A survey of the therapeutic landscape in peripheral T-cell lymphomas: the importance of expert hematopathology review in the era of targeted therapies and precision medicine

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Abstract: Peripheral T-cell lymphomas (PTCL) remain a diagnostic challenge, and the most common subtype remains "unspecified". However, improved understanding of the transcriptional and genetic landscape among the PTCL's supports an ontological classification scheme that is based on the "cell of origin" and facilitates the identification of subset-specific therapeutic vulnerabilities. Therefore, it is anticipated that identification of the "cell of origin" will become increasingly important as a predictive biomarker as targeted agents become increasingly available, thus highlighting the need for expert hematopathology review and appropriate disease classification. Herein, we present a PTCL case as a framework within which to review recent developments in PTCL classification and survey the current therapeutic landscape.

Keywords: Peripheral T-cell lymphomas (PTCL); precision medicine; hematopathology

Sir William Osler, a "father of modern medicine", and a towering figure in the late 19th and early 20th centuries, revolutionized post-graduate medical education, emphasizing the importance of patient-centered and bedside teaching. He famously quipped: "*Each case has its lesson—a lesson that may be, but is not always, learnt, for clinical wisdom is not the equivalent of experience. A man who has seen 500 cases of pneumonia (or PTCL) may not have the understanding of the disease which comes with an intelligent study of a score of cases, so different are knowledge and wisdom.*"

Osler's long shadow lingers still, and so we will utilize a peripheral T-cell lymphoma (PTCL) case to not only survey the current therapeutic landscape, but also highlight the importance of both expert hematopathology review and clinical trial participation.

Case presentation

A 55-year-old gentleman with no significant past medical history presented with B symptoms, dyspnea, and diffuse pruritus. On physical exam, diffuse lymphadenopathy, splenomegaly and bilateral pleural effusions were noted. An excisional lymph node biopsy, performed locally, revealed large and morphologically atypical CD30+CD15+ cells with Hodgkin and Reed-Sternberg (HRS)-like morphology (*Figure 1*). These findings were interpreted as classical Hodgkin lymphoma (cHL). With stage IIIB disease, he completed 6 cycles of ABVD, achieving a complete response. However, recurrent lymphadenopathy was noted 8 months later, and biopsies obtained. A similarly aberrant population of CD30+CD15+ large cells was noted, but further immunohistochemical studies
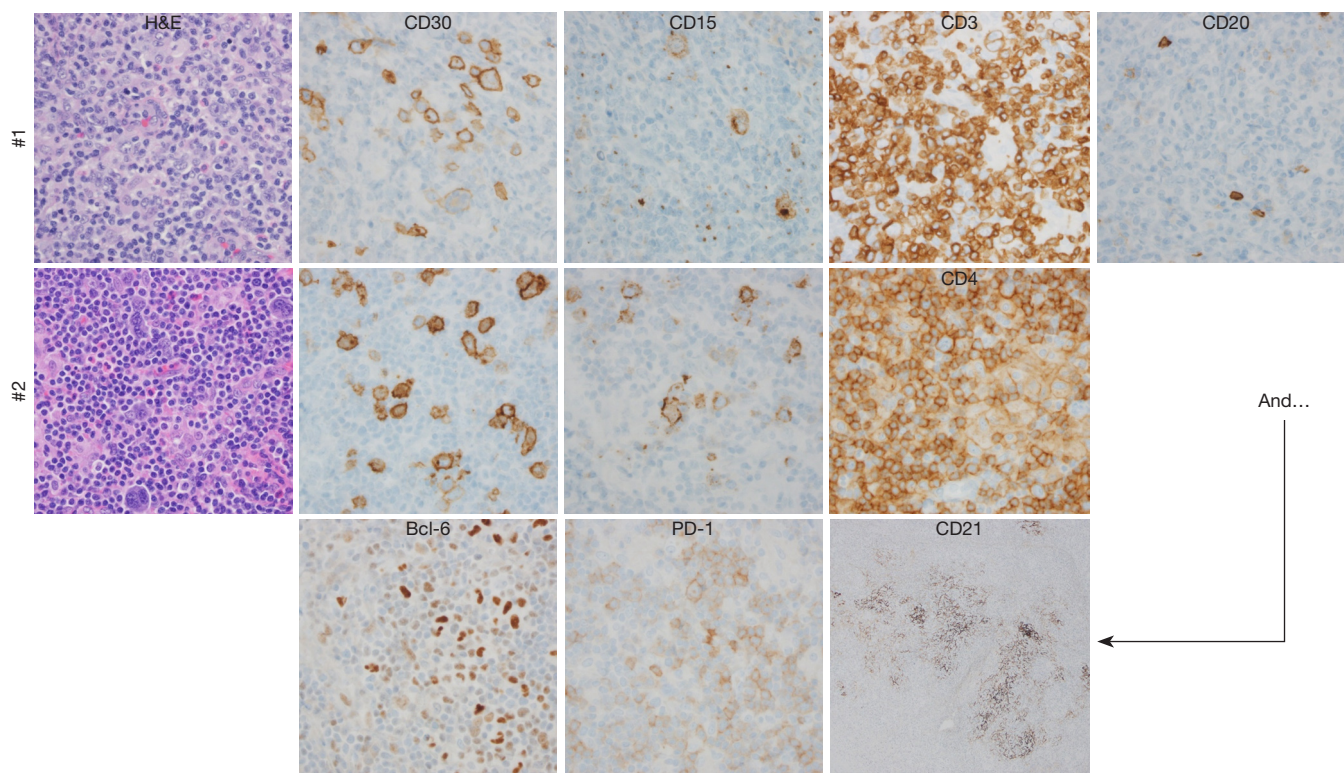
Figure 1 Patient's excisional lymph node biopsy. Note large and morphologically atypical CD30+CD15+ cells with Hodgkin and Reed-Sternberg (HRS)-like morphology. Complete immunophenotyping, including the inclusion of TFH markers, is critically important in proper classification (200× magnification).

