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Cytogenetics in the management of mature T-cell and NK-cell neoplasms: Guidelines from the Groupe Francophone de Cytogénétique Hématologique (GFCH)

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ABSTRACT

Mature T-cell and natural killer (NK)-cell neoplasms (MTNKNs) are a highly heterogeneous group of lymphomas that represent 10–15 % of lymphoid neoplasms and have usually an aggressive behavior. Diagnosis can be challenging due to their overlapping clinical, histological and immunophenotypic features. Genetic data are not a routine component of the diagnostic algorithm for most MTNKNs. Indeed, unlike B-cell lymphomas, the genomic landscape of MTNKNs is not fully understood. Only few characteristic rearrangements can be easily identified with conventional cytogenetic methods and are an integral part of the diagnostic criteria, for instance the t(14;14)/inv(14) or t(X;14) abnormality harbored by 95 % of patients with T-cell prolymphocytic leukemia, or the *ALK* gene translocation observed in some forms of anaplastic large cell lymphoma. However, advances in molecular and cytogenetic techniques have brought new insights into MTNKN pathogenesis. Several recurrent genetic alterations have been identified, such as chromosomal losses involving tumor suppressor genes (*SETD2, CDKN2A, TP53*) and gains involving oncogenes (*MYC*), activating mutations in signaling pathways (JAK-STAT, RAS), and epigenetic dysregulation, that have improved our understanding of these pathologies. This work provides an overview of the cytogenetics knowledge in MTNKNs in the context of the new World Health Organization classification and the International Consensus Classification of hematolymphoid tumors. It describes key genetic alterations and their clinical implications. It also proposes recommendations on cytogenetic methods for MTNKN diagnosis.

1. Introduction

Mature T-cell and natural killer (NK)-cell neoplasms (MTNKNs) constitute a highly heterogeneous group that accounts for 10–15 % of non-Hodgkin lymphomas and usually exhibits an aggressive course with poor prognosis. The fifth world health organization (WHO) classification of Hematolymphoid Tumors (WHO-HAEM5) recognizes more than 30 entities [1]. According to their presentation, MTNKNs can be divided into nodal, extranodal, cutaneous, and leukemic types. Currently, MTNKN diagnosis is based on histopathological and immunophenotypic findings, with little contribution by genomic data. Indeed, in MTNKN, the classical cytogenetic investigations are difficult due to the low proliferative rate resulting in low mitotic index and karyotyping failure. When successful, complex and heterogeneous karyotypes are commonly observed, without specific chromosomal abnormalities (CAs), except for some neoplasms, such as T-cell prolymphocytic leukemia (T-PLL) and anaplastic large cell lymphoma (ALCL). In the other MTNKN types, the genomic alteration complexity makes difficult to determine the precise contribution of individual CA and their role in the disease pathophysiology [2]. Nevertheless, recent technical advances, including chromosomal microarray (CMA) and next-generation sequencing (NGS), have allowed a more detailed analysis of the genetic, epigenetic, and transcriptional changes in rare T-cell lymphomas with primary cutaneous or intestinal localization. These novel findings improve our understanding of MTNKN tumorigenesis.

Here, we report the main cytogenetic data and gene mutations described in MTNKNs that help to reach an accurate diagnosis and risk stratification. We also provide cytogenetic guidelines and technical recommendations.

Cytogenetics and main molecular alterations in mature T-cell and NK-cell neoplasms

Table 1 summarizes the frequency, characteristics, and potential clinical relevance of CAs detected in MTNKNs.

2. Nodal peripheral T/NK-cell lymphomas

2.1. Systemic anaplastic large cell lymphoma

ALCL is a rare T-cell/null neoplasm that strongly expresses the activation marker CD30 and includes systemic ALK-positive ALCL (ALK^+ sALCL), systemic ALK-negative ALCL (ALK^-sALCL), primary cutaneous ALCL (pcALCL, see chapter on primary cutaneous T-cell lymphomas) and breast implant-associated ALCL (BIA-ALCL).

2.1.1. ALK^+ sALCL

ALK^+ sALCL represents less than 2 % of non-Hodgkin lymphomas

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Table 1
Characteristics of recurrent cytogenetic abnormalities in T/NK-cell lymphomas.

