

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 dys-regulation 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 epithelioid 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

Introduction

AITL is cogitated as a peripheral T cell lymphoma with characteristic components of systemic disease, polymorphic lymphoid infiltration of the lymph nodes accompanied by significant proliferation of high endothelial venules and follicular dendritic cells. The nodal T cell lymphoma (AITL) depicts a malignant T follicular helper phenotype. Nodal architecture can be partly to completely obliterate. Immune reactivity to CD4+, CD10+, PD1+, CXCL3+ is demonstrated along with the presence of T cell immunoblast, CD21+ reactive follicular dendritic cells and B lymphocytes immune reactive to Epstein Barr virus (EBV+). Additionally, genetic recombination of T cell receptor (TCR) and immunoglobulin heavy (IGH) genes can be enunciated. Angio-immunoblastic T cell lymphoma (AITL) (Figure 1) is designated as a lymph node based T cell lymphoma which originates from a T follicular helper cell phenotype by the world health organization in 2016 [1]. Angio-immunoblastic T cell lymphoma (AITL) constitutes

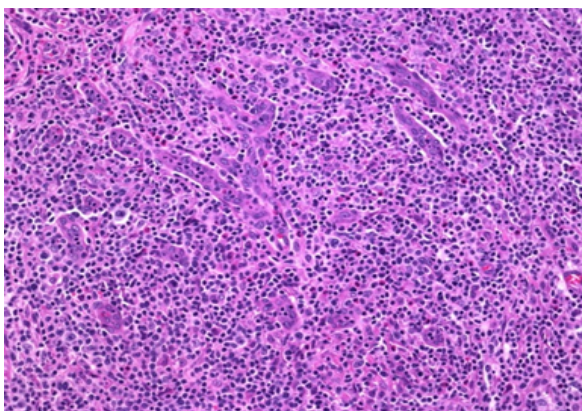


Figure 1: AITL mixture of immunoblasts and small, atypical lymphocytes (Image Courtesy: Web-pathology).

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 obscure initial diagnosis [2]. Angio-immunoblastic T cell lymphoma (AITL) is simultaneously cogitated as angio-immunoblastic lymphadenopathy with dysproteinaemia (AILD), immunoblastic lymphadenopathy or lympho-granulomatosis X [2,3]. The disorder was initially labelled as a benign immune activation of B lymphocytes despite the fatal course of disease. Evaluation of clone specific T and B lymphocytes confirms a malignant and T lymphocytic manifestation of the neoplasm. Hence the current terminology of angio-immunoblastic T cell lymphoma (AITL) is 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) is 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%). B lymphocytes denominate a perpetual viral infection whereas the malignant T lymphocytes lack the viral trigger [2,3]. The lymphoma (AITL) generally displays

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an aggressive clinical course with a median survival of below 3 years irrespective of the therapeutic intervention. AITL progresses 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 ensues due to infections and immunological compromise [2,3].

Clinical elucidation

Subjects enunciate non-specific constitutional symptoms, transient physical signs and inconclusive serological or radiographic features, thus detection of the disorder is delayed by several weeks or months. Individuals incriminated with the non-Hodgkin's lymphoma (AITL) exemplify B symptoms (70%) such as fever, weight loss greater than 10% of the body weight, drenching night sweats, lymph node enlargement, hepatic-splenomegaly (74%) and skin involvement (50%) [2,3]. Angio-immunoblastic T cell lymphoma (AITL) or previous Angio-immunoblastic lymphadenopathy with dysproteinaemia (AILD) with clinical features characteristic of a lymphoma display a maculopapular rash (simulating a viral rash), poly-arthritis (sero-positive), fever, pruritus, lymph node enlargement, night sweats and weight loss. Additionally oedema, acute abdomen, disseminated bacterial infection and herpes virus type 6 or associated viral infections are demonstrated. Discordant clinical manifestations such as a sick sinus syndrome and collagen vascular disease such as rheumatoid arthritis and dermatomyositis indicate the presence of an AITL. AITL simulates an infection by *M. tuberculosis* with the consequent initiation of anti-tubercular therapy. Proliferative glomerulo-nephritis concomitant to the lymphoma (AITL) is exceptional. Pulmonary involvement is indicated by hypoxemia, interstitial pneumonia or bronchopneumonia. Subjects with bronchopneumonia demonstrate co-existent opportunistic infections such as pneumonia due to *Pneumocystis jirovecii*, dyspnoea and peripheral oedema. The lymphoma is 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 centimetres on computerized tomography (CT) and diverse standard uptake values (SUVs) on a positron emission tomography (PET) are 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 is initially moderate. Antecedent skin rash appears in approximately 20-50% instances. Dermal manifestations appear as urticarial rash or tumour like nodules. Administration of antimicrobial agents or the exceptional overt, cutaneous variant of AITL delineates multitudinous skin rashes. Extra-nodal incrimination is infrequent with AITL [4]. Immune hyperactivity is 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 depicts the polyclonal nature of dys-proteinemia and gammopathy [3,5]. A clone specific plasmacytosis infrequently concurs with a monoclonal gammopathy in an estimated 10% instances. Autoimmune induced warm antibody (direct anti-globulin test DAT) haemolytic anaemia appears as the presenting symptom. Eosinophilia emerges with or without a concomitant infectious aetiology. Peripheral blood smear rarely depicts circulating malignant cells which is 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 exemplifies a

