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Introductory Chapter: Updates and New Insights from WHO 2017 Peripheral T-Cell Lymphoma Classification

Pier Paolo Piccaluga

1. Introduction

Peripheral T-cell lymphomas (PTCLs) are relatively rare disorders, representing around 10% of all lymphomas worldwide; however, they are relatively common in specific geographic areas, including Asia, the Caribbean basin, and scattered areas in Europe where HTVL1 is endemic.

In the latest edition of the World Health Organisation (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues, edited in 2017, nodal, extra nodal and leukaemia forms are listed. Specifically, as many as 31 entities are listed among PTCLs [1]. Compared with the previous edition, in the current classification, a few but quite relevant novelties have been introduced. Generally speaking, as already observed for B-cell derived malignancies, recent discoveries from molecular genetic studies led to a better definition of certain entities and clearly defined a pivotal role for cellular derivation in tumour classification. In the following, the main updates concerning non-cutaneous PTCLs will be briefly discussed.

2. T-follicular helper cell-related lymphomas

Among nodal PTCLs, that overall constitute the majority of PTCL cases, a new subgroups has been defined based on the corresponding to a specific cellular counterpart, namely the T-follicular helper (TFH) lymphocytes. The latter is physiologically represented within germinal centres of secondary follicles, providing costimulatory signalling to B-lymphocytes through many different signaling pathways [2]. These cells, at immunophenotyping, are characterised by the expression of selected markers, including BCL6, SAP, ICOS, CXCL13 and CD10. Consistently, tumors derived from TFH cells express these molecules. However, likely due to the aberrancy in phenotype, which is typical of PTCLs [3], some of them may lack in a single case. Therefore, an extended panel should be tested to confirm the diagnosis. On the other hand, since non-TFH-derived PTCLs may express one of these markers, it is recommended to detect positive staining for at least two (better would be three) of them to claim a TFH derivation [4]. TFH-related PTCLs currently include three main nodal PTCL types, namely angioimmunoblastic T-cell lymphoma (AITL, the commonest PTCL in northern Europe), follicular T-cell lymphoma (FTCL, formerly accounted among PTCLs not otherwise specified/NOS), and PTCL/NOS not fulfilling the diagnostic criteria for the previous tumors but showing

a clear TFH-phenotype. Such cases were characterised and associated to TFH-lymphocyte at both transcriptional and protein level [5–7].

Beside the cell of origin, *per se* relevant criteria for tumour classification, TFH-related PTCLs also share, at least for a certain extent, the genetic background and, therefore, the molecular pathogenesis. Particularly, genes controlling epigenetic regulation of gene expression as well as gene involved in T-cell receptor (TCR) signalling appeared to be more commonly deregulated [8, 9]. The presence of *TET2*, *IDH2* and *DNMT3A/B* somatic mutations is detected in about 20–80% of cases [10, 11]. Intriguingly, it was recently shown that treatment with 5-azacytidine, a well-known demethylating agent, currently approved for acute myeloid leukaemia therapy, was strikingly effective in patients affected by TFH-PTCL, with sustained clinical responses observed in previously relapsed/refractory cases [12]. Second, mutations affecting *RHOA* were observed in up to 70% of AITL cases and in a variable percentage of other PTCLs [9, 11]. By deregulating the *RHOA* GTPase protein, the TCR signalling is eventually affected. Similar effects are determined by *VAV1* rearrangements that are mutually exclusive with *RHOA* mutations. Less frequently, other genetic events can inter with TCR singling, including *PLCG1* (14%), *CD28* (9–11%) and *FYN* (3–4%) [8].

Finally, *ITK/SYK* rearrangements, due to the t(5;9) translocation, are quite common in FTCL, being only occasionally recorded in AITL.

Therapeutic strategies designed against aberrant TCR are currently under investigation.

3. Extra-nodal, non-cutaneous PTCL

As far as this category of PTCLs is concerned, the main novelties regard anaplastic large cell lymphomas (ALCLs) and intestinal PTCLs.

Among ALCLs, first of all, ALCL ALK-negative has been regarded as an independent entity, mainly based on gene expression data [13–15] and more recent genetic data acquired through next generation sequencing [16]. In fact, ALCL ALK-negative was shown to have a global gene expression profile (GEP) different from other PTCLs and specially PTCL/NOS, carrying recurrent genetic rearrangements eventually leading to *STAT3* activation [16]. Noteworthy, this finding provides the molecular basis for the similarities between ALCL ALK-positive and negative, since *STAT3* is the main downstream of *ALK* as well.

Second, a new provisional entity has been introduced, the breast-implant-associated (BI) ALCL. This tumour, although very uncommon, solicited great attention for the social impact. In fact, it selectively arises in patients who received a breast implant after oncologic or simply aesthetic surgery. The tumour can present as wither a serum (i.e. with malignant cells floating in a serous fluid around the capsule) or as tumbrel mass, the latter cases being more aggressive. Of note, recent GEP studies indicated that BI-ALCL is distinct from ALK-positive and negative cases, but presents with the same typical features including *STAT3* activation and TCR singling downregulation [17]. The genetic background of the disease needs, however, to be fully elucidated.

As far as intestinal PTCLs are concerned, it has become apparent that the two subtypes formerly designated as variants of enteropathy-associated T-cell lymphoma (EATL) are distinct [18–20]. Type I EATL, now designated as EATL, is closely related to coeliac disease and is mainly encountered in people from the northern part of Europe. Type II EATL, now designated as *monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)*, shows no link with coeliac disease and appears relatively more common in Hispanic and Asian populations. Genetically,

gains in chromosome 8q24 involving MYC are seen in a high proportion of cases of MEITL but not EATL. On the clinical ground, both forms of intestinal T-cell lymphoma are aggressive and almost always occur in adults [18].

Overall, a new road towards molecular classification and possibly more targeted therapy has been initiated for PTCLs, as it happened for acute leukemias and B-cell lymphomas in the last decade. Despite the large amount of still unsolved issues, hopefully, this will be translated soon into significant benefit for patients and communities.

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