Pathology	Abnormalities	Frequency	Target genes	Commercial FISH probe(s)	Main associated features	Main associated gene mutations[a]	References
ALK-positive systemic anaplastic large cell lymphoma (ALK^{+} sALCL)	t(2;5)(p23;q35)	80 %	*NPM1::ALK*	ALK	Diffuse ALK staining (cytoplasmic, nuclear)		[4–6]
	t(1;2)(q25;p23)	15 %	*TPM3::ALK*	ALK	Cytoplasmic ALK staining		
	t(2;v)(p23;v)	5 %	*v::ALK*	ALK	Cytoplasmic and/or cell membrane ALK staining		
	+2q, +7p, +17p, +17q, del(4q), del (11q), del(13q)	10–20 %/each	unknown				
ALK-negative systemic anaplastic large cell lymphoma (ALK^{-} sALCL)	*DUSP22* (6p25) rearrangement	20–30 %	*DUSP22::mir29b* t(6;7) (p25;q32)	DUPS22	Typical morphological features		[10]
	TP63 (3q28) rearrangement	2–8 %	Mostly *TBL1XR1::TP63* inv(3)(q26q28)	TP63/TBL1XR1	Poor prognosis (OS) Non-specific marker of ALK- ALCL		[16]
	+1q, del(6q), del(13q), del(17p)	30–35 %/each	*PRDM1* (6q21), *TP53* (17p13)	TP53			[5,7]
	+5q, +6p, +7p, +7q, +8q, +12q, +17q, del(4q), del(11q)	15–20 %/each	unknown				
Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)	del(20q) (CMR : 20q13.13)	66 %	unknown				[21]
Nodal T-follicular helper (TFH) cell lymphoma	t(5;9)(q33;q22)	17 %	*ITK::SYK*				[23,24]
Nodal TFH cell lymphoma angioimmunoblastic-type	+*X*, +3, +5, +19, +21, del(6q)	50 %	unknown		Combined in low CK (≤5 CA) Co-occurrence of +5 (43 %) and +21 (23 %) with *IDH2 R172* variant		[2,25,26]
Peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS)	+7/+7q	48 %	unknown			**PTCL-GATA3 subgroup**	[32]
	+8/+8q	45 %	*MYC* (8q24)	MYC		*TP53* (29 %)	
	+17q	52 %	*STAT3* (17q21)			**PTCL-TBX21 subgroup**	
	del(5q)	39 %	unknown			Epigenetic regulators	
	del(6q)	23 %	*PRDM1* (6q21)			(*TET1, TET3, DNMT3A*)	
	del(9p)	30 %	*CDKN2A/2B* (9p21)	CDKN2A	Unfavorable prognosis (OS)	(36 %)	
	del(10q)	35 %	*FAS* (10q23), *PTEN* (10q23)				
	del(13q)	42 %	*RB1* (13q14)	RB1			
	del(17p)	70 %	*TP53* (17p13)	TP53	Co-occurrence with del(6q), del(9p) and del(10q)		
T-cell prolymphocytic leukemia (T-PLL)	t(14;14)(q11;q32) inv(14)(q11q32)	39–70 %	TRA-TRD::*TCL1A/B*	TCL1,TCRA	Disease hallmark Same rearrangements as in ataxia	*JAK3* (30 %) *STAT5B* (21–36 %)	[35,37,40]
	t(7;14)(q34;q32)	<1 %	TRB::*TCL1A/B*	TCL1,TCRB	telangiectasiaDisease hallmark	*SAMHD1* (20 %)	[39]
	t(X;14)(q28;q11)	3–20 %	TRA-TRD::*MTCP1*	TCRA	Same rearrangements as in ataxia telangiectasia		[43]
	t(X;7)(q28;q34)	<1 %	TRB::*MTCP1*	TCRB			
	+8q	67 %	*AGO2* (8q24)	MYC	i(8)(q10), +8, unbalanced translocations, r(8)		[46,47]
	del(11q)	37–57 %	*ATM* (11q22)	ATM	Bi-allelic inactivation by mutation on the second allele (77 %)		[35,44]
	CK (≥3CA)	70–90 %			Unfavorable prognosis (OS) if HCK (≥5CA)		[35,44]

(*continued on next page*)

Table 1 (*continued*)

Pathology	Abnormalities	Frequency	Target genes	Commercial FISH probe(s)	Main associated features	Main associated gene mutations[a]	References
Adult T-cell leukemia/ lymphoma	CK	Up to 100 %			Aggressive type (80–100 %), Indolent type (0–33 %) Unfavorable prognosis (OS)	**Indolent type** *STAT3* (40 %) **Aggressive type**	[61]
	CD28 gain/amplification	28 %	*CD28* (2q33)		Unfavorable prognosis (OS) in indolent types	*TP53* (20 %) *IRF4* (20 %)	[59]
	CDKN2A deletion	40–50 %	*CDKN2A* (9p21)	CDKN2A			[62]
	CD274 (*PD-L1*) amplification	10–20 %	*CD274 (PD-L1)* (9p24)	CD274/ PDCD1LG2	Prognostic impact (OS) in both aggressive and indolent types		[58,62]
Sézary syndrome	+8/8q, +17q, del(17p), del(10q)	50–70 % each	*MYC* (8q24), *STAT3/5* (17q21), *TP53* (17p13)	TP53, MYC		*TP53* (41 %) *CD28* (23 %)	[63,64]
	del(1p)	63 %	*ARID1A* (1p36.1)		Focal deletion	*DNMT3A* (23 %)	
	del (9p)	40 %	*CDKN2A* (9p21)	CDKN2A	Focal deletion	*PLCG1* (23 %)	
Mycosis fungoides	+7p, +7q, +17q, del(9p), del(10q), del (13q)	30–50 % each	*STAT3/5* (17q21), *CDKN2A/B* (9p21)	CDKN2A			[64,67,68]
Primary cutaneous anaplastic large cell lymphomas	t(2;v)(p23;v)	2 %	*v::ALK*	ALK			[69,70,73]
	DUSP22 (6p25) rearrangement	30 %		DUPS22			
	+1p	25 %	*TNFRSF8* (1p36.2)		Focal gain		
	+7q	50 %	*EZH2* (7q36)		Focal gain		
	del(6q)	50 %	*PRDM1* (6q21)		Focal deletion		
Lymphomatoid papulosis	*DUSP22* (6p25) rearrangement	5 %		DUPS22			[71]
Hepatosplenic T-cell lymphoma	i(7q)	Up to 62 %	*ABCB1* (7q21), *PPP1R9A* (7q21)	7q22/7q31 probe	+8	*STAT5B* (33 %) *SETD2* (25 %)	[74]
	+8	Up to 50 %	unknown	cen8			[76]
	+1q	13 %	unknown				[79]
	del(10p)	19 %	unknown				
Indolent T-cell lymphoma of the gastrointestinal tract	t(9;17)(p24;q21)	Depending on the phenotype	*STAT3::JAK2*	JAK2	25–80 % in CD4+ forms Absent in CD8+ forms	*STAT3* (30 %) *KMT2D* (20 %)	[84,85]
Enteropathy-associated T-cell lymphoma	+9q (CMR : 9q33q34.1)	46–80 %	*NOTCH1* (9q34)	ASS1		*JAK1* (20 %)	[87,88,90, 94]
	+1q	16–20 %	unknown		Up to 94 % in RCDII without association with +9q	*STAT3* (20 %)	
	+5q (CMR: 5q34–35.2), +7q, del(8p) (CMR : 8p22–23.2), del(9p), del(13q), del(16q)	15–30 % each	unknown				
	CK (≥3CAs)	68 %			Unfavorable prognosis (OS)		
Monomorphic epitheliotropic intestinal T-cell lymphoma	+9q	58–77 %	unknown	ASS1		*SETD2* (77–96 %)	[95,96]
	+7q, +19q, del(7p), del(8p), del(18p)	33–75 % each	unknown			*JAK3* (33–67 %)	
	+8q	20–70 %	*MYC* (8q24)	MYC	Associated with *TP53* mutations	*STAT5B* (33–60 %)	[98,100]
	t(8;v)(q24;v)	4–6 %	*MYC* (8q24)	MYC			
EBV-positive extranodal NK/T-cell lymphoma	del(6q)	17–27 %	*PRDM1* (6q21)		Associated with TSIM subtype	*DDX3X* (14–44 %)	[103,104, 106]
	del(17p)	10 %	*TP53* (17p13)	TP53		*STAT3* (22 %)	
	+1q, +2q, +9p,+17q	10–17 % each	*JAK2* (9p24), *STAT3/5* (17q21)		Associated with TSIM type (+9p, +17q)	*TP53* (11–12 %)	

