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Review Article

Biology of peripheral T cell lymphomas – Not otherwise specified: Is something finally happening?

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ABSTRACT

Introduction: Peripheral T-cell lymphomas represent a rare, heterogeneous group of nodal and extra-nodal mature T-cell lymphomas. Among those, the subtype of PTCL not otherwise specified (PTCL-NOS) account for about 25% of all PTCL. While other PTCL subtypes are increasingly recognized as discrete entities based on specific genotypic and phenotypic alterations, the diagnosis of PTCL-NOS is currently performed on an "exclusion criteria" model, since PTCL-NOS lack pathognomonic features.
Methods: In this review, we describe the classical pathological features of PTCL-NOS and integrate them with the most recent molecular findings.
Results: Thanks to gene expression profiling and next generation sequencing approaches, we have recently improved our knowledge of PTCL in general and PTCL-NOS in particular. Indeed, specific patterns of gene expression were reported to segregate PTCL into more homogeneous subtypes associated with distinct clinical outcome. Furthermore, we describe how immunophenotypic, expression and mutational data helped to better define a new subgroup of PTCL-NOS displaying a global profile close to T Follicular Helper cell elements. Finally, we review how these new acquisitions are changing the current diagnostic approach to PTCL-NOS, and how phenotypic features and oncogenic pathways operative in these lymphomas are becoming targets of novel treatments.
Conclusion: Although no recurrent and specific biological aberrations have been discovered yet, novel integrated genomic and transcriptomics approaches are significantly improving our knowledge of PTCL biology and support the development of new powerful diagnostic and prognostic markers, as well as targets of future therapies.

1. Introduction

Peripheral T-cell lymphomas (PTCL) represent a relatively rare disease that account approximately for 15% of all Non-Hodgkin lymphomas in Western countries [1–3].

The current WHO classification recognizes several distinct PTCL subtypes, among which the most frequent are angioimmunoblastic lymphoma (AITL), anaplastic large T cell lymphoma (ALCL) with or without *ALK* gene translocations, and PTCL-not otherwise specified (PTCL-NOS) (Table 1 and Fig. 1). Overall, these entities encompass approximately 60% of all PTCL [2–5]. With the exception of anaplastic large cell lymphomas with ALK translocation, PTCLs are recognized for their aggressive clinical course and poor response to conventional chemotherapy [1,3,6–9].

For many years, the differential diagnosis between PTCL subtypes on pathological morphological, phenotypic and molecular grounds has posed a great challenge. Aside from *ALK*-translocated ALCL (ALK pos), which represents to date the only PTCL entity defined by a recurrent chromosomal translocation [2], many different studies aimed at the identification of distinctive biological markers of ALK-negative (ALK neg) ALCL, AITL and PTCL-NOS have largely failed. The diagnostic discordance rate between pathologists still accounts for about 30% of cases, representing a big issue for the correct diagnosis and treatment of each patient [10]. Several studies have recently described novel biological features of ALCL and AITL, providing significant contributions to the pathological characterization of these en-

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Table 1
WHO 2008 classification of mature T cell and NK cell neoplasm.

Leukemic
T-cell prolymphocytic leukemia T-cell large granular lymphocytic leukemia Adult T cell leukemia/lymphoma Aggressive NK cell leukemia
Cutaneous
Mycosis fungoides Sezary Syndrome Primary cutaneous CD30+ T-cell lymphoproliferative disorder Lymphomatoid papulosis Primary cutaneous anaplastic large-cell lymphoma Primary cutaneous peripheral T-cell lymphomas rare subtypes *Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma** *Primary cutaneous gamma-delta T-cell lymphoma* *Primary cutaneous small/medium CD4+ T-cell lymphoma**
Extranodal
Hepatosplenic T-cell lymphoma Subcutaneous panniculitic-like T cell lymphoma *Entheropathy associated T-cell lymphoma* *Extra nodal NK/T-cell Lymphomas*
Nodal
Peripheral T-cell lymphoma not otherwise specified Angioimmunoblastic T-cell lymphoma Anaplastic large cell lymphoma, ALK+ *Anaplastic large cell lymphoma, ALK–**

* These represent provisional entities or provisional subtypes of other neoplasm. Disease shown in italic are newly included in the 2008 WHO classification.

tities. High-throughput techniques such as gene expression profiling (GEP) and next generation sequencing (NGS) [11–15] have found shared genomic and transcriptomic features that justify the existence of ALK-neg ALCL and AITL as distinct clinico-pathological entities, whereas PTCL-NOS still remains an "orphan" disease, without any pathognomonic feature. For these reasons, a diagnosis of PTCL-NOS is currently based on an "exclusion criteria" model not defined by specific morphologic, phenotypic or molecular features, and it is likely that within this diagnostic group lie distinct PTCL subtypes not yet identified [4,7,16,17]. In this review, we will discuss the recent advances on the understanding of the biology of PTCL and we will specifically focus on the PTCL-NOS subtype where future findings have the potential to improve diagnostic markers, change current classification criteria and even direct efforts for future therapeutic approaches.