were performed, demonstrating aberrant co-expression of multiple T-cell associated antigens and absent PAX5 expression. An expanded follicular dendritic cell (FDC) network was observed, as was Bcl-6 and PD-1 expression. Flow cytometric immunophenotyping further identified an aberrant population of $CD2^+CD4^+CD5^+CD3^-$ T cells. Concordant T-cell receptor gene rearrangements were observed in both biopsies. Collectively, these findings were consistent with angioimmunoblastic T-cell lymphoma (AITL) or T_{FH}-derived PTCL (PTCL-TFH).

The importance of expert hematopathology review

The importance of expert pathologic review was recently demonstrated in a large, prospective study in which well over 30,000 lymphoma biopsies that had been interpreted locally were referred to a reference center within the French Lymphopath Network (1). The rate and clinical impact of pathologic reclassification following a second,

centralized review by expert hematopathologist was reported (1). The vast majority (≈85%) of referral and expert diagnoses were concordant among the most common B-cell NHL (i.e., DLBCL, FL). In stark contrast, ≈65% of the most common PTCL diagnoses (PTCL, NOS and AITL) were concordant. Cases initially classified as cHL were among the approximately one in three PTCL cases that were reclassified, as HRS-like B-cells may be observed in AITL and PTCL-TFH (2,3). These HRS-like B cells are frequently EBV positive and may pose a diagnostic challenge, particularly when immunophenotyping is incomplete (4).

The role of HDT-ASCT : missed therapeutic opportunity?

Few prospective studies have addressed the role of high-dose therapy (HDT) and autologous stem-cell transplantation (ASCT) as a consolidation strategy in first remission or as a salvage strategy in second remission (5,6). The largest