genetic concurrence by molecular mechanisms. Follicular helper T lymphocyte (TFH) functions as a critical controlling mechanism of B cell differentiation and activation within the germinal centre (Figure 2). Antigenic stimulation of the germinal centres incites a B cell hyperactivity [4,5]. Follicular helper T lymphocytes (TFH) catalyses the evolution of peripherally dispersed secondary lymphoid tissue containing centroblasts into centrocytes. 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 is critical for restricting the genesis of auto immune disorders. Nevertheless, a comprehensive dys-regulation of the follicular T helper (TFH) lymphocytes ensues within the disorganized germinal centres with a subsequent emergence of angio-immunoblastic T cell lymphoma (AITL) [5,6].

Morphological elucidation

Lymph node biopsy discerns the emergence of AITL. Malignant follicular helper T (TFH) lymphocytic component constitutes a miniscule fraction of the lymph node neoplasm similar to the Reed Sternberg cells denominated in Hodgkin's disease. Lymph node architecture is obliterated with an absence of follicles. Immunological cells such as immunoblasts, B lymphocytes, plasma cells, eosinophils, histiocytes and epitheloid cells are abundant (Figure 3). Follicular

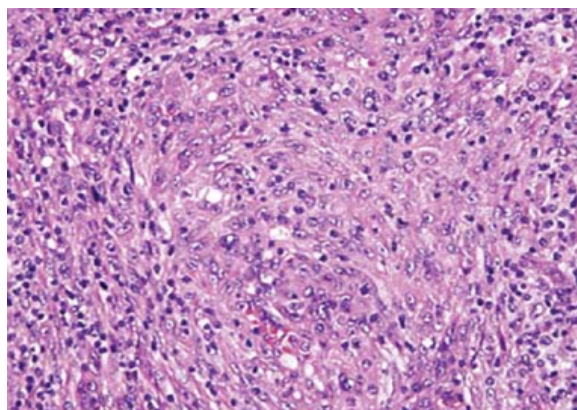


Figure 2: AITL burned out germinal centre with pale staining immunoblasts (Image Courtesy: Basic medical key).

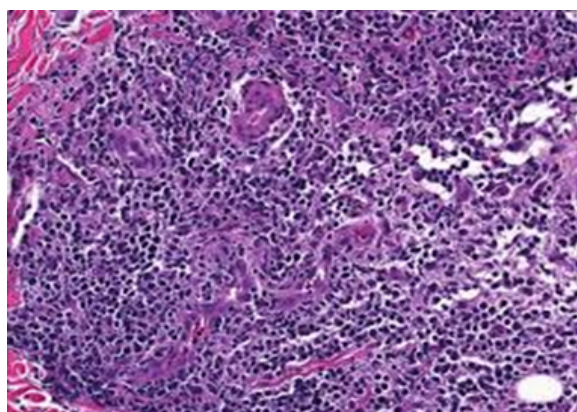


Figure 3: AITL eosinophilic PAS+ material in the lymph node (Image Courtesy: aad.com).

