may be indicated by hypoxemia, interstitial pneumonia or bronchopneumonia. Subjects with bronchopneumonia may demonstrate co-existent opportunistic infections such as pneumonia due to *Pneumocystis jirovecii*, dyspnoea and peripheral edema. The lymphoma may be preceded by an allergic reaction, infection, drug exposure or penicillin administration [2,3]. Minimal lymph node enlargement of the magnitude of 1.5 to 3.0 cm on computerized tomography (CT) and diverse standard uptake values (SUVs) on a positron emission tomography (PET) may be elucidated. Majority (70%) of the individuals demonstrate an implicated bone marrow. AITL exhibits an infrequent preliminary stage disease at an estimated (10%). Hepatomegaly and splenomegaly may initially be moderate. Antecedent skin rash may appear in approximately 20%-50% instances. Dermal manifestations arise as urticarial rash or tumor like nodules. Administration of antimicrobial agents or the exceptional overt, cutaneous variant of AITL may delineate multitudinous skin rashes. Extra-nodal incrimination may be infrequent with AITL. Immune hyper-activity may be enunciated with an elevation of the erythrocyte sedimentation rate (ESR), reactive autoimmune rheumatoid factor (RF), anti-smooth muscle antibody and coexistent circulating immune complexes or a cold agglutinin reaction. Serum protein electrophoresis may depict the polyclonal nature of dysproteinemia and gammopathy [3,5]. A clone specific plasmacytosis may infrequently concur with a monoclonal gammopathy in an estimated 10% instances. Autoimmune induced warm antibody (direct anti-globulin test - DAT) hemolytic anemia may appear as the presenting symptom. Eosinophilia may emerge with or without a concomitant infectious etiology. The peripheral blood smear rarely depicts circulating malignant cells which may be suitably enunciated on a flow cytometry of the peripheral blood [2,3].

GENESIS OF THE LYMPHOMA

Angio-immunoblastic T cell lymphoma (AITL) as engendered from the follicular helper T lymphocyte (TFH) subset may exemplify a genetic concurrence by molecular mechanisms. The follicular helper T lymphocyte (TFH) functions as a critical controlling mechanism of B cell differentiation and activation within the germinal centre. Antigenic stimulation of the germinal centres may incite a B cell hyperactivity [4,5]. The follicular helper T lymphocytes (TFH) catalyses the evolution of peripherally dispersed secondary lymphoid tissue containing centroblasts into centrocytes. The lymphocytic interrelation consequently activates the differentiation of lymphoid cells into plasma cells or memory B cells. Inception of immune tolerance within the follicular helper T (TFH) lymphocyte compartment may be critical for restricting the genesis of auto immune disorders. Nevertheless, a comprehensive dysregulation of the follicular T helper (TFH) lymphocytes may ensue within the disorganized germinal centres with a subsequent emergence of angio-immunoblastic T cell lymphoma (AITL) [5,6].

MORPHOLOGICAL ELUCIDATION

A lymph node biopsy may discern AITL. The malignant follicular helper T (TFH) lymphocytic component may constitute a miniscule fraction of the lymph node neoplasm similar to the Reed Sternberg cells denominated in Hodgkin's disease. Lymph node architecture may be obliterated with an absence of follicles. Immunological cells such as immunoblasts, B lymphocytes, plasma cells, eosinophils, histiocytes and epitheloid cells may be abundant. The follicular dendritic cells (FDCs) and vasculature with proliferative, plump endothelium may propagate aberrantly and randomly [4,5]. The aggregates of malignant follicular helper T (TFH) lymphocytes may about the high endothelial venules (HEVs). The lymphoma may enunciate as a systemic disease with lesions confined to the lymph node, bone marrow, spleen, liver and skin. Malignant conversion of the lymph node with characteristic manifestations may delineate an effaced nodal architecture, focally preserved lymphoid sinuses, a polymorphic infiltration of lymphoid cells and a prominent proliferation