2. Morphology and phenotype

PTCL-NOSs encompass cases that don't fulfill diagnostic criteria for specific PTCL entities. Therefore, PTCL-NOSs are generally characterized by very heterogeneous histological and immunistochemical (IHC) profiles. In fact, the old Working Formulation listed PTCL-NOS

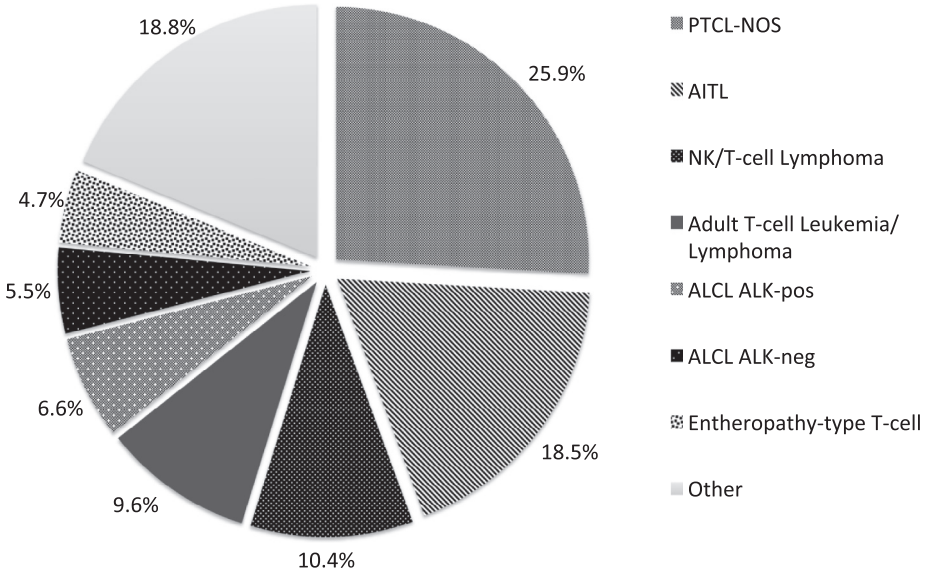

Fig. 1. Relative frequencies of non cutaneous mature T-cell lymphoma subtypes in an adult patient population.

Table 2
Differential diagnosis of nodal peripheral T-cell lymphoma, not otherwise specified, adapted from WHO 2008 classification.

Disease	Immunophenotypic features
PTCL-NOS	CD4>CD8, Antigen loss frequent (CD7, CD5, CD4/CD8, CD52), CD30+/–, CD56–/+, CD10–, BCL6–, CXCL13–, PD1–
PTCL-NOS TFH	CD10+, BCL6+, PD1+ and CXCL13+
AITL	CD4+ or mixed CD4/CD8, CD10+/–, BCL6+/–, CXCL13+, PD1+, Hyperplasia of FDC, EBV+, CD20+ B blasts
ATLL	CD4+, CD25+, CD7–, CD30–/+, CD15–/+, FoxoP3+/–
ALCL	CD30+, ALK+/–, EMA+. CD25+, cytotoxic granules+, CD4+/–, CD3–/+, CD43+
T zone Hyperplasia	Mixed CD4/CD8, intact architecture, variable CD25 and CD30, scattered CD20+B cell

cases as either diffuse small cleaved, mixed, large cell or immunoblastic lymphomas [5,18]. Lymph node involvement is frequent, as only 13% of cases present with extranodal disease only [19]. The normal lymph node architecture is usually effaced by a paracortical or diffuse proliferation of small, medium and large atypical cells in variable proportions, admixed with variable degrees of vascular proliferation and inflammatory background of non-neoplastic cells (eosinophils, plasma cells, and histiocytes) [7,20–22]. Differential diagnosis of PTCL-NOS can be challenging and requires extensive immunophenotyping to exclude AITL, ALK-neg ALCL or Adult T-cell Leukemia/Lymphoma (ATLL) given the lack of characteristic histological features. Although PTCL-NOSs are usually characterized by specific aberrant T-cell phenotypes (i.e. loss of CD5 and CD7 and expression of CD2, CD3, CD4 and/or CD8, the T-cell receptor (TCR) beta-chain (BetaF1)), all investigated markers have revealed a very low positive and negative predictive value, that do not help differential diagnosis of PTCL-NOS [7] (Table 2). PTCL-NOS may show confounding features such as presence of Red-Stemberg-like cells and distinct microenvironment alterations typically associated with AITL, such as clonal restriction of infiltrating B-lymphocytes, sometimes with evidence of Epstein–Barr virus (EBV) integration, in almost 30% of the cases [4,23–25]. Furthermore, EBV virus is usually negative in tumor cells (detectable only in 5% of cases). Proliferation rate is usually high and Ki-67 rates exceeding 80% of the tumor cells are associated with a worse prognosis [25–27]. Prompted by a promising anti-tumoral activity of the anti-CD52 monoclonal antibody Alemtuzumab [28], authors have investigated the prevalence of CD52 expression among PTCL-NOS and reported it at about 40% of total [2,29]. However, the widely divergent CD52 expression by IHC has made it quite difficult to reliably identify the CD52+ PTCL-NOS cases across laboratories. Furthermore, the availability of new treatments and the high toxicity of Alemtuzumab have decreased the enthusiasm for this molecule in recent years [30].