prospective and PTCL specific study to address the role of HDT-ASCT in the frontline setting was conducted by the Nordic Lymphoma Group (7). Out of 166 enrolled patients, 115 achieved a partial or complete remission following CHOP or CHOEP induction and underwent HDT-ASCT. Treatment-related mortality was low (4%), and despite early treatment failures in ≈25% of patients, long-term progression-free survival (PFS) was 44%. Despite the acknowledged limitations of the available retrospective and prospective data, most notably the absence of a randomized-controlled trial addressing the absolute benefit of HDT-ASCT in first remission, this approach is endorsed by NCCN guidelines and by many experts in the field for the most common PTCL subtypes (8). Nonetheless, HDT-ASCT in first remission is likely underutilized, as fewer than 25% of patients underwent HDT-ASCT in a large, prospective cohort study examining practice patterns in the United States (9). Consequently, many patients with recurrent disease will not have undergone HDT-ASCT. In this setting, outcomes comparable to those achieved following HDT-ASCT in relapsed diffuse large B-cell lymphoma may be anticipated with this approach for PTCL, NOS/AITL patients achieving a complete remission following salvage therapy. The largest study to specifically address the role of HDT-ASCT in AITL was retrospectively conducted by the European Group for Blood and Marrow Transplantation (10). Approximately 75% of the 146 patients examined underwent HDT-ASCT after ≥2 lines of prior therapy, and 48% were transplanted in first or second complete remission. The remaining patients were transplanted with chemotherapy-sensitive (38%) or refractory (14%) disease. For patients achieving a complete remission prior to HDT-ASCT, 4-year PFS was 56%, and was significantly higher compared with the 4-year PFS observed in patients with chemotherapy-sensitive (30%) or refractory disease (23%) at the time of transplant. However, it is worth noting that 70% of those transplanted in complete remission underwent transplant following their first complete remission. Therefore, achieving a complete response (CR) prior to HDT-ASCT is an important goal.

While the therapeutic goal—achieving a CR—in the setting of relapsed PTCL, NOS or AITL is clear, the optimal salvage regimen is not, and clinical trial participation should be encouraged. Nonetheless, at the time of relapse, our patient was treated locally with CHOP, and achieved a partial response after 4 cycles of therapy. Given his suboptimal response and complicated course (i.e., neutropenia, sepsis, and atrial fibrillation), he

was referred to our center for evaluation and treatment recommendations, at which time allogeneic stem cell transplantation was considered, but a suitable related or matched unrelated donor was not available.

What is the optimal salvage therapy in relapsed/refractory PTCL: does the "cell-of-origin" matter?

The cell-of-origin is best appreciated for AITL and PTCL-TFH (11). Follicular helper T cells (T_{FH} cells) regulate humoral immunity via the production of cytokines (e.g., IL-4, IL-21) and expression of cell-surface ligands (e.g., CD40L) that regulate somatic hypermutation and isotype switching. Immunophenotyping and gene-expression profiling studies demonstrated that malignant T cells in AITL/PTCL-TFH are T_{FH} cell derived (12-22). Understanding AITL ontogeny explains the classic histologic findings (e.g., expansion of germinal-center B cells and an expanded meshwork of FDCs) characteristic of this PTCL. Similarly, the differentiation of conventional $CD4^+$ T-cell subsets, from which PTCL, NOS subsets are derived, is controlled by "master" transcription factors, including GATA-3 and T-bet (12,13). For example, the zinc-finger transcription factor GATA-3, while regulating the growth and survival of post-thymic T cells, is classically associated with Th2 differentiation (14). Interrogation of these transcription factors and their respective gene targets led to the observation that a majority of morphologically classified PTCL, NOS cases are characterized by the expression of the transcription factors T-bet or GATA-3 and their respective gene targets (12). GATA-3 expression was associated with dismal survival, and may be attributed, at least in part, to GATA-3-dependent cell-autonomous and non-cell-autonomous effects (12,15). These adverse prognostic implications associated with GATA-3 expression were independently validated in two subsequent studies (16,17). A more robust gene expression profiling study similarly identified these distinct subtypes, demonstrating that PTCL, NOS cases highly expressed either GATA-3 and its gene targets or TBX21 (T-bet) and its gene targets (13). Collectively, these findings demonstrate that PTCL, NOS, when excluding PTCL-TFH or morphologically misclassified cases, is comprised of two dominant subtypes: "GATA-3" and "T-bet" PTCL (11).