dendritic cells (FDCs) and vasculature with proliferative, plump endothelium propagates aberrantly and randomly [4,5]. Aggregates of malignant follicular helper T (TFH) lymphocytes about the high endothelial venules (HEVs). The lymphoma enunciates 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 delineates an effaced nodal architecture, focally preserved lymphoid sinuses, a polymorphic infiltration of lymphoid cells and a prominent proliferation of post capillary venules. Cellular infiltrate comprises of miniature lymphocytes, plasma cells, immunoblast, eosinophil and multinucleated giant cells. The lymph node is persistently devoid of normal, uninvolved germinal centres. Germinal centres are constituted of disordered aggregates of pale histiocytes, immunoblast and enlarged epithelial cells, appropriately termed as the “burnt out germinal centres”. Germinal centres focally recapitulate the appearance of granulomas. Conventional germinal centres exceptionally display hyperplasia of the surrounding lymphoid follicles [4]. Proliferation of dendritic reticulum cell clusters which are immune reactive for desmin can be elucidated. An amorphous, eosinophilia intercellular substance reactive for periodic acid Schiff’s (PAS) stain is disseminated through the lymph node architecture. Capsular and peri-capsular infiltration of tumour cells is frequent. A polyclonal immunoglobulin configuration is elucidated by the immuno-peroxidase stain. B lymphocytes with immune reactivity to the Epstein Barr virus (EBV⁺) are detected in a majority (75%) of instances. Lymphoid aggregates vary from reversible and reactive to malignant and aggressive in countenance [4,6]. Clone specific proportions of B and T lymphocytes are discerned. An aberrant cellular composition is discerned such as immunoblasts, miniature lymphocytes with convoluted nuclei and thick membrane or clear cells. Particular subtypes denominate an aggravated clinical course (Figure 4).

Immune phenotype and *in situ* hybridization

Immune reactivity to diverse T cell antigens are employed to ascertain the presence of tumour cells such as CD3⁺, CD4⁺, CD8⁻, CXCL13⁺, CD10⁺, BCL6⁻, CD19⁺, C20⁺, CD1a⁺, CD21⁺, CD23⁺ and TdT. Clone specific T lymphocyte population is elucidated in the majority (75%) instances [6,7]. Malignant follicular helper T (TFH) lymphocytes depict a phenotype of immune reactive CD3⁺, CD4⁺, CD10⁺. An alpha /beta T cell receptor is elucidated with a frequent, anomalous negativity for CD5⁻ and/or CD7⁻. An estimated one fifth (20%) instances display a CD30⁺ immune expression. Immune reactive CXCL13⁺ is particularly specific and consistently elucidated in the

cytoplasm of malignant lymphocytes, in contrast to CD10. Follicular helper T (TFH) lymphocytes manifest the program death receptor-1 (PD-1), ICOS, BCL6 and CD200 [3]. Aforementioned immune molecular expression demarcates the lymphoma (AITL) (Figure 5) from diverse benign lympho-proliferative disorders and subcategories of PTCL with an identical genesis from a follicular helper T (TFH) cell. Immune reactive CD21⁺ segregates the follicular dendritic cells (FDCs) from the intermingled follicular helper T (TFH) cells and high endothelial venules (HEVs) [7,8]. Majority of enlarged B lymphocytes depict a reactive Epstein Barr virus encoded small RNAs (EBER) by *in situ* hybridization, indicating an on-going viral infection (EBV), whereas the malignant follicular helper T (TFH) lymphocytes are non-reactive to EBER.