Abbreviations: CK, complex karyotype; OS, overall survival; CA, cytogenetic abnormality; CMR: Critical Minimal Region, RCDII: Refractory celiac disease type II, TSIM: tumor-suppressor/immune-modulator subtype.

[a] Main associated gene mutations (>20 % of patients) or classifying gene: molecular markers that may help to reach a diagnosis.

and is more frequently diagnosed in children and young adults. In children, ALK$^+$ sALCL is the most common T-cell lymphoma subtype (20–30 % of cases). ALK$^+$ sALCL generally has a good prognosis. *ALK* rearrangements are theranostic markers, potentially targeted by crizotinib, an inhibitor of ALK, ROS1, and MET receptor tyrosine kinases, in refractory or relapsed patients ALK$^+$ sALCL [3]. The t(2;5)(p23;q25) translocation is observed in ~80 % of cases; it leads to the *NPM1::ALK* fusion transcript that results in the constitutive activation of the ALK kinase. *ALK* (2p23) can also be fused with other partner genes, including *TPM3* (1q25) (15 %), and less frequently *ATIC* (2q35), *CLTC* (17q23), *TPM4* (19p13), *TFG* (3q12), *RNF213* (17q25), *MYH9* (22q12), *MSN* (Xq12), or *TRAF1* (9q33) [4]. Using CMA, recurrent additional chromosomal aberrations (ACAs) are reported in 58 % of cases, including loss of 4q, 11q, 13q, and gain of 17p, 17q, 2q and 7p [5]. The *NPM1::ALK* fusion transcript has been associated with diffuse (cytoplasmic, nuclear, and nucleolar) ALK staining in cancer cells. Conversely, cytoplasmic and/or cell membrane ALK staining have been observed in samples harboring other *ALK* fusion events [6].

2.1.2. ALK$^-$ sALCL

ALK$^-$ sALCL occurs in older patients (40–70 years) and displays a more aggressive course than ALK$^+$ sALCL. In ALK$^-$ sALCL, recurrent chromosomal imbalances identified using CMA include gain of 1q, 17q, 5q, 6p, 8q, 12q, 7p, 7q, and loss of 4q, 6q, 11q, 13q and 17p. The most common deletions are 6q21 (*PRDM1*) and 17p13.3p12 (*TP53*) [5,7].

Recently, two novel rearrangements that target *DUSP22* (6p25) and *TP63* (3q28) have been identified in patients with ALK$^-$ sALCL. The *DUSP22* rearrangements are observed in 20 to 30 % of patients with ALK$^-$ sALCL and are mainly the consequence of a t(6;7)(p25;q32) translocation [8,9] that results in *DUSP22* downregulation and *MIR29B* upregulation at 7q32 [10]. Some morphological features are associated with *DUSP22* rearrangements, such as a sheet-like growth pattern with numerous “doughnut” cells and few pleomorphic cells [11]. The prognosis of patients carrying a *DUSP22* rearrangement was initially considered favorable, similar to that of ALK$^+$ sALCL [8,12]. However, recent studies, while confirming the biological and clinical distinctiveness of DUSP22+/ALK- sACLCL, modulate this good outcome [13,14]. These clinical, morphological, and genetic features have led to the identification of sALCL with *DUSP22* rearrangements as a distinct genetic subtype of ALK$^-$ sALCL by the International Consensus Classification committee [15].

Rearrangements that targets *TP63*, which belongs to the *TP53* gene family, are less frequently observed (2 to 8 % of cases) and mainly generate the *TBL1XR1::TP63* fusion transcript as a result of a cryptic inversion inv(3)(q26q28). The concomitant use of break-apart and dual-fusion probes is often needed for fluorescence in situ hybridization (FISH) analysis due to the proximity of the *TBL1XR1* and *TP63* loci. *TP63* rearrangements are rare and appear to be associated with dismal outcome, with the limitation that the prognosis is assessed on small cohorts. *TP63* rearrangements are detected in 9.4 % of peripheral T-cell lymphomas and 10.5 % of pcALCL, but also in 1.2 % of diffuse large B-cell lymphoma, suggesting the absence of diagnostic specificity [16]. Although *DUSP22* and *TP63* rearrangements were initially described as mutually exclusive in ALK$^-$sALCL, “double-hit” cases have been described [17].

Other fusion events that involve the tyrosine kinases *ROS1* (6q22) and *TYK2* (19p13) are sporadically found in ALK$^-$ sALCL. They lead, for instance, to the *NFKB2::ROS1* or *NFKB2::TYK2* fusion transcripts (*NFKB2*, 10q24). These rearrangements also are mutually exclusive with *DUSP22* and *TP63* abnormalities. In addition and similarly to *ALK* and *DUSP22* rearrangements, all these gene fusions result in the constitutive activation of the JAK-STAT pathway [18].