Different studies have described potential IHC markers related with overexpression of proteins within PTCL-NOS oncogenic pathways. One of the most important is the PDGFRA protein that was recently reported to be aberrantly expressed in more than 90% of PTCL-NOS [31]. Interestingly, PDGFRA is activated by the PDGF-AA ligand secreted by the tumor cells themselves, creating an autocrine stimulation loop that involved STAT1 and STAT5 activation, resulting in tumor proliferation. Another study has described a high NOTCH1 expression and activation in more than 50% of PTCL-NOS by IHC, suggesting an involvement of this pathway in mature T-lymphoproliferative disorders [32]. While the role of these aberrantly expressed proteins in the differential diagnosis of PTCL spectrum diseases remains to be established, they may also represent potential targets for known drug classes such tyrosine kinase inhibitors and NOTCH-inhibitors.

The PTCL-NOS heterogeneity was further refined by the introduction, in the last WHO classification, of specific and distinct morphological variants such as the lymphoepitelioid (Lennert) Lymphoma, the T-zone and the T Follicular Helper (TFH) variants [2]. The latter was particularly important accounting to approximately 20–41% of PTCL-NOS and encompasses all cases expressing TFH cell markers and exhibiting some, but not all, of the morphological features of AITL [33–36]. Morphologically, this variant is usually characterized by atypical clear cells forming intrafollicular aggregates, small nodular aggregates in a background of progressively transformed germinal centers or enlarged perifollicular zone nodular aggregates surrounding hyperplastic follicles [2,33]. Despite a TFH phenotype, early stage disease, partial lymph node involvement, lack of enlarged follicular dendritic cell meshworks and lack of prominent high endothelial venules helps the distinction from typical AITL. In the past, this variant was described by different terms including: perifollicular. intrafollicular, paracortical nodular and expanded mantle zone [2].

3. CD30+ PTCL-NOS

A hot topic in the field of PTCL is currently represented by CD30 expression. It is well known that CD30 is highly expressed in all ALCL and in a significant fraction of PTCL-NOS [2,7,37,38]. Although CD30 staining in PTCL-NOS is typically focal and more variable than that observed in ALCL, CD30 positivity may make the distinction of PTCL-NOS from ALK-neg ALCL problematic. Furthermore, among a large series of 376 non-cutaneous PTCLs, CD30 was reported to be expressed in 58% and 63% of PTCL-NOS and AITL, respectively [22]. However a strong CD30 positivity (>50% of tumor cells) was detected only in 23% and 5% of PTCL-NOS and AITL, respectively (Table 3). Interestingly, gene expression and IHC data suggested that all CD30+ PTCL share distinct biological profile across WHO subgroups [38–41]. In fact, CD30+ PTCL-NOS and ALK-neg ALCL shared an expression signature that was not present in CD30- PTCL-NOS, and consisted in downregulated expression of T-cell receptor-associated proximal tyrosine kinases (Lck, Fyn, Itk) and of proteins involved in T-cell differentiation/activation (CD69, ICOS, CD52, NFATc2), and upregulation of JunB and IRF4 [39]. Interestingly, CD30 has been recently reported to promote

Table 3
CD30 ICH expression among PTCLs.

	Score 0 (0%)	Score 1 (1–25%)	Score 2 (25–50%)	Score 3 (50–75%)	Score 4 (75–100%)	Score > 2
ALCL ALK pos [37]	0	0	5%	2%	93%	95%
ALCL ALK neg [38]	0	0	0	0	100%	100%
AITL [37]	37%	47%	10%	5%	0	5%
AITL [38]	51.14%	21.42%	11.9%	9.52%	-	9.52%
PTCL-NOS [37]	42%	26%	9%	10%	13%	23%
PTCL-NOS [38]	35.63%	12.64%	20.69%	12.64%	18.39%	31.03%

IRF4 expression through activation of the NF-kB subunits p52 and RelB [40]. In turn, IRF4 activates MYC in a positive feedback loop that was also described among ALCLs, suggesting a shared oncogenic pathway [27]. In line with heterogeneity of its expression pattern, the prognostic value of CD30 expression in PTCL-NOS has raised controversy as well. While reported as a favorable prognostic marker by some [39], Savage et al. [42] have shown that the survival of patients with high expression of CD30+ (≥80% of tumor cells) was extremely poor with 5-year overall survival of 19%. Therefore, the clinical relevance of the expression of CD30+ should be investigated in larger cohorts of patients, stratified for expression levels.

Clearly, the great interest on CD30 expression is due to the high clinical efficacy of the conjugated monoclonal antibody anti-CD30 Brentuximab Vedotin (BV) in naïve and relapsed PTCL patients [28,32–35]. Interestingly, some reports have suggested that BV may even be active in IHC negative CD30 cases of DLBCL and PTCL [6,43,44]. The disease-specific variability in such an effect could be explained by the specifics of the inflammatory background of each neoplasm, or by the poorly reproducible evaluation of CD30 expression by IHC [6,7,43,45]. While there is an obvious need for biomarkers and standardized techniques that can help predict response to BV, this molecule presently represents one of the most attractive novel therapeutic opportunities in the field.