Molecular assay

Majority (90%) of instances of angio-immunoblastic T cell lymphoma (AITL) depict an anomalous karyotype, which may or may not belong to particular clone of malignant T lymphocytes. Trisomy of chromosomes 3 and 5 is a frequent aberration. *TP53* oncogene is infrequently decimated [2,3]. However, occurrence of clone specific complications indicates a poor prognosis. As the lymphoma (AITL) is devoid of characteristic anomalies, development of therapeutic possibilities remains lacking. Immune reactivity to clone specific CD4⁺ T cells is delineated in a majority (80%) of instances of angio-immunoblastic T cell lymphoma (AITL). A clone specific population of B lymphocytes is demonstrated in an estimated 41% instances with concomitant angio-immunoblastic T cell lymphoma. Competent molecular investigation of the lymphoma discerns genetic manifestations of AITL and demarcates it from categories of peripheral T cell lymphoma (PTCL) [8,9]. Molecular fabrication of AITL comprises of follicular dendritic cells (FDCs), B lymphocytes and an interwoven stroma. Tumour specific microenvironment defines the prognostic outcomes of the lymphoma (AITL). Gene expression profiling (GEP) appropriately delineates multitudinous genetic aberrations such as Tet2 47-73%, DN MT 3A (33%) and IDH2-R172 20-40%. Anomalies can distinguish AITL from certain B cell lymphomas with the recapitulation of specific myeloid malignancies [2,3]. However, these mutations are inadequate to initiate the specific lymphoma. Functional mutations with chromosomal gains within the T cell receptors of AITL are exemplified. RHOA, a specific GTPase, incriminated in the rearrangement of cellular cytoskeleton is mutated (G17v) in an estimated 60% instances of AITL. RHOA and TET2 mutation coexist, thereby inciting multitudinous genetic aberrations within AITL, which are enunciated in various stages of T cell development [2,3] (Figure 6).

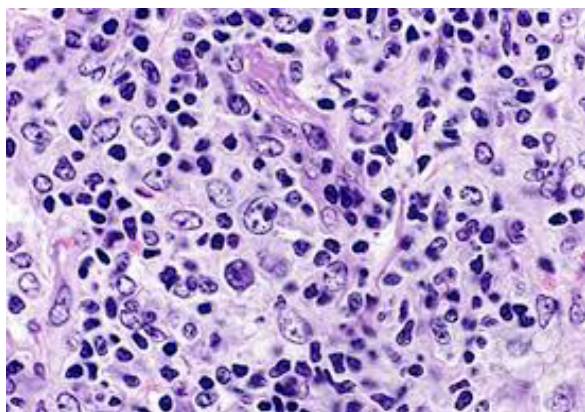


Figure 4: AITL immunoblasts with convoluted nuclei and post capillary venule (Image Courtesy: Image Bank Haematology).

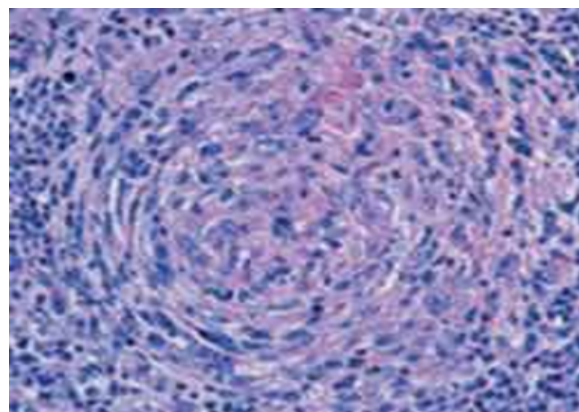


Figure 5: AITL burnt out germinal centre with histiocytes and immunoblasts (Image Courtesy: Healio.com).

Investigative assay

Diagnostic manifestations include pancytopenia, circulating immune complexes, anti-smooth muscle antibodies, autoimmune haemodialysis, and the presence of cold agglutinin, para-protein and emerging anti-cardiolipin antibodies. Appearance of rheumatoid factor and cryo-globulins is exceptional. Majority of instances display an elevated erythrocytes sedimentation rate (ESR) with elevated serum lactate dehydrogenase (LDH). Polyclonal gamma-globulins concur with a reactive direct coombs/antiglobulin test (DAT) [8,9]. Attributes favouring a diagnosis of AITL incorporates itching, rashes, fever, weight loss, cervical lymph node enlargement, pancytopenia, autoimmune haemolysis, 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 discerns a bilateral mediastinal and hilar lymph node enlargement, pleural effusion, interstitial and alveolar opacities with atelectasis. Plain X-ray chest demonstrates bilateral reticulo nodular opacities. Computerized tomography (CT) scan of the thorax exhibits bilateral nodular opacities with patchy consolidation of the lung parenchyma. Mediastinal lymph node enlargement coexists [9,10]. Computerized tomography (CT) scan of the abdomen depicts a lymph node enlargement with a concomitant histology of cervical lymph nodes [10,11]. Whole body computerized tomography can be employed for evaluating lymphomas. Overall inter-observer agreement (94.9%) of the modality appears superior within staging of lymphoma, with superlative inter-observer agreement as cogitated in for stage I (96.4%), stage II (94.8%), stage III (94.6%) and stage IV (94.0%). Comprehensive inter-observer agreement for evaluating therapeutic response sequential to a complete therapeutic regimen emerges at 95.8%. Progressive disease depicts an inter-observer agreement at 97.1%, stable disease at 95%, partial response at 98.1% and inter-observer agreement of complete response of 93.3% [12]. Whole body multi-detector computerized tomography appears preferable to the application of conventional radiography for discerning bony lesions particularly of the spine and thoracic cage. Focal or diffuse incrimination of the bony medulla is concordant with disease staging and overall prognostic indices. Fractures of the spine, cortical lesions and extra-osseous spinal lesions are suitably discerned. Whole body multi-detector computerized tomography influences therapeutic protocol and outcomes in specified subjects [13]. Computerized tomography as a modality can be employed to expose partial therapeutic response