It is not known whether this molecular sub-classification driven by distinct cytogenetic abnormalities (*DUSP22, TP63, ROS1, TYK2*) is clinically relevant. However, recent studies showed that these molecular entities have distinct prognoses and may be managed differently in the future [13,14].

In the ALK$^-$ sALCL subtype, the most common mutations concern the *MSC* (15 %), *JAK1* (15 %), *PRDM1* (12 %), *STAT3* (10 %), and *TP53* (6 %) genes. *MSC E116K* variant mutation occurs exclusively in ALK− ALCLs and coexists with *DUSP22* rearrangements in 93 % of cases [19].

2.1.3. BIA-ALCL

BIA-ALCL is a rare type of ALCL now considered as a distinct entity in the WHO-HAEM5 classification. It usually develops in the capsule of scar tissue that surrounds a textured breast implant. The prognosis is generally excellent.

Translocations involving *ALK, DUSP22* or *TP63* have never been reported in BIA-ALCL. Karyotyping data revealed a CK in the few studied cases, always in association with an aggressive clinical course [20]. Whole-genome sequencing revealed a high frequency of 20q loss (66 % of cases), differentiating BIA-ALCL from other ALCL and PTCL-NOS types [21]. Additionally, the JAK-STAT pathway in BIA-ALCL is frequently dysregulated, with mutations found in *JAK1, JAK2, STAT3, STAT5B* and *SOCS1* genes, as well as JAK2 gains or *STAT3::JAK2* activating fusion [22].

2.2. Nodal T-follicular helper cell lymphoma

The novel nodal T-follicular helper (nTFH) cell lymphoma family in the WHO-HAEM5 classification includes three entities: nTFH cell lymphoma angioimmunoblastic-type (nTFH-AILT), nTFH cell lymphoma follicular-type, and nTFH cell lymphoma not otherwise specified.

The rare, but recurrent t(5;9)(q33;q22)*/ITK::SYK* translocation has been reported in few patients with nTFH cell lymphoma [23,24]. In nTFH-AILT, half of patients present a CK, but with a lower chromosomal complexity than other peripheral T-cell lymphomas, that include 2 or 3 trisomies among chromosomes 3, 5, 19, or 21, +*X* and del(6q) [2,25,26]. Besides this typical cytogenetic presentation, the other patients harbor more complex and various karyotypes.

NGS has allowed identifying somatic mutations in epigenetic modifiers, such as *IDH2*, almost exclusively in patients with nTFH-AITL who harbor the *IDH2 R172* variant (20–40 %) [27], *TET2* (50–80 %), *DNMT3A* (20–30 %) [28] and *RHOA* (60–70 %; *RHOA G17V* variant in more than 90 % of cases). The combination of these mutations may have diagnostic significance, as it is only described in the context of nTFH-AITL and is uncommon in other PTCL [29]. However, particular caution is required when interpreting isolated *TET2* and/or *DNMT3A* variants, which may be related to clonal hematopoiesis.

2.3. Nodal EBV-positive NK/T-cell lymphoma

Nodal EBV-positive NK/T-cell lymphoma is a new entity in the WHO-HAEM5 classification that was formerly included in the peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) group.

Very few cytogenetic data are available. A cryptic del(14)(q32q32) was initially described as highly prevalent, but this should be interpreted as a clonality marker and not as a CA because it is the consequence of VDJ recombination with lack of specificity [30].

2.4. Other T-cell lymphomas

PTCL-NOS is a heterogeneous category and is mainly a diagnosis of exclusion. Recent data show, nevertheless, that there are two transcriptionally defined subgroups: TBX21-overexpressing (PTCL-TBX21) and GATA3-overexpressing (PTCL-GATA3), distinguishable in clinical practice using an immunohistochemistry (IHC) algorithm [31]. The PTCL-GATA3 subgroup is characterized by higher genomic complexity as assessed using CMA with +7/+7q, del(5q), del(9p), and del(12p). Other ACAs in PTCL-GATA3 are: +8/+8q, +17q and del(1q), del(6q21), del(10q), del(13q) and del(17p). Most deletions affect tumor suppressor genes with bi-allelic inactivation either by mutation, such as in *TP53* and

PRDM1, or by homozygous deletion, such as in *CDKN2A*. Therefore, the PTCL-GATA3 subgroup is distinct from other PTCL-NOS and is associated with high risk of poor outcome. Moreover, in this subgroup, *CDKN2A* deletion has an additional unfavorable effect on overall survival (OS) [32,33].

3. Leukemic T-cell lymphomas

3.1. T-cell prolymphocytic leukemia

T-PLL is a rare mature T-cell neoplasm with an aggressive clinical course that occurs in elderly patients. The T-PLL International Study group defined standardized diagnostic criteria that partly rely on cytogenetic findings. Specifically, $>5 \times 10^9$/L cells with the T-PLL phenotype in peripheral blood (PB) or bone marrow (BM), T-cell clonality, and 14q32.1/Xq28 abnormalities or *TCL1A/B* or *MTCP1* overexpression (assessed by flow cytometry or IHC) constitute the major criteria. Other chromosome abnormalities constitute minor criteria as well as the involvement of T-PLL specific site (e.g., splenomegaly, effusions). T-PLL diagnosis is established when all three major criteria or when the first two major criteria and one minor criterion are present [34].