of post capillary venules. The cellular infiltrate may comprise of miniature lymphocytes, plasma cells, immunoblasts, eosinophils and multinucleated giant cells. The lymph node may be persistently devoid of normal, uninvolved germinal centres. The germinal centres may be constituted of disordered aggregates of pale histiocytes, immunoblasts and enlarged epitheloid cells, appropriately termed as the "burnt out germinal centres". The germinal centres may focally recapitulate the appearance of granulomas. The conventional germinal centres may exceptionally display hyperplasia of the surrounding lymphoid follicles [4]. Proliferation of dendritic reticulum cell clusters, immune reactive for desmin, may be elucidated. An amorphous, eosinophilic intercellular substance reactive for periodic acid schiff's (PAS) stain may be disseminated through the lymph node architecture. Capsular and peri-capsular infiltration of tumour cells may be frequent. A polyclonal immunoglobulin configuration may be elucidated by the immunoperoxidase stain. B lymphocytes with immune reactivity to the Epstein Barr virus (EBV+) may be detected in a majority (75%) of instances. The lymphoid aggregates may vary from reversible and reactive to malignant and aggressive in countenance [4,6]. Clone specific proportions of B and T lymphocytes may be discerned. An aberrant cellular composition may be discerned such as immunoblasts, miniature lymphocytes with convoluted nuclei and thick membrane or clear cells. The particular subtypes may denominate an aggravated clinical course.

IMMUNE PHENOTYPE AND *IN SITU* HYBRIDIZATION

Immune reactivity to diverse T cell antigens may be employed to ascertain the presence of tumor cells such as CD3+, CD4+, CD8-, CXCL13+, CD10+, BCL6-, CD19+, C20+, CD1a+, CD21+, CD23+ and TdT. A clone specific T lymphocyte population may be elucidated in the majority (75%) instances [6,7]. The malignant follicular helper T (TFH) lymphocytes may depict a phenotype of immune reactive CD3+, CD4+, CD10+. An alpha /beta T cell receptor may be elucidated with a frequent, anomalous negativity for CD5- and/or CD7-. An estimated one fifth (20%) instances may display a CD30+ immune expression. An immune reactive CXCL13+ may be particularly specific and consistently elucidated in the cytoplasm, in contrast to CD10, for denominating the lymphoma. The follicular helper T (TFH) lymphocytes may manifest the program death receptor 1 (PD-1), ICOS, BCL6 and CD200 [3]. The aforementioned immune molecular expression may demarcate the lymphoma (AITL) from diverse benign lympho-proliferative disorders and subcategories of PTCL with an identical genesis from a follicular helper T (TFH) cell. An immune reactive CD21+ may demarcate the follicular dendritic cells (FDCs) from the intermingled follicular helper T (TFH) cells and high endothelial venules (HEVs) [7,8]. Majority of the enlarged B lymphocytes may depict a reactive Epstein Barr virus encoded small RNAs (EBER) by in situ hybridization, indicating an ongoing viral infection (EBV), whereas the malignant follicular helper T (TFH) lymphocytes may be non-reactive to EBER.

MOLECULAR ASSAY

A majority (90%) of instances of angio-immunoblastic T cell lymphoma (AITL) may depict an anomalous karyotype, which may or may not belong to the particular clone of malignant T lymphocytes. Trisomy of chromosomes 3 and 5 may be a frequent aberration. The TP53 oncogene may be infrequently decimated [2,3]. However, occurrence of clone specific complications may indicate a poor prognosis. As the lymphoma (AITL) may be devoid of characteristic anomalies, the development of therapeutic possibilities may be lacking. Immune reactivity to clone specific CD4+ T cells may be delineated in a majority (80%) of instances of angio-immunoblastic T cell lymphoma (AITL). A clone specific population of B lymphocytes may be demonstrated in an estimated 41% instances with concomitant angio-immunoblastic T cell lymphoma. Competent molecular investigation of the lymphoma may discern genetic manifestations of AITL and demarcates it from categories of peripheral T cell lymphoma (PTCL) [8,9]. The molecular fabrication of AITL comprises of follicular dendritic cells (FDCs), B lymphocytes and an interwoven stroma. Tumor specific microenvironment defines the prognostic outcomes of the lymphoma (AITL).

