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MOLECULAR ETIOLOGY OF MATURE T-CELL NON-HODGKINS LYMPHOMAS

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TABLE OF CONTENTS

1. ABSTRACT

T-cell Non-Hodgkin's lymphomas (NHL) represent approximately 10-15% of all lymphomas diagnosed in Western countries. Significant progress has been made over the last 2 decades in defining non-random chromosomal abnormalities. Cytogenetic and molecular analyses have enhanced diagnostic capabilities as well as improved classification and prognostication for T-cell NHL. Gamma-delta T-cell receptor (TCR) clonality now represents the more common TCR rearrangement in subcutaneous panniculitis-like T-cell lymphoma (SCPTCL), hepatosplenic T-cell lymphoma (HSTCL), extranodal NK/T-cell lymphoma, nasal type and enteropathy-type intestinal T-cell lymphoma (EITCL). Non-random, recurrent chromosome abnormalities such as isochrome 7 with HSTCL, complex karyotypes with peripheral T-cell lymphoma, not otherwise characterized (PTCL-NOC), trisomies 3 and 5 with angioimmunoblastic lymphoma (AIL) and t(2;5) with systemic anaplastic T-cell lymphoma have been recognized. Furthermore, identification of relevant protooncogenes and tumor suppressor genes involved in the pathogenesis of T-cell NHL such as the NPM/ALK fusion protein, p53, cyclin dependent kinase inhibitors (p15, p16, p21) and EBV as well as their interplay with the various regulatory pathways of cell cycle progression and apoptosis represent potential candidates for molecular-based therapy. This review presents a detailed analysis of the molecular and genetic perturbations present in mature T-cell lymphomas including discussion of how tumor-specific alterations impact on clinical outcome. Future studies in T-cell NHL are likely to provide additional disease-specific chromosomal translocations and molecular alterations with important translational implications.

INTRODUCTION

Many lymphomas have documented genetic abnormalities (1). Recurrent chromosome aberrations and associated protooncogenes have been identified in non-Hodgkin's lymphoma (NHL), such as the t(8;14)(q24q32) translocation and associated c-myc oncogene with Burkitt's and Burkitt-like lymphoma (2). These alterations have been recognized to have diagnostic, prognostic and potential therapeutic importance. T-cell NHL represents approximately 10-15% of all lymphomas in Western countries (3-6). B-cell NHL is 4 times as common as T-cell lymphoma in Western countries, so smaller databases are available for cytogenetic and molecular analysis. Updated classifications have recognized specific clinical and pathologic entities within the T-cell lymphoma category (5)

Table 1. T-cell lymphomas according to WHO classification

Mature (peripheral) T-cell lymphoma/neoplasms[1]
• Peripheral T-cell lymphoma, not otherwise characterized
• Angioimmunoblastic T-cell lymphoma
• Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type
• Subcutaneous panniculitis-like T-cell lymphoma
• Hepatosplenic gamma-delta T-cell lymphoma
• Extranodal NK/T-cell lymphoma, nasal type
• Enteropathy-type T-cell lymphoma
• Adult T-cell lymphoma/leukemia (HTLV1+)
• Mycoses Fungoides/Sezary Syndrome
Precursor T-cell lymphoma/neoplasms
• Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)

[1]T-cell prolymphocytic leukemia, T-cell granular lymphocytic leukemia and Aggressive NK-cell leukemia are also included in this category. Abbreviations: WHO, World Health Organization; HTLV1+, human T-cell leukemia virus; NK, natural killer.

(See Table 1). T-cell lymphomas commonly present with extranodal disease and often contain varying amounts of necrosis/apoptosis on biopsy specimens making differentiation between a reactive process and diagnosis of neoplasm challenging (7). Moreover, the confirmation of a diagnosis of T-cell lymphoma may be problematic based on clinical, morphologic and immunophenotypic grounds as this data is often identifiable for a malignant process, but not specific for a particular NHL or for an exact subtype of T-cell lymphoma (8). Over the last two decades, significant advances have been made in the field of molecular biology. Cytogenetic and molecular analyses have not only enhanced diagnostic capabilities (NHL vs reactive process), but have also allowed for the differentiation and prognostication of particular subgroups within the T-cell NHL category (9, 10). This data has also permitted further study into the details of the varied oncogenic pathways of NHL including chromosome rearrangements, disruption of tumor suppressor genes, gene amplification and viral infection. The predominant mechanism of protooncogene activation and gene expression deregulation in NHL is chromosomal translocation. These molecular and genetic characteristics are defined and reviewed for selected mature T-cell lymphomas in this paper. The disease entities, cutaneous T-cell lymphoma (Mycoses Fungoides/Sezary Syndrome) and adult T-cell lymphoma/leukemia (HTLV-I), are beyond the scope of this chapter and have been reviewed elsewhere (11-13).