3.1.1. Major cytogenetic criteria

The *TCL1* oncogene (*TCL1A/B*, 14q32.1) or its paralog *MTCP1* (Xq28) are involved in more than 95 % of cases [35,36]. The inv(14)(q11q32) is found in up to 2/3 of patients and less frequently the t(14;14)(q11;q32). Both result in the juxtaposition of the enhancer of the TRA-TRD loci with the *TCL1* cluster gene leading to its overexpression [37,38]. A sporadic case of T-PLL with a TCRB*::TCL1* rearrangement was recently documented [39]. FISH studies showed that *TCL1* is involved in 85 % of T-PLL. Measurement of TCL1 expression by flow cytometry or IHC may replace cytogenetic analysis in suspected T-PLL, as specified by the T-PLL International Study Group. However, chromosome banding analysis (CBA) or FISH can be considered as a gold standard in the detection of *TCL1* rearrangements due to their high sensitivity and specificity. Notably, IHC has a false negative rate of 4 % compared to FISH [40]. Furthermore, TCL1 overexpression may lack specificity since it's not limited to T-PLL; it has also been observed in B-cell malignancies such as chronic lymphocytic leukemia and B-cell lymphoma [41]. The translocation t(X;14)(q28;q11)/TRA-D::*MTCP1* is detected in 3–20 % of patients and leads to *MTCP1* upregulation [42]. Very rare t(X;7)(q28;q34)/TRB::*MTCP1* translocations have been reported [43].

3.1.2. Minor cytogenetic criteria

The second most frequent genetic hit is mono- or bi-allelic *ATM* inactivation due to 11q deletion and/or mutation in ~81 % of patients. *TCL1* rearrangement, leading to constitutive activation of TCL1, contributes to transformation in cooperation with ATM dysfunction, although the kinetics of appearance of both abnormalities has not been established yet [44,45].

An 8q gain due to different mechanisms (i.e. i(8q), +8, unbalanced translocations, or even a ring chromosome 8) is the most frequent ACA (67 % of cases) [46]. This 8q gain systematically involves *AGO2*, and at a lower frequency *MYC* (70 % of cases) [47]. Other recurrent ACAs have been described using CMA: del(6q), del(12p), del(13q), del(17p), del (22q), and +4q, +5p, +22q, leading to a complex karyotype (CK) in 70–90 % of patients [48,49]. The precise contribution of these abnormalities to T-PLL pathophysiology is not known, except for the putative role of *CDKN1B* haploinsufficiency in patients with del(12p) and of *TP53* in del(17p) [50]. Moreover, while no individual cytogenetic abnormality has an independent prognostic value for OS, high CK (≥5CA) is associated with shorter OS [35].

The T-PLL International Study group retains chromosome 11 aberrations, abnormalities of chromosomes 8, 5, 12, 13, 22, and CK as minor criteria.

A high number of somatic mutations accumulates during T-PLL pathogenesis. The mutation frequency is challenging to establish accurately due to the wide variety of techniques and small cohort sizes. However, a meta-analysis of 275 T-PLL have reported that mutations in *JAK* or *STAT* genes were present in 62 % of cases overall, and could be associated in about 10 % of cases. *JAK3, STAT5B*, and *JAK1* are the most recurrently *JAK/STAT* mutated genes. They are predominantly subclonal [51]. Moreover, mutations affecting genes implicated in DNA repair (*CHEK2, SAMHD1*) and epigenetic regulation (*EZH2, TET2, BCOR*) are also described [52,53].

3.2. Large granular lymphocytic leukemia (LGL)

CAs have been reported in individual patients with T-LGL, but none is considered recurrent.

Gain-of-function *STAT3* mutations have been described in 28–40 % of patients with T-LGL and have been associated with poor outcome [54]. *STAT5B* mutations are observed in 2 % of patients [55] but in up to 66 % of patients with the $CD4^+$ T-LGL subtype, characterized by an indolent form [56].

Cytogenetic data for NK-LGL are limited, and no recurrent CAs have been identified. Mutations in *CCL22* gene have been described in 27 % of patients with NK-LGL [57].

3.3. Adult T-cell leukemia/lymphoma

Adult T-cell leukemia/lymphoma is a mature T-cell neoplasm caused by human T-cell leukemia virus type 1 (HTLV-1). It includes four clinical subtypes: acute and lymphomatous subtypes, which are aggressive forms, and chronic and smoldering subtypes, which are indolent forms. Recurrent *CD28* alterations have been described. They lead to CD28 activation by different mechanisms: gain or amplification (28 %), in-frame *CTLA4::CD28* and *ICOS::CD28* (10 %) fusion events, and point mutations (2 %). Moreover, CKs are frequent, especially in the aggressive subtypes, and are associated with shorter OS [60,61].

CMA- and NGS-based studies have identified somatic alterations that are preferentially associated with a specific subtype. *STAT3* mutations are found in 40 % of indolent forms, whereas *TP53* (20 %) and *IRF4* (20 %) mutations as well as *CD274* amplification (10–20 %) and *CDKN2A* deletion (40–50 %) [62] have been associated with aggressive forms. *CD274* amplification is associated with poor prognosis in indolent and aggressive forms through T-cell function suppression by binding to PD-1 [58].

3.4. Sézary syndrome

Sézary syndrome (SS) is an aggressive disease defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of clonal CD4+ T cells with cerebriform nuclei (Sézary cells) in the skin, lymph nodes, and peripheral blood. It is considered as the leukemic form of mycosis fungoides (MF) (see below).

CMA studies have revealed recurrent loss of 17p, 9q, 10q and gain of 17q, 8/8q and 10p [63,64]. It has been shown that the co-occurrence of more than three of these recurrent CAs is significantly correlated with poor prognosis [63]. Analysis of NGS data confirmed the involvement of these regions and showed the relevance of alterations in genes involved in T-cell activation and apoptosis, NFκB signaling, chromatin remodeling, epigenetic regulation and DNA damage response, including TP53, ARID1A, CDKN2A, NFKB2, PLCG1, CD28, MYC, TET2, JAK1/3, STAT3/5B (JAK-STAT pathway : 11 %) [65,66], in SS physiopathology.

4. Primary cutaneous T-cell lymphomas

Primary cutaneous T-cell lymphomas (pcTCL) constitute a heterogeneous group of T-cell lymphomas that concern primarily the skin. MF and cutaneous $CD30^+$lymphoproliferative disorders account for 80 % of all pcTCL. In these lymphomas, CAs have been identified mostly using

CMA and NGS and are not included in the diagnostic process.