The utility of the "cell-of-origin" as a predictive biomarker in the setting of relapsed/refractory disease, while poorly understood, is best appreciated for AITL/PTCL-TFH. In the PROPEL study, 32% of PTCL, NOS patients achieved a response with pralatrexate, whereas only a single AITL patient achieved a response with pralatrexate,
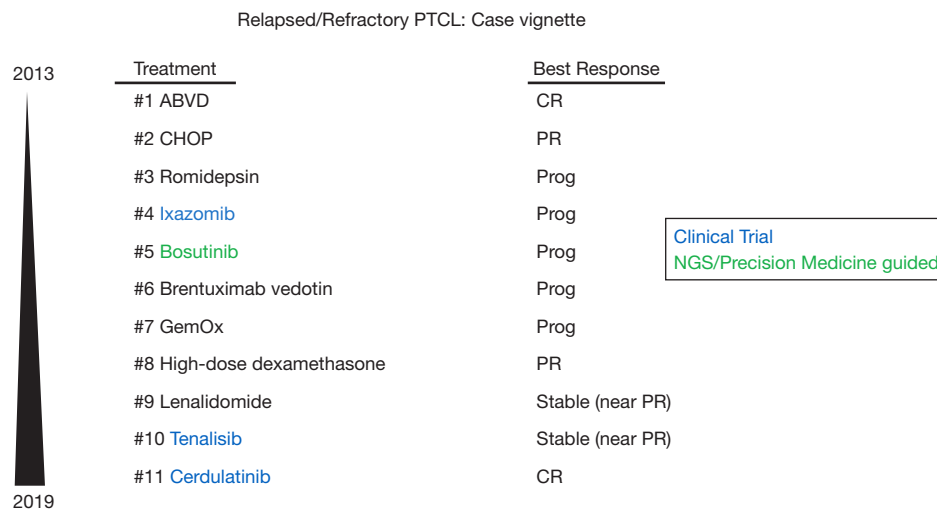
Relapsed/Refractory PTCL: Case vignette

	Treatment	Best Response
2013	#1 ABVD	CR
	#2 CHOP	PR
	#3 Romidepsin	Prog
	#4 Ixazomib	Prog
	#5 Bosutinib	Prog
	#6 Brentuximab vedotin	Prog
	#7 GemOx	Prog
	#8 High-dose dexamethasone	PR
	#9 Lenalidomide	Stable (near PR)
	#10 Tenalisib	Stable (near PR)
2019	#11 Cerdulatinib	CR

Clinical Trial
NGS/Precision Medicine guided

Figure 2 Summary timeline of patient's treatments. A chronologic timeline of patient's therapies and responses to summarize his treatment history.

and a partial response at that (18). In contrast to the 8% overall response rate (ORR) observed with pralatrexate, the ORR observed in AITL with romidepsin, belinostat, or brentuximab vedotin range from 30–54% (19-21). Among the≈15% of PTCL, NOS/AITL patients achieving a CR with romidepsin, a majority achieved a durable CR, lasting at least 1 year in 60%, and >2 years in 40% (22). As such, romidepsin was elected, but he progressed after receiving three cycles of therapy with PET imaging demonstrating disease progression, with nodal disease above and below the diaphragm (summarized in *Figure 2*). In a phase II study, an ORR of 54%, most of which were complete, was observed in AITL patients treated with brentuximab vedotin, irrespective of CD30 expression (21). He subsequently received brentuximab vedotin, but nodal progression was observed on PET.

What is the optimal management of multiply relapsed or refractory PTCL?

Survival outcomes are dismal for most patients with refractory PTCL with currently available therapies. For example, a recent retrospective, single institution study examined outcomes following salvage therapy in the setting of primary refractory disease (n=93). As anticipated, outcomes were dismal, with median event-free and overall survival of <4 and 9 months, respectively, observed (23). A significant difference in survival was not observed when comparing patients who received "traditional" salvage regimens (e.g., ICE) with those

who received single agents. While the benefits of clinical trial participation have not been systematically examined in PTCL, one study performed in Hodgkin lymphoma and selected B-cell non-Hodgkin lymphomas (NHL) examined outcomes between clinical trial participants and matched patients who met eligibility criteria but did not participate in a clinical trial (24). Significant improvements in event-free survival were observed for clinical trial participants among all the lymphomas examined. Among the 47 phase I–III trials included in this study, 17 trials included novel agents that subsequently received FDA approval. As clinical trial participation should be highly encouraged in patients with relapsed/refractory PTCL, our patient was enrolled in a phase II trial with the oral proteasome inhibitor ixazomib (25). Unfortunately, nodal disease progression was observed (by PET).

