T and NK Cell Lymphomas

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T cell lymphomas are a heterogeneous group of neoplasms with different morphological patterns, phenotype and clinical presentations. These tumors account for about 10-15% of non-Hodgkin’s lymphomas in Western countries, but are more frequent in Asia. Historically, the classification of malignant lymphomas was based on histology, which included cytological features and growth patterns. The Kiel classification was the first to recognize some histopathological entities among T-cell neoplasms, with relatively well defined characteristics (Aagioimmunoblastic, lymphoblastic...). However, several studies have recognized the limitations of the morphology as the defining criteria for these entities. The use of phenotypic and molecular tools has proved to be essential in the diagnostic strategy. Unfortunately, till now, the primary molecular event involved in their pathogenicity is recognized in only a few entities such as the translocation involving ALK (anaplastic lymphoma kinase) in anaplastic large cell lymphoma. Thus, the phenotype, the site of origin, the clinical presentation, and the relationship with certain antigens (EBV, gliadin) seem to be very important aspects in the definition of these entities. It appears that these tumors may originate in different subsets of T (CD4, CD8, cytotoxic, α/β, γ/δ) or NK cells, sometimes tissue-specific. This has lead to the concept of clinicopathologic entities, which often are obviously organ-specific (ie mycosis fungoides, enteropathy-type, hepatosplenic, nasal NK/T). As for B-cell lymphomas, the concept of clinicopathologic entities has been introduced in the REAL classification, with a list of ‘T-cell and putative NK-cell neoplasms’, which has been slightly modified in the WHO classification (Table 1). Due to the phenotypic and functional properties shared by some cytotoxic T-cells and NK cells, the list includes T and NK cell tumors, some entities showing some diversity in term of cell lineage.

The clinical evolution of the patients with T-cell lymphomas is usually aggressive and the present therapeutic strategies are limited. It appears that therapies which have cured a significant proportion of other aggressive subtypes of lymphoma, such as diffuse large B-cell lymphomas, have proved to be less efficient in most peripheral T-cell lymphomas (PTCL). The heterogeneity of these tumors and their relatively low incidence are important difficulties in the assessment of more satisfactory protocols.

We will successively describe the different morphologic, biological and clinical aspects of the different entities. These are divided into precursor T-cell lymphoblastic neoplasm, with a thymic origin, and mature (peripheral, ie post-thymic) tumors. The latter comprises several entities which are divided into 3 groups according to their predominant leukemic, nodal or extranodal clinical presentation.

**PREDOMINANTLY LEUKEMIC T/NK CELL NEOPLASMS**

These are rare diseases. Their diagnosis is mainly based on combined cytologic and phenotypic features, not on histopathology. They will be only shortly described in this chapter.

**T-cell proymphocytic leukemia:**

On the basis of clinical features (splenomegal...
skin localizations), high number of circulating leukemic cells and cytogenetic data (recurrent abnormality on 14q32.1 involving the TCL-1 gene), this very rare entity comprises most, if not all, «lymphocytic» leukemia without azurophilic granules. On cytology, they are indeed heterogeneous including classical «prolymphocytic» and «lymphocytic» variants, and usually disclose a CD4 + phenotype. On histology, they disclose diffuse interstitial infiltration of the bone marrow, of the red and with pulps of the spleen.

**T-cell large granular lymphocytic (L.G.L.) leukemia:**

They constitute the most frequent entity among chronic lymphocytic leukemia. On blood smears, they show increase in the number of mature lymphocytes containing azurophilic cytoplasmic granules. Most cases have a CD 8 T αβ phenotype. The bone marrow infiltration is usually mild and better recognize using immunohistochemistry (CD3+, CD8+, TIA-1+, Granzyme B+). Clinically, splenomegaly is common, associated with neutropenia, sometimes in a context of auto-immune disease. The course is very indolent.

**NK-cell leukemia:**

NK-cell leukemia are very rare with a common monomorphic more or less «blastic» cytoplastic appearance and a phenotype and genotype of NK cells. Clinically, in addition to leukemic pictures and interstitial often moderate bone marrow infiltration, tumour involvement in extranodal sites (skin, digestive tract...) are common. The disease may be revealed by clinical (including severe B symptoms) and biological (cytopenia, increased ferritinemia and/or triglyceridemia) manifestations related to hemophagocytic syndrome.. EBV association is a comon finding. The clinical course is very aggressive.