4. Cytogenetic aberrations

The karyotype of PTCL was first evaluated in the 90s by conventional cytogenetic approaches. At the time data were limited by the rarity of these malignancies in Western countries and interpretation was hampered by issues related to histological classification [7]. These studies have reported the frequent presence of complex karyotypes [20], with distinct recurrent cytogenetic aberrations such as losses in chromosomes 6q, 13 or 13q, and gains in 7q. Overall, abnormal clones were identified in 71% of PTCL cases, and 1p36 breakpoints were observed in almost half of the cases [46–48]. More recently, the spectrum of copy-number abnormalities in PTCL-NOS has been investigated by means of microarray-based comparative genomic hybridization (aCGH) and by genome-wide human single nucleotide polymorphism (SNP) arrays resulting in a much larger and more detailed catalogue of abnormalities, some of which shared by different studies [49–52]. Among these were deletion of the 9p21 region, containing the tumor suppressor locus *CDKN2A/B*, deletions in 10p11 (*ZEB-1*) and 17p13 (*TP53*). Conversely, chromosome regions with recurrent gain were: 1q32–43, 2p15–16 (*REL*), 7q22, 8q24, 11q14–25, 17q11–21 and 21q11–21 (*NRIP*). However, the three main studies showed important differences in prevalence of specific copy number aberrations suggesting the low reproducibility of this approach (Table 4).

Table 4
PTCL-NOS copy number aberrations data according with the main next studies.

	[52]	[50]	[49]
Series size	36	51	47
Imbalanced Cases	97%	57%	47%
LOSS			
1p31	–	10%	–
2q37	–	12%	–
5q21	25%	–	2%
6q14/6q23	19%	10%	–
6q21	31%	10%	8%
6q22	25%	–	8%
6q24-qte/6q15-q16	22%	–	2%
6q14/6q23	19%	–	
7p14	–	–	36%
8p21	19%	–	10%
9p21	31%	31%	13%
10cen-p12	17%	12%	19%
10q23-24	28%	10%	–
12q21-q22	28%	–	–
13q14	–	10%	8%
13q21	36%	21%	–
14q11	–		74%
Del17p13	17%	21%	10%
GAIN			
1p36	5%	–	–
1p31	–	10%	
1q32-qter	17%	–	10%
2p15-16	–	–	10%
2q37	–	12%	–
3p21,	17%	–	–
4q21-28	–	14%	–
6p25	5%	–	–
7q22-qter	31%	31%	15%
8q24	19%	–	10%
9q33-qter	19%	12%	–
11cen-q13	17%	–	–
11q14.1	–	13.7%	10%
11q23	–	–	13%
12p13	8%	–	–
12q21-q22	–	–	–
17cen-q21;	25%	–	13%
16p	22%	14%	–

Few recurrent translocations have been described in PTCL-NOS. One of the most important and well characterized is the t(5;9)(q33;q22), causing the overexpression of a chimeric protein where the N-terminus of ITK, a tyrosine kinase required for T-cell development, is fused to the C-terminus portion of *SYK*, a non-receptor protein kinase [53]. The resulting ITK-SYK protein retains the N-terminal pleckstrin homology and proline-rich domains of ITK and the C-terminal kinase domain of SYK. This translocation was found to be associated mainly with TFH PTCL-NOS, and was not detected in AITL or ALK-neg ALCL, so that it was even proposed as a molecular diagnostic marker defining a distinct PTCL-NOS subgroup [53,54]. Interestingly, further observations have shown high SYK levels by IHC in 133 (94%) PTCL cases, regardless of the presence of the *ITK/SYK* translocation, but not in normal T cells [54]. Specifically, this study revealed SYK overexpression in 35/35 (100%) AITLs, 62/66 (94%) PTCL-NOS, 6/6 (100%) ALCL ALK-pos, 11/12 (92%) ALCL ALK-neg and 19/22 (86%) of other subtypes, making it one of the most widely expressed oncogenes in PTCLs. In fact, transgenic expression of the *ITK/SYK* translocation in mice was able to recapitulate a disease resembling human PTCL, thus underscoring the relevance of this event for disease pathogenesis [55]. This evidence, combined with the availability of orally available SYK inhibitors [56,57], suggests that SYK merits further evaluation as a candidate target for pharmacologic inhibition in patients with PTCL.

Another translocation associated with PTCL-NOS is the t(6;14) (p25;q11.2), resulting in overexpression of the transcription factor *IRF4* under the control of the T-cell receptor-alpha (*TCRA*) locus [58]. This translocation was detected in 12/169 (7%) PTCL-NOS cases that where all characterized by distinct clinical features with skin and bone marrow involvement at diagnosis.

