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Original Research Article

Pitfalls and major issues in the histologic diagnosis of peripheral T-cell lymphomas: results of the central review of 573 cases from the T-Cell Project, an international, cooperative study

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Abstract

Peripheral T-cell lymphomas (PTCLs) comprise a heterogeneous group of neoplasms that are derived from post-thymic lymphoid cells at different stages of differentiation with different morphological patterns, phenotypes and clinical presentations. PTCLs are highly diverse, reflecting the diverse cells from which they can originate and are currently subclassified using World Health Organization (WHO) 2008 criteria. In 2006 the International T-Cell Lymphoma Project launched the T-Cell Project, building on the retrospective study previously carried on by the network, with the aim to prospectively collect accurate data to improve knowledge on this group of lymphomas. Based on previously published reports from International Study Groups it emerged that rendering a correct classification of PTCLs is quite difficult because the relatively low prevalence of these diseases results in a lack of confidence by most pathologists. This is the reason why the T-Cell Project requested the availability of diagnostic material from the initial biopsy of each patient registered in the study in order to have the initial diagnosis centrally reviewed by expert hematopathologists. In the present report the results of the review process performed on 573 cases are presented. Overall, an incorrect diagnosis was centrally recorded in 13.1% cases, including 8.5% cases centrally reclassified with a subtype eligible for the project and 4.6% cases misclassified and found to be disorders other than T-cell lymphomas; 2.1% cases were centrally classified as T-Cell disorders not included in the study population. Thus, the T-Cell Project confirmed the difficulties in providing an accurate classification when a diagnosis of PTCLs is suspected, singled out the major pitfalls that can bias a correct histologic categorization and confirmed that a centralized expert review with the application of adequate diagnostic algorithms is mandatory when dealing with these tumours. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: **peripheral T-cell lymphomas; pitfalls; misdiagnosis; expert hematopathologist review**

Introduction

Peripheral T-cell lymphomas (PTCLs) constitute a heterogeneous group of aggressive T- and NK-cell disorders arising via oncogenic transformation of mature (post-thymic) T and NK cells in peripheral lymphoid organs [1]. The different entities belonging to this group have different morphological and immunophenotypical patterns and can be recognized for the diverse clinical presentation, a usually aggressive clinical course and poor response to available chemotherapy [2]. High diversity of PTCLs reflects the diverse cells from which they can originate [2–7].

The 2008 WHO classification for hematopoietic malignancies [2] roughly divides the PTCLs into four categories according to their presentation: predominantly leukaemic (disseminated), nodal, extranodal and cutaneous. In each category, entities are further differentiated based on morphologic, genotypic, genetic and immunohistochemical criteria, as well as clinical behaviour.

Mature T-cell and NK-cell neoplasms usually affect middle-aged or elderly adults and have a higher incidence in males than in females. The median age at diagnosis is between 55 and 60 years [8,9].

Compared to B-cell lymphomas, mature T/NK-cell lymphomas are uncommon malignancies, representing 10–15% of new non-Hodgkin's lymphomas cases per year [10], with relevant geographic differences [2,11]. An impressively typical epidemiological distribution among geographic areas of PTCLs is well documented [9,12–16]. PTCLs are rare in Western hemisphere [15,17], and their incidence is slightly higher in Asia [11,18,19] and in Central and South America [12,20–23].

By some estimates, the incidence of PTCLs has increased significantly in recent years in some industrialized countries, the growth being driven by an ageing population [24] or because of an apparent growth in incidence because of improvements in diagnosis techniques [25].

Moreover, even if standard operating procedures and the appropriate panel of all needed immunochemistry tests would be applicable, the relatively low prevalence of these diseases and the resulting lack of confidence by most hematopathologists wouldn't allow in many circumstances a correct diagnosis. Thus, expert hematopathology review with the application of adequate diagnostic algorithms is essential when dealing with these tumours.

We report here on pitfalls and on difficulties in correctly diagnosing PTCLs out of referral centres according to results and observations coming from the initial diagnosis central review process of patients registered in the T-Cell Project.