3. MECHANISMS OF ONCOGENESIS

Random genomic instability, as seen in many epithelial cancers, is not a characteristic of the more stable lymphoma genome. Furthermore, defects in DNA mismatch repair that manifest as genomic microsatellite instability are less recognized in lymphoma, as compared to various hereditary solid tumor syndromes and rare sporadic cancers (14-17). Genetic alterations involved in lymphoma oncogenesis include chromosome rearrangements, disruption of tumor suppressor genes and an increase in the number of copies of genes (gene amplification). Moreover, infection of cells by viruses such as human T-cell leukemia virus (HTLV-I), Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV-8) may also contribute to lymphogenesis (13, 18, 19). Chromosome rearrangements contribute to altered gene function through varied mechanisms such as protooncogene activation and deregulation of gene expression. The primary mechanism of protooncogene activation in lymphoma is reciprocal and balanced chromosomal translocations. These translocations are mostly recurrent and non-random in NHL. The majority of chromosome translocations in NHL involve the juxtaposition of a protooncogene from one chromosome next to regulatory sequences of a partner chromosome. This contributes to control of the protooncogene by a promoter usually associated with an immunoglobulin (Ig) or T-cell receptor (TCR) gene. The two subtypes of TCR's that T-cell lymphocytes may express are gamma-delta ($\gamma\delta$) or alpha-beta ($\alpha\beta$) (20). Approximately 95% of normal T lymphocytes express the $\alpha\beta$ heterodimer, while the minority of T lymphocytes express the $\gamma\delta$ heterodimer (21, 22). Alpha-beta T-cells develop predominantly in the thymus, while $\gamma\delta$ T-cells may develop in extra-thymic locations such as the skin, intestinal epithelium and spleen (23, 24). The four TCR genes are arranged in germline configuration in non-continuous segments of variable (V), diversity (D), joining (J) and constant (C) regions. The precise mechanism by which translocation of TCR and Ig genes occur is not known, but it appears to in part involve dysfunctional gene remodeling including V-D-J recombination, isotype switching and somatic hypermutation (25, 26). T-cell neoplasms may have rearrangements involving the site of TCR α and δ genes on chromosome 14 (14q11) (27, 28), or more rarely, chromosome 7 (7q34-36 and 7p15), the site of TCR β and γ genes (29-31). Many of the genes located at the breakpoints of recurring chromosome translocations have been documented (32). The majority of translocated genes encode transcription factors (32, 33). Transcription factors are involved in the initiation of gene transcription and cell differentiation. The most common result of chromosome translocations in lymphomas that involve TCR and/or Ig genes is deregulation of gene expression with over-expression of a normally tightly regulated gene. Few lymphomas have been recognized to contain translocations that produce a fusion protein, such as the t(2;5)(p23;q35) translocation in anaplastic large cell lymphoma (ALCL) that results in expression of the nucleophosim (NPM)-anaplastic lymphoma kinase (ALK) protein. Inactivation of tumor suppressor genes may also play a role in lymphogenesis. The most common mechanism of tumor suppressor inactivation occurs through the Knudson two-hit model where a reduction of homozygosity leads to tumor formation, for example, following germline deletion of one allele and somatic mutation of the other (34, 35). Tumor suppressor genes associated with NHL include p53, p15 and p16 (36, 37). Moreover, specific chromosomal deletions that have been detected in NHL (including some

T-cell lymphomas), such as 3p, 6q, 13q and 17p, may represent sites of candidate tumor suppressor loci (38-40). Other mediators that may be involved in lymphogenesis include the cyclin-dependent kinase (cdk) inhibitors, such as $p21^{(Waf1)}$ (41, 42). A function of the $p21^{(Waf1)}$ protein includes the arrest of cells in G_1-phase checkpoint by associating with cyclin-cdk complexes, but the exact factors critical for apoptosis have not been clearly defined (43). The gene for the $p21^{(Waf1)}$ protein has been identified as a downstream target of p53 in regulating cell cycle progression through G_1 (44). Induction of $p21^{(Waf1)}$ has also been demonstrated to occur through a p53-independent pathway (45). Gene amplification leads to an increase in the number of copies of a gene in the genome of a cell, which may contribute to lymphogenesis (46). Gene amplification has been identified mostly in B-cell lymphomas (e.g., REL gene)(46-49), although amplification of TCR genes in varied T-cell lymphomas has been described (50-52). Detailed descriptions of the varied techniques available for the molecular characterization of NHL such as Southern blot assays (52, 53), reverse transcriptase-polymerase chain reaction (RT-PCR) (54, 55) and fluorescent *in situ* hybridization (FISH) (56) have been reviewed elsewhere (53, 57).

