Biology and genetics of extranodal mature T-cell and NK-cell lymphomas and lymphoproliferative disorders

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Abstract

The extranodal mature T-cell and NK-cell lymphomas and lymphoproliferative disorders represent a unique group of rare neoplasms with both overlapping and distinct clinicopathological, biological, and genomic features. Their predilection for specific sites, such as the gastrointestinal tract, aerodigestive tract, liver, spleen, and skin/soft tissues, underlies their classification. Recent genomic advances have furthered our understanding of the biology and pathogenesis of these diseases, which is critical for accurate diagnosis, prognostic assessment, and therapeutic decision-making. Here we review clinical, pathological, genomic, and biological features of the following extranodal mature T-cell and NK-cell lymphomas and lymphoproliferative disorders: primary intestinal T-cell and NK-cell neoplasms, hepatosplenic T-cell lymphoma, extranodal NK/T-cell lymphoma, nasal type, and subcutaneous panniculitis-like T-cell lymphoma.

Introduction

Mature T-cell and NK-cell lymphomas and lymphoproliferative disorders are uncommon and heterogeneous with variable clinical presentations, histopathology, genomic alterations, biological foundations, and clinical behavior. A rare subset has a predilection for extranodal sites and demonstrates several unique clinicopathological, genomic, and biological features. Complementing the companion review by Stuver *et al.*,[1] focused on the clinical management of rare extranodal mature T-cell and NK-cell neoplasms that may require systemic therapy, here we summarize the clinicopathological and genomic features of the same group of disorders, emphasizing the pathobiological insights provided by recent genomic advances. While most of the entities reviewed here are classified similarly by the 2017 revised 4th edition of the World Health Organization (WHO) classification, the 2022 5th edition WHO, and the 2022 International Consensus Classification (ICC) systems, some updates to certain diseases have been made, which are noted. For simplicity, 2022 ICC terminology will be utilized when referring to specific entities.[2] Select key biological, immunophenotypic, and genomic features of these diseases are summarized in Table 1.

Refractory celiac disease

Clinicopathological features

Celiac disease (CD) is an immune-mediated condition that arises in genetically predisposed individuals in whom gluten ingestion triggers small bowel damage. Refractory celiac disease (RCD) is a rare, long-term complication of CD and is defined as the persistence of gastrointestinal symptoms and small bowel villous atrophy despite adhering to a strict gluten-free diet for 6-12 months.[3] RCD is classified into two types. Type I RCD (RCD-I) is histologically similar to classic CD, demonstrating villous atrophy and increased polyclonal intraepithelial lymphocytes with a normal immunophenotype, and follows a relatively benign course. Type II RCD (RCD-II) morphologically resembles active CD and RCD-I, but is distinguished by clonal, immunophenotypically aberrant intraepithelial lymphocytes. The abnormal intraepithelial lymphocytes demonstrate dual T- and NK-cell traits, expressing cytoplasmic CD3 and the NK receptor NKp46[4] typically without surface CD3, CD5, CD8, or T-cell receptor (TCR) expression,[5] but carrying clonal TCR gene rearrangements. The intraepithelial lymphocytes also typically express CD103 (αE integrin), a receptor for E-cadherin that is thought to promote ad-

hesion of intraepithelial lymphocytes to epithelial cells.[5] The clonal T cells in RCD-II commonly disseminate within the intestine (stomach, colon), to the peripheral blood and bone marrow, as well as to extra-intestinal solid organs, including skin, lung, and mesenteric lymph nodes.[6] The prognosis of patients with RCD-II is poor, with there being a 30-50% chance of transformation into enteropathy-associated T-cell lymphoma (EATL) within 5 years.[6,7] This risk and the detection of shared TCR gene rearrangements and other somatic genomic alterations among individual RCD-II and their corresponding EATL support RCD-II as the neoplastic precursor of EATL.[8] As such, RCD-II was newly added as a distinct entity to the 2022 ICC of mature lymphoid neoplasms.[2]

Genomic and biological features

Abnormal intraepithelial lymphocytes in RCD-II are believed to arise from lymphoid precursors differentiating in the gut epithelium but are subsequently reprogrammed toward an NK/T innate-like fate in response to interleukin-15 (IL-15).[9,10] IL-15 exerts this effect by switching off NOTCH-dependent T-cell differentiation and diverting the lymphoid precursors from adaptive to innate-like cell differentiation.

The chromosomal aberrations in RCD-II include trisomy 1q, which is highly prevalent (90%), and recurrent 4q and 6q losses.[6,8] The JAK-STAT pathway, known to regulate intraepithelial lymphocyte function and play pathogenic roles in several T/NK-cell neoplasms, is the most frequently mutated pathway. Indeed, 85% of cases show at least one somatic gain-of-function mutation in *JAK1* or *STAT3*, with the *JAK1* p.G1097 hotspot mutation being particularly prevalent (~50%).[5,8] Deleterious mutations in negative JAK-STAT regulators (e.g., *SOCS1*, *SOCS3*) are common in patients without *JAK1* or *STAT3* mutations.[8] NF-κB signaling is the second most affected pathway. Loss-of-function mutations in negative regulators of NF-κB, such as *TNIP3* and *TNFAIP3/A20*, are detected in ~20%, although the prevalence increases (90%) when abnormal intraepithelial lymphocytes are purified. Recurrent somatic events affecting epigenetic regulators (*TET2*, *KMT2D*), DNA damage repair proteins (*POT1*), and the translational regulator *DDX3X* are also reported.[5,8]

Enteropathy-associated T-cell lymphoma

Clinicopathological features

Three types of aggressive primary intestinal T-cell lymphomas are recognized: EATL, monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), and intestinal T-cell lymphoma, not otherwise specified (ITCL-NOS). EATL is the most common and has a strong association with CD, arising in 1% in this population. MEITL is less common and has no association with CD while ITCL-NOS is a diagnosis of exclusion when EATL, MEITL, and other defined T/NK-cell lymphomas have been ruled out. ITCL-NOS is likely a heterogeneous category with poorly characterized biological and genetic features and thus will not be covered further in this review. EATL occurs almost exclusively in adults (median age >60 years) with a male predominance. A minority of patients present without a clinical history of CD but demonstrate histological or serological evidence of celiac enteropathy, suggesting subclinical or latent CD. The small bowel is most commonly affected while involvement of colon or stomach is rare (8%).[11] Dissemination to extra-intestinal sites is common, and, in up to one-third of RCD-II patients, the initial lymphoma develops at an extra-intestinal site, such as mesenteric lymph nodes, spleen, liver, lung, bone marrow, or skin.[6,12] Such extra-intestinal presentations of EATL may arise from pre-existing extra-intestinal RCD-II clonal T cells. The clinical course is unfavorable, with a median survival of ~10 months.[13]

Tumor cells are typically medium-sized to large and pleomorphic, occasionally with anaplastic or bizarre multinucleated cells (Figure 1A). A polymorphic inflammatory background is often present, occasionally obscuring the lymphoma cells. Angiocentricity and angioinvasion, extensive necrosis, and a high mitotic rate are common. CD-related pathological features in remote intestinal mucosa are a diagnostic aid (Figure 1B). The tumor cells are immunophenotypically similar to the intraepithelial lymphocytes in RCD-II, including frequent CD103 expression[11] (Figure 1C-H), with the exception of CD30, which is commonly expressed in EATL but rare in RCD-II in which it is considered a sign of progression to EATL.[14]

Genomic and biological features

The pathogenesis of EATL remains incompletely understood; however, multiple lines of evidence point to RCD-II as its precursor. In addition to shared TCR gene rearrangements, their genetic profiles overlap significantly, with EATL also commonly harboring trisomy 1q and mutations in JAK-STAT and NF-κB pathway genes (e.g., *JAK1*, *STAT3*, *TNFAIP3/A20*), particularly the *JAK1* p.G1097 hotspot (68%). *KMT2D*, *TET2*, and *DDX3X* are among other common mutations in both conditions. In contrast to RCD-II, however, EATL exhibits higher genomic complexity, consistent with disease evolution. Multiple chromosomal imbalances are frequent in EATL but rare in RCD-II, and included gains at 9q33-34 and 5q34-35, and losses involving 8p22-23.2, 9p21.2-p21.3, 11q14.1-q14.2, 13q31, and 16q21.1. Multiple *JAK1* or *STAT3* mutations are observed in ~40% of EATL but only 10% of RCD-II,[8] suggesting JAK1-STAT3 mutations act as founders as well as drivers of

Table 1. Key biological, phenotypic, and genomic features of select mature extranodal T-cell and NK-cell lymphomas and lymphoproliferative disorders.