of hepatic metastasis. The procedure displays a superior inter-observer agreement at 89.29%. Additionally, stable disease demonstrates an inter-observer agreement at 89.29%, progressive disease at 100% with a comprehensive inter observer agreement at 89.29% [14]. Therefore, whole body computerized tomography remains a cogent and consistent imaging technique in the application of staging and therapeutic evaluation of lymphoma- as categorized with Lugano classification along with response assessment of hepatic metastasis in breast cancer according to response evaluation criterion in solid tumours (RECIST) criterion [12,14].

Prognostic outcomes

Angio-immunoblastic T cell (AITL) (Figure 7) is considered as a diverse peripheral T cell lymphoma (PTCL). Median 5 year survival of the lymphoma (AITL) appears at an estimated (32%). International prognostic index (IPI), as applicable for aggressive B lymphocyte non-Hodgkin's lymphoma, exhibits 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. Prognosis in AITL (PIA) score incorporates 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 $150 \times 10^9/L$. A "low risk group" is defined with manifested 0-1 probable factors and a 5 year overall survival (OS) of 44%. A concomitant "high risk group" is distinguished with the emergence of 2-5 probable factors and a concordant overall survival (OS) of 24%. Applicability of a prognostic index elucidates appropriate adaptations of risk specific therapeutic options [2,3].

Therapeutic approach

Angio-immunoblastic T cell lymphoma (AITL) responds to suitable induction therapy. Therapeutic options include single agent oral therapy or a combination of intensive chemotherapeutic agents. Treatment protocols induce primary progression of disease or brief periods of remission. Recent diagnosed lymphoma (AITL) lack the application of specific chemotherapeutic agents. Prognosis in AITL (PIA) can be benefitted by application of risk adapted therapeutic strategies. Clinical trials are appropriately employed. First line treatment with an anthracycline based regimen delineates a complete remission (CR) of 61% and 5 year survival of 32% with a recurrence free survival of 18% [11,12]. Classic combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) singularly appears as

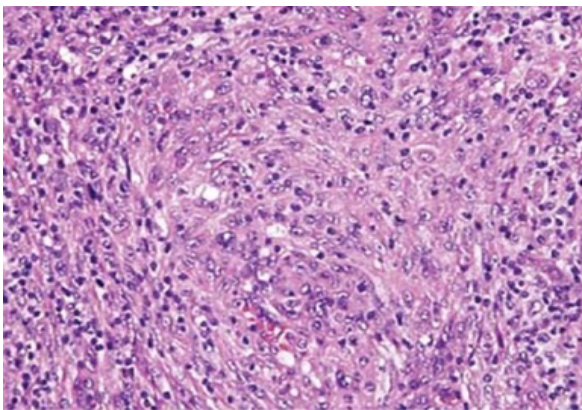


Figure 6: AITL germinal centre with immunoblasts, histiocytes and epitheloid cells (Image Courtesy: Red news wire).