Gene expression profiling (GEP) may appropriately delineate multitudinous genetic aberrations such as TET2 (47%-73%), DN MT 3A (33%) and IDH2-R172 (20-40%). The anomalies may distinguish AITL from certain B cell lymphomas with the recapitulation of specific myeloid malignancies [2,3]. However, these mutations may be inadequate to initiate the specific lymphoma. Functional mutations with chromosomal gains within the T cell receptors of AITL may be exemplified. RHOA, a specific GTPase, incriminated in the rearrangement of cellular cytoskeleton may be mutated (G17v) in an estimated 60% instances of AITL. RHOA and TET2 mutation may coexist thereby inciting multitudinous genetic aberrations within AITL, which may be enunciated in various stages of T cell development [2,3] **(Figures 1-13)**.

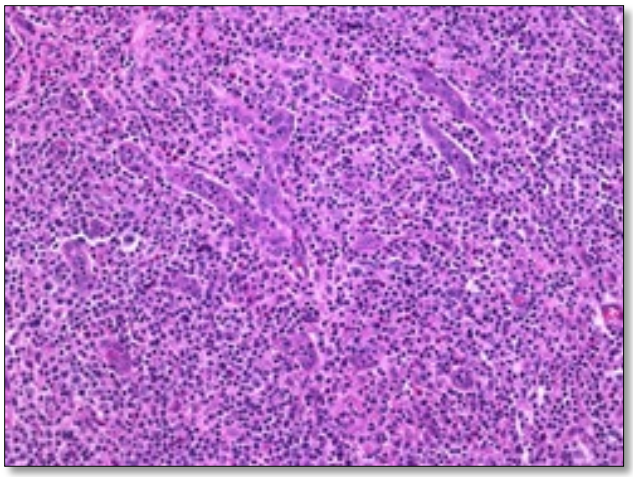

Figure 1. AITL mixture of immunoblasts and small, atypical lymphocytes [14].

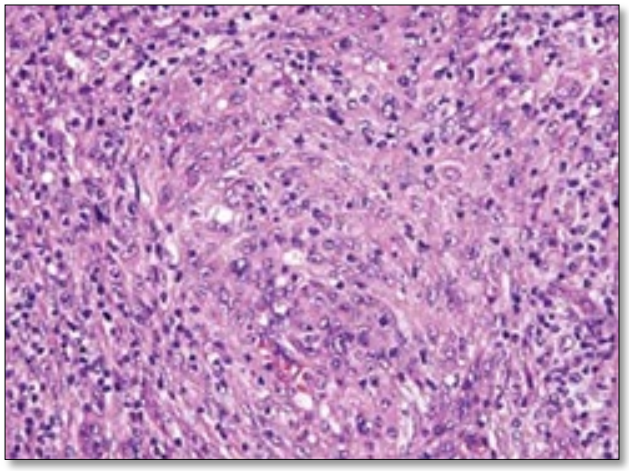

Figure 2. AITL burned out germinal centre with pale staining immunoblasts [15].

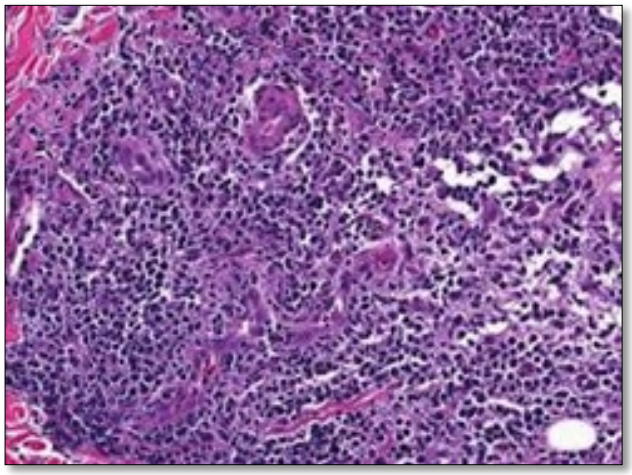

Figure 3. AITL eosinophilic PAS+ material in the lymph node [16].