Many of the identified driver genes are shared by MF and SS. It is still debated whether these diseases represent distinct disorders or whether they are the extremes of the same disease spectrum in which SS would be the leukemic form of MF. CMA studies revealed common recurrent loss of 17p and gain of 17q and 8q24. Inactivation/deletion of the *CDKN2A/B* locus is more frequent in MF than in SS, whereas *TP53* alterations are less common [63,64,67,68].

Cutaneous CD30$^+$ lymphoproliferative disorders include pcALCL and lymphomatoid papulosis (LyP) that usually have an indolent clinical behavior. Unlike sALCL that appears to be driven by various genetic alterations leading to STAT3 activation, the molecular pathogenesis of pcALCL and LyP remains largely unknown. Translocations involving the *ALK* gene (2p23) have been detected in 2 % of patients with pcALCL, but are not found in LyP [69]. Rearrangement of the *DUSP22* locus (6p25) occurs in ~30 % of patients with pcALCL [70] and is also found in a LyP subtype (5 %) [71]. *TP63* rearrangements and the *NPM1::TYK2* (5q35 and 19p13 respectively) gene fusion are exceptional, and only few cases have been reported [16,72,73]. Mutations in the JAK1-STAT3 pathway that are common in ALK$^-$sALCL are found only in 5 % of patients with pcALCL [18]. The most commonly affected cellular processes and pathways are cell cycle, T-cell physiology regulation, transcription, and mainly signaling through the PI-3-K and MAPK pathways [73].

5. Other extranodal peripheral T/NK-cell lymphomas

5.1. Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma (HTCL) is a rare entity with poor prognosis that represents approximately 2 % of all peripheral T-cell lymphomas, mostly derived from cytotoxic T cells usually of gamma-delta T-cell receptor type (rarely alpha-beta). It predominantly affects men and in the context of immunosuppression (20–30 % of cases) [74]. It is characterized by hepatosplenomegaly, related to infiltration of liver and spleen sinusoids, without adenopathy. Bone marrow invasion is variable (15–64 %), but cytopenia is observed in most patients [75].

The most frequent CAs are i(7q) and +8. They are found in approximately 50 % of patients and sometimes are in co-occurence [76]. Rare cases of r(7) have been described [77], usually leading to an aberrant TRB::TRG (7q34, 7p14 respectively) rearrangement. Two minimal critical regions have been defined using CMA: 7p22.2p14.1 loss and 7q21.11q31.33 gain [78]. The *ABCB1* and *PPP1R9A* gene gain on 7q21 may be involved in the pathogenesis. The other recurrent CAs are del(10p) and +1q [79].

T-LGL/NK-LGL represents the primary differential diagnosis and differentiating an LGL from an HTCL can be challenging, particularly if spleen and liver histology is unavailable (aggressive LGL variants have been described with hepatosplenomegaly or with atypical morphology). Rare T-cell receptor types, such as HTCL alpha-beta or T-LGL gamma-delta, can further complicate the situation. However, i(7q) seems specific to HTCL, since it is absent in LGL and is therefore considered a criterion that supports the diagnosis of HTCL [80,81]. Like in LGL, somatic mutations in the *STAT5B* (33 %) and *STAT3* (8–10 %) genes have been reported [82]. In addition, *SETD2* mutations have been described in 25 % of patients [79].

5.2. Intestinal T-cell lymphoid proliferation and lymphomas

Intestinal T-cell lymphomas are rare and represent only 4–6 % of primary gastrointestinal lymphomas. This group includes four entities: indolent T-cell lymphoma of the gastrointestinal tract (ITLGT), enteropathy-associated T-cell lymphoma (EATL), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), and intestinal T-cell lymphoma not otherwise specified.

5.2.1. Indolent T-cell lymphoma of the gastrointestinal tract

ITLGT is a distinct entity that was initially considered as a lymphoproliferation in the WHO-2017 classification and now as a lymphoma in the WHO-HAEM5 classification. It is a clonal proliferation of T cells in the gastrointestinal tract, most often in the small intestine and colon, with symptoms similar to those of EATL and MEITL but without the association with celiac disease. ITLGT are usually indolent lymphoid neoplasms, unlike EATL and MEITL that are aggressive. It is essential to distinguish them because, despite their indolent clinical behavior, ITLGT are usually refractory to symptomatic treatment and conventional chemotherapies. They are easily misdiagnosed as inflammatory bowel disease or other T-cell lymphomas. They are immunophenotypically heterogeneous: CD4$^+$ (40 %), CD8$^+$ (40 %), CD4$^+$/CD8$^+$ (10 %), and CD4$^-$/CD8$^-$ (10 %) [83].

Recently, the recurrent t(9;17)(p24.1;q21.2), translocation has been identified in 25–80 % of CD4+ ITLGTs. It leads to the creation of a *STAT3::JAK2* fusion transcript. This transcript, through homodimerization, induces phosphorylation of STAT5 via JAK2, and not of STAT3 that is destabilized by the C-terminal domain loss [84,85].

The *STAT3::JAK2* rearrangement has not been found in CD8+ ITLGT and in other forms of intestinal T-cell lymphomas by FISH using a JAK2-targeting probe. However, it is not a specific hallmark because it is also described in BIA-ALCL [22].

Somatic variants in ITLGTs differ according to the cell origin. Mutations in *STAT3* and *SOCS1* are found in CD4$^+$forms, in addition to *STAT3::JAK2* rearrangements. The JAK-STAT pathway is altered in 82 % of CD4$^+$ and CD4$^+$/CD8$^+$ or CD4$^-$/CD8$^-$ ITLGTs. They also harbor concomitant mutations in epigenetic modifier genes (*TET2, DNMT3A*, and *KMT2D*). There is little information on the CD8$^+$ forms, but they do not appear to present any recurrent mutations. A study described two patients with structural abnormalities involving the untranslated region of the *IL2* gene (4q27) [86].