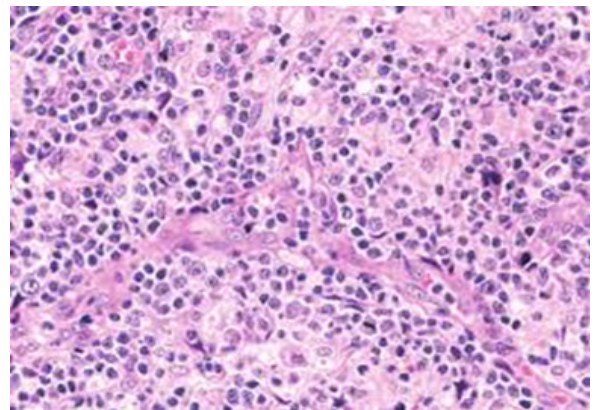


Figure 7: AITL high endothelial venules with proliferative endothelium (Image Courtesy: Wiley online library).

a gold standard of therapy with AITL, though specific subclasses of lymphoma elucidate an inferior prognosis. Chemotherapeutic regimen of CHOP is considered suitable for first line management of AITL, particularly when administered subsequent to ineffective anthracycline based therapies. Regimen of CHOP induces a complete remission (CR) of 53% with AITL (39% with PTCL) [3]. Competent induction therapy for PTCL with an objective response rate (ORR) of 82% and complete remission (CR) of 51% is constituted by concomitant employment of cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone (CHOEP). However, remission and response rates of AITL subjected to a CHOEP therapy are not currently available. Therapeutic CHOEP enhances the remission for subsequent application of an elevated chemotherapeutic dosage and autologous stem cell rescue (HDT-ASCR) [3]. Solitary agents can be employed in combination with CHOP regimen such as romidepsin (romidepsin CHOP or Ro CHOP). Complete remission (CR) of 51% and median progression free survival (PFS) of 21 months is achieved in PTCL. Belinostat is employed as a singular drug along with CHOP. Complete remission (CR) induced by the combination extends up to 67% with PTCL [12,13]. Pralatrexate is an alternative sole agent adjunctive to CHOP and employed in clinical trials. Concurrence of doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (ACVBP) proves to be superior to chemotherapy with CHOP. Bortezomib (proteasome inhibitor) as a singular therapy is employed concomitantly with CHOP and ACVBP regimens. Objective response rate (ORR) of 76% and complete remission (CR) of 65% is elucidated with PTCL. An estimated 17% incidence of AITL (Figure 8) depicts an augmented 3 year overall survival (OS) [15,16]. Regimen of dose adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA- EPOCH) is recommended by the national comprehensive cancer network (NCCN) guidelines [11,13]. It can be surmised that a non anthracycline regimen proves to be superior for managing PTCL. Regimen of cisplatin, etoposide, gemcitabine and methylprednisolone (PEGS) delineates an inadequate objective response rate (ORR) of 39% with AITL. Median progression free survival (PFS) is exhibited at 7 months. Regimen of alternating cyclophosphamide, etoposide, vincristine and prednisone (CEOP) with pralatrexate depicts 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) can be combined with the CHOP regimen (Av- CHOP). The combination therapy depicts a complete response (CR) of 49% and a progression free survival (PFS) of 44% at 1 year. However, the particular regimen is significantly cardio-toxic. Anti CD20 monoclonal antibody termed as rituximab is utilized with the regimen of CHOP (R- CHOP). Combination therapy displays an objective response rate (ORR) of 80%, complete remission (CR) of 44% or the CR remains unconfirmed. Overall survival (OS) at 2 years is observed at 62% [10,12]. Anti CD52 monoclonal antibody Alemtuzumab is employed with the therapeutic regimen of (CHOP). Monoclonal antibody adheres to the T and B lymphocytes which enunciate the CD52 molecule. Complete response (CR) of 66% is achieved. Lymphomas engendered by the opportunistic virus's cytomegalovirus (CMV) or Epstein Barr virus (EBV) are concomitantly elucidated. Superimposed infections and non-haematological complications additionally ensue following immune suppression with chemotherapy. Immunomodulatory agent such as lenalidomide is beneficial when employed singularly. It is successfully combined with CHOEP regimen. Lenalidomide is used singularly as maintenance therapy. Recent instances of AITL (Figure 9) can be managed with concurrent lenalidomide and CHOP [12,13]. AITL is chemo-sensitive to 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). Chemo-sensitive instances of AITL exhibit a definite survival advantage. Induction regimen employing CHOEP along with HDT- ASCR is applicable for individuals of AITL with intent to treat or transplant. Subjects comprehensively delineate a 5 year progression free survival (PFS) of 49% and an overall survival (OS) of 52%. Such individuals are described as having a "maximal chemotherapeutic exposure" [3].