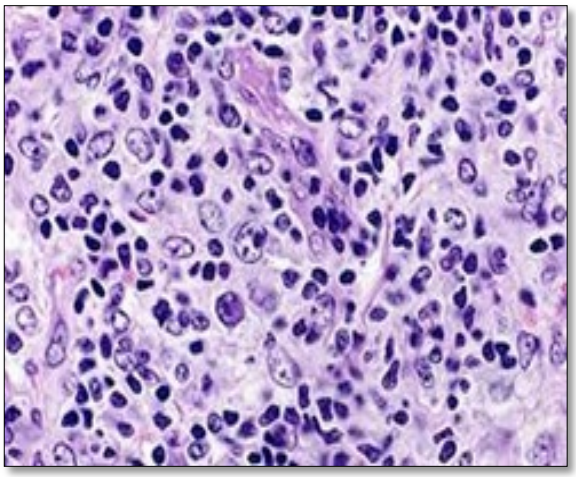

Figure 4. AITL immunoblasts with convoluted nuclei and post capillary venule [17].

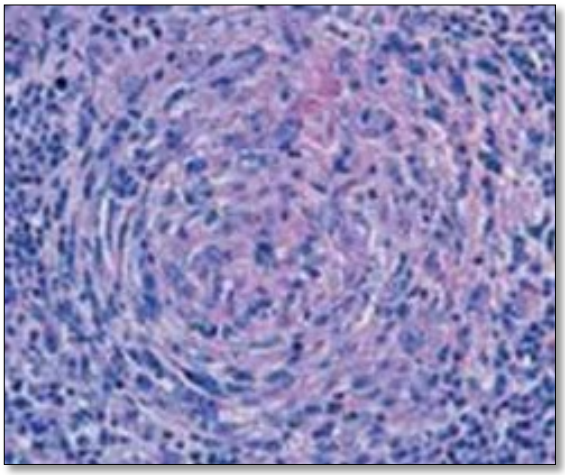

Figure 5. AITL burnt out germinal centre with histiocytes and immunoblasts [18].

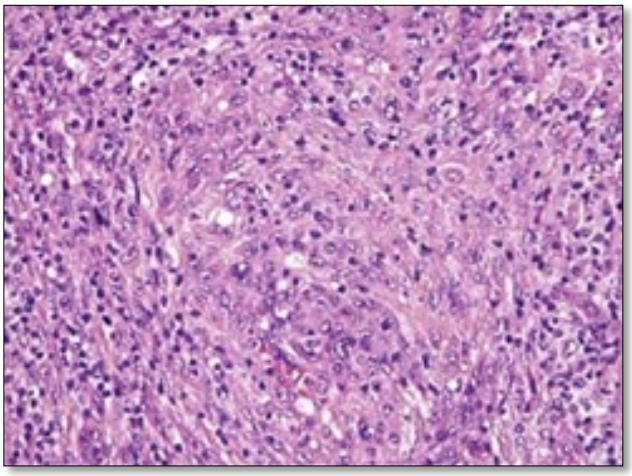

Figure 6. AITL germinal centre with immunoblasts, histiocytes and epitheloid cells [19].

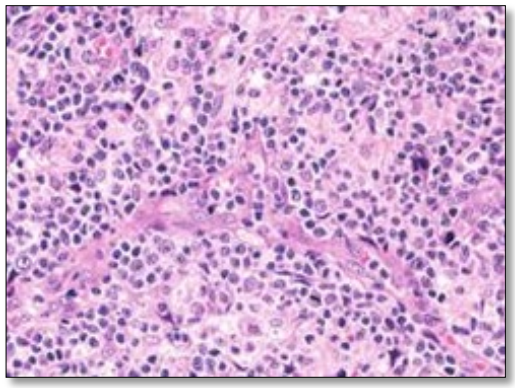

Figure 7. AITL high endothelial venules with proliferative endothelium [20].