The genetic landscape in AITL and its therapeutic implications.

Epigenetic dysregulation is a hallmark of T_{FH}-derived malignancies. Ten-Eleven-Translocation (TET) 2 promotes DNA demethylation and recurrent loss-of-function mutations affecting its catalytic domain are observed in the majority of AITL. In addition, isocitrate dehydrogenase (IDH) 2 catalyzes the decarboxylation of isocitrate to α-ketoglutarate (α-KG) and indirectly regulates α-KG dependent dioxygenases, including TET2. IDH2 is recurrently mutated at arginine-172 in
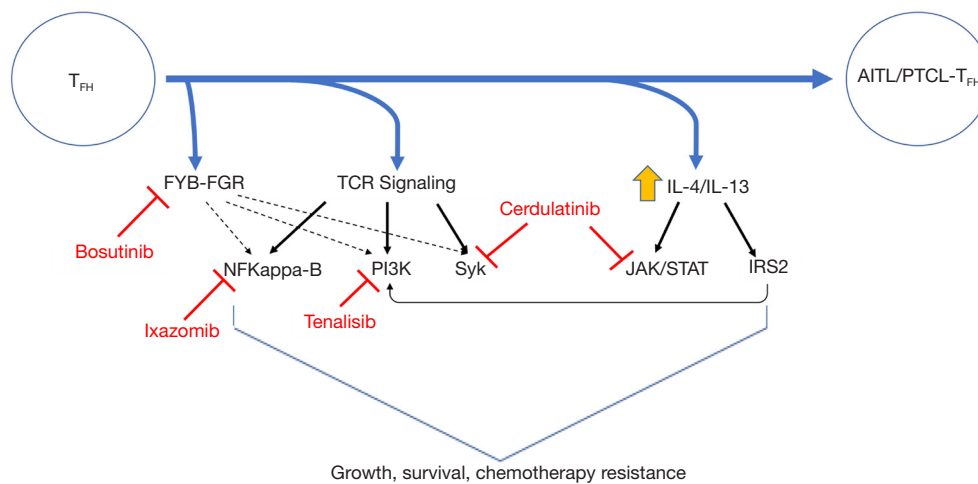
Figure 3 Relevant signaling pathways and novel therapies in our AITL/PTCL-TFH patient. Aberrant Src family kinase (SFK) activity may be redundant with downstream effectors of conventional T-cell receptor (TCR) signaling (dashed arrow), in this patient's case provided by a novel FYB-FGR fusion protein. The novel therapies and targeted agents utilized in this case are indicated in red.

approximately one-third of AITL, conferring neomorphic activity such that α-KG is converted to the R-enantiomer of 2-hydroxyglutarate, an oncometabolite that antagonizes TET2 and histone demethylases. Loss-of-function mutations in the DNA methyltransferase DNMT3A are also observed, and usually occur with TET2 mutations, in approximately one-third of AITL cases. Interestingly, TET2 and DNMT3A mutations are observed in hematopoietic stem and progenitor cells in patients with clonal hematopoiesis (26-28), and are not restricted to malignant T cells in AITL, but are also present in progenitor cells and constituents of the tumor microenvironment (29,30). In contrast, other recurrent mutations (e.g., RhoA, IDH2) are restricted to malignant T cells (30), suggesting that TET2 and/or DNMT3A mutations are early events in disease pathogenesis that promote the malignant transformation of T cells following the acquisition of additional genetic hits. Conventional T cells are dependent upon the integration of both antigen-dependent and antigen-independent (e.g., costimulation and cytokine-dependent) signals. These pathways are prime candidates for the "second hits" that promote T-cell transformation (31) and ripe for therapeutic exploitation. The constellation of mutational profiling and next-generation sequencing studies completed to date generally support this contention (32-37).

