Peripheral T cell lymphoma, not otherwise specified: the stuff of genes, dreams and therapies

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ABSTRACT
Peripheral T cell lymphomas (PTCL) account for about 12% of lymphoid tumours worldwide. Almost half show such morphological and molecular variability as to hamper any further classification, and to justify their inclusion in a waste-basket category termed “not otherwise specified (NOS)”. The latter term is used for neoplasms with aggressive presentation, poor response to therapy and dismal prognosis. In contrast to B cell lymphomas, PTCL have been the subject of only a limited number of studies to elucidate their pathobiology and identify novel pharmacological approaches. Herewith, the authors revise the most recent contributions on the subject based on the experience they have gained in the extensive application of microarray technologies. PTCL/NOS are characterised by erratic expression of T cell associated antigens, including CD4 and CD52, which have recently been proposed as targets for ad hoc immunotherapies. PTCL/NOS also show variable Ki-67 marking, with rates >80% heralding a worse prognosis. Gene expression profiling studies have revealed that PTCL/NOS derive from activated T lymphocytes, more often of the CD4+ type, and bear a signature composed of 155 genes and related products that play a pivotal role in cell signalling transduction, proliferation, apoptosis and matrix remodelling. This observation seems to pave the way for the use of innovative drugs such as tyrosine kinase and histone deacetylase inhibitors whose efficacy has been proven in PTCL primary cell cultures. Gene expression profiling also allows better distinction of PTCL/NOS from angioimmunoblastic T cell lymphoma, the latter being characterised by follicular T helper lymphocyte derivation and CXCL13, PD1 and vascular endothelial growth factor expression.

Peripheral T cell lymphomas (PTCL) represent approximately 12% of lymphoid neoplasms. Their incidence varies among countries, and it is higher in human T-cell lymphotropic virus-1 endemic areas. PTCL are a heterogeneous group of tumours that can be roughly subdivided into: specified and not otherwise specified (NOS) (Box 1). While specified tumours correspond to distinct but rare entities often occurring at extranodal sites, NOS represent the commonest type of TCL (40–50%), followed by the angioimmunoblastic (AITL) and the anaplastic large cell (ALCL) types.

PTCL/NOS cannot be further classified based on morphology, phenotype and molecular biology in most instances, although rare distinctive variants have been reported (ie, follicular and lymphoepitheliod). Usually, PTCL/NOS occurs in the fifth to sixth decade of life, and there is no evidence of sex predilection. PTCL/NOS more often presents in stage III–IV, with nodal, skin, liver, spleen, bone-marrow or peripheral blood involvement.

The tumour is highly variable in terms of cell morphology and may contain prominent reactive components. Immunohistochemistry usually shows T cell associated molecule expression, although the phenotypic profile is aberrant in about 50% of cases.

Clonal rearrangements of T cell receptor encoding genes are generally detected. The karyotype is aberrant in most cases, and is often characterised by complex abnormalities. Recently, recurrent chromosomal gains and losses have been documented in PTCL/NOS by comparative genomic hybridisation, and these have been found to differ from those seen in AITL and ALCL.

The molecular pathobiology of PTCL/NOS, as in general in all T cell neoplasms, is poorly understood. In particular, only limited numbers of studies have explored the gene expression profile (GEP).

On clinical grounds, PTCL/NOS are among the most aggressive non-Hodgkin lymphomas. Their response to conventional chemotherapy is indeed poor, with 5-year relapse-free and overall survival rates of 26% and 20%, respectively. Neither the morphology nor the international prognostic index (IPI) significantly correlates with the outcome. Clinical or clinicobiological scores have been proposed to identify cases with different prognoses. However, the molecular bases of PTCL/NOS drug resistance and aggressiveness remain elusive.

In the following, the results recently obtained by our group through the extensive application of microarray technologies will be summarised and commented on, with the scope of defining the pathobiological characteristics of PTCL/NOS, tracing the borders between it and AITL on the one hand and anaplastic large cell lymphoma kinase (ALK)-negative ALC on the other, and drawing attention to potentially novel prognosticators and therapeutic targets.