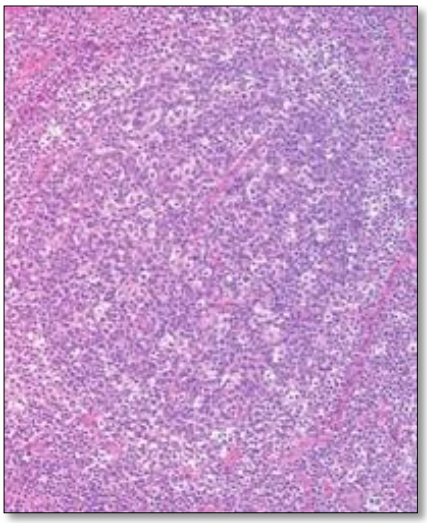

Figure 8. AITL germinal centre with histiocytes, small lymphocytes and immunoblasts [20].

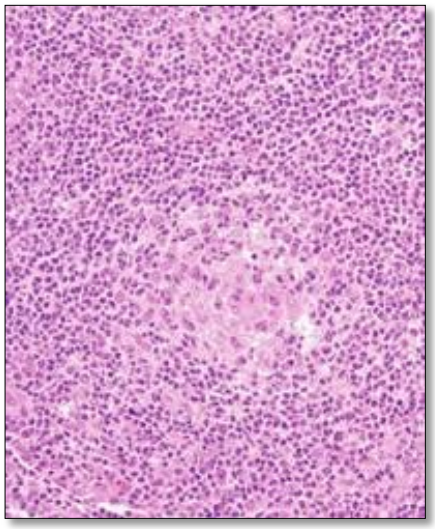

Figure 9. AITL burnt out germinal centre with pale staining immunoblasts and peripheral, malignant T lymphocytes [20].

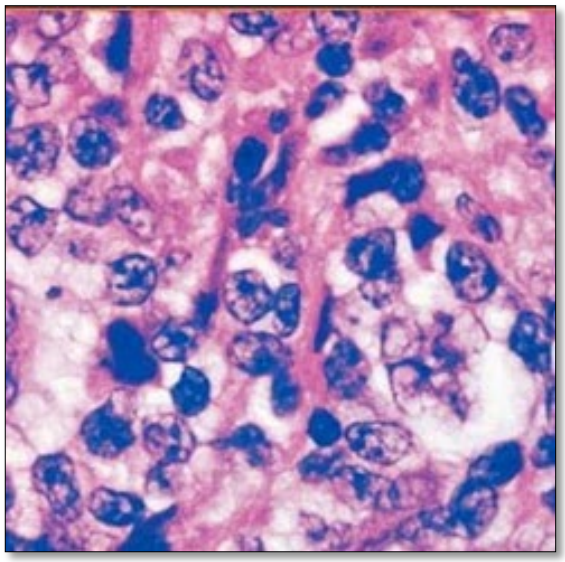

Figure 10. AITL pleomorphic cells with convoluted nuclei and prominent nucleoli [21].

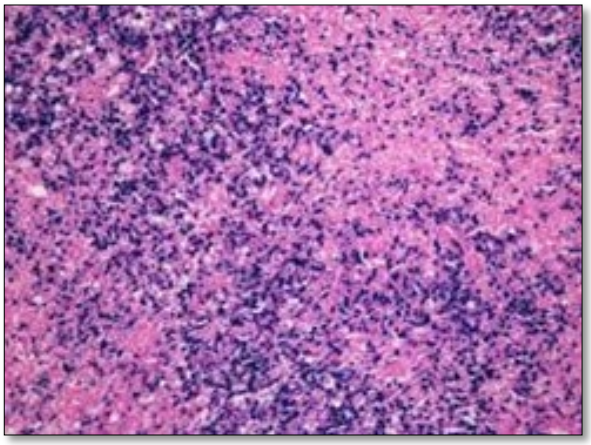

Figure 11. AITL eosinophilic, PAS+ substance in the lymph node stroma [22].

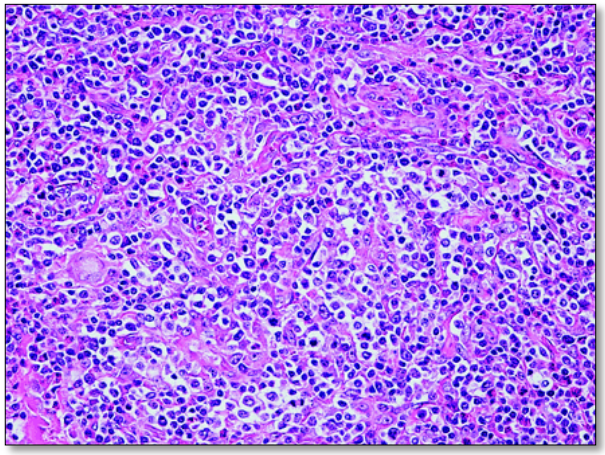

Figure 12. AITL high endothelial venules with plump endothelium [23].