5.2.2. Enteropathy-associated T-cell lymphoma

EATL represents about 5 % of T-cell mature lymphomas and is the most common form of primary intestinal T-cell lymphoma. This aggressive lymphoma is usually associated with celiac disease, of which it is main neoplastic complication. It can be preceded by refractory celiac disease type II (RCDII) that is considered a low-grade T-cell lymphoma.

Array-based comparative genomic hybridization (aCGH) studies showed the presence of non-specific CAs in approximately 87 % of patients. Gain of 9q is the most common (46–80 % of patients), with a minimal region at 9q33q34.1 that includes the *NOTCH1* gene [87]. Other observed imbalances are gains in chromosomes 7q (24–29 %), 5q (18 %), 1q (16–20 %) and losses in 8p (25 %), 13q (24 %), 16q12.1 (23 %, almost mutually exclusively with 9q gain), 9p (18 %) [88–90]. Loss of heterozygosity in the 9p21 region, which contains *CDKN2A/CDKN2B*, is detected in 56 % of patients [91]. The presence of a complex profile on aCGH (≥3 CAs) is associated with a negative effect on OS [88].

RCDII has a simpler imbalance profile. Unlike EATL, 9q gain is not found, but there is a predominance of 1q gain (17–94 % of patients) [92,93].

EATL is characterized by the involvement of the JAK-STAT pathway in ~50 % of cases, with variants mainly in *JAK1* (20 %), *STAT3* (20 %), and *SOCS1* (12 %). Mutation in the JAK-STAT pathway could enhance EATL sensitivity to cytokine stimulation. Mutations in the RAS pathway are found in approximately 20 % of patients [90,94].

RCDII presents a similar mutations pattern in *JAK1* (75 %) and *STAT3* (25 %), concomitantly with variants in *TET2* and *KMT2D,* two epigenetic regulator genes (78 %) [93].

5.2.3. Monomorphic epitheliotropic intestinal T-cell lymphoma

MEITL, formerly type II EATL, is another aggressive lymphoma. Unlike EATL, it is unrelated to celiac disease and is the main form of primary intestinal T-cell lymphoma in Asia.

MEITL shares many CAs with EATL, including the 9q gain detected in 58–77 % of patients [95,96]. However, 1q and 5q gains, which are usually observed in EATL, are rare, whereas 8q gains are over-represented in MEITL (20–70 % of patients) [97,98]. Translocations involving the *MYC* gene have been occasionally reported (4–6 %) [99,100]. The deregulation of the *MIR17HG* (*MIR17–92*) cluster mediated by *MYC* abnormalities may play a role in MEITL development [101]. *MYC* rearrangements seem to correlate with *TP53* mutations that negatively affect OS in multivariate analysis [98].

Other described CAs, assessed using CMA or derived from whole exome sequencing, are 7q (44–63 %), 19q (33 %) gains, and 7p (44–75 %), 8p (33 %), and 18p (33 %) losses [95,96].

Mutations affecting the JAK-STAT pathway are common in MEITL (80 %), like in EATL, but involve preferentially *JAK3* (33–67 %) and *STAT5B* (33–60 %). The MAP kinase pathway also is affected, but less frequently (32 %) [96,98]. Moreover, mutations in the tumor suppressor gene *SETD2* are more frequent in MEITL (77–96 %) than EATL (22 %). These are mostly truncating mutations or deletions of the 3p21.31 region (often biallelic) that contains *SETD2* [95,98,102].

Specific mutation patterns can be considered for the differential diagnosis between EATL and MEITL: *JAK1/STAT3* for EATL and *JAK3/STAT5/SETD2* for MEITL.

5.3. EBV-positive extranodal NK/T-cell lymphoma

Extranodal forms (75 % NK- and 25 % T-cell lymphomas) are aggressive diseases primarily located in the upper aerodigestive tract. The prognosis is variable, and non-nasal forms generally have a worse outcome.

NGS-based studies, with copy number variant calling, and by CMA, have identified recurrent copy-number abnormalities that include gain of 1q (17 %), 2q (13 %), 9p24.1-*CD274* (*PD-L1*)/*PDCD1LG2* (*PD-L2*) (14 %), 9p24.1-*JAK2* (11 %), 17q21.2 (9–15 %), which contains *STAT3*, and losses of 6q21-q25/*PRDM1* (17–27 %), and 17p13-p11/*TP53* (10 %). The 6q deletion was also confirmed by karyotyping in patients with bone marrow involvement [103,104].

NGS identified mutations in three main gene categories: i) tumor suppressor genes (48 %), including *DDX3X* (14–44 %), *TP53* (11–12 %; mutually exclusive with the *DDX3X* mutation), and *MGA* (8 %); ii) chromatin modifier genes (45 %), such as *KMT2C* (16 %), *KMT2D* (13–15 %) and *BCOR* (9–11 %); and iii) genes of the JAK-STAT pathway (31 %) such as *STAT3* (22 %), *JAK2* (11 %), *STAT5A/5B* (9 % each). In vitro studies have shown that *PRDM1* deletion cooperates with *STAT3* mutations to promote NK-cell growth and survival [105].

Despite the genetic heterogeneity, Xiong et al. demonstrated a clustering of mutations and copy number alterations that defines three subtypes: i) tumor-suppressor/immune-modulator subtype (del6q, gain 9p24.1/17q21.2, and JAK-STAT pathway or *TP53* mutations), ii) aberrant histone acetylation subtype (*HDAC9-EP300-ARID1A* mutations), and iii) MB subtype (*MGA* mutations and *BRDT*/1p22.1 loss of heterozygosity). These three subtypes have different OS: MB forms have a poorer prognosis than the others [106].

6. Technical aspects and recommendations

6.1. Chromosome banding analysis

Table 2 lists the optimal culture conditions for MTNKN cytogenetic analysis.