PHENOTYPIC PROFILE OF PTCL/NOS
As mentioned above, PTCL/NOS usually carry phenotypic aberrations, the exact prevalence and spectrum of which have remained unresolved. In 2006, we reported PTCL from 198 Italian patients (148 NOS and 45 AITL) that had been collected on tissue microarrays and tested by immunohistochemistry and Epstein–Barr virus encoded RNA 1 (EBER1) and EBER2 in situ.
Recently, we published a GEP study based on the analysis of 28 PTCL/NOS, all corresponding to lymph node biopsy samples containing an amount of neoplastic cells exceeding 70% value of the whole examined population. The mRNA extracted from these cases was hybridised on the HG U133 2.0 Plus gene chip. The results obtained were compared with those of six AITL, six ALCL (two ALK-positive and four ALK-negative) and 20 samples of normal T lymphocytes, which were purified from the peripheral blood and tonsil and corresponded to the main T cell subsets (CD4+, CD8+, resting and activated). Such a study significantly differed from most previous reports in terms of methodology and selection criteria. In addition, for the first time it provided the rationale for possible targeted therapies.

CD50 was recorded in 6% of cases (see fig 1B), CD15 in 4%, and CD20 in 1%; these rates of positivity may undoubtedly cause diagnostic difficulties. In particular, CD20 was detected in only two PTCL/NOS that were negative for CD79a, in keeping with previous observations of CD20 positivity in isolated PTCL/NOS, and CD79a aberrant expression in "specified" PTCL. Co-expression of CD15 and CD30 was found in only 3/183 of cases that were able to be evaluated. This is the first reliable estimate of the random incidence of such a phenomenon in a large cohort of patients with PTCL; in fact, the previous reports of Barry et al}

and Gorczycka et al\textsuperscript{22} referred to a highly selected series. In spite of its rarity, such a finding raises the question of how to differentiate between PTCL and classic Hodgkin lymphoma (CHL) under these circumstances: the polymorphism of neoplastic elements, the possible lack of Reed-Sternberg cells and CD cell specific activator protein negativity favour the diagnosis of PTCL and vice versa. In particular, B cell specific activator protein is a valuable B cell marker that is found in about 90% of cases of CHL,\textsuperscript{56} but it is exceptional in PTCL/NOS.\textsuperscript{57}

In our hands, the mean percentage of Ki-67+ neoplastic cells was around 50%, with 11% of PTCL/NOS exceeding the 50% value. Finally, EBV integration was found at the neoplastic cell level in 5% and 3% of PTCL/NOS and AITL respectively; this value is definitely lower than the one recorded by Dupuis et al\textsuperscript{13} in a French cohort.\textsuperscript{13}

**Box 1: Mature T cell and NK cell neoplasms**

**Peripheral T cell lymphoma, not otherwise specified (PTCL/NOS)**

**Peripheral T cell lymphoma, specified**

**Leukaemic:**
- T cell prolymphocytic leukaemia
- T cell large granular lymphocytic leukaemia
- Aggressive NK cell leukaemia
- Systemic Epstein–Barr virus positive T cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)
- Hydroa vaccineforme-like lymphoma
- Adult T cell leukaemia/lymphoma

**Extranodal:**
- Extramedullary NK/T cell lymphoma, nasal type
- Enteropathy-associated T cell lymphoma
- Hepatosplenic T cell lymphoma
- Subcutaneous panniculitis-like T cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous anaplastic large-cell lymphoma
- Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T cell lymphoma (provisional entity)
- Primary cutaneous γδ T cell lymphoma
- Primary cutaneous small/medium CD4+ T cell lymphoma (provisional entity)

**Prevalently nodal:**
- Angioimmunoblastic T cell lymphoma
- Anaplastic large cell lymphoma (ALCL), anaplastic large cell lymphoma kinase (ALK) positive
- ALCL, ALK negative (provisional entity)