	RCD-II	EATL	MEITL	IC-TLPD-GI	I-NKLPD-GI	HSTCL	ENKTL	SPTCL
Localization	Small bowel	Small bowel > colon, stomach	Small bowel > colon, stomach	Small bowel, colon > upper GI tract	Stomach, small bowel > colon	Spleen, liver, BM	Upper aerodigestive tract > skin, GI tract, others	Subcutaneous adipose tissue
Associated conditions	Celiac disease	Celiac disease	NA	NA	NA	Immune compromise, possibly thiopurine, TNF-α inhibitor therapy	*IL18RAP, HLA-DRB1, HLA-DPB1* germline SNP	Autoimmune disease (e.g., SLE), *HAVCR2* germline mutations
Immunophenotype (%)	+: CD2, cCD3, CD7, CD103, TIA1, NKp46	+: CD2, cCD3, CD7, CD103, TIA1	+: CD3, CD7, CD8, CD56, TIA1, MATK (>85), TCRγδ > TCRαβ	+: CD2, CD3, CD4 or CD8, CD5, TIA1 ($CD8^+$ cases), TCRαβ	+: CD2, cCD3, CD7, TIA1, granzyme B	+: CD2, CD3, CD7, CD56, TIA1, granzyme M, TCRγδ > TCRαβ	+: CD2, cCD3, CD56, TIA1, granzyme B, perforin, EBER	+: CD3, CD8, TIA1, granzyme B, perforin, TCRαβ
	±: CD8, granzyme B, perforin, TCRαβ (20)	±: CD8, CD30, granzyme B, perforin	±: CD2, CD20, CD103, granzyme B, perforin, MYC	±: CD7, CD103	±: CD8	±: CD8	±: CD5, CD7, CD8, CD30, TCRαβ, TCRγδ	±: CD2, CD5, CD7
	-: sCD3, CD4, CD5, CD56, CD30, TCRγδ, EBER	-: sCD3, CD4, CD5, CD56, TCRαβ, TCRγδ, EBER	-: CD4, CD5, CD30, EBER	-: CD30, CD56, granzyme B, TCRγδ, EBER	-: sCD3, CD4, CD5, TCRαβ, TCRγδ, EBER	-: CD4, CD5, granzyme B, perforin, CD57, EBER	-: CD4, CD16, CD57	-: CD4, CD56, CD30, TCRγδ, EBER
Chromosomal abnormalities (%)	Gains: 1q (90)	Gains: 1q (73) 5q34-35.2 (80) 7q33-34 (33) 8q24 (*MYC*, 27-40) 9q (67)	Gains: 1q (20) 5q34-35.2 (20) 7q33-34 (60) 8q24 (*MYC*, 60-73) 9q31.3-qter (73)	$CD4^+$ cases: *STAT3::JAK2* (80) $CD8^+$ cases: *IL2* structural alterations (50)	-	i(7q) (25-80) Trisomy 8 (10-50)	*CD279* alterations (23)	Gains: 2q (83) 4q (83)
	-	Losses: 7p14.1 (29) 8p22-23.2 (27) 9p21.2-21.3 (13) 11q14.1–q14.2 (13) 16q12.1 (33)	Losses: 7p14.1 (75) 8p22-23.2 (47) 9p21.2-21.3 (33) 11q14.1–q14.2 (27) 16q12.1 (13)	-	-	-	Losses: 6q21-25 (~40)	Losses: 1p (100) 2p (83) 5p (83) 9q (83) 10q (83) 11q (83) 12q (83) 16 (83) 20 (100) 22 (100)

Continued on following page.

	RCD-II	EATL	MEITL	IC-TLPD-GI	I-NKLPD-GI	HSTCL	ENKTL	SPTCL
Mutations (%)								
JAK/STAT	*JAK1* (48) *STAT3* (38) *JAK3* (11) *SOCS1* (11) *SOCS3* (8)	*JAK1* (74) *STAT3* (47) *SH2B3* (16) *SOCS1* (10) *JAK3* (5) *STAT5B* (5)	*STAT5B* (60) *JAK3* (35-50) *SH2B3* (20) *STAT3* (15) *JAK1* (12)	CD4⁺ cases: *STAT3* (50) *SOCS1* deletion (17)	*JAK3* (30)	*STAT5B* (30) *STAT3* (10)	*STAT3* (18) *JAK3* (9) *STAT5B* (<5)	*JAK3* (10)
MAPK	-	*BRAF* (10) *NRAS* (5) *KRAS* (0-5)	*BRAF* (26) *KRAS* (20) *NRAS* (5)	-	-	-	-	-
NF-κB	*TNIP3* and *TNFAIP3/A20* (together 20)	*TNIP3* and *TNFAIP3/A20* (together 31)	-	-	-	-	-	-
Epigenetic regulators	*TET2* (30) *KMT2D* (22) *KMT2C* (10) *BCOR* (10) *CREBBP* (8) *SETD2* (4)	*KMT2D* (37) *TET2* (32) *BCOR* (32) *ASXL1* (16) *ARID1A* (16)	*SETD2* (>90) *BCOR* (11) *KMT2D* (6) *TET2* (6)	CD4⁺ cases: *TET2* *DNMT3A* *KMT2D* (together 67)	-	*SETD2* (25) *INO80* (21) *TET3* (15) *SMARCA2* (10)	*KMT2D* (13) *BCOR* (11) *TET2* (9) *KMT2C* (8) *EP300* (7) *ARID1A* (7)	*CDC27* (25) *TET2* (15) *KMT2C* (15) *KMT2D* (15) *ASXL1* (10) *BAZ2A* (10)
DNA damage repair	*POT1* (20)	*POT1* (26) *TP53* (5-10)	*TP53* (35) *ATM* (11)	-	-	*TP53* (5-10)	*TP53* (10)	-
PI3K/AKT/ mTOR	-	-	-	-	-	*PIK3CD* (9)	-	*PIK3CD* (10) *MTOR* (5)
Others	*DDX3X* (20) *PRDM1* (6)	*DDX3X* (32) *PRDM1* (16)	*GNAI2* (9-21) *DDX3X* (3)	-	-	*UBR5* (5-10) *IDH2* (5-10)	*DDX3X* (14) *MGA* (8)	*HAVCR2* (25-85) *NAV3* mutation/loss (44) *PLCG2* (15) *CBL* (5) *IDH1* (5)

RCD-II: type II refractory celiac disease; EATL: enteropathy-associated T-cell lymphoma; MEITL: monomorphic epitheliotropic intestinal T-cell lymphoma; IC-TLPD-GI: indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract; I-NKLPD-GI: indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract; HSTCL: hepatosplenic T-cell lymphoma; ENKTL: extranodal NK/T-cell lymphoma, nasal type; SPTCL: subcutaneous panniculitis-like T-cell lymphoma; GI: gastrointestinal; BM: bone marrow; NA: not applicable; SNP: single nucleotide polymorphisms; SLE: systemic lupus erythematosus; cCD3: cytoplasmic CD3; sCD3: surface CD3.

transformation. JAK1-STAT3 pathway targeting may offer a potential therapeutic approach to suppress growth of RCD-II cells, preventing progression to EATL. EATL also harbor additional mutations uncommon in RCD-II, including those in the MAPK pathway (e.g., *KRAS*, *NRAS*, *BRAF*) (20%) and *TP53*.[8,15] Additional pathogenic mutations in EATL include *SH2B3*, *BCOR*, *ARID1A*, *SETD1B*, *PTPRC*, *PRD*, *NF1*, and *NOTCH1*, the value of which in predicting progression is unclear.[8]

It is postulated that EATL lymphomagenesis follows a multi-step process, initiated by CD-associated cytokines that trigger polyclonal expansion of intraepithelial lymphocytes. IL-15, which is upregulated in CD intestinal epithelium, triggers a powerful anti-apoptotic cascade involving *JAK3* and *STAT5* phosphorylation, hindering T-cell elimination after activation.[16] Subsequent acquisition of *JAK1* or *STAT3* mutations in an intraepithelial lymphocyte clone confers hyper-responsiveness to IL-15 and other cytokines and, in concert with alterations in negative regulators of NF-κB, provides a selective advantage and promotes clonal outgrowth.[9,17] The synergy between cytokines and mutations also triggers autonomous cytokine production in abnormal intraepithelial lymphocytes and epithelial cytotoxicity, resulting in self-sustaining inflammation that leads to loss of response to gluten-free diets and progression to RCD-II. This process also creates a genotoxic inflammatory environment that fosters genomic instability, enabling the