**Adult T-cell leukemia/lymphoma (HTLV 1 +)**

This entity occurs in patients originating from endemic areas for the HTLV1 retrovirus (Japan, Caribbean...). From the time of viral infection to the occurrence of the lymphoma, there is a long latency (20 to 40 years). Clinical presentation is heterogeneous : besides the acute form characterized by leukemia, usually associated with hypercalcemia, the tumor can present with lymphadenopathies, skin and other tumour localizations. A smoldering form is described usually characterized by cutaneous involvement.

Morphological aspects are heterogeneous. The most characterizing feature is a pleomorphic tumor cell population with variable size cells showing lobated nuclei («flower cells»). They have a CD4 T-cell phenotype and strongly express CD25 (Il-2 receptor). Southern Blot analysis may be useful to demonstrate the clonal integration of the virus in neoplastic cells.

The prognosis is usually poor. However, it differs in chronic and acute forms of the disease. The use of α-Interferon and Zidovudine (AZT) in combination to chemotherapy improve the clinical course.

**PREDOMINANTLY NODAL PERIPHERAL T-CELL LYMPHOMAS**

Most PTCL present as nodal neoplasms. Among different morphologic types which can be recognized, they comprise 2 distinct and relatively frequent entities with clinical and biologic significance: Angioimmunoblastic T-cell lymphoma (AIL) and primary systemic Anaplastic Large Cell Lymphoma (ALCL).

**Angioimmunoblastic T-cell lymphoma (AIL)**

Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) was first described around 1972 by several groups giving different names (immunoblastic lymphadenopathy, angioimmunoblastic lymphadenopathy, lymphogranulomatosis X, etc). In 1979, Shimujama et al described AILD as being a T-cell lymphoma. It was thus called immunoblastic-like T-cell lymphoma. During the next
years, it was thought that AILD might be in part re-active and in part neoplastic. Molecular genetic studies for clonality documented around 10 years ago that the vast majority if not all cases of AILD are monoclonal T-cell proliferations. Thus it was concluded to designate this lesion as a peripheral node based T-cell lymphoma - « AILD-type T-cell lymphoma or angioimmunoblastic T-cell lymphoma ». To our experience, AILD represent one of the most frequent entity among T/NK cell neoplasms, accounting for about 25%-30% of peripheral T-cell lymphomas.

**Histopathology and Immunophenotype:**
Histologically, the major common features of AIL-type T-cell lymphoma are:
- the total effacement of the lymph node architecture, with frequent spreading throughout the lymph node capsule, but preservation of the peripheral sinuses;
- a proliferation of arborizing epithelioid venules frequently associated with PAS positive material;
- an admixture of non neoplastic cells (plasma cells, eosinophils, histiocytes or epithelioid cells), including an increase of follicular dendritic cells with large irregular networks recognized by staining with CD35, CD21, CD23, or CNA-42 antibodies; the presence of scattered large CD20+ B-cells (blasts) is very common;
- A variable neoplastic cellular content, with a predominance of small to medium sized lymphoid cells with often large clear cytoplasm. This tumour component is sometimes minimal and difficult to recognize on morphology alone. CD3 and/or CD5 stainings may be very useful, as well as the search for CD10 expression which has been recently shown as a characteristic feature of AIL. Depending on cases, a variable number of large cells is present and, occasionally, these cells may resemble Hodgkin and Sternberg-Reed cells.

**Morphologic variants :**
Besides the « classical » AIL as described above, morphologic variants have been recognized, such as AIL with hyperplastic follicles (also called « early phases »), « Epithelioid-rich » AIL, or « AIL with cytological features of progression to pleomorphic lymphoma », ie disclosing borderline features with the PTCL unspecified category. Some cases may show small or large sheets of large B-cells and even develop a diffuse large cell B-cell lymphoma, usually EBV-associated.

**Clinical features :**
The clinical manifestations of AIL-type lymphomas are relatively well known. Patients present with generalized polyadenopathies, skin rash, fever, and weight loss. Splenomegaly is frequent, as well as bone marrow involvement. Hypergammaglobulinemia and autoimmune biological manifestations are common. The clinical behavior is aggressive with a 30% 5-year overall survival rate despite aggressive chemotherapy. However, some patients may have a past history with ondulating lymph node enlargement, and spontaneous remissions during such episodes.