4. SPECIFIC DISEASE TYPES

4.1. Peripheral T-cell lymphoma, not otherwise characterized (PTCL-NOC)

Peripheral T-cell lymphoma (PTCL), not otherwise characterized (NOC), is predominantly a nodal lymphoma that represents the most common T-cell lymphoma comprising approximately 50-60% of all T-cell lymphoma diagnoses (58). Some studies have suggested that TCR gene rearrangements are rare in PTCL-NOC, although these findings may be dependent on the laboratory techniques employed to determine TCR clonality (59-61). Reports using more sensitive techniques such as PCR have documented TCR genes in PTCL-NOC to be rearranged in many cases (62, 63). Moreover, analysis of γ TCR loci may provide a higher diagnostic yield than β TCR loci for the study of PTCL-NOC clonality (64). Lepretre *et al* analyzed 49 consecutive cases of PTCL-NOC and demonstrated that only 3 cases involved chromosome 7q35 rearrangement (none for 7p15) and 2 cases were associated with 14q11 (60). Importantly, chromosome analysis in this study was performed using metaphase cytogenetics, thereby likely decreasing the sensitivity for detecting TCR gene rearrangements. Overall, cytogenetic aberrations in PTCL-NOC are common with approximately 70-90% of abnormal metaphases documented in most series (10, 60, 65) (See Table 2). Schlegelberger *et al* reported that chromosome analysis in PTCL allowed for separation of PTCL into low and high-grade categories, but the prognostic significance of this distinction has not been established (9, 10, 66, 67). Moreover, many studies reporting on cytogenetics of PTCL-NOC have included very small numbers of patients and used older lymphoma disease classifications. Lepretre *et al* recently described their results in 71 untreated patients with PTCL, of which included 49 patients with PTCL-NOC diagnosis (2 patients with hepatosplenic and 20 patients with AIL). Good-quality metaphases were obtained in 90% of PTCL-NOC patients and 78% of these patients had documented chromosome abnormalities. Moreover, 25 of 38 (90%) of cases with chromosome abnormalities contained complex karyotypes ($\geq$ 3 changes). Of all 71 cases in their series (including 20 cases of AIL), 40 patients demonstrated numerical abnormalities with the most common changes being trisomies 3 (15.7%), 5 (14%), 7 (14%), 21 (14%), 8 (12.2%) and 19 (12.2%) and losses of chromosomes 13 (14%), 10 (10.5%) and Y (10.5%). Trisomies 3, 5 and 7 have been reported commonly to be associated with the broad category of T-cell lymphoma (9, 68, 69). Moreover, these trisomies are not unique to specific T-cell lymphoma subtypes (70-72). The most common chromosomal structural abnormalities identified in Lepretre *et al* series were chromosome 6 (31.5%; mainly due to 6q deletions, 19.2%), 1q (22.8%), 7q (22.8%), 9p (19.4%), 9q (19.2%), 4q (19.2%), 3q (19.2%), 2p (17.5%), 1p (17.5%) and 14q (17.5%). Chromosome 1 changes and 6q deletions have been commonly associated with both B and T-cell NHL (73-76). Age greater than 60, stage III/IV and elevated lactate dehydrogenase (LDH) were associated with significantly shorter survival in the 71 patients from the Lepretre *et al* study. No significant statistical difference was found with overall survival and chromosomal abnormalities with regards to the entire population in their series or for independent histologic subtypes. It has been suggested that a tumor suppressor gene(s) on 6q may be involved in this and other T-cell lymphomas, although this putative tumor suppressor gene has not been identified (77, 78). A Japanese study documented p53 gene mutations in 5 of 5 peripheral T-cell lymphoma cases (post-renal transplant) with most cases involving transition mutations (79). Their study also demonstrated that 25% of cases had k-ras mutations and one-third of cases showed mutations of c-kit and beta-catenin genes. Other studies have established that significant minorities of PTCL-NOC have elevated levels of p53 protein, while p53 mutations have been documented less commonly (42, 80, 81). Furthermore, as compared to p53-negative cases, p53-positive cases have been shown to contain significantly higher proliferative activity, less frequent expression of the downstream $p21^{(Waf1)}$ protein and frequent expression of Bcl-2 (41, 42). Prognostic studies in PTCL-NOC have demonstrated that p53 protein overexpression and mutation of p53 correlate significantly with increased treatment failure and worse overall and disease-free survival in multivariate analysis (with 1-year survival rates in one study of 0% versus 64% with mutated and normal p53, respectively) (41, 81). Some studies in PTCL-NOC have documented abnormalities of retinoblastoma (Rb) gene expression at the transcriptional and/or post-transcriptional level (42, 80). Further study is needed into the molecular pathogenesis of PTCL-NOC specifically regarding abnormalities in the p53 and Rb gene pathways.

4.2. Angioimmunoblastic T-cell lymphoma (AIL)

AIL, otherwise known as angioimmunoblastic lymphadenopathy with dysproteinemia, is one of the more common T-cell lymphomas accounting for 15-20% of cases and 4-6% of all lymphomas (58). AIL is commonly a systemic disease with nodal involvement and various