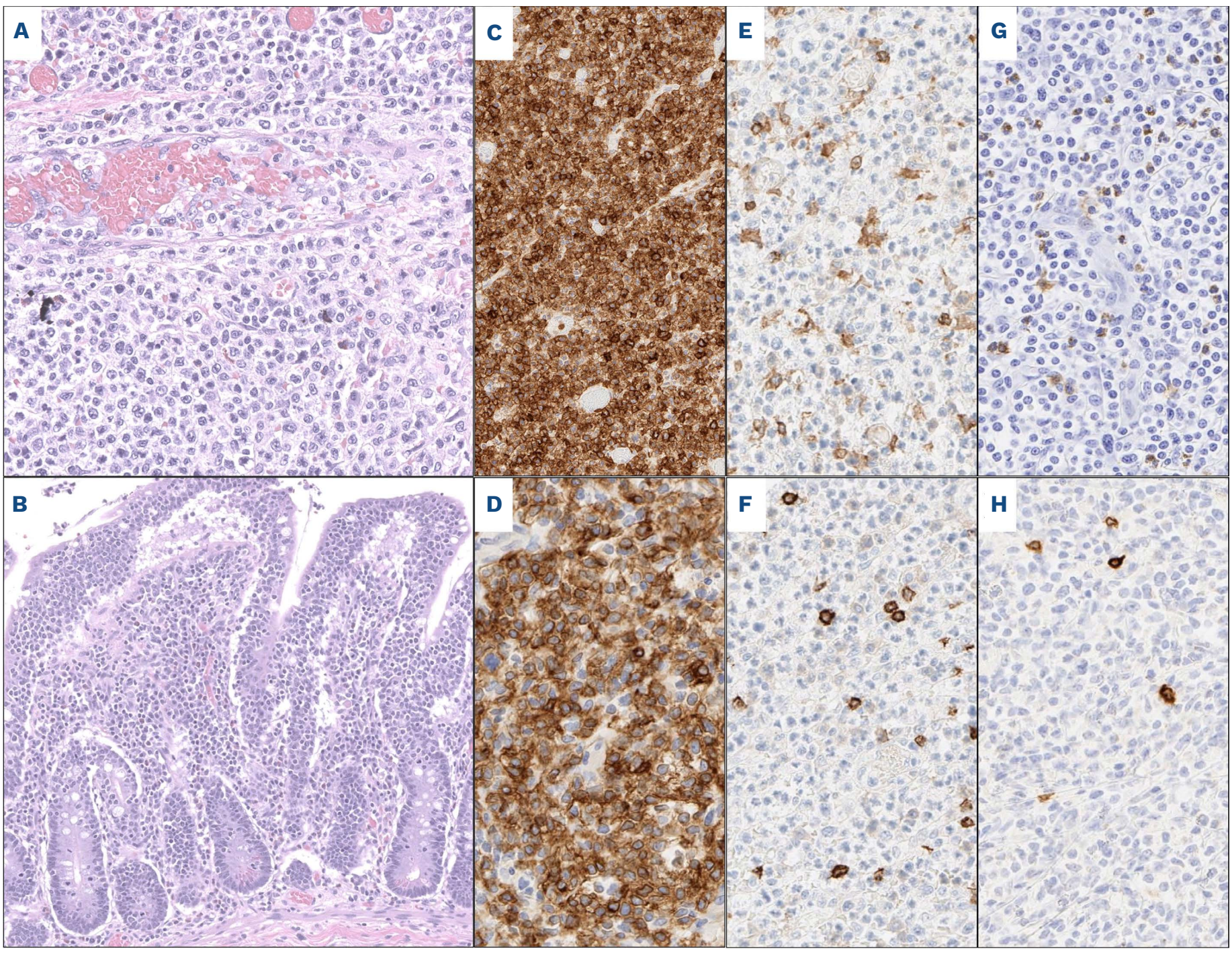

Figure 1. Enteropathy-associated T-cell lymphoma. (A-H) This case was composed of intermediate-sized to large cells with high mitotic activity, abundant apoptotic debris, and angioinvasion (A, H&E). Although the patient had not reported a history of gastrointestinal symptoms prior to presentation, the small bowel distant from the mass showed villous blunting and marked intraepithelial lymphocytosis (B, H&E) while serological evaluation detected anti-gliadin IgA, anti-gliadin IgG, anti-tissue transglutaminase IgA, and anti-endomysial IgA antibodies, consistent with subclinical celiac disease. The neoplastic cells showed a typical phenotype of enteropathy-associated T-cell lymphoma, expressing CD30 (C), and CD103 (D), and lacking CD4 (E), CD8 (F), TCRβ (G), and TCRδ (H) expression. H&E: hematoxylin and eosin.

accumulation of additional genetic aberrations and ultimately leading to the development of EATL.

Monomorphic epitheliotropic intestinal T-cell lymphoma

Clinicopathological features

Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) constitutes <5% of gastrointestinal lymphomas; however, it is the predominant form of primary intestinal T-cell lymphoma in people of Asian and Hispanic descent. The low incidence of CD in both populations indicates that MEITL is not related to CD. MEITL primarily affects older adults, has a male predominance, and typically localizes to small bowel (jejunum more frequently than ileum or duodenum) and rarely the colon or stomach. Dissemination to regional lymph nodes and distant organs can occur.[11] The prognosis is dismal, with a median survival of 7-15 months.[18] Tumors usually consist of monotonous, small to medium-sized lymphoid cells that show prominent epitheliotropism (Figure 2A). However, variant morphology, including cellular pleomorphism, larger cell size, or prominent nucleoli, has been described in a minority of cases.[19,20] Unlike EATL, MEITL typically lacks angiotropism, necrosis, and extensive background inflammation, although these can occasionally occur.[20] Villous blunting may be seen but is mostly confined to the peritumoral mucosa. The phenotype of MEITL differs from that of EATL in that the neoplastic cells are typically positive for CD8 and CD56 but negative for CD30, irrespectively of histological appearance[11,19,20] (Figure 2B-E). Occasional cases with atypical immunophenotypes (negative for CD8 and/or CD56) are described.[19,20] Aberrant CD20 expression is reported in 20%. MATK expression is reported as a characteristic marker, although it is not widely used in practice.[21] TCR is generally expressed, TCRγδ more commonly than TCRαβ. A small subset is TCR-silent, and co-expression of both TCR isoforms is rare. One-third of cases express MYC, which partly reflects underlying *MYC* alterations (Figure 2F-G). Epstein-Barr virus (EBV) is absent in tumor cells.

Genomic and biological features

The genetic profile of MEITL is distinct from that of EATL. Compared to EATL, MEITL shows a significantly higher frequency of gains in the *MYC* locus (73% *vs.* 27%) (Figure 2G) and a lower frequency of gains in 1q and 5q, although the two conditions share several recurrent chromosomal abnormalities, such as gains of 9q34 and 7 and losses of 8p22-23, 11q14, and 16q12.[15,22-24]

Recent studies have suggested that a combination of epigenetic deregulation and cell signaling activation may play a central role in the pathogenesis of MEITL. Deleterious mutations or deletions of *SETD2*, observed in nearly all cases (97%), have emerged as a genetic hallmark of MEITL.[20,25,26] *SETD2* is a lysine methyltransferase that is exclusively responsible for catalyzing the trimethylation of lysine 36 in histone H3 (H3K36me). H3K36me is a key modification that regulates gene expression at multiple levels (e.g., histone and DNA methylation, transcriptional activities, RNA splicing). Additionally, H3K36me plays a role in DNA damage repair, facilitating recruitment of DNA repair machinery. SETD2 loss of function results in reduced or absent H3K36me, presumably interrupting the above-mentioned activities. SETD2 also methylates non-histone substrates such as α-tubulin, whose methylation by SETD2 during mitosis and cytokinesis is essential for proper chromosome segregation and genomic stability. Additionally, SETD2 binds to TP53, enhances its stability, and upregulates expression of some of its target genes.[27] Considering the broad and multilayered roles of SETD2, it is difficult to predict which genes and pathways are critically affected by *SETD2* inactivation in lymphomagenesis. One phenotypic consequence is the expansion of γδ T cells, as demonstrated in a T-cell-specific *SETD2* knockout mouse model, which may explain the dominance of γδ T-cell origin in MEITL.[15] Given its role in DNA damage repair and TP53 stabilization, *SETD2* inactivation conceivably increases genomic instability and facilitates the acquisition of collaborating genetic events, which predominantly affect cell signaling pathways.

In common with EATL, MEITL frequently harbors mutations in the JAK-STAT pathway, albeit in different genes, namely *STAT5B* and *JAK3*.[20,22] Genes in the MAPK pathway (e.g., *BRAF*, *KRAS*, *NRAS*) are altered in 30-50% and are mutually exclusive.[25,28] *GNAI2*, which encodes a guanine nucleotide binding protein subunit, is mutated in 9%-21%.[22] One study identified *SYK* overexpression, likely due to promoter hypomethylation, as a distinctive marker of MEITL (95% prevalence *vs.* 0% in EATL), suggesting enhanced TCR signaling[29] (Figure 2E). Approximately one-third of cases exhibit *TP53* mutations, which are frequently associated with atypical morphology, concurrent *MYC* aberrancies (40% of *TP53*-mutated cases), and particularly dismal outcome, suggesting that *TP53* and *MYC* aberrations may cooperatively drive MEITL progression.[20]

Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract

Clinicopathological features

Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract (IC-TLPD-GI) was upgraded from a provisional entity in the 2017 revised 4th edition of the WHO