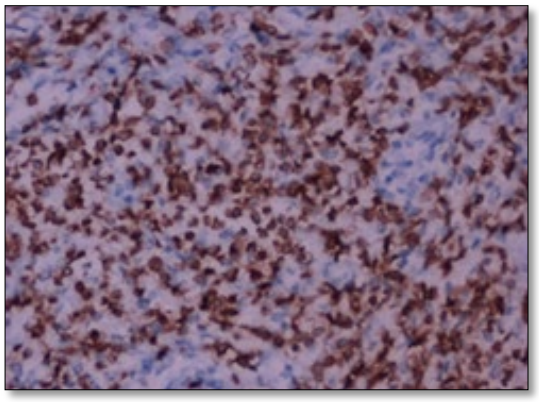

Figure 13. AITL immune reactive CD3+ [24].

INVESTIGATIVE ASSAY

Diagnostic manifestations may include pancytopenia, circulating immune complexes, anti-smooth muscle antibodies, autoimmune hemodialysis, the presence of cold agglutinin, para-protein and emerging anti-cardiolipin antibodies. The appearance of rheumatoid factor and cryo-globulins may be exceptional. Majority of instances display an elevated erythrocytes sedimentation rate (ESR) with elevated serum lactate dehydrogenase (LDH). Polyclonal gammo-globulins may concur with a reactive direct coombs/anti-globulin test (DAT) [8,9]. Attributes favoring a diagnosis of AITL may incorporate itching, rashes, fever, weight loss, cervical lymph node enlargement, pancytopenia, autoimmune hemolysis, a positive direct coombs test (DCT+), elevated erythrocyte sedimentation rate (ESR), serum lactate dehydrogenase (LDH) and total serum protein, a decline in serum albumin, a positive C-reactive protein (CRP) and reactive anti-nuclear antibodies (ANA) [2,3]. Radiographic elucidation of the lymphoma may discern a bilateral mediastinal and hilar lymph node enlargement, pleural effusion, interstitial and alveolar opacities with atelectasis. A plain X-ray chest may demonstrate bilateral reticulo-nodular opacities. Computerized tomography (CT) scan of the thorax may exhibit bilateral nodular opacities with patchy consolidation of the lung parenchyma. Mediastinal lymph node enlargement may coexist [9,10]. Computerized tomography (CT) scan of the abdomen may depict a lymph node enlargement with a concomitant histology of cervical lymph nodes [10,11].

PROGNOSTIC OUTCOMES

Angio-immunoblastic T cell (AITL) may be considered as a diverse peripheral T cell lymphoma (PTCL). Median 5 year survival of the lymphoma (AITL) appears at an estimated (32%). The international prognostic index (IPI), as applicable for aggressive B lymphocyte Non-Hodgkin's lymphoma, may exhibit a 5 year overall survival (OS) of 56% for individuals with an IPI score of 0/1 and a 5 year overall survival (OS) of 25% for an IPI score of 4/5. The prognosis in AITL (PIA) score may incorporate distinct parameters such as age above 60 years, Eastern Cooperative Oncology Group (ECOG) performance status greater than two, site of extra-nodal disease greater than one, occurrence of B symptoms and a platelet count below 150 × 10^9/L. A "low risk group" may be defined with manifested 0-1 probable factors and a 5 year overall survival (OS) of 44%. A concomitant "high risk group" may be distinguished with the emergence of 2-5 probable factors and a concordant overall survival (OS) of 24%. The applicability of a prognostic index may elucidate appropriate adaptations of risk specific therapeutic options [2,3].