Relapsed and refractory angio-immunoblastic T cell lymphoma

A challenging disease to treat, refractory or relapsed AITL (Figure 10) enunciates 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, cytarabine, cisplatin (DHAP) or etoposide, methyl-prednisone, cisplatin, cytarabine (ESHAP) are employed for

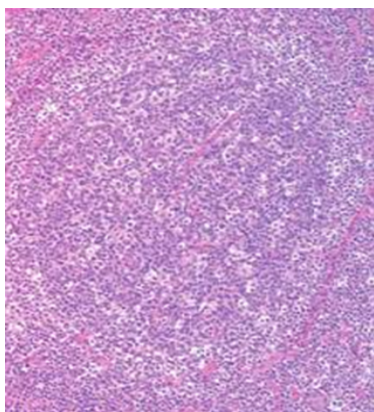


Figure 8: AITL germinal centre with histiocytes, small lymphocytes and immunoblasts (Image Courtesy: Wiley online library).

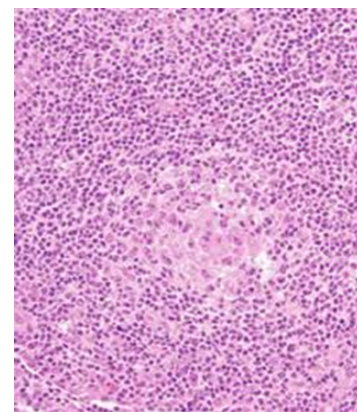


Figure 9: AITL germinal centre with histiocytes, small lymphocytes and immunoblasts (Image Courtesy: Wiley online library).

managing the refractory/relapsed instances [3]. Regimens applicable to our patients incorporate gemcitabine, cisplatin, methylprednisolone (Gem-P) and gemcitabine, cisplatin dexamethasone (GDP). Singular agent bendamustine are also advantageous. Aforementioned efficacious regimens mandate additional evaluation in patients of AITL [11,13-16] (Figure 11).

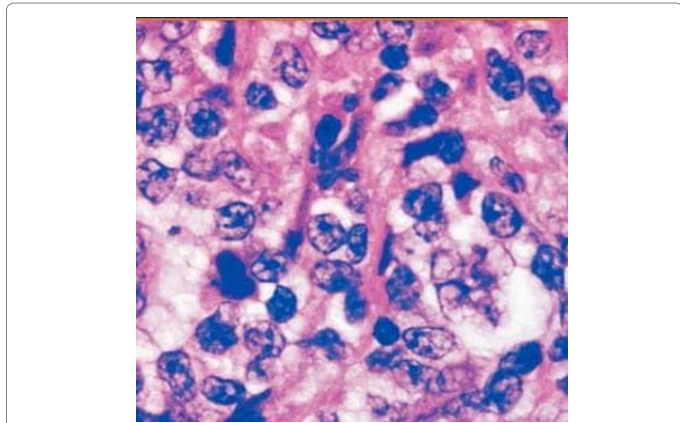


Figure 10: AITL pleomorphic cells with convoluted nuclei and prominent nucleoli (Image Courtesy: aol.co.uk).

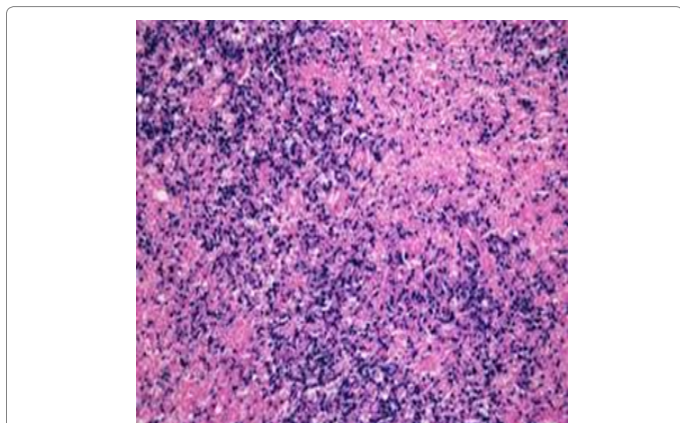


Figure 11: AITL eosinophilic, PAS+ substance in the lymph node stroma (Image Courtesy: mistaken for internal medicine).