CBA can be performed using any infiltrated fresh samples: PB, BM, lymph nodes and other tissues. However, culturing presents two major limitations: low mitotic index and no specific immunomodulation. Unlike B-cell lymphomas, there is no mitogen, such as ODN-CpG+IL2, to induce tumor cell division. Phytohemagglutinin (PHA) can promote the division of malignant T cells, but this effect is not restricted to tumor cells and concerns also normal lymphocytes. In addition, PHA can ever inhibit tumor cell growth in some cases [107].

For MTNKNs (except T-PLL), a short culture (<24 h) is preferred first, with the possibility of a second long culture in the presence of PHA, if sufficient material is available. In NK-cell lymphomas, several studies have shown higher abnormal metaphase rate following stimulation with IL2 compared with PHA [108], because IL2 induces activation and expansion of the NK-cell contingent. Therefore, for NK-cell hemopathies, a second long culture with IL2 may be preferred.

For T-PLL, various studies did not find any significant difference in chromosome abnormality detection rate between short culture and long culture with PHA. Thus, a long culture with PHA is preferred to obtain higher resolution metaphases and better detect relevant abnormalities, such as inv(14).

6.2. FISH

FISH can be performed on metaphases, if available. If not, interphase FISH can be used on touch preparations or formalin-fixed paraffin-embedded (FFPE) tissue sections. Special attention should be given to the interpretation of FFPE sampling techniques, which need prior identification of the tumor areas by histological staining of the same section. In addition, the use of split probes is recommended. These probes produce less complex fluorescence profiles than fusion probes, particularly in cases of unbalanced abnormalities. Moreover, they allow the identification of rearrangements for a target gene, irrespective of its partner. To note, there is no precise cutoff for interphase FISH on FFPE tissue sections, since it is influenced by the degree of invasion in the examined tissue area and possible artifacts related to the protocol used (section thickness, hybridization rate).

6.3. Chromosomal microarray analysis

CMA is an alternative approach for MTNKNs and can be performed on fresh tissue or formalin-fixed paraffin-embedded tissue sections (with lower hybridization quality in this case). It allows obtaining the chromosomal abnormality profile that can guide the diagnosis. Moreover, it

Table 2
Sample management: optimal conditions, cell culture duration and cell concentration.

Suspected diagnosis	Culture time and specifications	Cell concentration for bone marrow and peripheral blood	Cell concentration for tissue samples and fluids [a,b]
T-cell lymphomas	Short culture without mitogens: 17 to 24 h Long culture with PHA: 72 h [c]	1 to 2 M/ml	3 to 5 M/ml
T-PLL	Long culture with PHA: 72 h [c]	1 to 2 M/ml	/
NK-cell lymphomas	Short culture without mitogens: 17 to 24 h Long culture with IL2: 72 h [c]	1 to 2 M/ml	3 to 5 M/ml

Abbreviations: IL2: interleukin 2; M: million; PHA: phytohemagglutinin; T-PLL: T-cell prolymphocytic leukemia.
[a] In highly proliferative lymphomas, a lower concentration frequently results in an informative karyotype.
[b] If material is limited, short culture should be preferred.
[c] Culture time can be adapted: 48 h to 96 h.

Table 3
Indications of cytogenetic analyses and recommendations for each disease.

Entity	Karyotype [a]	Mandatory (in bold) or recommended molecular cytogenetic analyses based on karyotype data	
		Abnormal karyotype consistent with the diagnosis	Normal karyotype, failure, not performed, or diagnostic discrepancy
ALCL	Recommended	**FISH ALK** If ALK negative: FISH DUSP22 and/or TP63	
T-PLL	Mandatory	FISH: TCL1A TCRA-D or TCRB ATM	**FISH:** **TCL1A** **TCRA-D and TCRB if TCL1A negative** ATM
ATLL	Optional	FISH: CDKN2A, CD274/PDCD1LG2	
HTCL	Recommended	/	FISH 7q22/7q31
ITLGT	Optional	FISH JAK2	
Other	Optional	CMA	

Abbreviations: ALCL, anaplastic large cell lymphoma; T-PLL, T-cell prolymphocytic leukemia; ATLL, adult T-cell leukemia/lymphoma; HTCL, Hepatosplenic T-cell lymphoma; ITLGT, Indolent T-cell lymphoma of the gastrointestinal tract; CMA, chromosomal microarray.
[a] if fresh invaded sample (bone marrow, peripheral blood, fluid or tissue) is available.

is performed using the same DNA used for NGS, which is now implemented in clinical practice. However, CMA is limited by its sensitivity, which requires a tumor infiltrate of at least 20 %, and its inability to detect balanced chromosomal abnormalities.

6.4. Recommendations

The implementation of cytogenetic results in the diagnostic work-up is restricted to few MTNKN types, for which we propose recommendations (Table 3).

Karyotyping is mandatory when suspecting T-PLL to identify the main primary abnormality. Without the demonstration of inv(14) or t(14;14) by CBA, FISH using a TCL1A break-apart probe is required. In the absence of a *TCL1A* rearrangement, the TCRAD and TCRB probes may represent an alternative to detect t(X;14) and t(X;7) in the absence of a commercial MTCP1 probe.

In ALCL, CBA is recommended if fresh material is available. Metaphase or interphase FISH using a break-apart ALK probe is mandatory to identify ALK^+ sALCL with good prognosis, even in the case of negative ALK IHC. If ALK FISH is negative, FISH using a DUSP22 break-apart probe and/or an appropriate TP63 probe is recommended.

In HTCL, CBA is recommended and FISH can be useful to identify i(7q). FISH using a JAK2 break-apart probe is recommended in patients with suspected ITLGT because the differential diagnosis with celiac or intestinal immune diseases can be difficult. It is essential to identify this rearrangement that could represent a therapeutic target for JAK inhibitors [109].

7. Conclusions

Cytogenetic analyses are crucial for the diagnostic work-up of T-PLL and ALCL. In other MTNKN subtypes, they are of secondary importance and are not included in the primary diagnostic criteria. However, in the case of atypical histology or immunophenotype, FISH and/or CMA can provide arguments for diagnostic classification or prognosis stratification, together with molecular studies.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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