**Molecular studies, pathogenesis :**
The pathogenesis of this lymphoma is not clear. The inflammatory background and the follicular dendritic cell proliferation suggest the involvement of different chemokines. In cytogenetic studies, T-cell lymphomas of AIL-type show characteristic although not specific abnormalities like trisomy 3 and trisomy 5. The tumour originates from \( \alpha \beta \) CD4 T cells, most probably from a minor CD10+ mature T cell. In addition, the role of EBV has been postulated in view of the frequent –if not constant - positivity of EBV, detected by EBERs in situ hybridization. However, it is to note that EBV is only found in a few scattered, most often B-blasts, not in the (majority) of T cells which may rather reflects some degree of dysimmune regulation observed in these patients. In this regard, besides clonal T-cell population which is found in the majority of cases using PCR studies, small B-cell clones are present in a proportion (15-40%) of cases, specially among the EBV+ B cells. EBV could be implicated in the development of EBV-associated B-cell lymphomas occasionally observed in the course of the disease.

**Peripheral T-cell lymphomas, unspecified (PTCL, unsp)**
Around 30 to 40% of PCTL arising in lymph nodes would fall in the « unspecified » category, which is a heterogeneous group of T-cell lymphomas, without clear characteristic clinical, bilogical and cytogenetic features. It is likely that individual clinicopathologic entities will be delineated in the future from this broad group of malignancies.

**Histopathology and phenotype :**
On histopathology, PTCL unsp are characterized by a heterogeneous cellular composition. There is usually a mixture of small, medium and large atypical lymphoid cells. Cytological appearance is
very variable from case to case. An inflammatory background is frequent, although not constant, consisting of eosinophils, plasma cells, and histiocytes. They may show preferential involvement of the paracortical region of lymph nodes. The diagnosis relies on both morphology and immunohistochemistry using CD20 and CD3 antibodies. The latter demonstrates the T-cell phenotype (CD3+) of the neoplastic cells. Most cases have a mature T-cell phenotype, and express one of the major subset antigens: CD4> CD8. Deletion of one of the pan T-cell antigens (CD3, CD5, CD2, or CD 7) is seen in 75% of cases, with CD7 most frequently being absent. Different morphological aspects without clear clinical significance can be recognized:

**Morphologic variants:**
- most cases fall into the pleomorphic lymphoma category according to the Kiel classification, with a mixture of small, medium and large atypical lymphoid cells. Some of them may resemble Reed-Sternberg cells and may express CD30.
- Other rare cases correspond to lymphoepithelioid cell lymphoma (also referred as Lennert’s lymphoma), or to T-zone lymphoma.

**Clinical features:**
Clinically, PTCL unspecified present in adults. Most patients exhibit generalized lymphadenopathy, hepatosplenomegaly, and frequent bone marrow involvement. Constitutional symptoms, including fever and night sweats, are common. The clinical course is aggressive, although complete remission may be obtained with combination chemotherapy. However, the relapse rate is high and the overall survival is worse in PTCL than in B-cell lymphomas of comparable histologic grade.

**Anaplastic Large Cell Lymphoma (T and null cell types) (systemic)**
Anaplastic Large Cell Lymphoma (ALCL) (T and null cell types) is now a well recognized entity with defined morphology, phenotype, cytogenaics and clinical features. It accounts for about 20-30% of all adult PTCL. Despite some common morphologic and phenotypic (CD30) features, this entity is clearly distinct from the anaplastic subtype of diffuse large B-cell lymphoma, which are just considered as a morphologic variant of diffuse large B cell lymphomas.

**Morphology:** Several subtypes of T/null-cell ALCL, which are considered to represent variants of a morphological spectrum of the same entity, are recognized. Beside the “common-type”, they include a lymphohistiocytic form, a small cell variant, a rare giant cell-rich form and mixed subtypes. Whatever the subtype, a characteristic feature is the presence of a medium to large cell with an eccentric nucleus (horse-shoe or kydney shaped), nucleoli that are less prominent than in Reed-Sternberg cells and often eosinophilic Golgi region near the nucleus. These cells can realise a massive and diffuse infiltration by cohesive sheets of neoplastic cells. The typical intrasinusal infiltration is often more obvious at the periphery of a massive infiltrate. Neoplastic cells can also show a striking perivascular distribution.