THERAPEUTIC APPROACH

Angio-immunoblastic T cell lymphoma (AITL) may respond to suitable induction therapy. Therapeutic options may include single agent oral therapy or a combination of intensive chemotherapeutic agents. The treatment protocols may induce primary progression of disease or brief periods of remission. Recent diagnosed lymphoma (AITL) may lack the application of specific chemotherapeutic agents. Prognosis in AITL (PIA) may be benefitted by risk adapted therapeutic strategies. Clinical trials may be appropriately employed. A first line treatment with an anthracycline based regimen may delineate a complete remission (CR) of 61% and 5 year survival of 32% with a recurrence free survival of 18% [11,12]. The classic combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) may singularly appear as a gold standard of therapy with AITL, though specific subclasses of lymphoma may elucidate an inferior prognosis. The chemotherapeutic regimen of CHOP may be considered suitable for the first line management of AITL, particularly when subsequent to ineffective anthracycline based therapies. The regimen of CHOP may induce a complete remission (CR) of 53% with AITL (39% with PTCL) [3]. A competent induction therapy for PTCL with an objective response rate (ORR) of 82% and complete remission (CR) of 51% may be constituted by concomitant employment of cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone (CHOEP). However, the remission and response rates of AITL subjected to a CHOEP therapy may not be currently available. Therapeutic CHOEP may enhance the remission for subsequent application of an elevated chemotherapeutic dosage and autologous stem cell rescue (HDT-ASCR) [3]. Solitary agents may be employed in combination with CHOP regimen such as romidepsin (romidepsin CHOP or Ro CHOP). A complete remission (CR) of 51% and a median progression free survival (PFS) of 21 months may be achieved in PTCL. Belinostat may be employed as a singular drug along with CHOP. The complete remission (CR) induced by the combination may extend up to 67% with PTCL [12,13]. Pralatrexate may be an alternative sole agent adjunctive to CHOP and employed in clinical trials. The concurrence of doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (ACVBP) may prove to be superior to chemotherapy with

CHOP. Bortezomib (proteasome inhibitor) as a singular therapy may be employed concomitantly with CHOP and ACVBP regimens. An objective response rate (ORR) of 76% and a complete remission (CR) of 65% may be elucidated with PTCL. An estimated 17% incidence of AITL may depict an augmented 3 year overall survival (OS). The regimen of dose adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-EPOCH) may be recommended by the National Comprehensive Cancer Network (NCCN) guidelines [11,13]. It may be surmised that a non anthracycline regimen may prove to be superior for managing PTCL. The regimen of cisplatin, etoposide, gemcitabine and methyprednisolone (PEGS) may delineate an inadequate objective response rate (ORR) of 39% with AITL. A median progression free survival (PFS) may be exhibited at 7 months. A regimen of alternating cyclophosphamide, etoposide, vincristine and prednisone (CEOP) with pralatrexate may depict a 2 year progression free survival (PFS) of 39% and a complete remission (CR) of 25% with AITL [3]. Avastin as an antagonist of the vascular endothelial growth factor (VEGF) may be combined with the CHOP regimen (Av-CHOP). The combination therapy may depict a complete response (CR) of 49% and a progression free survival (PFS) of 44% at 1 year. However, the particular regimen may be significantly cardio-toxic. An anti CD20 monoclonal antibody termed as rituximab may be utilized with the regimen of CHOP (R-CHOP). The combined therapy may display an objective response rate (ORR) of 80%, a complete remission (CR) of 44% or the CR remains unconfirmed. Overall survival (OS) at 2 years may be observed at 62% [10,12]. An anti CD52 monoclonal antibody Alemtuzumab may be employed with the therapeutic regimen of (CHOP). The monoclonal antibody may adhere to the T and B lymphocytes which enunciate the CD52 molecule. A complete response (CR) of 66% may be achieved. Lymphomas engendered by the opportunistic viruses' cytomegalovirus (CMV) or Epstein Barr virus (EBV) may concomitantly be elucidated. Superimposed infections and non-hematological complications may additionally ensue following immune suppression with chemotherapy. An immunomodulatory agent such as lenalidomide may be beneficial when employed singularly. It may be successfully combined with the CHOEP regimen. Lenalidomide may be used singularly as maintenance therapy. Currently diagnosed AITL may be managed with concurrent lenalidomide and CHOP [12,13]. AITL may be chemo-sensitive to the employment of high dose chemotherapy with autologous stem cell rescue (HDT-ASCR) as discerned by computerized tomography (CT) or a positron emission tomography (PET-CT). The chemo-sensitive instances of AITL may exhibit a definite survival advantage. An induction regimen employing CHOEP along with HDT-ASCR may be applicable for individuals of AITL with intent to treat or transplant. The subjects may comprehensively delineate a 5 year progression free survival (PFS) of 49% and an overall survival (OS) of 52%. Such individuals may be described as having a "maximal chemotherapeutic exposure" [3].