Table 2. Characteristic genetic and molecular features of T-cell lymphomas

Lymphoma Histologic subtype	Chromosome Translocations	TCR gene rearrangement	Protooncogene involved	Protooncogene mechanism and function
Peripheral T-cell (not otherwise characterized)	Often complex Numerical: +3, +5, +21, -13, +8, +19, -10, -Y Structural: del(6q), 1q, 7q, 9p, 9q, 4q,2p, 1p, inv(14)(q11); t(7)(q35)	αβ > γδ	?p53 ?Rb gene TCR-A/D TCR-B/G ?c-kit ?k-ras ?beta-catenin	Functional inactivation and/or mutation TF—deregulation
Angioimmunoblastic	+3 and +5 >> +X	αβ = γδ	EBV (in many cases) ?p53 ?n-ras	?viral oncogenesis ?p21 related
Anaplastic T-cell (systemic)	t(2;5)(p23;q35); less common t(1;2), t(2;3), t(2;22) or inv(2)	αβ >> γδ	NPM/ALK* ?c-myc ?hypermethylation ?EBV	Fusion protein—ALK is a TK; ?PI3K activation
Subcutaneous panniculitis-like	t(1;6)(11q;21p) rarely	γδ > αβ	--	--
Hepatosplenic	i(7)(10q) and +8	γδ >> αβ	?EBV	?viral oncogenesis
Extranodal T-cell (nasal)	del 6 (q21~25) most frequent; Numerical: +13q, -1p, -17p, -12q, +2q, +10q, +X, and -11q Structural: isochromes 6p, 1q, 17q; del(11q)	γδ >> αβ	EBV (in nearly all cases) ?p53	?viral oncogenesis oerexpression, ?p21, p16
Enteropathy-type intestinal	ND	γδ > αβ > NK	EBV (geographic variation) ?p53	?viral oncogenesis

*See Table 3 for complete characteristics. Abbreviations: ND, None described; del, deletion; inv, inversion; TCR, T-cell receptor; A/D, alpha/delta; B/G, beta/gamma; TF, transcription factor; ALK, anaplastic lymphoma kinase; NPM, nucleophosim gene; EBV, Epstein-Barr virus; TK, tyrosine kinase; PI3K, phosphatidylinositol 3-kinase-Akt pathway; i, isochrome; NK, Natural Killer

disease features such as organomegaly, B symptoms, skin rash, pruritis, effusions, arthritis, eosinophilia and immunologic abnormalities (positive Coombs' test, cold agglutins, hemolytic anemia, antinuclear antibodies, rheumatoid factors, cryoglobulins and polyclonal hypergammaglobulinemia) (82-84). Histologic diagnosis of AIL may be difficult, therefore demonstration of TCR clonality is important in documenting a diagnosis of malignancy (85). The TCR genes (usually β) are rearranged in approximately 70-100% of patients with AIL when performing Southern blot analyses for rearranged alleles or detection of clonal products after PCR (86-90). Furthermore, these series documented Ig genes (heavy chain) to be rearranged in 0-15% of cases. Feller *et al* documented that specific patterns of clonal gene rearrangement correlate with prognosis in AIL (88). They showed that patients with concomitant TCR β-chain gene and Ig gene rearrangements often presented with hemolytic anemia, experienced spontaneous transient remissions (and remissions following steroids), but did not respond as well to chemotherapy and had worse overall survival compared to patients with "TCR-only" clonality (no Ig gene rearrangements). Some histologic cases of AIL may demonstrate oligo-clonality, while other cases may show regression or appearance of clonality (50, 91-94). One detailed retrospective pathologic study of 22 AIL biopsy

Table 3. Characteristics of fusion proteins associated with ALK-positive ALCL

Genetic aberration	Frequency	Fusion protein connected with TK domain of ALK 2p23	Size of fusion protein (kD)	Staining pattern
t(2;5)	73%	NPM	80	Cytoplasmic and nuclear
t(1;2)	17%	TPM3	104	Cytoplasmic and nuclear
t(2;3)	2.5%	TFG	97	Cytoplasmic
t(2;22)	2.5%	CLTCL	96	Granular cytoplasmic
inv(2)	2.5%	ATIC	250	Cytoplasmic

Abbreviations: TK, tyrosine kinase; ALK, anaplastic lymphoma kinase; ALCL, anaplastic large cell lymphoma; NPM, nucleophosim gene; TPM3, non-muscle tropomyosin; TFG, tropomyosin receptor kinase-fused gene; CLTCL, clathrin heavy polypeptide-like gene; ATIC, 5-aminoimidazole-4-carboxamide-1-beta-D-ribonucleotide transformylase/inosine monophosphate cyclohydrolase; inv, inversion.

cases, documented γ-TCR clonality in 16 of 22 patients, β-TCR clonality in 16 of 22, Ig clonality in 6/22, PCR oligoclonal products in 3/22 (92). Moreover, 'functional' γ-TCR, β-TCR and Ig clonality was demonstrated by sequence analyses of PCR products in 6 of 12, 9 of 11 and 8 of 8 cases respectively. 'Functional' TCR and/or Ig oligo-clones were detected in 6 of 20 cases with 11 cases showing 'nonfunctional' TCR and Ig sequences (92). Further study is warranted to determine the importance of the heterogeneous forms of clonality and the significance of functional versus non-functional sequences in AIL. B-cell EBV genomes are detected by PCR (for presence of EBV-DNA) and/or FISH analysis (for EBV-encoded small nuclear RNA's, or EBER-1) in approximately 80-100% of AIL-involved lymph nodes (18, 91) (95, 96). The exact role of EBV in the pathogenesis of AIL is not known, although recent research has demonstrated significant interplay between AIL and the survival and clonal expansion of EBV (97, 98). Reports studying the prognosis between EBV-positivity and the broad category of T-cell lymphomas have documented significantly inferior survival rates (versus EBV-negative T-cell lymphoma) (99, 100). Conventional cytogenetics (metaphase analysis) will detect chromosomal abnormalities in approximately 70-80% of patients with AIL (60, 69, 101, 102) (See Table 2). One study incorporating interphase FISH analysis increased the number of aberrant chromosomes identified to 90% of patients and more than 40% of patients were noted to have oligo-clonal clones (101). Trisomies 3 and 5 and an additional X chromosome are the most frequent cytogenetic abnormalities detected in AIL patients and complex karyotypes are common (60, 69, 101, 103). Fifty to seventy-five percent of patients with AIL will have trisomy 3 and/or trisomy 5 clones (60, 104). In a retrospective cytogenetic analysis of 50 patients with AIL, the presence of complex karyotype was associated with inferior survival in multivariate analysis (105). Other potential mechanisms of lymphogenesis such as downstream $p21^{(Waf1)}$ abnormalities either dependent or independent of p53 protein overexpression, (42, 106) and N-ras (107) have rarely been documented to be associated with AIL. Prospective studies are needed to confirm these results and to further explore potential proto-oncogenes involved in AIL.