**GEP of PTCL/NOS**

PTCL have been the subject of a limited number of GEP studies\textsuperscript{14–22, 30, 60} (table 1). In particular, Tracey et al\textsuperscript{14} reported that PTCL/NOS corresponded to a heterogeneous group of tumours whose GEP was difficult to interpret due to the amount of infiltrating reactive cells. According to those authors, the only clinically relevant information provided by GEP pertains the NF-κB activation and the possible lack of Reed-Sternberg cells, which is in line with those reported in previous publications.\textsuperscript{81, 12, 52, 82, 9}

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Interestingly, we found 32% of AITLs to be CD8+; this is in the upper range of reported values.\textsuperscript{27, 50–54} In contrast, the incidence of CD4 positivity (42%) was much lower than expected.\textsuperscript{27, 45} Interestingly, we found 32% of AITLs to be CD8+; this is in the upper range of reported values.\textsuperscript{27, 50–54} In contrast, the incidence of CD4 positivity (42%) was much lower than expected.\textsuperscript{27, 45} Interestingly, we found 32% of AITLs to be CD8+; this is in the upper range of reported values.\textsuperscript{27, 50–54} In contrast, the incidence of CD4 positivity (42%) was much lower than expected.\textsuperscript{27, 45}
in PTCL/NOS by offering clear evidence of their ex vivo effectiveness.

In particular, the GEP we detected indicated that PTCL/NOS are distinct from normal T and B lymphocytes and are more closely related to activated rather than resting T cells. As in normal mature T lymphocytes, it was possible to identify two main subgroups of PTCL/NOS, with GEPs related to either CD4 or CD8 elements. Notably, this characteristic did not reflect the expression of CD4 and CD8 molecules.

In addition to histogenetic information, our analysis provided several insights into the functional alterations of PTCL/NOS. A careful comparison of PTCL/NOS with the closest normal counterparts revealed the systematic deregulation of 155 genes controlling functions that are typically damaged in malignant cells, such as matrix remodelling, cell adhesion, transcription, proliferation and apoptosis. In particular, our findings might explain the dissemination pattern of PTCL/NOS, with frequent extranodal and bone-marrow involvement and spread to peripheral blood, by showing the upregulation of FN1, LAMB1, COL1A2, COL3A1, COL4A1, COL4A2, and COL12A1 (i.e., genes that promote local invasion and metastasis in different types of human cancer). In

Figure 1  (A) Lymphomatous cells do not express CD4; however, CD4 is detected in some reactive small lymphocytes (alkaline phosphatase anti-alkaline phosphatase (APAAP) technique, Gill’s haematoxylin nuclear counterstaining, ×250). (B) Partial CD30 expression; it should be noted that the tumour has no anaplastic morphology (APAAP technique, Gill’s haematoxylin nuclear counterstaining, ×250). (C) Positivity for platelet-derived growth factor receptor α (PDGFRα) (APAAP technique, Gill’s haematoxylin nuclear counterstaining, ×400). (D) PDGFRα is phosphorylated (APAAP technique, Gill’s haematoxylin nuclear counterstaining, ×400). (E) CXCL13 expression by neoplastic elements in angioimmunoblastic T cell (EnVision+ technique, Gill’s haematoxylin nuclear counterstaining, ×100). (F) Ki-67 marking exceeds the 80% value (EnVision+ technique, Gill’s haematoxylin nuclear counterstaining, ×200). (G) CD52 positivity in a peripheral T cell lymphoma, not otherwise specified (APAAP technique, Gill’s haematoxylin nuclear counterstaining, ×100). (H) Strong expression of vascular endothelial growth factor in an angioimmunoblastic T cell lymphoma (EnVision+ technique, Gill’s haematoxylin nuclear counterstaining, ×200).
addition, it revealed the deregulation of genes involved in apoptosis (eg, \(\text{MOAP1} \), \(\text{ING3} \), \(\text{GADD45A} \text{ and } \text{GADD45B}\)) and chemoresistance (such as \(\text{CYR61} \text{ and } \text{NNMT}\)).