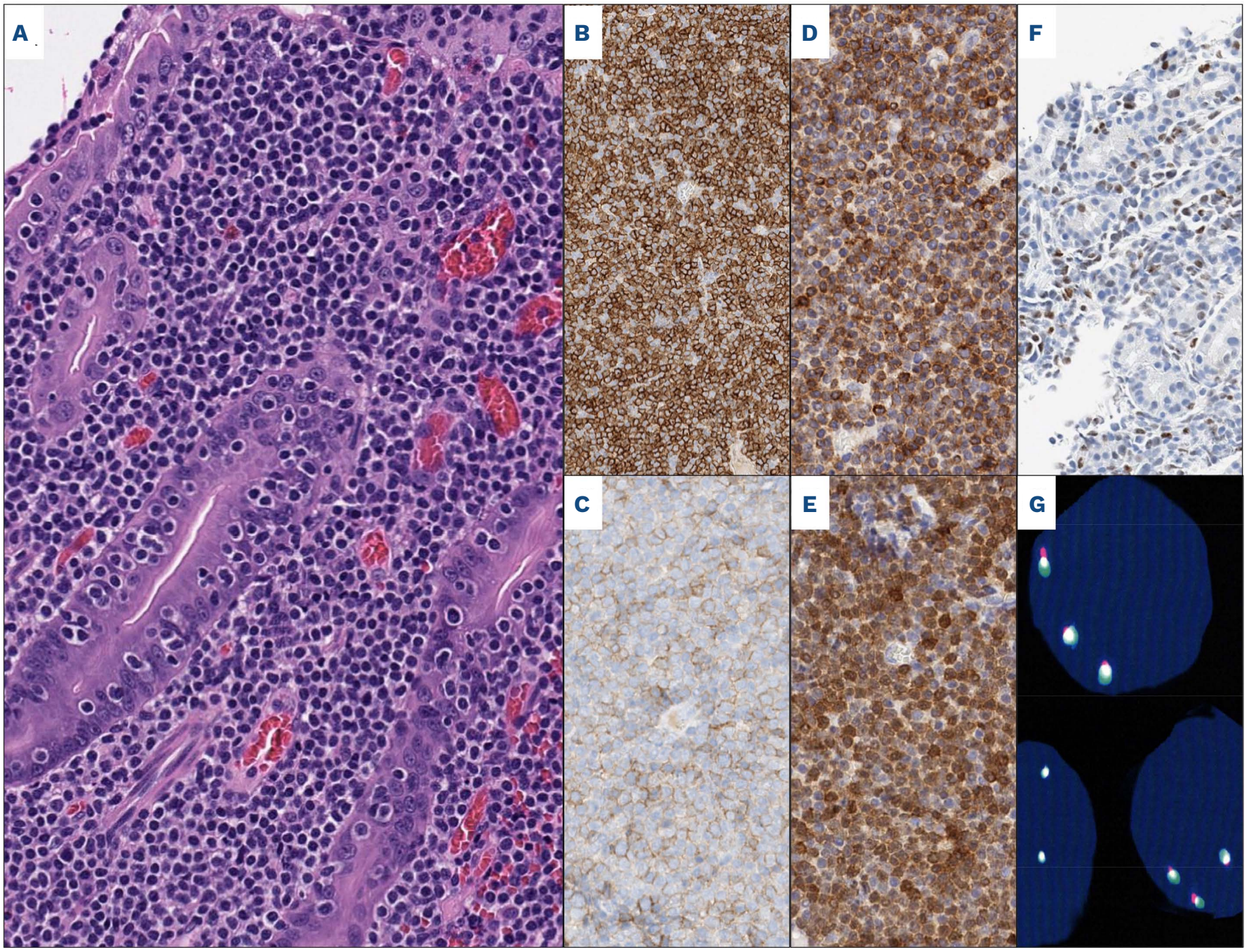

Figure 2. Monomorphic epitheliotropic intestinal T-cell lymphoma. (A-E) A dense infiltrate of monotonous small to intermediate-sized neoplastic cells with condensed chromatin and a rim of pale cytoplasm which infiltrates the small bowel epithelium is typical of monomorphic epitheliotropic intestinal T-cell lymphoma (A, hematoxylin and eosin). The cells expressed CD8 (B), CD56 (C), and TCRδ (D), and overexpressed SYK (E). (F, G) Another case showed increased MYC expression (F) and gain of the *MYC* locus on chromosome 8q24, as determined by fluorescence *in situ* hybridization (G).

classification to a definite entity in both the 2022 5th edition of the WHO and ICC systems.[2,30] The 5th edition of the WHO classification, however, changed the terminology from "lymphoproliferative disorder" to "lymphoma" due to the disease's significant morbidity and ability to disseminate.[30] It is most common among 50- to 60-year-olds and has a slight male predominance. It typically affects the small bowel and colon and is often multifocal. Mesenteric lymph node involvement is uncommon and distant dissemination is rare. While most patients experience chronic persistent/relapsing disease without progression for up to 14 years, death due to large cell transformation, occurring 10-27 years after diagnosis, has been reported.[31] Limited data suggest that CD4+ cases may have a higher risk of progression.[32]

Histologically, IC-TLPD-GI shows a dense, non-destructive proliferation of bland, monomorphic, small to intermediate-sized lymphocytes in the lamina propria with displacement of the intestinal epithelium without invasion. Mitotic figures and apoptosis are scarce, and vascular invasion and necrosis are absent. The tumor cells express CD3 and CD2 and may downregulate CD5 and/or CD7. Equal numbers of CD4+ and CD8+ cases are reported, with rare occurrences of double-negative or double-positive immunophenotypes. IC-TLPD-GI expresses TCRαβ and occasionally CD103. The Ki-67 proliferation index is low (< 5%) and EBV is absent.

Genomic and biological features

Despite limited published data, evidence suggests that IC-TLPD-GI has a lower burden of genetic aberrations compared to EATL or MEITL.[15,25,33] CD4+ and CD8+ cases exhibit distinct molecular signatures, which may partly explain

their different risks of progression. Recurrent alterations in the CD4$^+$ cases include JAK/STAT pathway alterations (e.g., *STAT3-JAK2* fusion, *STAT3* mutation, *SOCS1* deletion) and loss-of-function mutations in epigenetic modifiers (e.g., *TET2*, *DNMT3A*, *KMT2D*).[34] Conversely, CD8$^+$ cases are enriched with IL2 structural alterations.[33]

Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract

Clinicopathological features

Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract (I-NKLPD-GI) is an entity newly added to both the 2022 5th edition WHO and ICC systems.[2,30] It encompasses cases previously designated as NK-cell enteropathy or lymphomatoid gastropathy. I-NKLPD-GI is extremely rare with fewer than 80 cases having been documented.[35] Most occur in middle-aged to older individuals and affect the stomach or duodenum. I-NKLPD-GI follows a protracted but indolent clinical course, with some lesions undergoing spontaneous resolution while others persist for years despite treatment. Unlike IC-TLPD-GI, I-NKLPD-GI is not known to progress to a more aggressive disease or to disseminate to lymph nodes or other organs.

Histological examination reveals a diffuse infiltrate of medium-sized to large lymphoid cells expanding the lamina propria, which may exhibit epitheliotropism, ulceration, glandular destruction, or accompanying acute inflammation but typically lacks angiocentricity and necrosis. Tumor cells demonstrate an activated NK-cell immunophenotype and variable Ki-67 proliferative index. EBV is absent, distinguishing it from extranodal NK/T-cell lymphoma, nasal type (ENKTL).[11]

Genomic and biological features

Despite initial debates, the identification of somatic mutations in a subset of I-NKLPD-GI supports its neoplastic nature and justifies its classification as a lymphoproliferative disorder.[2,36,37] A recent study identified a recurrent, somatic, small, in-frame deletion in exon 12 of *JAK3*. Non-recurrent mutations involving *PTPRS, AURKB, AXL, ERBB4, IGF1R, PIK3CB, CUL3, CHEK2, RUNX1T1, CIC, SMARCB1*, and *SETD5* are also reported.[37] Clonal TCR gene rearrangements are absent.