4.3. Anaplastic large-cell lymphoma, T/null cell, primary systemic and cutaneous type

Primary systemic ALCL and primary cutaneous ALCL represent identical morphologic CD30+ entities, but they are clinically distinct diseases (108, 109). T-cell/null ALCL accounts for approximately 2.4% of all NHL (110). Studies applying Southern blot techniques to detect TCR gene rearrangements in ALCL have shown inconsistencies between TCR rearrangements and immunophenotype (111-115). More updated studies using PCR analysis for TCR rearrangements have demonstrated clonal rearrangements in most cases of T-cell and null-type ALCL (70-90%) with clonal β genes being more commonly detected than γ gene rearrangements (116-119). Furthermore, genotypic studies have improved the classification of the varied ALCL disease subtypes. Clonal rearrangements of the TCR in Histologically designated "B-cell ALCL" has rarely been documented confirming that "B-cell ALCL" is genetically different than T-cell ALCL and likely represent a variant of diffuse large, B-cell lymphoma (116, 120-122). Beginning in 1988, it was demonstrated that ALCL is associated with the chromosome translocation t(2;5) (123-126). This nonrandom t(2;5) chromosome translocation has been cloned and is known to cause the fusion of the nucleophosim (NPM) gene located at 5q35 to the gene at 2p23 encoding the receptor tyrosine kinase anaplastic lymphoma kinase (ALK) resulting in the fusion protein NPM-ALK (127-131) (See Table 3). The transcription of the 80-kd chimeric fusion protein NPM-ALK (also known as p80) results as a consequence of the ALK gene coming under the control of the NPM promoter (132-135). Further characterization of the properties of NPM, ALK and NPM-ALK has been described in detail elsewhere (109). The presence of NPM-ALK may be detected by RT-PCR (129, 136-139) and FISH techniques (140, 141), but there are limitations to these tests such as they are relatively labor intensive. Polyclonal (ALK11) and monoclonal (ALK1 and ALKc) antibodies specific for the ALK portion of the molecule have been established that stain both the cytoplasm and nucleus in tissues containing the NPM-ALK translocation, which is documented in approximately 50-90% of primary systemic ALCL cases (131, 133, 142, 143). When heterogeneous patient populations are analyzed, the prevalence of ALK-positivity in primary systemic ALCL cases is 50-60% (144, 145). Several series have documented that up to 30% of ALK-positive ALCL cases are found to be negative for the t(2;5) translocation, suggesting that other fusion proteins and chromosome translocations are involved with the 2q23 ALK gene other than NPM (131, 142, 146-148). Other fusion partners to the ALK gene include non-muscle tropomyosin (TPM3) forming t(1;2)(q21;23) creating the chimeric protein TPM3-ALK (135, 149-152), tropomyosin receptor kinase-fused gene (TFG) forming t(2;3)(p23;q21) resulting in the TFG-ALK protein (135, 152, 153), clathrin heavy polypeptide-like gene (CLTCL) forming t(2;22) resulting in the CLTCL-ALK protein (154) and 5-aminoimidazole-4-carboxamide-1-beta-D-ribonucleotide-transformylase/inosine-monophosphate- cyclohydrolase enzymatic activities (ATIC) caused by the inversion(2) (p23;q35) resulting in ATIC-ALK (155-159) (See Table 3). The determination of ALK-positivity is important as it denotes a significant favorable

