

Review

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Posted Date: 27 October 2025

doi: 10.20944/preprints202510.1938.v1

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Review

Indolent T- and Natural Killer-Cell Lymphomas and Lymphoproliferative Diseases – Entities in Evolution

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Abstract

Indolent lymphoproliferative diseases or disorders (LPD) derived from T cells or Natural Killer (NK) cells may be neoplastic or non-neoplastic, which are often difficult to distinguish from each other and from the aggressive counterparts. The etiology and pathogenesis are mostly nebulous and may be related to infections or immune dysfunction. Indolent lymphomas differ from the high-grade aggressive counterparts by a prolonged clinical course of persistent or relapsing disease, histology, immunophenotype and genetics. In the recent decades, indolent lymphomas or LPD of T or NK cell derivation have been increasingly recognized, causing diagnostic and nosologic confusion. The issue is particularly challenging in the arena of indolent intestinal lymphomas and LPD, as evidenced by the myriad of names given to the indolent intestinal T- and NK-cell lymphomas and LPD. Confounding the picture are also reports of Epstein-Barr virus (EBV)-positivity in various indolent non-intestinal LPD and rarely even in indolent intestinal T-cell lymphoma, which have been widely accepted to be typically EBV-negative. This review aims to curate current information and understanding of these diseases with the goal to resolve these issues. The recently described indolent T-lymphoblastic proliferation (iTLP) and the re-classified indolent primary cutaneous CD4-positive small or medium T-cell LPD and primary cutaneous acral CD8-positive T-cell LPD also require greater awareness and recognition. It is important to diagnose these indolent entities in order to avoid over-treatment and unnecessary therapeutic intervention, and to provide for accurate prognostic prediction and appropriate follow up.

Keywords: indolent; T-/NK- cell; lymphoma; lymphoproliferative diseases; intestinal; EBV

1. Introduction

Most primary gastrointestinal (GI) NK- or T-cell lymphomas are aggressive high-grade lymphomas [1]. In the recent 3 decades, there have been reports of indolent T- and NK-cell LPD of the GI tract, designated by a plethora of names. The myriad names given to these entities reflect the enigma of their biology, behavior and nosology. These are clonal proliferations and widely accepted to be EBV-negative [2–49]. This compares with their high grade counterparts which may be EBV+ (in extranodal NK/T-cell lymphoma of the GI tract - ENNKTL) [50] or EBV- (in monomorphic epitheliotropic intestinal T-cell lymphoma- MEITCL and enteropathy-associated T-cell lymphoma- EATCL) [51,52]. Interestingly, there are also rare reports of EBV-positivity in indolent intestinal T-cell lymphoma (iTCL) [8,27,30]. This subjects the widely accepted belief that indolent T-cell GI lymphomas are EBV-negative to question. Furthermore, EBV-positive indolent non-intestinal NK- or T-cell LPD have also been reported [54–62], despite also isolated reports of indolent EBV-negative NK-cell LPD in two non-intestinal sites, the nasopharynx [49] and the vagina [63]. The reported molecular features of indolent GI LPD also differ from those of ENNKTL, MEITCL and EATCL [2–4,8,20,23,26–29,31,32,48–50], though there is some overlap in alterations of genes related to the JAK/STAT pathway. There are other recently recognized or re-categorized indolent T-cell LPD, including indolent T-lymphoblastic proliferation (iTLP), primary cutaneous CD4+ small or medium T-cell LPD (PcutCD4+TLPD) and primary cutaneous acral CD8+ T-cell LPD (PcutacCD8+TLPD) that

require greater attention [32,64–71]. This review summarizes the hitherto reported clinical, morphologic and immunophenotypic features, the evolving genetic landscape and the dubious possible role of EBV in these entities.