A recent paper applying next generation sequencing (NGS) to the detection of gross structural changes in 16 PTCL (including 4 PTCL-NOS) highlighted recurrent abnormalities involving p53-related genes, including inversions and translocations of the *TP63* locus and deletions of *CDKN2A*, *WWOX*, and *ANKRD11*. In particular, *TP63* rearrangements were further validated by FISH in a larger series and were found in 9.4% of PTCL-NOS cases (5/53), characterized by higher CD30 and Ki-67 expression, and inferior survival [59]. Thus suggest that, while *TP53* mutations and/or deletions are quite rare in PTCL and PTCL-NOS compared to other lymphoid malignancies [60,61], disruption of its pathway is a frequent oncogenic event that may contribute to the frequent treatment failures in this class of lymphomas.

Cytogenetic aberrations in general are therefore frequently involved in PTCL-NOS pathogenesis, and play a pivotal role in their biological complexities. However, the heterogeneity of the neoplastic infiltrate and the inconsistencies in histological PTCL classification could clearly hamper the discovery of recurrent aberration with significant prevalence. The use of novel methodologies could provide insights into the genetic complexity of PTCL-NOS, as recently shown in CTCL and ATLL where whole genome sequencing has highlighted a number of previously unreported recurrent micro-deletions with clear implications for disease pathogenesis [62,63].

5. Gene expression profiling

Gene expression profiling (GEP) has been widely used to improve PTCL diagnosis accuracy and to better understand its pathogenesis. Specific and robust signatures have been identified for AITL and ALCL, and this has proven so far to be the best approach to distinguish those entitles from PTCL-NOS [12,33,39,64–68]. In the largest cohort to date, Iqbal et al. have recently confirmed the power of GEP-derived expression signatures in assigning each PTCL case to the correct subtype, confirming previous reports [12]. This approach proved to be superior to standard histology/immunohistochemistry, leading to reclassification of a number of patients. As expected, the group with most reclassified patients was represented by PTCL-NOS, where 55/150 (37%) were classified as either AITL (21), ALK-neg ALCL (17), γδ-PTCL (13) or ATLL (4) (Fig. 2). Conversely, 26/117 (22%) AITL cases were reclassified as PTCL-NOS based on GEP.

By gene expression profiling many groups described a common PTCL-NOS expression profile, more evident in supervised analysis comparing PTCL-NOS with other entities (i.e. AITL and ALCL) [34,68–71]. Conversely, when PTCL-NOSs were considered alone, GEP revealed a

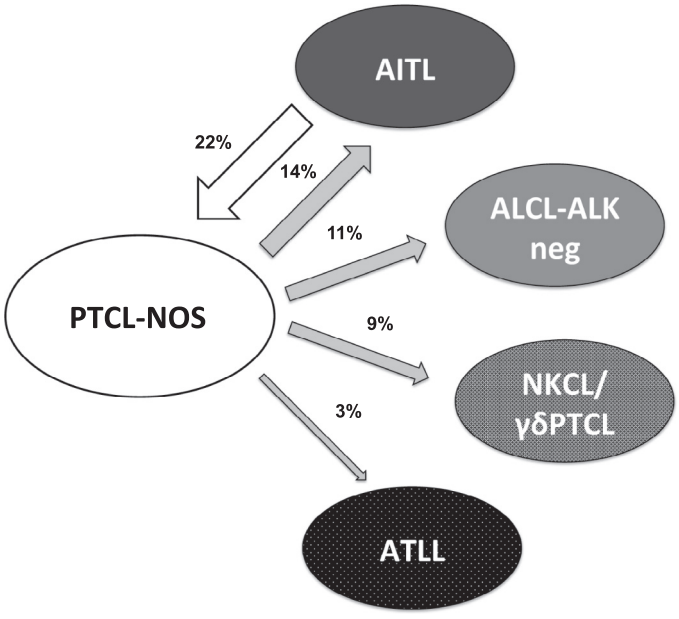

Fig. 2. Percentage of reclassified patients according to gene expression signatures by Iqbal et al. [12]. A total 37% of PTCL-NOS were classified thought other WHO entities: (i) AITL (n = 21, 14%); (ii) ALCL ALK-neg (n = 17, 11%); (iii) ATLL (n = 4, 3%); (iv) γδ-PTCL (n = 13, 9%). Twenty-six (22%) AITL cases were not molecularly classifiable and changed to PTCL-NOS.