RELAPSED AND REFRACTORY ANGIOIMMUNOBLASTIC T CELL LYMPHOMA

A challenging disease to treat, refractory or relapsed AITL may enunciate a median overall survival (OS) of 5.5 months, particularly in subjects lacking HDT-ASCR following acceptable induction therapy. Regimens such ifosphamide, carboplatin, etoposide (ICE) dexamethasone, cytarabin, cisplatin (DHAP) or etoposide, methyl-prednisone, cisplatin, cytarabine (ESHAP) may be employed for managing the refractory/relapsed instances [3]. Regimens applicable to out-patients may incorporate gemcitabine, cisplatin, methylprednisolone (Gem-P) and gemcitabine, cisplatin dexamethasone (GDP). Singular agent bendamustine may also be advantageous. The aforementioned efficacious regimens may mandate additional evaluation in patients of AITL [11,13]. Concurrent chemotherapies may depict an augmented objective response rate (ORR), such as that of 70% with the administration of ICE. Emerging hematological toxicities may restrict the combined chemotherapies to 3-4 cycles with a diminished progression free survival (PFS). Patients who are "transplant eligible" may benefit from the combined therapeutic option which permits an appropriately timed HDT-ASCR in chemo-sensitive subjects. Continuous therapy applicable until progression of disease or therapeutic intolerance may be opted for treating AITL. The technique may be applicable to singular agents with an objective of maintenance of quality of life [10,12]. Drug conjugate pralatrexate may depict an objective response rate (ORR) of 8% in AITL, thus may be acceptable for a combination therapy or a clinical trial. Romidepsin as a solitary agent may demonstrate an objective response rate (ORR) of 30% in AITL. A median duration of response (DOR) of 17 months may be achieved with romidepsin. Belinostat as a second histone deacetylase (HDAC) inhibitor may be administered in AITL. An objective response rate (ORR) of 45% may be elucidated as AITL delineates a minimally intense CD30+ phenotype, in contrast to a greater CD30+ enunciation with anaplastic large cell lymphoma (ALCL). Drug conjugate brentuximab vedotin may depict an objective response rate (ORR) of 54% with AITL [3]. Cyclosporine as an immune suppressive agent may be utilized in AITL with an objective response rate (ORR) of 75%. Immune-modulatory agent lenalidomide may be appropriate for managing refractory or relapsed AITL. The achieved objective response rate (ORR) may be at 29% with the emergence of partial remission. Romidepsin and Belinostat may be employed as FDA approved singular therapies for treating refractory or relapsed instances of AITL. However, the agents may not be efficacious as front line therapy for treating refractory AITL in combination with CHOP. Novel therapies such as Janus Kinase (JAK 2) inhibitors, hypo-methylating agents and isocitrate

dehyrogenase 2 (IDH2) inhibitors may prove to be efficacious in clinical trials [3] **(Table 1)**.

Table 1. Estimates of clinical and laboratory aspects of AITL [3].

Attributes	Proportions
B symptoms	55-77%
Performance status>1	37-50%
LDH levels	60-86%
Advanced stage (III/IV)	81-92%
Low probability IPI (0-1)	11-21%
Multiple lymph node involvement	76-99%
Bone marrow	28-70%
Skin rash	31-45%
Anaemia	33-65%
Coombs' test (positive)	13-75%
Thromobocytopenia	20-31%
Hypergammaglobulinaemia	50-84%
Hypereosinophilia	32-34%

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