prognosis with reported 5-year overall survival rates of 71-80% versus 15-46% for ALK-negative ALCL cases when treated with anthracycline-based therapy (133, 144, 148). Moreover, the prognosis for ALK-positive and ALK-negative ALCL groups may be further divided based on CD56 positivity (neural cell-adhesion molecule), which portends a significantly worse outcome when it is expressed in either ALCL subgroup (145). ALK-positive ALCL is typically diagnosed in men prior to age 40 with frequent systemic symptoms, extranodal and advanced stage disease (148). Of note, the t(2;5) (p23;q35) translocation does not appear to be involved in the molecular pathogenesis of primary cutaneous ALCL or lymphomatoid papulosis as it is rarely detected in these diseases (160-163). The prognosis for primary cutaneous ALCL is overall excellent (164-166). Furthermore, there appears to be significant clinico-pathologic and genotypic overlap between primary cutaneous ALCL and the benign entity of lymphomatoid papulosis (167-170). The expression of the ALK gene is not confined to ALCL thus decreasing the positive predictive value of this testing. Other disease entities that rarely express the ALK gene include neuroblastoma, rhabdomyosarcoma and inflammatory myofibroblastic tumors (127, 142, 171-173). Furthermore, the detection of t(2;5) and/or chimeric ALK-protein has been reported in other lymphomas, but this remains a controversial topic (142, 148, 174-176). There are also reports of the detection of ALK genes in non-neoplastic and "normal" peripheral blood cells (131, 177, 178). This data confirms that indiscriminate molecular testing should be avoided and this testing should be a compliment to a detailed clinical and histologic workup. Other mechanisms of oncogenesis in ALCL include apoptosis (179), hypermethylation (180), c-myc expression (181), and EBV infection (182-184). Furthermore, the NPM/ALK fusion protein has been demonstrated to constitutively activate the downstream phosphatidylinositol 3-kinase (PI3K)-Akt pathway suggesting that this pathway may be involved in the molecular pathogenesis of ALCL (185, 186). DNA gene array technology is recently being applied in an attempt to identify critical genes relevant to the initiation/progression of ALCL (187).

4.4. Subcutaneous panniculitis-like T-cell lymphoma (SCPTCL)

SCPTCL is a rare T-cell lymphoma with cytotoxic CD-8+ phenotype that infiltrates the subcutaneous fat causing erythematous to violaceous nodules and/or plaques and is often associated with a systemic hemophagocytic syndrome (188, 189). Histologic diagnosis is not precise for SCPTCL and may be associated with a broad morphologic differential diagnosis including erythema nodusum, lupus profundus, erythema induratum and benign lobular panniculitis (190). Genotypic studies are often critical in confirming a neoplastic diagnosis (191, 192). Moreover, a controversial entity known as cytophagic histiocytic panniculitis (CHP) has been described as an inflammatory disease (also often associated with hemophagocytic syndrome) with possible connection to SCPTCL (193, 194). CHP is a disease that has been recognized to have diverse outcomes ranging from indolent to aggressive/fatal clinical courses (193-195). PCR gene rearrangement studies have recently demonstrated that CHP is likely part of the same clinicopathologic spectrum of SCPTCL, with SCPTCL representing a neoplastic clonal process, while CHP represents pre-malignant lymphoid disease (191, 194, 196). Gonzalez *et al* first documented in 1991 a subcutaneous T-cell lymphoma associated with hemophagocytic syndrome and β-TCR chain clonality (197). Since then, numerous small case reports have documented the entity of SCPTCL and it has been recognized as a separate T-cell lymphoma in the REAL and current WHO classification (198-204). Most of these case reports demonstrated a monoclonal TCR (commonly γ-gene rearrangement) and many cases were EBV positive (See Table 2). Retrospective case series with somewhat larger patient numbers have corroborated the clonality of TCR in the majority of cases of SCPTCL, but have not validated an association with EBV (188, 191, 192, 205). Kumar *et al* study of 16 cases of SCPTCL showed 8 of 9 cases had clonal TCR-γ gene rearrangements while 10 cases were negative for EBV sequences (188). Moreover, molecular usage studies of TCR γ-gene segments in SCPTCL have demonstrated that the Vγ2 gene is primarily expressed (192, 205-207). This is in contrast to other T-cell lymphomas such as hepatosplenic lymphoma where the Vγ1 gene is preferentially expressed (205, 207). The TCR-γ gene consists of 6 varied Vγ gene segments, although γδ T-cells express the Vγ1 or Vγ2 genes in approximately 95% of cases (22, 30, 207-209). It has been documented that normal γδ T-lymphocytes that reside in the intestine, spleen and thymus mainly express the Vγ1 gene, while normal γδ T-lymphocytes present in the skin, tonsils and peripheral blood primarily express Vγ2 genes (22, 206, 207). This indicates that γδ T-cell lymphomas such as hepatosplenic and SCPTCL are derived from local lymphoid tissue. This data may be potentially helpful not only for accurate diagnosis, classification and monitoring of minimal residual disease (MRD) with γδ T-cell lymphomas, but also may contribute to discovery of molecular directed therapies for these often difficult-to-treat diseases (192, 197, 210, 211). Chromosome abnormalities and proto-oncogenes associated with SCPTCL have been rarely reported in the literature. Mizutani and colleagues documented t(1;6)(11q;21p) in one patient with SCPTCL (212).