**Phenotype and genotype** - The classic phenotype of these lymphomas is T or null cell type with expression of CD30 (in virtually all tumour cells), EMA and cytotoxic molecules (TIA1, Granzyme B). On the contrary, CD15 and EBV are negative. Extensive loss of T-cell antigens (CD2, CD3, CD5, CD7) are frequent. This argues for the fact that ALCL with a null-cell phenotype, in addition with their usual cytotoxic protein expression and TCR clonal gene rearrangement, correspond to tumours of T-cell origin. TCR gene studies show that most of the cases of T/null cell ALCL have clonal TCR gene rearrangement.

**Cytogenetic features** - Cytogenetic studies have shown the presence of a recurrent t(2; 5) (p23; q35) translocation. Interestingly, the latter was initially reported in malignant histiocytosis, and is now thought to be characteristic, although not entirely specific, of ALCL of T-and null-cell phenotype. This translocation creates a new chimeric gene composed of the nucleolar phosphoprotein gene, or nucleophosmin (NPM) on chromosome 5q35, and of the novel tyrosine kinase gene, called the anaplastic lymphoma kinase (ALK) gene on chromosome 2p23 and generates a novel protein. Recent data support the oncogenic properties of ALK rearrangement since retrovirus-mediated gene transfer of NPM-ALK has been shown to induce lymphomas in mice. The cloning of the breakpoint has provided new molecular probes to demonstrate this translocation using Southern blot and polymerase chain reaction (mostly RT-PCR) techniques. Variant translocations implicating the Alk gene but not the nucleophosmin partner.(ie t(1;2) translocation,...) are observed in about 20% of cases. Whatever the variant translocation, it induces overexpression of ALK protein, which can also be detected using antibodies, which have been produced against the cytoplasmic kinase domain of ALK (ALK-1, ALK-c).
Although ALK is expressed in some normal tissues, recent studies indicate that its expression in lymphoid cells can be regarded as a reliable method for detecting ALK rearrangement, even in routinely fixed tissues. Altogether, these techniques are of great diagnostic value, specially for the differential diagnosis with Hodgkin's disease. Several studies indicate that ALK expression, which is present in about 50-80% of T/null cell ALCL, could be more frequent in young patients and related to a better prognosis.

**Clinical features -** ALCL of T- and null-cell type appear to be frequent in children and young adults. T- and null-cell types ALCL bear peculiar clinical features. There is evidence to separate forms with a single primary cutaneous presentation (see above) from primary systemic ALCL. Typically, the systemic form has a bimodal age distribution, involves lymph nodes and/or extranodal sites (including but not limited to skin), has frequent B symptoms and is spontaneously clinically aggressive. Despite aggressive clinical features, several studies show that ALCL of T- and null-cell phenotype have a better prognosis than other peripheral T-cell lymphomas and can be cured with conventional polychemotherapy regimen.

**Putative normal counterpart -** Based on the fact that ALCL are composed of tumor cells that have reached the activation state defined by the CD30 antigen, CD30+ ALCL have been proposed to represent the neoplastic counterpart of large lymphoid T cells which are preferentially localized around B-cell follicles in reactive lymph nodes. Both normal interfollicular CD30+ cells and anaplastic lymphoma cells, have usually a CD4 phenotype and frequently express bcl-6.

**EXTRANODAL AND T/NK CELL LYMPHOMAS**

Extranodal T and NK cell lymphomas are relatively rare diseases, with the important exception of high frequency of nasal-type NK/T cell lymphomas in Asian populations. They comprise several recently recognized clinicopathologic entities which were included in the REAL classification as distinct or provisional entities. Among them, angiocentric lymphoma was renamed «nasal NK/T-cell lymphoma» following a recent workshop. It appears that several entities are defined by their site of origin, their clinical features, their cell origin and/or their possible association with some antigen, whereas morphology is not specific.

**Mycosis fungoides (MF), Sézary syndrome**

MF is the most common subtype among primary cutaneous lymphoma. MF is an epidermotropic cutaneous T-cell lymphoma characterized by a proliferation of small or medium-sized T-lymphocytes with cerebriform nuclei showing, typically, epidermotropic and band-like infiltration of the papillary dermis. Neoplastic cells are CD3+, CD4+ αβ T cells. Clinical features are characteristic and important for the diagnosis: indolent course with slow progression over years from patches to more infiltrated plaques, and eventually tumours (tumour stage). Lymph nodes can become involved.