Hepatosplenic T-cell lymphoma

Clinicopathological features

Hepatosplenic T-cell lymphoma (HSTCL) is an aggressive lymphoma of mature, cytotoxic T cells with a predilection for spleen, liver, and bone marrow. It accounts for ~1-2% of T/NK-cell lymphomas, occurring more commonly in North America and Europe than in Asia,[38,39] and has a dismal prognosis.[40-43] It shows a male preponderance and most commonly affects young adults (median age early to mid 30s) but can develop across a wide age range. Approximately 20% occur in immunocompromised individuals (e.g., those with autoimmune disease, inflammatory bowel disease, prior solid organ or stem cell transplant, or who take immunosuppressive drugs).[43,44] Most patients present with hepatosplenomegaly, B symptoms, cytopenias, and bone marrow involvement without significant lymphadenopathy. While peripheral blood involvement is common, lymphocytosis at initial diagnosis is rare.[40-43] Hemophagocytic syndrome is a well-recognized but uncommon complication.[43]

Neoplastic T cells are usually small to intermediate in size with mature chromatin, inconspicuous nucleoli, and moderate amounts of pale agranular cytoplasm (Figure 3A). However, variable cytomorphology, including large cell size, cellular pleomorphism, or blastic appearance with dispersed chromatin resembling acute leukemia, can be seen.[40-43] Lymphoma cells typically involve cords and sinusoids of the splenic red pulp as well as sinusoids of the bone marrow and liver. They typically express the T-cell markers CD2, CD3 and CD7 and aberrantly lack CD5 (Figure 3B). They usually lack both CD4 and CD8, but a minor subset expresses CD8. CD56 is positive in ~70% while CD57 is usually negative (Figure 3C).[45,46] Most cases show a non-activated cytotoxic T-cell phenotype, expressing T-cell intraellular antigen (TIA1) and granzyme M without perforin or granzyme B (Figure 3D). EBV is typically absent.[45,46]

Most HSTCL express TCR$\gamma\delta$ (~75%) (Figure 3E), typically with Vδ1 gene usage,[47] but variants expressing TCR$\alpha\beta$ (~20%) or lacking TCR expression (~5%) occur.[46] TCR$\alpha\beta^+$ cases are clinically and pathologically similar to TCR$\gamma\delta^+$ cases but have been associated with female sex, older age, and poorer outcomes in some studies.[43,48]

Genomic and biological features

The most common cytogenetic alterations include isochromosome 7q [i(7q)] and trisomy 8, which often co-occur and have been reported in ~25-80% and 10-50% of cases, respectively, as determined by karyotype or fluorescence *in situ* hybridization analysis[40-43,45,48,49] (Figure 3F-I). Less frequent alterations include ring chromosome 7, losses in 4p, 10p, and 10q, and gains in 1q and 17q.[49,50] Isochromosome 7q likely represents a primary event while other alterations, including trisomy 8, are postulated to occur secondarily.[51] The pathogenic role of i(7q), which results in loss in 7p and gain in 7q, is still unclear. The 7p loss has been associated with enhanced *CHN2* expression and its encoded signal transduction protein β2-chimerin, which may downmodulate the NFAT pathway and enhance

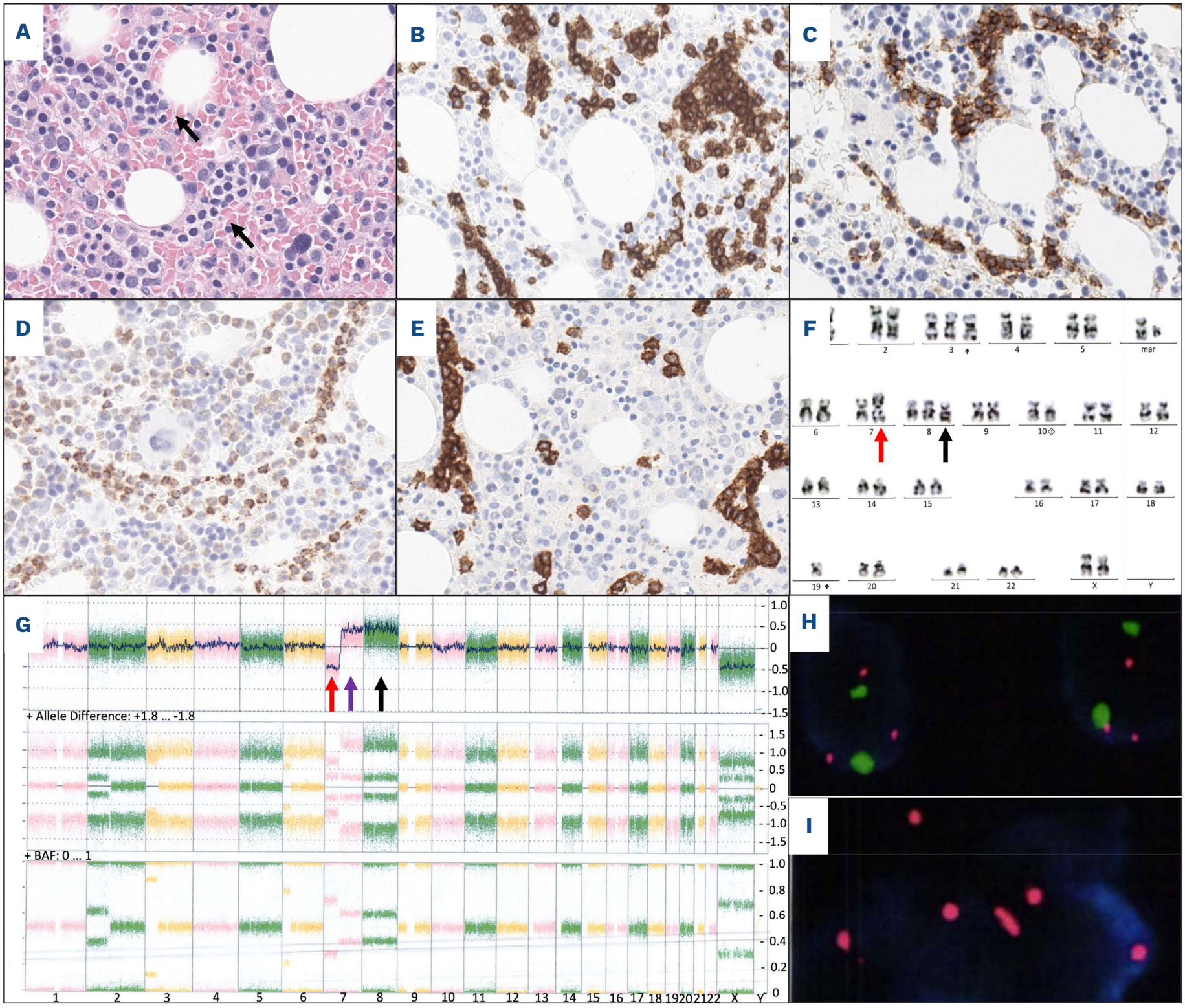

Figure 3. Hepatosplenic T-cell lymphoma. (A-F) Bone marrow biopsy in this patient with hepatosplenic T-cell lymphoma showed an infiltrate of intermediate-sized atypical lymphoid cells with condensed chromatin and pale cytoplasm involving and expanding the sinusoids (A, hematoxylin and eosin, black arrows). The cells expressed CD3 (B), CD56 (C), TIA1 (D), and TCRδ (E). Karyotyping detected multiple characteristic chromosomal abnormalities, including isochromosome 7q (red arrow) and trisomy 8 (black arrow) (F). (G-I) In another case of hepatosplenic T-cell lymphoma, both isochromosome 7q and trisomy 8 were detected by single nucleotide polymorphism array analysis (G, red arrow indicates 7p loss, purple arrow indicates 7q gain, black arrow indicates gain of 8) and fluorescence *in situ* hybridization (H, 3 signals of 7q31 [red probe] and 2 signals of CEP 7 [green probe] indicate gain of 7q; I, 3 signals of CEP 8 [red probe] indicates gain of 8). BAF: B-allele frequency.

cell proliferation, while the 7q gain is associated with increased expression of several genes at that locus implicated in tumorigenesis, such as *RUNDC3B*, *PPP1R9A* and *ABCB1*, which may impart an intrinsic growth advantage and chemoresistance.[50]

Gene expression profiling has demonstrated that HSTCL cluster separately from other T-cell lymphoma types.[52] TCR$\gamma\delta^+$ and TCR$\alpha\beta^+$ HSTCL cluster together and show highly similar gene signatures.[52] Genes upregulated in HSTCL as compared to peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) and ENKTL include *S1PR5*, involved in homing of NK cells to the spleen (potentially contributing to tumor cell localization within spleen and marrow sinusoids), and *ABCB1* (alias *MDR1*), which encodes a P-glycoprotein multidrug transporter (potentially contributing to tumor chemoresistance by extruding drugs from tumor cells), while the tumor suppressor *AIM1* is underexpressed. In addition, genes encoding NK-cell associated molecules are overexpressed in HSTCL compared to PTCL-NOS, while genes involved in immunomodulation

and *CD5* are underexpressed. Several categories of genes are differentially expressed as compared to normal γδ T cells, suggesting their importance in pathogenesis.[52,53] Overexpressed genes involve NK-cell-associated molecules (e.g., *KIR2DL2, KIR2DL3*) and those related to oncogenes (e.g., *FOS, VAV3*), cell adhesion (e.g., *VCAM1*), tyrosine kinases (e.g., *SYK*), signal transduction (e.g., *SPRY2*), the sonic hedgehog and WNT pathways, and *S1PR5*, while underexpressed genes include those associated with cytotoxicity (e.g., *GZMB*), cytokines, *AIM1*, and *CD5*. Pre-treatment tumor cells have been shown to demonstrate genetic heterogeneity, despite derivation from a common ancestral clone, with differential chemoresponsiveness.[53] Chemoresistance was associated with increased expression of genes associated with tumor survival (e.g., *IL32*, *TOX2*) and drug resistance (e.g., *AIF1*, *AKAP12*), suggesting potential mechanisms of treatment failure.[53]