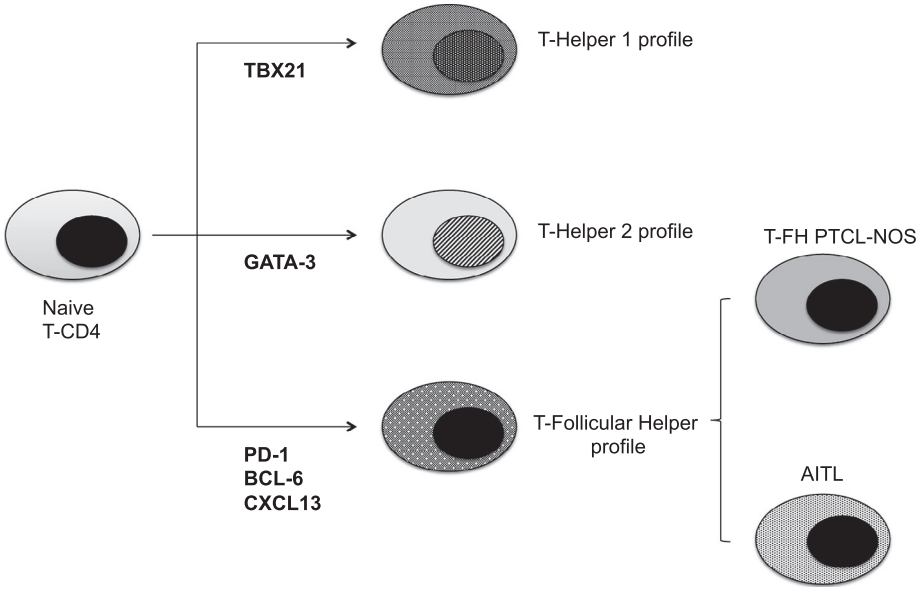

Fig. 3. Hypothetical cell-of-origin model for PTCL-NOS based on gene expression data.

significant heterogeneity, again reinforcing the notion that discrete entities are still grouped in this category [12,34]. For example, the existence of a distinct PTCL-NOS sub-group has been postulated that has a poor prognosis and expresses a unique repertoire of transcripts enriched for pathways associated with T-CD8+ cell differentiation [34]. Among these, transcripts encoding cytotoxic molecules and the transcription factor *TBX21*, which has a pivotal role in Th1 cell differentiation at the expenses of Th2 cells, and in the development of CD8+ effector cells (Fig. 3) [72]. A more recent and larger study on reclassified PTCL-NOS cases confirmed that GEP analysis identified a *TBX21*-overexpressing subgroup (49% of patients), but also reported the presence of a second group (33%) characterized by overexpression of *GATA3* [12]. Although *GATA3* and *TBX21* gene expression levels showed a significant inverse correlation, more than 20% of PTCL-NOS did not meet criteria for either group and were defined as "unclassified." Biological and phenotypic features of these "unclassified" PTCL-NOS patients are still unknown. Conversely, the *TBX21* group confirmed a cytotoxic profile and significant enrichment of IFN- and NFkB-related gene expression signatures, while samples characterized by overexpression of *GATA3* and of its known target genes (*CCR4*, *IL18RA*, *CXCR7*, *IK*) were enriched for PI3K-, mTOR- and MYC-related signatures. Furthermore, these patients showed a profile compatible with a T-CD4+ cell origin, where *GATA3* is known to have a critical role in differentiation and maturation [64,73]. Contrary to the early study [34], subsequent analyses [12,71] showed that *TBX21* overexpression by GEP or IHC was associated with a much better prognosis than *GATA3* overexpressing cases.

MicroRNA expression profiles have also recently been investigated and highlighted the enrichment of different sets of microRNA in the various PTCL subtypes when compared to normal mature T-cells [74]. A microRNA-based classifier was then developed that was able to assign each PTCL case to its correct subgroup with 97.5% concordance when compared with other molecular classifiers, suggesting that the use of microRNA profiling may improve the diagnosis and classification of PTCL.

6. Mutational spectrum

Different groups have recently investigated the mutational landscape of PTCL by NGS approaches, mainly whole exome sequencing (WES). Among ALCL and AITL, different genes were reported to be recurrently mutated [7,11,13–15,75]. In ALK-neg ALCL, Crescenzo et al. recently published a comprehensive characterization of driver genetic alterations converging to STAT3 activation, providing evidence that inhibition of STAT3 has therapeutic efficacy in vivo [11]. Specifically, STAT3 could be activated by direct mutations and/or *JAK1* mutations in ~20% ALK-neg ALCL. In *JAK1/STAT3* WT cases, RNAseq analysis identified novel recurrent oncogenic translocations where the 3' end of the tyrosine kinases *ROS1* or *TYK2* was fused to the 5' portion of *NFkB2*, *NCOR2* or *PABPC4* (all genes with high expression levels in T-cells), resulting in oncogenic STAT3 activation. Interestingly, these recurring alterations were not found in PTCL NOS with overexpression CD30+ that shared morphological and phenotypic features with ALK-neg ALCL.

Among AITL patients, recent studies surprisingly described mutations in genes previously involved in myeloid malignancies: *TET2* (70%), a methylcytosine dioxygenase that catalyzes the conversion of methylcytosine to 5-hydroxymethylcytosine, *DNMT3A* (26%), a DNA methyltransferase, and *IDH2* (30%), an enzyme of the Krebs cycle that produces a TET2-inactivating oncometabolite when mutated [13–15,75]. While this suggests a common theme of DNA methylation as a recurrently affected pathway across hematological malignancies, these mutations tended to frequently co-occur in the same patient in PTCL, differently from what previously reported for example in myelodisplastic syndromes [76,77]. In addition, mutations in *RHOA*, a member of the Rho family of small GTPases that control the cytoskeleton actin, were identified in 50–70% of patients affected by AITL (Table 5). Interestingly, *RHOA* and *IDH2* mutations where found at lower allelic frequencies and in tumor cells only, while co-occurring *TET2* and *DNMT3A* mutations were also found in white cells not belonging to the lymphoma clone [14]. This suggests an intriguing multi-step tumorigenesis process where first *TET2* and/or *DNMT3A* mutations at the progenitor level/stem cell level drive the expansion of a hematopoietic clone, likely of the same nature as those recently described in age-related clonal hematopoiesis [78–80]. This would create a favorable genetic background in mature clonal T-lymphocytes for the development of

Table 5
Mutational landscape of AITL and PTCL-NOS according with recent next generation sequencing data.