Immunohistochemistry provided in situ validation of the genomic data by showing correspondence between mRNA and protein expression, as seen, for example, with GEP, PDGFR\(x\) (see fig IC and D) and BCL10. In addition, by comparison with normal tissues, immunohistochemistry allowed the identification of staining patterns corresponding to the synthesis of ectopic or parapophysiological products by neoplastic cells. Finally, the phenotypic test highlighted the possibility that some of the results obtained by GEP may depend on non-neoplastic components present in the analysed sample, as seen for Calsendin.

In the course of the same study, we found that all ALCLs tended to cluster together – irrespective of their ALK positivity or negativity – showing a signature distinct from those of PTCL/NOS andAITL.\(^{20}\)

More recently, we succeeded in identifying a gene signature discriminating between PTCL/NOS and AITL (fig 2).\(^{21}\) In addition, the observed AITL global profile strengthened its derivation from the follicular T helper lymphocyte (FTHL), as originally proposed by Rüdiger et al.\(^{22}\) and de Leval et al.\(^{23}\) Among upregulated genes, those encoding for CXCL13, PD1 and vascular endothelial growth factor (VEGF).

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<tr>
<th>Reference</th>
<th>Disease(s) explored</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Tracey et al.(^{20})</td>
<td>FM</td>
<td>The GEP of FM was investigated, and it showed concurrent deregulation of multiple genes involved in the tumour necrosis factor signalling pathway.</td>
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<tr>
<td>Martinez-Delgado et al.(^{24})</td>
<td>PTCL/NOS</td>
<td>The authors found significant differences between the peripheral and lymphoblastic T cell lymphomas. The differences included a deregulation of the nuclear factor-(\kappa)B signalling pathway.</td>
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<tr>
<td>Martinez-Delgado et al.(^{24})</td>
<td>PTCL/NOS</td>
<td>The authors found two different subgroups of PTCL based on the expression of NF-(\kappa)B related genes. One-third of PTCL clearly showed reduced expression of NF-(\kappa)B genes, while the other group was characterised by high expression of these genes. Of interest, the expression profile associated with reduced expression of NF-(\kappa)B genes was significantly associated with shorter survival of patients.</td>
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<tr>
<td>Ballester et al.(^{25})</td>
<td>PTCL/NOS, AILT, ALCL</td>
<td>According to this study, PTCL/NOS could be divided into three molecular subgroups: U1, U2 and U3. The U1 gene expression signature included genes known to be associated with poor outcome in other tumours, such as CD262. The U2 subgroup was associated with overexpression of genes involved in T cell activation and apoptosis, including NF-(\kappa)B1 and BCL-2. The U3 subgroup was mainly defined by overexpression of genes involved in the IFN- (\kappa)/ JAKSTAT pathway. Notably, such distinction possibly reflected, at least in part, the presence of reactive components in the PTCL samples.</td>
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<td>de Leval et al.(^{27})</td>
<td>AILT</td>
<td>The molecular profile of AILT was characterised by a strong microenvironment and overexpression of several genes characteristic of normal follicular helper T (THF) cells: CXCL13, BCL10, PDDC1, CD40L and NFATC1. Such a finding was reinforced by gene set enrichment analysis, which demonstrated that the AITL molecular signature was significantly enriched in THF-specific genes.</td>
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<tr>
<td>Piccaluga et al.(^{28})</td>
<td>PTCL/NOS</td>
<td>The authors showed that PTCL/NOS are most closely related to activated peripheral T lymphocytes, either CD4+ or CD8+, based on the GEP. In addition, PTCL/NOS displayed deregulation of relevant functional cell programmes. In particular, among others, PDGFR(a), a gene encoding for a tyrosine kinase receptor, turned out to be aberrantly expressed by PTCL/NOS. Notably, phosphorylation of PDGFR(a) and sensitivity of cultured PTCL cells to imatinib were demonstrated.</td>
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<tr>
<td>Piccaluga et al.(^{29})</td>
<td>PTCL/NOS</td>
<td>The authors found that CD52 is expressed in approximately 40% of PTCL/NOS at the same level as in normal T lymphocytes, being aberrantly downregulated in the remaining cases. Notably, they concluded that the estimation of CD52 expression may provide a rationale for the selection of patients with a higher probability of response to the anti-CD52 antibody alemtuzumab.</td>
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<tr>
<td>Piccaluga et al.(^{30})</td>
<td>AILT</td>
<td>In this manuscript, the authors reported that AILT and other PTCL have rather similar GEP, possibly sharing common oncogenic pathways. In addition, they found that the molecular signature of follicular T helper cells was significantly overexpressed in AILT. Finally, several genes, such as PDGFR(a) and VEGF, which are deregulated in AILT and represent potential therapeutic targets, were identified.</td>
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<td>Lamant et al.(^{31})</td>
<td>ALC1</td>
<td>This was the first study to focus on ALC1. Unsupervised analysis classified ALCL in two clusters, corresponding essentially to morphological subgroups and clinical variables. Supervised analysis showed that ALK-positive ALCL and ALK-negative ALC1 have different GEP, further confirming that they are different entities.</td>
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<tr>
<td>Cuadros et al.(^{32})</td>
<td>PTCL/NOS</td>
<td>Five clusters of genes were identified, and their expression varied significantly among the samples. Genes in these clusters were mainly related to different cellular processes such as proliferation, inflammatory response, and T cell or B cell lineages. Notably, overexpression of genes in the proliferation signature was significantly associated with shorter survival of patients.</td>
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AILT, peripheral T cell lymphoma, angioimmunoblastic type; ALCL, anaplastic large cell lymphoma; ALK, anaplastic large cell lymphoma kinase; FM, mycosis fungoides; GEP, gene expression profiling; PDGFR\(a\), platelet-derived growth factor receptor \(\alpha\); PTCL/NOS, peripheral T cell lymphoma, not otherwise specified.