Somatic mutations occur in several gene types. Mutations of chromatin-modifying genes occur in ~62% of cases, the most common being inactivating mutations of *SETD2* followed by mutations of *INO80*, *TET3*, and *SMARCA2*.[49] Activating mutations of the signaling pathway genes *STAT5B*, *STAT3*, and *PIK3CD* are reported in nearly half of cases.[45,49,54] Recurrent mutations in other driver genes, such as *TP53*, *UBR5*, and *IDH2*, are less common.[49]

Recurrent DNA methylation changes in HSTCL preferentially affect regulatory regions such as promotors and enhancers. These include hypermethylation of *AIM1*, *BCL11B*, *CD5, CXCR6, GIMAP7, LTA, SEPT9, UBAC2*, and *UXS1*, some of which have been implicated in the pathobiology of T-cell neoplasms and associated with aberrantly absent protein expression (e.g., CD5). Recurrently hypomethylated genes include *ADARB1*, *NFIC*, *NR1H3*, and *ST3GAL3*.[52,55] Some of these alterations, such as chromatin-modifying gene mutations and *AIM1* promotor methylation, *STAT3/5B* mutations, *PIK3CD* mutations, and SYK overexpression may represent therapeutic targets, potentially amenable to epigenetic modifiers, JAK/STAT pathway inhibitors, PI3K inhibitors, and SYK inhibitors, respectively.[49,52,54]

Given the association with immunocompromise, it has been postulated that immune suppression/dysregulation may play an etiological role, potentially by reducing an individual's ability to clear pathogens leading to chronic antigenic stimulation of T cells, particularly γδ T cells that have more limited antigenic specificity.[56] The resultant polyclonal γδ T-cell outgrowth may subsequently acquire genomic alterations leading to clonal expansion and malignant transformation. Approximately 10% of HSTCL arise in patients treated with thiopurines and/or tumor necrosis factor-α inhibitors for inflammatory bowel disease.[44] While a causal role of these drugs in HSTCL development has been suggested, this remains controversial. The risk of developing lymphoma, including HSTCL, is reported to increase following treatment with these drugs.[57] Tumor necrosis factor-α inhibitor therapy has been associated with clonal expansion of γδ T cells in patients with high baseline γδ T-cell counts and can induce γδ T-cell proliferation *in vitro* in a dose-dependent manner, suggesting that it may contribute to early pre-neoplastic clone development.[58] However, tumor necrosis factor-α inhibitors are not essential for the development of HSTCL among patients with immunodysregulatory disorders, suggesting that other factors may be more pathogenically important in such patients, such as other immunosuppressive drugs, genetic predisposition, and chronic antigenic stimulation.[59]

Extranodal NK/T-cell lymphoma, nasal type

Clinicopathological features

Extranodal NK/T-cell lymphoma (ENKTL) is an aggressive EBV-associated lymphoma derived from NK cells or T cells. Of note, the qualifier "nasal-type" was dropped from the name in the 5th edition of the WHO classification as the disease can present at extra-nasal sites.[30] It accounts for ~10% of T/NK-cell lymphomas worldwide but is significantly more common in Asia and Latin America than in western countries.[38,39,60] It typically arises in middle-age and most commonly affects the upper aerodigestive tract, with other sites of involvement including the gastrointestinal tract, skin, and testes. Secondary lymph node involvement, bone marrow infiltration, B symptoms, and hemophagocytic syndrome occur in a subset of patients.[61] The prognosis is generally poor but variable, with worse outcomes reported for patients with non-nasal presentation.[61]

Tumors show a diffuse infiltration of pleomorphic cells with irregular nuclei, frequently with an angiocentric and angiodestructive growth pattern and necrosis (Figure 4A). They typically express cytoplasmic CD3, CD2, CD56, and cytotoxic markers (TIA1, granzyme B, perforin) and lack CD4 (Figure 4B, C). Those of NK-cell lineage lack surface CD3 expression and a clonal TCR gene rearrangement while T-cell-derived cases typically express surface CD3, may variably express CD5 or CD8, and show monoclonal TCR gene rearrangements. EBV is detected in most tumor cells by *in situ* hybridization for EBV-encoded RNA (EBER) (Figure 4D). While unique clinicopathological features can typically distinguish ENKTL among other EBV$^+$ diseases, such as chronic active EBV disease and aggressive NK-cell leukemia, when widespread dissemination occurs, discrimination may not be possible.

Genomic and biological features

Recurrent gains involving chromosomes 1q, 2q, 7q, 17q and 20q and losses involving 6q, 11q, 13q and 17p are re-

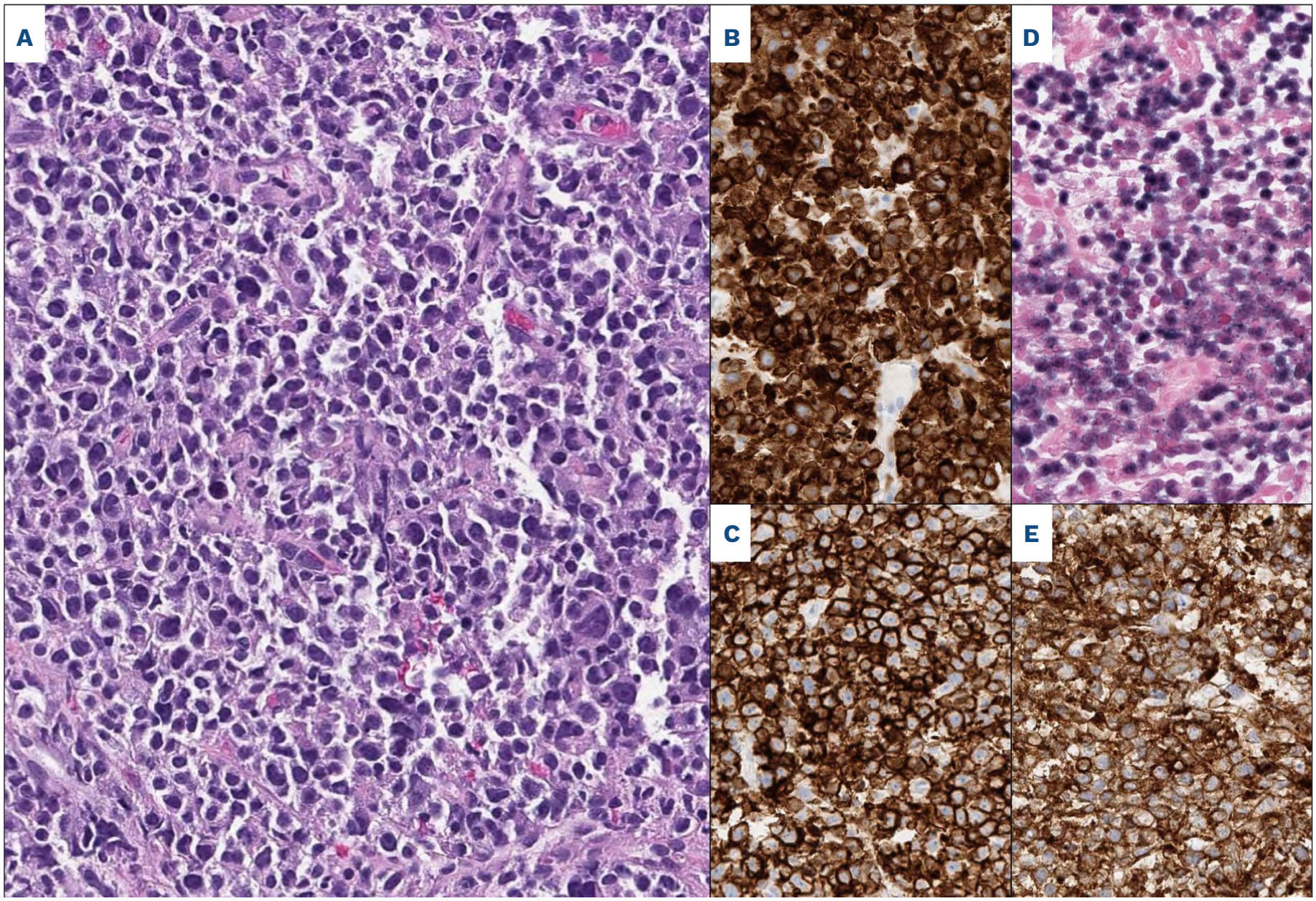

Figure 4. Extranodal NK/T-cell lymphoma, nasal type. (A-E) This extranodal NK/T-cell lymphoma, nasal type showed sheets of atypical lymphoid cells ranging from small to large in size with irregular nuclei (A, hematoxylin and eosin). The cells were diffusely positive for CD3 (B), CD56 (C), and EBER (D). High PD-L1 expression was also present (E).