Ref	RHOA		TET2		DNMT3A		IDH2	
	AITL	PTCL-NOS	AITL	PTCL-NOS	AITL	PTCL-NOS	AITL	PTCL-NOS
[15]	53.3% (24/45)	7.7% (1/13)	nd	nd	nd	nd	nd	nd
[13]	67% (22/35)	18% (8/44)	73% (22/30)	29% (5/17)	23% (7/30)	12% (2/17)	13% (4/30)	0% (0/17)
[14]	71% (51/72)	17% (15/87)	82.6% (38/46)	48.5% (16/33)	26% (12/46)	27.3% (9/33)	30.5% (14/46)	0% (0/33)
[82]	71.8% (28/39)	27% (11/41)	59% (23/39)	46% (19/41)	38.5% (15/39)	36.6% (15/41)	33% (19/58)	4% (1/24)

subsequent *RHOA* mutations that can then divert the phenotype toward a PTCL, similar to what happens in AML where *NPM1* mutations are thought act at in a similar way downstream of pre-existing, non-clinically apparent mutations (Fig. 4) [81].

A similar mutational profile to AITL was also detected in the small number of PTCL-NOSs analyzed by WES (n = 6), and in subsequent extension cohorts (n = 44) by candidate targeted sequencing [13]. Specifically, 48.5%, 17.2% and 27.3% of PTCL-NOS samples harbored *TET2*, *RHOA* and *DNMT3A* mutations, respectively, and similar to AITL, all these mutations frequently co-occurred in the same patients. On the contrary, no *IDH2* mutations were initially described among PTCL-NOSs [13]. A comparable mutational spectrum was found in *GATA3* and *TBX21* GEP subgroups, thus not providing any insight on the causal relation between the tumor genotype and its expression profile [82]. Interestingly, 13 of 15 PTCL-NOS cases harboring *RHOA* mutations were characterized by an AITL-like phenotype and had a T-follicular helper gene expression profile [83]. Furthermore, *IDH2* mutational analysis of the large PTCL cohort annotated by GEP [12] showed that *IDH2* mutations were frequent in PTCL-NOS reclassified as AITL (4/11) but almost absent in AITL reclassified as PTCL-NOS (1/14). In retrospect, it is likely that the presence of PTCL NOS cases with TFH profile, which are now known to share more biological and pathological features with AITL than with PTCL-NOS, was responsible for the asymmetric exchange of *IDH2* mutated patients between PTCL-NOS and AITL prompted by gene expression profiling [33,39,70]. Together, these data suggest that the TFH PTCL-NOS subgroup shares genomic as well as phenotypic features with AITL more than it does with PTCL-NOS, and stresses the challenges of the current PTCL histologic classification (Fig. 3).

In light of the above, no specific and recurrent mutations have been found in PTCL-NOS by WES so far. This was recently challenged by a targeted deep sequencing approach for candidate driver gene mutations in a series of 28 PTCL-NOS samples that excluded cases with AITL features [84]. With the limitations of a gene-discovery analysis based on a prespecified list of candidate drivers without matched germline DNA, the report highlighted frequent mutations in genes related to epigenetics. Regulators of histone methylation were mutated in 25% of cases, including mutations in *KMT2D* (4/28 cases), *KDM6A* (3/28) and *KMT2A* (2/28), and were associated with a poorer survival. Regulators of DNA methylation were also affected in 25% of cases, including *TET2* (3 cases) and *DNMT3A* (2 cases). Moreover, genes related to chromatin remodeling mediated by the *SWI/SNF* complex activity were mutated in 18% of cases and 46% of the cases, respectively. (Table 5).