**PRACTICAL IMPLICATIONS OF PHENOTYPIC AND MOLECULAR FINDINGS**

**Diagnosis**

Along with clonality studies, the phenotype plays a basic role in the distinction of PTCL from reactive conditions—such as paracortex hyperplasia—that can mimic malignant lymphoma. In fact, the lack of one or more T cell associated antigens (see above) is a hallmark of neoplastic cells as opposed to the complete phenotype of normal T lymphocytes. Immunohistochemical and molecular findings are also of great value for differential diagnosis among PTCL.

**PTCL/NOS versus AILT**

Such distinction may be problematic in about 25% of cases, based on conventional criteria.\(^{34}\) Also CD10 staining, proposed as characteristic of AILT,\(^{35} - 36\) is actually seen in less than 50% of cases in our experience.\(^{37}\)

Notably, the AITL gene signature recently reported by de Leval et al.\(^{37}\) and our group\(^{2} \) (see above) provides a rationale to the immunohistochemical observations of Dupuis et al.\(^{38}\) Grogg et al.\(^{39}\) and Roncador et al.\(^{40}\) who found that most, if not all, AITL stain for typical FTL-related antigens, such as CXCL13 (see fig 1E) and PD-1. Such molecules can actually represent a powerful tool for the distinction of AITL from PTCL/NOS, due to the exceptional positivity of the latter, a finding also
EBV, CD15 and proliferation

In our series of Italian patients, we found that high Ki-67 expression (see fig 1F), EBV status and CD15 staining were associated with the worst outcome in PTCL/NOS. Interestingly, a proliferation signature has recently been reported to correlate with an aggressive clinical course, and EBV has repeatedly been proposed as a negative prognosticator in PTCL. No other phenotypic marker alone or in combination was associated with a poor outcome, although patients with tumours expressing a CD57 or CD4+/CD8+ profile showed a tendency towards a more favourable outcome, as also observed by others.

Clinicopathological score

Based on our collective results and those published in the literature, we developed a new score that integrates patient- and tumour-specific characteristics (age ≥ 60 years, performance status, lactate dehydrogenase, and Ki-67 marking > 80%) and identifies three clear-cut groups of patients with different prognosis. Such a score seems to be more effective than previous indices, including international prognostic index and prognostic index for peripheral T cell lymphoma, not otherwise specified.