**Sézary syndrome, which is strongly similar to MF on histology and phenotype,** is a peculiar form characterized by erythroderma, generalized lymphadenopathy and the presence of a substantial number of neoplastic T-cells in the blood. Clinical behavior is aggressive.

**Primary cutaneous anaplastic large cell lymphoma**

Primary cutaneous anaplastic large cell lymphoma is now considered as a clinicopathologic entity, distinct from the classical systemic ALCL, although showing many similar histologic and phenotypic features. It occurs usually in adults and is characterized by a unique skin involvement (usually solitary nodule or tumour), a proliferation in the dermis of large CD30+ “anaplastic” cells (sometimes with some epidermotropism), a T-cell phenotype with frequent expression of cytotoxic molecules, the common expression of the cutaneous lymphocyte antigen (CLA, HECA), an indolent course with possible spontaneous regression, and a probable overlapping with lymphomatoid papulosis. This tumour does not show EMA expression, as well as the t(2; 5) translocation or its consequence on ALK expression.

**Nasal and “nasal type” NK/T cell lymphomas**

They mostly present as a localized disease in the nasal cavity, maxillary sinuses or palate. These lymphomas are characterized by:

- a more or less pleomorphic lymphoid proliferation (cytological spectrum from rather monomorphic small/medium-sized to large cell lymphoma with anaplastic features) with frequent features of angioinvasion and angiocentrism, and common extensive necrosis. The latter can explain the diagnostic difficulties on small biopsies.
- a phenotype (CD2+, CD3ε+/CD3complex-, CD5-, CD56+, TCR-) and a genotype (absence of rearrangement of the T-cell receptor genes) in agreement with NK cell origin,
- a common expression of cytotoxic (TIA1+, perforin+, granzyme B+) proteins,
- a striking association with EBV found in the majority of neoplastic cells.

Clinically, some of the patients may show the dramatic features of » lethal midline granuloma ». Most studies indicate a poor prognosis with a tendency to involve other extranodal sites (skin, gastrointestinal tract). The extensive necrosis characteristic of these lymphomas has been attributed to angioinvasion by tumor cells, as well as upregulation of chemokines and cytokines, such as TNF-α, NFκB, Mig and IP-10. Cytogenetics studies suggest an association to a recurrent 6q abnormality.

A few recent studies have pointed out the existence of nonnasal lymphomas that are morphologically, phenotypically and biologically very similar to the nasal NK/T cell lymphomas. Such cases can present with major intestinal tumors or other extranasal manifestations. They disclose common features with nasal NK cell lymphomas, i.e. angiocentrism and angioinvasion. EBV association in most tumor cells, and a NK cell immunophenotype. Due to the marked similarity with typical nasal NK/T cell lymphoma, it is proposed to refer them to as » nasal-type NK/T cell lymphoma ».

**Enteropathy-type T-cell lymphoma (ETL).**

Peripheral T-cell lymphoma may arise in the small intestine. Some of these are associated with malabsorption and appear to be a complication of coeliac disease or gluten-sensitive enteropathy and are called »enteropathy-type intestinal T-cell lymphoma » (ETL). Many data support the fact that ETL constitutes a distinct clinicopathologic entity, which presents as multiple jejunal tumours or ulcers, and is commonly revealed by intestinal perforation. Other sites of involvement in the gastrointestinal tract, and other mucosa (lung, breast...) have been reported.

ETL exhibits a morphological spectrum. The most characteristic appearance is that of pleomorphic tumour, but histology is often complicated by the presence of necrosis and a large inflammatory component. The demonstration of the presence of atypical T-cells may require immunohistochemistry. The presence of intraepithelial tumour cells is very characteristic. ETL is typically associated with villous atrophy and increase in intraepithelial lymphocytes. However, these features may be lacking, specially when the patient is on a gluten-free diet or when the tumour occurs in the distal small intestine.

ETL is derived from intraepithelial cytotoxic lymphocytes as supported by their CD103 (HML-1/αβ7) phenotype. It shows expression of TIA-1, Perforin and Granzyme B molecules indicating their derivation from activated cytotoxic cells. The great majority of the reported cases have an αβ T-cell origin although rare gd cases have been reported. They can be CD4 -/CD8-, CD8+ or even CD4 +.