Methods

The T-Cell Project (NCT01142674) was incepted in 2006 as a prospective registry of patients with PTCLs. The study was conducted in compliance with the Helsinki Declaration of 1975 as revised in 1983, was approved by the appropriate research ethics committees and required each patient to provide written informed consent before registration. This study is designed as a prospective collection of information that are potentially prognostic for newly diagnosed patients with the more frequent subtypes of PTCL, not otherwise specified (PTCL-NOS) and Angioimmunoblastic T-Cell Lymphoma (AITL) and to better define clinical characteristics and outcome of the more uncommon subtypes (Extranodal NK/T-cell lymphoma; Enteropathy-type T-cell lymphoma; Hepatosplenic T-cell lymphoma; Peripheral gamma-delta T-cell lymphoma; Subcutaneous panniculitis-like T-cell lymphoma; Anaplastic large-cell lymphoma, T/null cell, primary systemic type) [26]. Data collection was done via electronic Case Report Forms (eCRFs) at a dedicated website (www.tcellproject.org), with the adoption of SSL03 technology assuring protection in web communications of subject's clinical data. Data access and management were regulated by the use of passwords with different level of admittance, providing that subject confidentiality was respected. An exhaustive set of information at baseline including clinical, laboratory and disease extent data, therapy details and outcome data were collected. Moreover, a dedicated electronic pathology form allowed sites to enter detailed biomarkers profile as from the results of the tests performed at peripheral sites reported in the local pathologist report. Data management and study management were performed at the study Trial Office in Modena, Italy.

Central review of diagnostic biopsy was planned for each patient registered. Four regional review sites were identified for the project, including Italy, Germany, US, and South Korea. In a second step two further expert pathologists agreed to serve as reviewers. Material needed for review process was forwarded by the Trial office staff to one of the regional site for central review.

The oncologist and pathologist at each local site were asked to select consecutive cases seen at their institution which met the following study criteria: diagnosis of peripheral T/NK-cell lymphoma/leukaemia (excluding Mycosis Fungoides/Sezary Syndrome and lymphoblastic subtypes); adult patients (≥18 years old); de novo cases diagnosed after 1 September 2006; diagnosis made from a tissue biopsy with available phenotype data, glass slides and formalin-fixed tissue blocks; clinical data available. Adequate clinical data at the time of initial diagnosis was required for all cases, including patient characteristics and treatment data. Long-term follow-up was required for at least 5 years for surviving patients. Tissue biopsies adequate for diagnosis and classification were required for all cases. Fresh tissue samples were to be processed by ordinary fixation in 10% buffered formalin for 24 h at room temperature. For each case, an adequate and representative formalin-fixed tissue block should be selected to be sent to

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the regional review site for additional stains; in the case a block was not available, 20 unstained sections cut on electrically charged slides (to allow usage in an immunostainer) at 3-micron of thickness were to be provided instead from each block, if possible with two cores (measuring 1 mm across) taken from each block using a tissue microarryer. An exception would be cases with good clinical data, but where the blocks have been exhausted or were no longer available: in this situation, such cases could be included if adequate H&E slides and immunostains, or phenotype data by flow cytometry, were available for review and allow proper diagnosis and classification. Cases where the bone marrow was the primary site of lymphoma were also considered eligible.

All samples and reports were to be de-identified by the peripheral site staff and labelled with the code assigned in the study.

As to the central review process, the expert pathologists at regional sites had to review the pathological material by strictly applying the criteria of the most recent edition of the WHO Classification of the Tumours of Haematopoietic and Lymphoid Tissues [2]. The initial diagnosis was classified by each pathologist on the basis of examination of the hematoxylin–eosin- and/or Giemsa-stained slides, the immunostains performed by local pathologist and the pathology form data. Clinical data were also available for examination. The cases were to be studied with a panel of immunostains including CD20, PAX5, CD2, CD3, CD4, CD5, CD7, CD8, CD30, CD56, TCR-β, TCR-gamma, PD1, BCL6, CD10, CXCL13, TIA-1, Granzyme B, Perforin, CD21 and Ki-67, and in situ stains for EBV-encoded RNAs, as well as any additional immunostains and polymerase chain reaction analyses, and fluorescence in situ hybridization studies if needed, and each case was to be classified by the expert hematopathologist at the regional site. If the diagnosis rendered by the central reviewer confirmed initial diagnosis the review process was considered completed. If a case was considered unclassifiable, the expert was required to give a reason, and the case retained temporarily in the study with the initial diagnosis. If the case was reclassified with an histology ineligible for the study, all the material was to be returned to the Trial Office and then sent to a second regional site; in case of discrepancy between the result rendered by the first and second central reviewers, the material was to be re-centralized at Trial Office and evaluated during a consensus meeting to be performed at the end of the central review process.