ported.[62-65] Multiple potentially pathogenically important tumor suppressor genes lie within the most commonly deleted 6q21-25 region, including *PRDM1, HACE1, PTPRK, FOXO3, ATG5*, and *AIM1*.[63,64,66,67] The gene expression profiles of both NK- and T-cell-derived ENKTL cluster together, separate from PTCL, NOS, and are characterized by upregulation of genes of the JAK/STAT, NF-κB and Notch pathways and *MYC*.[63,68] Mutations most commonly affect the JAK/STAT pathway (e.g., *STAT3, JAK3, STAT5B*), tumor suppressors (e.g., *TP53, DDX3X, MGA*), and epigenetic modifiers (e.g., *KMT2D, KMT2C, BCOR, TET2*).[62,69,70] JAK/STAT pathway activation, occurring through gene mutations or phosphorylation of JAK3 or STAT3, is pathogenically critical in ENKTL and a potential therapeutic target.[63,71] RAS/MAPK (e.g., *NRAS, KRAS, BRAF, MAP3K5*), Notch (e.g., *NOTCH1/2*), NF-κB (e.g., *ECSIT, BIRC3*), and immune surveillance (e.g., *CIITA, HLA-A*) pathway mutations are less frequent.[62,69,70] ENKTL commonly exhibit global promoter hypermethylation, including that of pathologically important tumor suppressor genes (e.g., *BCL2L11, DAPK1, PTPN6, TET2*).[72] They also commonly express programmed cell death ligand-1 (PD-L1) (Figure 4E), which is mediated by *CD274* alterations (amplification or 3'-untranslated region truncation) or upregulation driven by LMP1 or STAT3.[73-76] It is still unclear whether PD-L1 expression or *CD274* alterations can predict response to anti-PD-1/PD-L1 therapy, a treatment used with some success in the relapsed/refractory setting.[75,77]

Several genomic subtypes of ENKTL are reported. A multi-omics study described three molecular subtypes associated with differential EBV transcriptional patterns and sensitivities to targeted therapies: (i) TSIM (alterations in tumor suppressor and immune modulator genes), characterized by JAK-STAT pathway activation, NK-cell origin, and PD-L1 overexpression; (ii) MB (*MGA* mutations and *BRDT* loss of heterozygosity), associated with MYC overexpression and poor outcomes; (iii) HEA (*HDAC9*, *EP300*, and *ARID1A* mutations), defined by epigenetic alterations, NF-κB activation and T-cell origin.[78] Through consensus clustering analysis of mutations and copy number alterations, another study identified seven genetic clusters (C1-C7) with differential survival outcomes.[62] Patients in the C6

group (characterized by RAS/RAF/MAPK pathway, *JAK3*, *BCOR*, and *TP53* aberrations, and chromosome 1 and 7 copy number alterations) had inferior outcomes while improved survival was associated with groups C5 (gains of *JAK3* and chromosome 19q/q13) and C7 (*TET2* loss and *ARID1B* mutations). Using gene expression profiling and immunohistochemistry, another study identified four immune microenvironmental subtypes (immune tolerance, immune evasion-A, immune evasion-B, immune silenced) which were associated with differential clinical outcomes, PD-L1 expression, and response to anti-PD-1 therapeutics.[79]

The identification of specific germline polymorphisms associated with risk and outcomes along with the ethnic/geographic bias of ENKTL suggest that genetic predisposition with or without environmental factors may play a pathogenic role. An increased risk of ENKTL development has been associated with single nucleotide polymorphisms in *IL18RAP* (which encodes the interleukin-18 receptor accessory β-subunit), *HLA-DRB1*, and *HLA-DPB1* in Asian individuals.[80,81] Specific single nucleotide polymorphisms have also been associated with differential survival.[82] Aside from minor differences in frequencies of genomic alterations, the genomic landscape is largely similar in Asian and Hispanic populations, suggesting similar oncogenic mechanisms.[62,70]

EBV invariably plays a critical pathogenic role given the strong association of ENKTL with the virus; however, the mechanisms are incompletely understood. The driver function of EBV is supported by the lower mutational burden in ENKTL and other EBV$^+$ neoplasms compared to other aggressive tumors (e.g., diffuse large B-cell lymphoma).[78] Most ENKTL harbor type A EBV with a 30 bp deletion in *LMP1*, although this is less common in Latin America, potentially due to geographic variation of EBV strains.[70,83] Tumor cells usually show type II latency with clonal episomal EBV, although type I latency and some integration of EBV DNA into the host genome can occur.[78,84] Viral LMP1-mediated activation of signaling pathways, such as NF-κB and MAPK, and epigenetic changes via modulation of host epigenetic machinery and EBV-encoded microRNA have been suggested as mechanisms of oncogenesis.[85,86] Small indels and long-fragment deletions of the EBV genome as well as integration of EBV fragments into the host genome which disrupt transcription of important host genes, such as *NHEJ1*, may also promote oncogenesis.

Subcutaneous panniculitis-like T-cell lymphoma

Clinicopathological features

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is an adipotropic lymphoproliferative disorder of TCRαβ$^+$, CD8$^+$, cytotoxic T cells that primarily involves subcutaneous tissue. It accounts for ~1% of T/NK-cell lymphomas,[38,39] affects a wide age range (median age 30-40 years), and occurs more commonly in females.[87-90] SPTCL is typically limited to subcutaneous adipose tissue with rare reports of involvement of extracutaneous fat-rich sites.[87-92] Patients typically present with multiple subcutaneous nodules or plaques, usually without ulceration, most commonly on the extremities or trunk. B symptoms and/or laboratory abnormalities are seen in over half of patients and hemophagocytic syndrome occurs in ~20-30%.[87,89,90] Approximately 20-40% of patients have an associated autoimmune disease, most commonly systemic lupus erythematosus,[87,89,90] although autoantibodies are reported in ~60% of patients, including in those without a history of autoimmune disease.[89,93] Given some overlapping clinical and morphological features, distinguishing SPTCL from lupus erythematosus panniculitis can be challenging. Although relapses are common, the clinical course is typically indolent with survival rates of >70%,[87-90,93] but worse outcomes in those who develop hemophagocytic syndrome are reported.[90] Historically, many patients were treated with combination chemotherapy, however, recent studies have demonstrated clinical responses to immunomodulatory drugs.[89,90,93]

Histologically, atypical lymphoid cells infiltrate subcutaneous fat lobules with sparing of the septa, superficial dermis, and epidermis.[87-90] The neoplastic cells are predominantly small to intermediate in size with irregular, hyperchromatic nuclei, which characteristically rim individual adipocytes (Figure 5A). Admixed small reactive T cells, histiocytes, karyorrhectic debris and fat necrosis are common while there are typically few background B cells, plasma cells, granulocytes, and plasmacytoid dendritic cells. The neoplastic cells express CD3, CD8, and cytotoxic markers (TIA1, granzyme B, perforin), show variable loss of CD2, CD5 and/or CD7, and typically lack CD4, CD30 and CD56 expression (Figure 5B, C). They express TCRαβ and lack expression of TCRγδ and EBV (Figure 5D). The Ki-67 proliferation index is often high (Figure 5E).

Genomic and biological features

Clonal TCR gene rearrangements are detected in most cases.[88-90] Chromosomal copy number alterations have been identified in isolated SPTCL cells, with the most common including losses in 1p, 2p, 5p, 9q, 10q, 11q 12q, 16, 20, and 22 and gains in 2q and 4q.[94] Gene expression profiling studies have suggested that inflammatory pathways and immune escape may be etiologically important in SPTCL. By gene expression profiling, cases of SPTCL group together and apart from cases of lupus erythematosus panniculitis, suggesting distinct biological backgrounds.[95] However, a subgroup of cases of lupus erythematosus