4.5. Hepatosplenic T-cell lymphoma (HSTCL)

HSTCL is an uncommon T-cell lymphoma that is seen mainly in young males (median age 35) presenting with B symptoms, prominent hepatosplenomegaly, mild anemia, neutropenia, thrombocytopenia (commonly severe), significant peripheral blood lymphocytosis, rare lymphadenopathy and is often associated with an aggressive clinical course (median survival 12 to 14 months) (213-216). Approximately 10-20% of HSTCL cases arise in immunocompromised patients, predominantly in the solid organ transplant setting (217). Similar to other T-cell lymphomas already discussed, detection of clonal TCR gene rearrangements may prove essential in establishing a diagnosis of HSTCL especially with complex histologic cases (210, 218). HSTCL likely arises from γδ T-cells of the hepatic sinusoids and splenic red pulp and

most cases of HSTCL are demonstrated to have clonal TCR γ-gene or δ-gene rearrangements with a cytotoxic T-cell phenotype (22, 205, 208, 210, 219, 220) (See Table 2). Moreover, the Vγ1 or Vδ1 genes are preferentially expressed in this disease reflecting in part the normal localization of γδ T-lymphocytes that reside in the spleen, intestinal tissue and thymus (205, 207, 215, 221). An αβ T-cell phenotype has been described with HSTCL (222-224). These infrequent αβ HSTCL cases interestingly occurred more commonly in women, but otherwise were characterized by similar clinicopathologic and cytogenetic features similar to γδ HSTCL. The primary recurrent chromosome abnormality in HSTCL demonstrated in many of cases is isochrome (i) 7(10q) (60, 213, 225-229), although not all series have documented i(7q) abnormalities in HSTCL (217, 230, 231). Furthermore, i(7q) is not specific for HSTCL as this karyotype has been reported in acute leukemia, prolymphocytic leukemia and Wilms' tumor (215, 232). Trisomy 8 has been frequently observed in HSTCL (60, 227-229). Other chromosome aberrations less frequently detected in HSTCL include deletion 11q, t(1;14)(q21;q13), der(21)t(7;21) and complex karyotype (215, 226, 230, 233). Abnormal expression of p21, p53 or other oncogenic gene pathways has not been identified in HSTCL (42, 234). Reports of associated EBV have been conflicting, but some reports have documented strong EBER-1 expression in cases of HSTCL (213, 222, 235). As previously discussed, a significant minority of HSTCL is recognized in post-transplant patients (217, 231, 236-241). Again conflicting results regarding EBV positivity in this post-transplant T-cell lymphoma population have been reported, but the majority of cases have not documented associated EBV or other viruses (231, 236, 237, 239, 241). Furthermore, post-transplant T-cell lymphoproliferative disorders typically do not respond to reduction in immunosuppression alone and often have a very aggressive clinical course with median survival commonly measured in weeks to months (217, 230, 242, 243).

4.6. Extranodal NK/T-cell lymphoma, nasal type

Extranodal NK/T-cell lymphoma-nasal type, formerly known as angiocentric lymphoma, is rare in Western countries being more prevalent in Asia and populations of Peru (244-246). It is designated "NK/T" secondary to the uncertainty of its cellular origin. Most molecular studies of this disease have included small patient numbers, but many studies have been reported. The rearrangement of TCR genes has been inconsistently identified in this disease, being described anywhere from 0 to 60% in various studies. (247-254). When present, γδ rearrangements are more common, while Ig rearrangements are germline (See Table 2). Studies have suggested that separation into distinct NK-cell and T-cell categories is feasible based on lineage-specific TCR rearrangements and immunophenotype (247, 251). Cytogenetic abnormalities are common in extranodal NK/T-cell lymphoma, nasal type. Most reports have identified deletions of chromosome 6 (q21~25) to be the most frequent recurrent cytogenetic abnormality (255-257). Siu and colleagues demonstrated consistent patterns of allelic abnormalities with loss of heterozygosity (LOH) at chromosome 6q in 91% of nasal lymphoma cases versus 50% of non-nasal NK lymphoma cases (258). Furthermore, they observed LOH at 13q in 33% of cases at presentation of disease, but in 100% of cases at relapse. A recent study by Ko *et al* documented frequent losses at 1p, 17p and 12q and gains at 2q, 13q and 10q with infrequent chromosome 6q aberration (253). Other reported non-random chromosome abnormalities include isochromes 6p, 1q, 17q and 7q, 11q aberrations, +X and +8 (256, 259) (See Table 2). Identification of oncogenes related to extranodal NK/T-cell lymphoma has been difficult, in part related to sufficient recovery of viable, non-necrotic tissue for appropriate analyses. p53 has been shown to be overexpressed in many cases of extranodal NK/T-cell lymphomas, nasal type (234, 246, 260). However, p53 mutations are much less frequently identified (234, 261, 262). Mutations of k-ras have been described in this lymphoma (79). Overexpression of p21 and p16 has been documented in NK/T-cell lymphoma, but the patterns of expression have been variable (234, 254, 261). It is not clear whether perturbations in p21 expression are directly involved in the pathogenic process. EBV may play a role in the oncogenesis of extranodal NK/T-cell lymphoma, nasal type. EBER-1 RNA transcripts are detectable in the majority of cells in nearly all cases (246, 249, 250, 253, 263). Moreover, EBV-latent membrane protein (LMP-1) is expressed in most cases (249, 264).