Results

From September 2006 to May 2015, 1,451 patients (pts) were registered in the T-cell Project by 74 sites from 14 countries worldwide, and 22 have been excluded for various reasons (10 for patient's consent missing/withdrawn; 8 after local review; 3 for lack of data, and one because of relapsed disease). The central diagnosis review process has pertained so far 573 cases out of the 1286 validated (44.6%).

The subtypes of lymphoma and other disorders identified after review are listed in Table 1.

A diagnosis of PTCL or NKTCL was confirmed in 461 of the cases (80.4%); 49 patients (8.5%) were misclassified locally and reclassified by central reviewers with a different subtype among those eligible for the study, and kept in the study with the central diagnosis. Among cases proved as eligible after review the most frequent subtype was found to be PTCL,NOS (34.6%); AITL (16.1%) and NKTCL (16.4%) were identified as the second most common subtypes. Anaplastic large-cell lymphoma (ALCL), ALK negative (ALK−) represented 12.9%, and ALCL, ALK positive (ALK+) 6.3%. Enteropathy-type PTCL was the most common subtype of the extranodal T-cell category (4.7%), while all the other specific subtypes of PTCL represented around 9% of the total.

Thirty-eight patients (6.7%) were excluded after review because 12 were reclassified with T-cell disorders not specifically included in the study population (2.1%) and 26 (4.6%) were centrally found to be disorders other than T-cell lymphoma, including B-cell lymphoma (1.4%), Hodgkin lymphoma (0.7%), disorders other than lymphomas, (0.2%), non-neoplastic lymphoproliferation (2.1%) or unclassifiable lymphoma (0.2%). Thus, a total of 13.1% of the cases were misclassified, including 8.5% centrally reclassified with an eligible subtype, and 4.6% excluded; 4.4% of the patients could not be adequately classified by central reviewers because of inadequate material or technical factors and were kept in the study with the diagnosis made by local pathologist and 2.1% were wrongly included in the study being T-cell disorders not eligible for the study.

Discrepancies between the local and central diagnosis are reported in Table 2. The subtypes for which the major difficulties in correctly diagnosing and classifying the disease by local pathologists were PTCL-NOS (35 misdiagnosed cases) and ALCL, ALK− (29 cases). Five and four cases of PTCL-NOS according to local diagnosis were reclassified as Enteropathy type and AITL, respectively; moreover, eight cases were found to be non-neoplastic lymphoproliferation, five were reclassified as immature T-cell lymphoblastic leukaemia/lymphoma and four as Adult T-cell leukaemia/lymphoma (ATLL). In 13 cases diagnosed peripherally as ALCL, ALK− the diagnosis rendered by the central reviewer was that of PTCL-NOS, and 6 cases were found to be B-cell lymphomas. With respect to NKTCL, the most frequent local mistake was confusion of nasal and extranasal forms. In two cases a local diagnosis of AITL was interpreted centrally as Hodgkin lymphoma.

Distribution of different subtypes by geographic region for the 535 eligible after central review is shown in

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Table 1. Distribution of the 573 cases by central review results