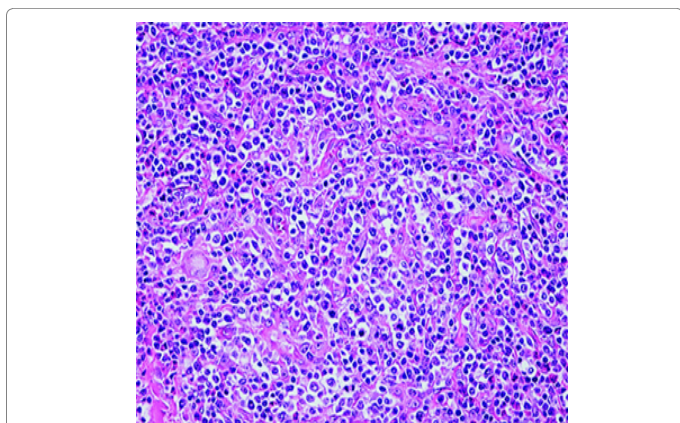


Figure 12: AITL high endothelial venules with plump endothelium (Image Courtesy: Pathology outlines).

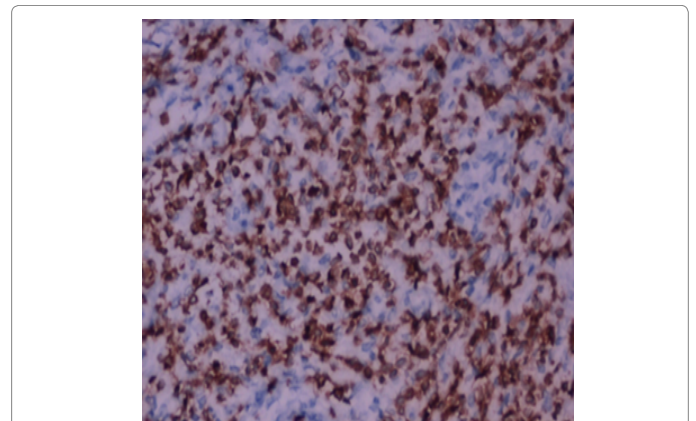


Figure 13: AITL immune reactive CD3+ (Image Courtesy: Internet Scientific Publications).

Attributes	Proportion
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%
Thrombocytopenia	20-31%
Hypergammaglobulinaemia	50-84%
Hypereosinophilia	32-34%

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

Discussion

Concurrent chemotherapies depict an augmented objective response rate (ORR), such as that of 70% with the administration of ICE. Emerging haematological toxicities restrict the combined chemotherapies to 3-4 cycles with a diminished progression free survival (PFS). Patients who are “transplant eligible” benefit from the combined therapeutic option which permits an appropriately timed HDT-ASCR in chemo-sensitive subjects. Continuous therapies applicable until progression of disease or therapeutic intolerance are opted for treating AITL. Technique is applicable to singular agents with an objective of maintenance of quality of life. Drug conjugate pralatrexate depicts an objective response rate (ORR) of 8% in AITL, thus remains acceptable or a combination therapy or a clinical trial. Romidepsin as a solitary agent demonstrates an objective response rate (ORR) of 30% in AITL. Median duration of response (DOR) of 17 months is achieved with romidepsin. Belinostat as a second histone deacetylase (HDAC) inhibitor is administered in AITL. An objective response rate (ORR) of 45% is 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 depicts an objective response rate (ORR) of 54% with AITL (Figures 12 and 13, Table 1).

Conclusion

Cyclosporine as an immune suppressive agent is utilized in AITL with an objective response rate (ORR) of 75%. Immune-modulatory

agent lenalidomide is appropriate for managing refractory or relapsed AITL. Achieved objective response rate (ORR) is at 29% with emergence of partial remission. Romidepsin and Belinostat are employed as FDA approved singular therapies for treating refractory or relapsed instances of AITL. However, the agents are not 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 dehydrogenase 2 (IDH2) inhibitors prove to be efficacious in clinical trials.

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