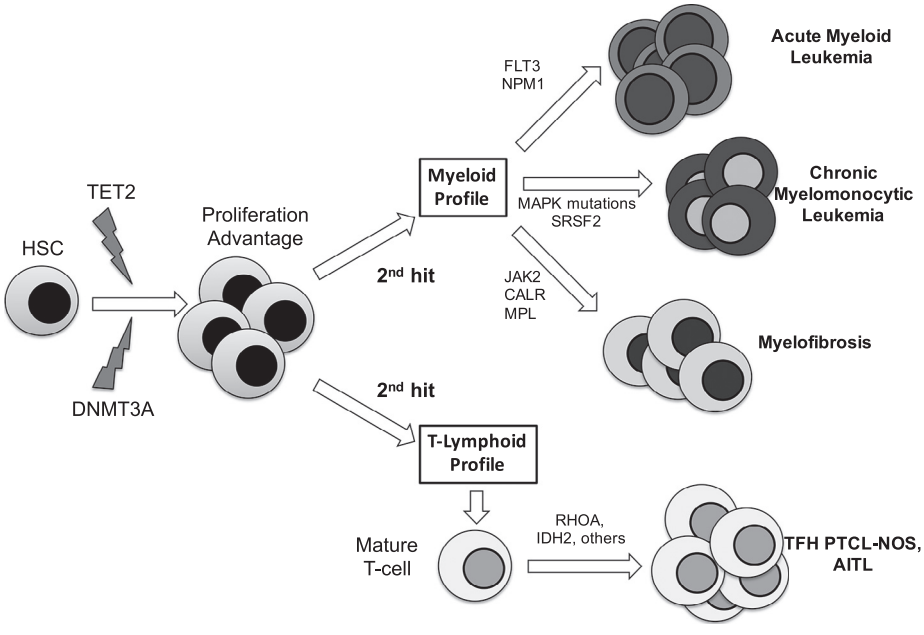

Fig. 4. Hypothetical model of T-cell lymphomagenesis based on recent mutational discoveries.

Table 6
Clinical trial efficacy results of novel single-agent treatment in relapse/refractory PTCL-NOS patients.

Drug	Drug Class	PTCL NOSs number	ORR	CR	Ref
Brenutximab	Conjugated MoAb anti-CD30	21	31%	14%	[91]
Alisertib	Aurora Kinasi i[a]	13	31%	7.5%	[88]
Romidepsin	HDACi[b]	38	29%	14%	[90]
Belinostat	HDACi[b]	77	23%	–	[92]
Pralatrexate	Antifolate CT[c]	53	32%	–	[93]
Mogamulizumab	MoAb anti CCR4[e]	16	19%	6%	[94]
Lenalidomide	IMIDs[d]	14	43%	14%	[95]
Bortezomib	Proteosome i[a]	2	50%	50%	[96]

[a] i = inhibitor
[b] HDACi = Histone Deacetylase Inhibitors
[c] CT = chemotherapy agent
[d] IMID = immunomodulatory drug
[e] MoAb = monoclonal antibody

7. Conclusions and future perspectives

Thanks to the availability of novel, often high-throughput analysis techniques, in the last decades we moved from a purely morphological description of PTCL cases to a much deeper understanding of their intrinsic biology. This has revealed that AITL and ALK-neg ALCL have a fairly homogeneous set of genotypic and phenotypic features, justifying their existence as distinct clinico-pathological entities [11–15]. However, PTCL-NOSs are still regarded to as a heterogeneous category encompassing every PTCL case that does not fit into other specific subtypes. As such, the group of PTCL-NOS is an interesting field of research either to find unifying features of its cases, or to resolve its heterogeneity into several distinct and more homogeneous subgroups. On this note, it is encouraging to observe how the existence of a subset of PTCL-NOS that have a follicular appearance and share morphologic and phenotypic features with AITL [85] has more recently been substantiated by the finding that such cases, grouped into the term TFH PTCL-NOS, are characterized by distinct cytogenetic, transcriptomic and genomic features that suggest they should be assigned to a distinct entity. We therefore believe that, given the similarities between TFH PTCL-NOS and AITL, the former subgroup should be excluded from future PTCL-NOS studies, as its inclusion could introduce a confounding factor and hamper the correct interpretation of the results. While we are gaining insight into those groups that show the most distinctive features, it will be harder to find relevant information on the residual cases that still lack unifying features. In the future, an integrated approach looking at the whole constellation of genomic features (mutations, structural variants, and mutational signatures), expression profiles and clinical outcomes of PTCL-NOS will hold the promise of shedding some light into this subgroup of PTCLs. Only such large-scale efforts have the potential to inform on the complex biology of such cases, providing rationale bases for a novel classification of PTCL based on real clinico-pathological entities, and possibly to provide novel prognostic markers and therapeutic targets.

While the recent advances described here have not yet translated into advances in clinical practice, it is likely that in the near future, specific gene mutation or expression patterns will be harnessed as novel diagnostic tests to overcome diagnosis issues related to cases not univocally classified on morphological grounds. As an example, the search for *RHOA* and *IDH2* mutations is already performed in some laboratories to distinguish AITL from PTCL-NOS. Furthermore, as increased GATA3 mRNA expression correlates with a poor prognosis, efforts are underway to validate standardized IHC methods to predict outcome of PTCL-NOS from routine trephines based on the expression of the GATA3 protein.

PTCL-NOS remains an aggressive disease with a poor survival [1]. Conventional chemotherapy approaches explored so far, including upfront autologous stem cell transplant, resulted in an unsatisfactory improvement of survival [3,86,87]. The use of novel, targeted treatments in PTCL has shown mixed results (Table 6) [30,88–96]. Nevertheless, biological evidence supporting the use of these novel therapeutic agents is lacking, and promising responses are admixed with complete failures. The future identification of recurrent genomic aberrations and aberrantly activated oncogenic pathways will thus help the clinician to prioritize novel targeted approaches to be validated in prospective trials, and provide markers of response that could inform on the best treatment approach in individual patients.

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Conflict of interest

There are no conflicts of interest to report.

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