Diagnosis	Confirmed		Reclassified		Review not possible[a]		Total		
	N	%	*N*	%	*N*	%	*N*	%	$\%_{VAL}$
PTCL-NOS	157		17		11		185	32.3	34.6
PTCL, unspecified type	*151*		*16*		*11*		178		
PTCL, lymphoepithelioid type	*4*		—		—		4		
PTCL, parafollicular type	*1*		*1*		—		2		
PTCL, T-zone type	*1*		—		—		1		
Angioimmunoblastic	80		5		1		86	15.0	16.1
NKTCL	77		8		3		88	15.4	16.4
Nasal NKTCL	*14*		*1*		*2*		17		
Extranasal NKTCL	*54*		*7*		*1*		62		
Unclassifiable NK-cell	*9*		—		—		9		
ALCL, ALK positive	28		4		2		34	5.9	6.3
ALCL, common type	*25*		*4*		*2*		31		
ALCL, small cell type	*1*		—		—		1		
ALCL, lymphohistiocytic type	*2*		—		—		2		
ALCL, ALK negative	57		5		7		69	12.0	12.9
Enteropathy-type	18		6		1		25	4.4	4.7
Hepatosplenic	10		1		—		11	1.9	2.1
Subcutaneous panniculitis-like	9		—		—		9	1.6	1.7
Peripheral γ/δ	5		—		—		5	.8	.9
Unclassifiable PTCL	20		3		—		23	4.0	4.3
Total	461	80.4	49	8.5	25	4.4	535	93.3	100.0
Excluded							**38**	**6.7**	
Other T-cell disorders							**12**	**2.1**	
ATLL							4		
T-cell lymphoblastic leukaemia/lymphoma							5		
Primary cutaneous lymphoma, indolent							2		
CD8+ epidermotropic cytotoxic							1		
Other disorders							**26**	**4.6**	
B-cell lymphoma							8		
Hodgkin lymphoma							4		
Unclassifiable lymphoma							1		
Acute myeloid leukaemia							1		
Non neoplastic lymphoproliferation							12		
Total							573	100.0	

Abbreviations: PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; NKTCL, natural killer/T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ATLL, adult T-cell leukaemia/lymphoma.
[a]Review not possible because of inadequate material or technical factors; cases kept in the study with local diagnosis.

Table 3. Unexpectedly, ALCL, ALK− are present in a higher proportion with respect to literature data: this is probably because of the large contribution of South American sites, where ALCL, ALK− is the most common subtype apart from PTCL-NOS.

Discussion

The results of the review of more than 500 cases of PTCLs confirm that a correct diagnosis is still a very critical issue that needs a painstaking attention. Clinical, immunophenotypic, histopathological, immunohistochemical, molecular and genetic findings must be correlated as none of them individually provides evidence for a certain diagnosis. As a result, these neoplasms can be easily misclassified or misdiagnosed in the daily practice.

The International T-Cell Lymphoma Project retrospectively evaluated a cohort of 1314 cases of PTCL and NKTCL diagnosed between 1990 and 2002, and represents the largest evaluation published to date in this subset of patients [9]. They reported 10.4% of the cases were either misclassified by the peripheral pathologists or could not be adequately classified by the experts and 1.8% were diagnosed as other T-cell disorders not specifically included in the study. Our results are superimposable, misclassification being found in 13.1% of patients, with an additional 2.1% of patients diagnosed by the expert pathologist with a T-cell lymphoma ineligible for the study. These findings indicate that we still lack reliable tools, specific markers

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Table 2. Local and central diagnosis of 49 reclassified and 38 excluded cases

Diagnosis of local pathologist	No cases	Diagnosis of expert pathologist	No cases
PTCL-NOS	35		
PTCL, unspecified type	34	Enteropathy type	5
		Angioimmunoblastic	4
		NKTCL, extranasal	2
		PTCL-NOS, parafollicular type	1
		ALCL, ALK–	1
		Unclassifiable PTCL	3
		T-cell lymphoblastic leukaemia/lymphoma	5
		ATLL	4
		Primary cutaneous lymphoma, indolent	1
		Acute myeloid leukaemia	1
		Non-neoplastic lymphoproliferation	7
PTCL,T-zone type	1	Non-neoplastic lymphoproliferation	1
ALCL, ALK–	29		
		PTCL-NOS, unspecific type	13
		ALCL, ALK+, common type	3
		Enteropathy type	1
		NKTCL, extranasal	1
		Primary cutaneous lymphoma, indolent	1
		B-cell lymphoma	6
		Hodgkin lymphoma	2
		Unclassifiable lymphoma	1
		Non-neoplastic lymphoproliferation	1
ALCL, ALK+	7		
ALCL, common type	6	PTCL-NOS, unspecific type	2
		ALCL, ALK–	2
		Angioimmunoblastic	1
		B-cell lymphoma	1
ALCL, lymphohistiocytic type	1	ALCL, ALK+, common type	1
NKTCL	7		
Nasal NKTCL	5	NKTCL, extranasal	3
		ALCL, ALK–	1
		Non-neoplastic lymphoproliferation	1
Extranasal NKTCL	2	NKTCL, nasal	1
		B-cell lymphoma	1
Subcutaneous panniculitis-like	4		
		ALCL, ALK–	1
		NKTCL, extranasal	1
		CD8+ epidermotropic cytotoxic	1
		Non-neoplastic lymphoproliferation	1
Angioimmunoblastic	3		
		PTCL-NOS, unspecific type	1
		Hodgkin lymphoma	2
Unclassifiable PTCL	2		
		Hepatosplenic	1
		Non-neoplastic lymphoproliferation	1