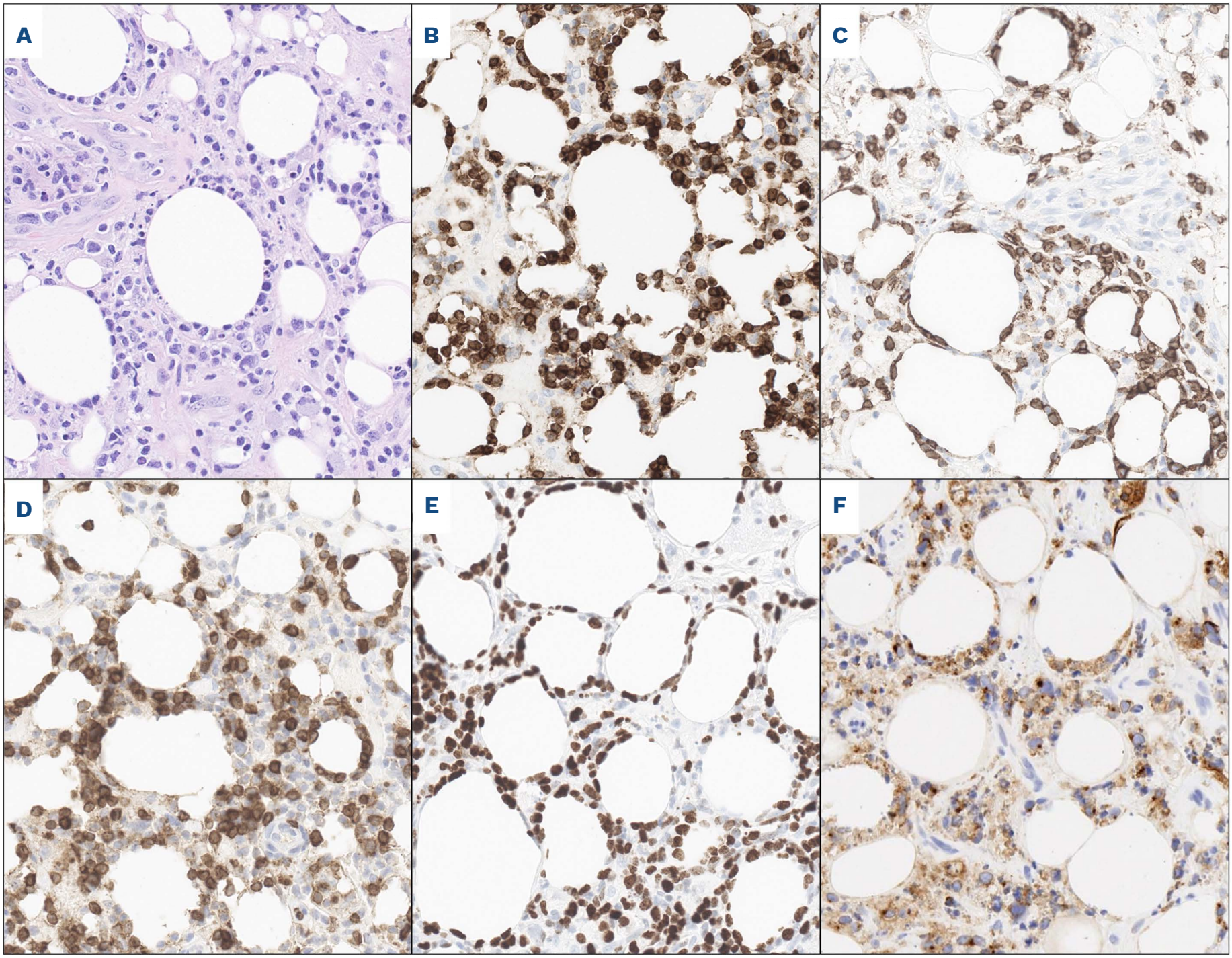

Figure 5. Subcutaneous panniculitis-like T-cell lymphoma. (A-E) A panniculitic lymphoid infiltrate composed of intermediate-sized atypical lymphoid cells with irregular nuclei and hyperchromatic chromatin are seen rimming individual adipocytes in this case of subcutaneous panniculitis-like T-cell lymphoma (A, hematoxylin and eosin). Foamy macrophages are present in the background. The atypical lymphocytes expressed CD3 (B), CD8 (C), and TCRα (D), and showed a high Ki-67 proliferative index (E). (F) Another similar case showed atypical cytoplasmic granular/paranuclear dot-like TIM3 staining, instead of the normal membranous/cytoplasmic staining pattern, raising suspicion of misfolded TIM3 protein, although *HAVCR2* mutational testing was not performed.

panniculitis has been shown to share some gene expression features with SPTCL, suggesting a potential molecular relationship. Genes reported to be overexpressed in SPTCL involve cytotoxicity (e.g., *PRF1, NKG7, GZMB*), cytokines and chemokines (e.g., *IFNG*, *CXCR3, CXCR6, CXCL9, CXCL10, CXCL11, CCL5, CCR5*), T-cell exhaustion/immune checkpoints (e.g., *IL10, LAG3, CD27, TIGIT, CTLA4, EOMES, TBX21, PDCD1*), and the immunotolerance-inducing enzyme indoleamine 2,3-dioxygenase 1 (*IDO1*), some of which have been associated with autoimmunity.[95-97]

Whole-exome and targeted sequencing studies identified a variety of somatic mutations, including those involving epigenetic modifiers (e.g., *CDC27, TET2, KMT2C, KMT2D, ASXL1, BAZ2A, ARID1B*), the PI3K/AKT/mTOR signaling pathway (e.g., *MTOR, PIK3CB, PIK3CD*), the JAK/STAT pathway (e.g., *JAK3, STAT3*), and other immune response pathways (e.g., *PLCG2, CBL, IDH1*).[98-102] Loss (deletion or loss of heterozygosity) and mutations of the tumor suppressor *NAV3* have been reported in 44%[94] and 10-15% of cases,[100,101] respectively.

Recent studies demonstrated a high frequency of predominantly biallelic missense mutations in *HAVCR2*, which encodes the protein T-cell immunoglobulin mucin 3 (TIM3).[93,99,100,102] The incidence among SPTCL patients ranged from 25% in a European study[93] to 85% within an Asian cohort.[102] Variants include p.Y82C (most common and enriched in Asian individuals), p.I97M, and p.T101I. These mutations were germline (mostly homozygous or com-

pound heterozygous) among patients in whom the germline could be assessed.[92,99,102] While *HAVCR2*-mutated (*HAVCR2*^{MUT}) SPTCL patients have typical clinical and histological features, they are reported to present at a younger age, suffer from more severe disease, including higher rates of hemophagocytic syndrome, and require more intensive therapy.[93,99,100] Testing for *HAVCR2* mutation in the clinical setting has been recommended to potentially identify patients at higher risk of aggressive disease and/or hemophagocytic syndrome who may benefit from more definitive therapy.[87,93]

TIM3 is a transmembrane receptor expressed in certain innate immune cells, including subsets of T/NK cells and macrophages. It acts as a negative immune checkpoint, terminating immune responses through interactions with ligands. *HAVCR2* mutations result in TIM3 protein misfolding which impairs its normal localization to the cell surface, a phenotype that can be seen with immunohistochemistry or flow cytometry[92,93,99] (Figure 5F). It is suggested that loss of normal TIM3 function leads to uncontrolled immune activation and excessive cytokine release, potentially promoting SPTCL along with development of hemophagocytic syndrome.

Compared to cases with wild-type *HAVCR2* (*HAVCR2*^{WT}), *HAVCR2*^{Y82C} SPTCL is enriched in genes involved in inflammation-associated cellular pathways, including IL6-JAK-STAT3 signaling and tumor necrosis factor-α signaling via NF-κB, consistent with enhanced inflammatory responses.[100] *HAVCR2*^{WT} SPTCL demonstrates upregulation of genes associated with lymphocyte homing (*CCR4, GPR183*) and autoimmunity (*STAB2*) and more frequently harbors several gene mutations (*ASXL1, CAPN1, UNC13D, PIAS3, PIK3CD, KMT2D, BRD2*), some of which (e.g., *PIAS3*) may function to deregulate immune pathways in the absence of deleterious *HAVCR2* mutations. *HAVCR2*^{WT} SPTCL also shows increased *CCR4* expression, a chemokine receptor that regulates T regulatory cell homing in skin, and higher numbers of CCR4^{+} and FoxP3^{+} cells in the microenvironment, suggesting that loss of intact CCR4-mediated T regulatory cell activity may propagate unchecked inflammation within *HAVCR2*^{MUT} SPTCL.

Despite the available data, the pathogenesis of SPTCL remains unclear. The concomitance of SPTCL with clinical, serological, and/or histological features of autoimmune disease, such as systemic lupus erythematosus, and/or indeterminate or overlapping histopathological features in some patients led to speculation that both disorders may co-occur, with either autoimmune disease predisposing patients to malignancy via immune dysregulation or SPTCL inducing autoimmune phenomena, or lie along a biological spectrum.[87,103-105] Reports of SPTCL arising after other immune-activating events, such as infection and vaccination, further suggests that immune stimulation may trigger T-cell dysregulation leading to the development of SPTCL.[89,102,106] Studies showing frequent expression of immune pathways, including those seen in autoimmune disorders, as well as the disease's indolent course that largely lacks extracutaneous dissemination and responds to immunomodulation have further linked the pathobiology of immune dysregulation and SPTCL. The discovery of frequent *HAVCR2* germline mutations in SPTCL patients at rates significantly higher than in the general population revealed a strong germline risk and furthered the understanding of SPTCL pathogenesis towards a disease of abnormal immune activation that fails to control a clonal T-cell outgrowth.[87,99] However, given the report of an unaffected patient with a known homozygous germline *HAVCR2* mutation,[99] these mutations alone may not be sufficient for disease development. Additionally, the detection of additional genomic alterations in significant proportions of *HAVCR2*^{MUT} tumors as well as the development of SPTCL in *HAVCR2*^{WT} individuals, some of whom have underlying diseases such as systemic lupus erythematosus or infections, suggests that additional genomic alterations and/or biological triggers may be involved in the pathogenesis.

Conclusion

The rarity of mature extranodal T-cell and NK-cell lymphomas and lymphoproliferative disorders makes their diagnosis, study, and biological understanding challenging. However, through the use of ever-advancing genomic and single-cell analytical techniques, insight into their pathogenesis continues to grow, and with it better opportunities to effectively diagnose, treat, and hopefully cure this unique group of challenging diseases.

Disclosures

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Contributions

NEL, TZ, and AD designed the manuscript, which NEL and TZ wrote. AD revised the manuscript. All authors approved the final version.

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