Lymphoma patients are increasingly subjected to next-generation sequencing (http://mctp.med.umich.edu/physicians/mi-oncoseq-study) at our institution (38,39), and this testing was performed for our patient. In contrast to the highly recurrent mutations commonly observed in AITL, which were not observed in our patient, a novel fusion between the SRC family kinase FGR, including its kinase domain, and a binding protein (i.e., FYB) for a related SRC family kinase (i.e., Fyn) was observed (*Figure 3*). While the function of this novel FYB-FGR fusion is unknown, activating mutations in the SRC family kinase Fyn are observed in ≤4% of AITL and PTCL, NOS (33,35). Treatment with bosutinib, a potent SRC family kinase inhibitor with IC_{50}'s <10 nM (40), was initiated, but he failed to respond with PET scan showing disease progression, including new nodal sites of disease. Mechanisms of resistance to most novel agents are poorly understood, and this is a fertile area for future study. Nonetheless, it is noteworthy that FGR was identified in 2016 as a mediator of resistance to vorinostat in B-cell NHL (41).

At this point, having relapsed or progressed after six prior lines of therapy, our patient had developed bulky and symptomatic retroperitoneal disease, prompting the selection of therapy that may rapidly debulk his disease. As gemcitabine, either alone or in combination, is associated with ORR exceeding 50% in PTCL (42-46), GemOx was initiated. Unfortunately, continued disease progression and clinical deterioration was observed, despite treatment. As durable remissions may be achieved with corticosteroids alone (47), and in the setting of continued clinical deterioration, high-dose dexamethasone (40 mg daily for 4 days) was initiated. Rapid and significant debulking of his disease and symptomatic improvement was observed.

After experiencing disease relapse or progression with seven prior lines of therapy, a partial response was achieved with corticosteroids. He appreciated use of an oral agent, and lenalidomide is associated with an ORR of 31% (15% CR) in AITL. Therefore, lenalidomide was initiated, as previously described (48). While stable disease was achieved for 7 months, and treatment well tolerated, he ultimately progressed, developing biopsy-confirmed bone marrow involvement.

Many of the recurrent mutations and other genetic alterations observed in AITL converge on the phosphoinositide 3-kinase (PI3K) pathway (*Figure 3*). The costimulatory receptor ICOS plays a fundamental role in T_{FH} cell biology (49), is highly expressed in AITL (31), and also culminates in PI3K activation. Among PTCL patients treated with the PI3Kγ/δ inhibitor duvelisib in a phase I study, 50% achieved a response, including an AITL patient (out of three treated) that achieved a durable and ongoing complete response. Therefore, our patient was enrolled in a clinical trial investigating a novel PI3Kγ/δ inhibitor (Tenalisib), but did not achieve a response. Similarly, many recurrent abnormalities observed in AITL implicate the T-cell receptor in disease pathogenesis (33), and suggest that downstream kinases, including Syk (50), among others (15), are suitable therapeutic targets. In addition, multiple cytokines (e.g., IL-4/IL-13) have been implicated in AITL pathogenesis (31), suggesting that inhibition of cytokine receptor-dependent activation of Janus kinases (JAK) is attractive. Therefore, our patient was enrolled in a phase I/II trial investigating the dual JAK/Syk inhibitor cerdulatinib, achieving a complete response. Whether the "cell of origin" and T_{FH}-cell derivation are predictive biomarkers for response to cerdulatinib is unknown, but will be investigated in a multinational phase IIb study (CELTIC-1, ClinicalTrials.gov Identifier: NCT04021082).

What's the optimal twelfth-line therapy?

We don't know what the future holds for our patient, but are convinced that clinical trial participation will continue to be an important consideration in his management. For example, PD-L1, while rarely expressed by malignant T cells in AITL, is commonly expressed by constituents of the tumor microenvironment (51). Furthermore, a significant mutational burden was observed in our patient (119 somatic mutations), which may portend a favorable response to checkpoint blockade (52). Therefore, checkpoint blockade, ideally in combination with additional immunomodulatory

strategies (52), is attractive.

The case presented (summarized in *Figure 2*) illustrates both the importance of expert hematopathology review and the significant benefits associated with clinical trial participation. In fact, clinical trial participation may become increasingly important, as we now face a challenge that was almost unimaginable 10 years ago. That is, the smorgasbord of therapeutic targets and novel agents continues to rapidly expand, necessitating the development of predictive biomarkers that will optimize the selection of patients for conventional and novel therapies, as a "good physician treats the disease", but "the great physician treats the patient who has the disease" (Sir William Osler).

Acknowledgments

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this article.

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