Abbreviations: PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; NKTCL, natural killer/T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ATLL, adult T-cell leukaemia/lymphoma.
Grey background identifies excluded cases.

and objective criteria to improve accuracy in the routinely diagnostic work-up for these entities.

As above mentioned, it has been predicted that PTCLs derive from distinct subpopulations of T lymphocytes with different functions and molecular profile. However, several confounding factors exist, and the rarity of the diseases, and frequent nonspecific morphologic and immunophenotypic features make often difficult to determine their cell of origin and restraint precise definition and a correct classification into distinct biologic subtypes for the single entities [27,28]. Studies published over the past decade relying on the use of conventional cytogenetic tests report limited recurrent karyotypic abnormalities, in most of the cases lacking disease specificity [29–31]. With the introduction of standardized techniques and validated standard operating procedures the identification of clonal T-cell

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Table 3. Distribution of the 535 cases eligible after central review by geographic region

Diagnosis	Europe		USA		South America		Asia		*Total*	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
PTCL-NOS	101	35.4	13	40.6	40	43.5	31	24.6	*185*	*34.6*
Angioimmunoblastic	55	19.3	4	12.5	6	6.5	21	16.7	*86*	*16.1*
NKTCL	25	8.8	3	9.4	12	13.0	48	38.1	*88*	*16.4*
ALCL, ALK positive	25	8.8	–	–	7	7.6	2	1.6	*34*	*6.4*
ALCL, ALK negative	44	15.4	4	12.5	18	19.8	3	2.4	*69*	*12.9*
Enteropathy-type	17	6.0	1	3.1	5	5.4	2	1.6	*25*	*4.7*
Hepatosplenic	7	2.5	1	3.1	1	1.1	2	1.6	*11*	*2.1*
Subcutaneous panniculitis-like	2	0.7	3	9.4	–	–	4	3.2	*9*	*1.7*
Peripheral γ/δ	2	0.7	1	3.1	–	–	2	1.6	*5*	*0.9*
Unclassifiable PTCL	7	2.5	2	6.3	3	3.3	11	8.7	*23*	*4.3*
Total	285		32		92		126		*535*	

populations has entered into the routine approach to these diseases [32,33]. It is now well recognized that the application of a defined panel of immunohisto/cytochemistry could limit the rate of diagnostic errors, thus allowing the recognition of the majority of the PTCLs [34]. Recently, state-of-the-art technology studies of comparative genomic hybridization, gene expression profiling and gene sequencing have helped outline differences and similarities at the genetic levels of different PTCLs subtypes [35–44].

Notwithstanding, new techniques are not available to the most of hematopathologists, and the analyses allowed by these up-to-date tests are mainly restricted to research protocols and not devoted to routine practice when a PTCLs is suspected.

In conclusion, the T-Cell Project experience highlights that expert hematopathology review with the application of adequate diagnostic algorithms is essential when dealing with these tumours, because a misdiagnosis could have a crucial impact on a correct treatment choice and consequently on patient care [45,46]. Moreover, with the advent of the updated WHO classification, which will increase the number of markers and molecular tests required for a correct identification and classification of PTCLs, a new organization of the diagnostic process should be planned, favouring the activation of referral centres for offering the patients the best chances to be correctly diagnosed and treated as well.

Conflict of interest

The authors declare that they have no competing interests.

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