4.7. Enteropathy-type intestinal T-cell lymphoma (EITCL)

EITCL (also known as intestinal T-cell lymphoma) is a rare T-cell lymphoma of intraepithelial lymphocytes that commonly presents with multiple circumferential jejunal ulcers in adults with a prior brief history of gluten-sensitive enteropathy (265, 266). EITCL may present without antecedent celiac history, but most patients have abdominal pain and weight loss. Evidence of celiac serologic markers and/or HLA types such as anti-gliadin antibodies and DQA1*0501/DQB1*0201/DRB1*0304, respectively, may be present at diagnosis of EITCL (267, 268). Moreover, these genotypes may represent celiac patients at higher risk for development of EITCL (268, 269). EITCL accounts for less than 1% of NHL's according to the International Lymphoma Study Group and has been recognized to have a poor prognosis with reported 5-year survival and disease-free survival rates of 20% and 3% respectively (110, 265, 270). This is in part related to many patients presenting with poor performance status and varied complications of locally advanced disease by the time a diagnosis of EITCL has been confirmed. Moreover, EITCL may be a difficult diagnosis to establish on histologic grounds alone. Earlier diagnosis is warranted and molecular and genetic techniques may expedite the diagnosis of this disease when applied in the appropriate clinical circumstance, which would hopefully translate into improved long-term outcomes (271). The TCR genes are rearranged in nearly all cases of EITCL (more commonly γ than β) (272-276). Moreover, TCR gene rearrangements are often present in patients with EITCL who have evolved from sprue (273, 276-279). Daum and colleagues compared 8 patients with overt EITCL to 13 patients of celiac disease caused by a defined disorder, 3 patients with refractory sprue evolving into overt EITCL and to 2

patients with ulcerative jejunitis (272). They demonstrated clonal TCR-γ gene rearrangement with PCR in all resected jejunal specimens of the EITCL patients. Furthermore, 4 of 8 duodenal biopsy specimens from overt EITCL patients demonstrated positive clonality compared to 2 of 3 with refractory sprue evolving into overt EITCL, 2 of 2 with ulcerative jejunitis (a disease associated with increased risk for development of EITCL)(280), 1 of 6 with refractory sprue and no patients with sprue caused by a defined disorder. Chromosomal aberrations have not been reported with EITCL (See Table 2). One report documented that 22 of 23 EITCL tumors stained for p53 with 9 of 19 cases studied having collections of small lymphocytes in the affected bowel expressing p53 (273). The role of p53 in the oncogenesis of EITCL is not known. Varied reports have documented EBV positivity (by PCR and FISH with EBER-1 analysis) in association with EITCL including cases of EBV-related EITCL PTLD suggesting a possible etiologic role of EBV in the pathogenesis of EITCL (281-289). Furthermore, analysis comparing the prevalence of EBV in Mexican versus European EITCL cases demonstrated that there are significant epidemiologic differences in EBV association (100% versus 10%, respectively) (288, 289).

5. CONCLUSIONS

A significant amount of data has been accumulated in the last decade regarding the molecular biology of T-cell lymphoma. Characterization of clonal TCR gene rearrangements has often allowed earlier detection of T-cell lymphoma and specific gene patterns may correlate with prognosis. Gamma-delta TCR clonality now represents the more common TCR rearrangement in SCPTCL, HSTCL, extranodal NK/T-cell lymphoma, and EITCL, and when present often represent cases with more aggressive clinical courses. Improved molecular techniques such as RT-PCR and FISH have allowed documentation of recurring, non-random chromosome abnormalities such as deletion 6q in extranodal NK/T-cell lymphoma, nasal type, i7(10q) in HSTCL, complex karyotypes in PTCL-NOC, trisomies 3 and 5 in AIL and t(2;5)(p23;35) with systemic anaplastic T-cell lymphoma. Furthermore, identification of the relevant genes involved in the pathogenesis of T-cell lymphoma such as the NPM/ALK fusion protein, p53, cdk inhibitors (including p15, p16 and p21), and EBV as well as their interplay with the various regulatory pathways of cell cycle progression and apoptosis represent potential candidates for molecular based therapy. Identification of specific fusion products such as NPM-ALK will facilitate the production of targeted treatments such as anti-sense oligodeoxynucleotides and monoclonal antibody therapies directed towards specific fusion proteins. Gene therapy using adenoviral vector-mediated wild-type p53 gene transfer is being evaluated and may have application in certain T-cell lymphomas (290). Cdk modulators such as Flavopiridol, which broadly inhibit cdk's promote cell cycle block. Importantly, these agents can induce apoptosis and modulate transcriptional events regardless of bcl-2 or p53 status (291, 292). Other intracellular signaling pathways such as the protein kinase C modulating agents, UCN-01 and Bryostatin, are also being examined alone or in combination with cytotoxic chemotherapy in NHL (293-295). Strategies such as cDNA microarray analysis should also facilitate the molecular characterization of T-cell lymphoma to improve classification, prognostication and to aid in the discovery of targeted molecular therapy (296-298). Future molecular studies in T-cell NHL are likely to provide additional disease-specific molecular perturbations and chromosomal translocations with important diagnostic and therapeutic implications.

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