CYP3A

Recently, Rodríguez-Antona et al measured tumour CYP3A mRNA content in 44 T cell lymphomas and found a large variation in its expression that might be due to gains affecting the corresponding gene. To test whether CYP3A could influence PTCL treatment outcome, its expression levels were compared with the patient clinical response and survival, and it was observed that a high CYP3A expression was significantly associated with a lower complete remission rate. These results indicate that CYP3A as a potential predictor of tumour chemosensitivity.

NF-κB pathway

Different GEP studies have suggested that PTCL/NOS may show up- or downregulation of NF-κB molecules, with possible prognostic implications (see above). However, these studies included a limited number of PTCL/NOS cases or were not controlled by prominent non-neoplastic components. By contrast, we found that PTCL/NOS mostly consisting of neoplastic cells present with global downregulation of NF-κB genes in comparison with normal T lymphocytes. This observation was corroborated by consistent cytoplasmic localisation of NF-κB molecules, the latter moving to the nucleus in the case of NF-κB pathway activation (unpublished observation).

Therapy

CD4 and CD52 expression

The in vivo administration of monoclonal antibodies targeted to CD4 and CD52 has recently been proposed for the treatment of patients with PTCL. However, in our experience this should be regarded with caution when referring to PTCL/NOS. The latter, in fact, characteristically lacks the expression of one or more T cell associated antigens, including those antigens that these antibodies are targeted towards. In particular, we found that CD4 is lacking at the neoplastic cell level in up to 50% of cases. CD52 is a molecule expressed by most peripheral blood lymphocytes, macrophages, and monocytes. Campath-1H (alemtuzumab) is a humanised antibody against CD52 currently approved for B cell chronic lymphocytic leukaemia therapy, and it has also shown interesting activity in T prolymphocytic leukaemia and cutaneous TCLs. Although other factors can affect its response in vivo, the lack of CD52 expression may play a major role in causing refractoriness to...
the compound. Few data are available regarding the use of alentuzumab in PTCL/NOS.\textsuperscript{108, 109} We studied the expression of CD52 on tissue microarrays containing 97 PTCL/NOS.\textsuperscript{21} In addition, in 28 cases for which frozen material was available, GEP were generated and compared with those of 20 samples of normal T lymphocytes.\textsuperscript{21} We found that 17/28 (60%) PTCL/NOS showed CD52 gene expression level lower than the lowest one recorded in normal T cells.\textsuperscript{21} In addition, the gene product was detected by immunohistochemistry in 40/97 (41%) PTCL (see fig 1G).\textsuperscript{21} Interestingly, such data are in keeping with the clinical results obtained by Enblad et al\textsuperscript{(2007)} who found an overall response rate of 36% in PTCL treated with alentuzumab. Based on these findings, we think that the estimation of CD52 expression may provide a rationale for the selection of patients with higher probability of responding to alentuzumab, by avoiding the risk of unwanted toxicity.\textsuperscript{21} Similar conclusions were achieved by Rodrig et al\textsuperscript{(2006)} and Chang et al,\textsuperscript{111} who reported immunohistochemical detection of CD52 in 0–40% of PTCL.

Histone deacetylation

Since silencing of certain genes (such as GADD45A and GADD45B) can be regulated by epigenetic mechanisms including acetylation, we tested a histone deacetylase inhibitor (HDACi) (ITF2357) against PTCL/NOS primary cells. Notably, the compound induced dramatic G0–G1 cell cycle arrest and apoptosis at therapeutic concentrations, suggesting a possible role for this class of drugs in PTCL/NOS therapy, as also supported by preliminary clinical observations.\textsuperscript{111} Interestingly, the combination of ITF2357 and daunorubicin apparently had a slight additive effect, as already observed with other HDACi.\textsuperscript{112}

CONCLUSIONS

For a long time, PTCL have represented an orphan pathology. This can be explained by their relatively low prevalence (which is in any case higher than that of a “common” tumour, such as CHL), diagnostic difficulties and dismal prognosis. Based on recent advances in the genomic and translational fields, a new scenario can now be envisaged leading the way to more successful therapeutic strategies. This may be the right time to live a dream, never forgetting however that “the truth is not always pure and never simple” (Oscar Wilde).

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