Different data support the role of gliadin hypersensitivity in the pathogenesis of the disease, specially the strong association with coeliac disease and the in vivo demonstration of increasing and activation of intraepithelial lymphocytes in coeliac disease. In addition, the HLA types of patients with coeliac disease and ETL are identical. The disease occurs in adults, often with a history of gluten-sensitive enteropathy or malabsorption, or in patients with asymptomatic villous atrophy. However, no clinical evidence of enteropathy is found in a number of intestinal T-cell lymphoma. In these cases, it is difficult to conclude a definitive diagnosis of ETL. The search for villous atrophy, an increase of intraepithelial lymphocytes in adjacent mucosa, a specific CD103 phenotype on fresh tissue and the absence of EBV are important features for the diagnosis of ETL, as well as the demonstration of specific (anti-endomysium,...) antibodies.

Overall, the prognosis is poor. Common sites of dissemination include mesenteric lymph nodes and, at a lower extend, spleen, liver, bone marrow and other extranodal sites such as skin or lung.. It must be noted that chronic ulcerative jejunitis which is another recognized complication of coeliac disease appears to be a condition closely related to ETL. This is supported by the recent finding of T-cell clonality in ulcerative jejunitis and by the observation that patients with ulcerative jejunitis may later develop ETL.

**Panniculitis-like subcutaneous T-cell lymphoma**

It is a rare entity which typically presents on the extremities or trunk with multiple subcutaneous masses. On histopathology, the lesion simulates a panniculitis with a mixture of neoplastic T (CD3+) cells of various sizes and benign macrophages. Tumour cell necrosis, karyorrhexis, and erythropagocytosis are frequent. Nearly all cases are cytotoxic CD8+ expressing the cytotoxic molecules...
TIA-1, granzyme B and perforin. Most are derived from α/β T-cells but a γ/δ origin is likely in approximately 25% of cases.

Nodal involvement is rare, either at presentation or during the course of the disease. A hemophagocytic syndrome is a common complication in up to two-thirds of patients and may result in the patient’s death. The hemophagocytic syndrome is most likely secondary to cytokine production by neoplastic cells. The prognosis seems poor, despite aggressive chemotherapy.

**Hepatosplenic (γ/δ) T-cell lymphoma**

This rare lymphoma entity has very peculiar clinical, morphological and phenotypic features. It occurs mainly in young adults, presenting with splenomegaly and hepatomegaly, but without lymphadenopathy. B symptoms are frequent. Thrombocytopenia is a constant feature. The neoplastic cells are monomorphic medium-sized, and located preferentially in the sinuses of the liver, the cords and the sinuses of the red pulp of the spleen and the sinuses of the bone marrow. The latter sinusal marrow infiltration, which often requires immunohistochemistry for its demonstration, is a very useful diagnostic criteria. They display a CD3+, CD5-., CD2+, usually CD4-/CD8-, often CD56+ phenotype and typically derive from γδ T cells (BF1-, TCRd1 +) which show a preferential distribution in the splenic red pulp. Very recently, rare similar cases with an αβ phenotype have been described. Another characteristic feature is the non activated cytotoxic profile (TIA-1+, perforin-, granzyme B-) of the γ/δ neoplastic cells. Cytogenetic analysis show a frequent association with isochromosome 7q. Some cases are found in patients with a context of immune defect, especially following organ transplantation. The disease has a highly aggressive course despite the use of intensive chemotherapy regimen.

**CONCLUSION**

Several clinicopathologic entities can now be recognized on the basis of combined morphology, phenotype and clinical informations. Within a single disease entity, there is often a morphologic spectrum. For some entities, clinical features appear to be of major importance in defining T-cell and NK-cell neoplasms, and in some cases the clinical syndrome may be more important than the precise cell of origin. In spite of the poor prognosis of most PTCL, the new classification system (WHO) has clinical, biological and prognostic value. Thus, ALCL appear to have a better prognostic than other PTCL. Several diseases appear to represent models of lymphomagenesis developed from tissue-restricted cytotoxic cells which have important functions in immune surveillance. However, to date, only a few cytogenetic abnormalities involving oncogenes (TCL-1, ALK) have been identified. Future classic and molecular, including DNA arrays, studies may help to localize new genes important for T-cell lymphomagenesis. Advances in the pathogeny of these PTCL entities could provide tools for the development of new therapies which are needed to improve the overall poor prognosis of T/NK cell neoplasms.

**SELECTED REFERENCES**