2. Indolent Intestinal Lymphoma and LPD

These received attention in the past 3 decades. This review retrieved papers on these entities by searching Scopus and Google Scholar for the period 1990 to 2025 with the keywords “indolent, intestinal, T-cell, NK-cell, lymphoma, lymphoproliferative disease, lymphomatoid gastropathy and enteropathy”. A total of 81 cases of indolent intestinal T-cell lymphoma (iTCL) and 56 cases of indolent intestinal NK-cell LPD (iINKLPD) were identified as a single case report or case series and were analyzed.

2.1. Indolent Intestinal T-cell Lymphoma

This was first described by Carbonnel et al in 1994 under the name of “extensive small intestinal lymphoma of low-grade malignancy associated with a new chromosomal translocation” [4]. The reported case manifested non-specific abdominal symptoms with insignificant intestinal endoscopic findings. The patient eventually developed acute small bowel obstruction and the resected small bowel featured dilatation, thickened wall and multiple 1-2 cm diameter serosal tumors associated with enlarged mesenteric lymph nodes. Small bowel histology revealed massive involvement that was limited to the mucosa by a diffuse infiltrate of small atypical lymphoid cells, associated with multiple non-caseating granulomas. The mesenteric lymph nodes and the liver portal tracts were involved by similar atypical lymphoid infiltrate. Immunophenotypically, the lymphoid cells are T-cells expressing CD3, CD4, betaF1, but negative for CD8. There was negligible Ki67 staining. A chromosomal translocation t(4;16)(q26;p13) involving the *interleukin-2* (IL-2) gene was also detected.

This report was followed by many other similar reports under designations of “small intestinal, gut, GI tract, stomach, indolent T-cell, CD4-positive lymphoma, lymphoproliferative disease” in varying word combinations [4–32]. This great variability in the use of designations reflects uncertainty within the then academia about the nature of this entity. This review collected 81 cases of iTCL. There were 55 males and 26 females with an age range 14-80 years and median age of 50 years. The reported cases had wide geographic distribution from Europe, Asia to Africa. As in the case reported in 1994 [4], all presented with non-specific abdominal symptoms including bloating, pain, diarrhea and weight loss. One was complicated by intestinal obstruction [4] and another by intestinal perforation [13]. Extraintestinal involvement or metastasis were reported in mesenteric lymph nodes [4,8,13,15,16,27–32], liver [4,8], peripheral blood [4,8,13,32], bone marrow [14,15,19,23,32], tonsil [15], lungs [4,8], skin [4,8,32] and epiglottis [32]. In 2 cases, inguinal lymph node involvement was reported [23], which was unusual as metastasis to peripheral lymph nodes has been regarded to be very rare or absent in iTCL. The histology of the reported iTCL cases was similar, namely non-destructive, diffuse infiltrates of small or medium atypical lymphoid cells often limited to the mucosa, though some cases show focal involvement of the muscularis mucosae and submucosa. There were differences in immunophenotypic expression of CD4 and CD8, in varying combinations. The Ki67 positivity rate was usually low [1,2,4–29,31,32].

2.1.1. Involved Sites and Gross Presentation

iTCL involves mostly the small intestine and the colon. However, other GI sites including the stomach, esophagus and oral cavity may also be involved [5,7,9,11,13–15,17,19,23–25,32]. Multifocal involvement of the GI tract is common [1–32], with gross presentations of polyps, folds, nodules, fissures or ulcers [1–32].

2.1.2. Histology

iITCL is characterized by non-destructive, partial involvement of the intestinal wall, often restricted to the lamina propria of the mucosa. A proportion of cases, however, may also show involvement of the muscularis mucosae or submucosa. There is usually no epitheliotropism and the surface and glandular epithelium are usually spared. In some cases, there are non-caseating granulomas or conspicuous eosinophils [2,4–32]. The infiltrate is typically composed of atypical small to medium lymphoid cells with irregular dark nuclei and infrequent mitotic activity. There is no angiocentricity or angioinvasion (Figure 1)[2,4–32].

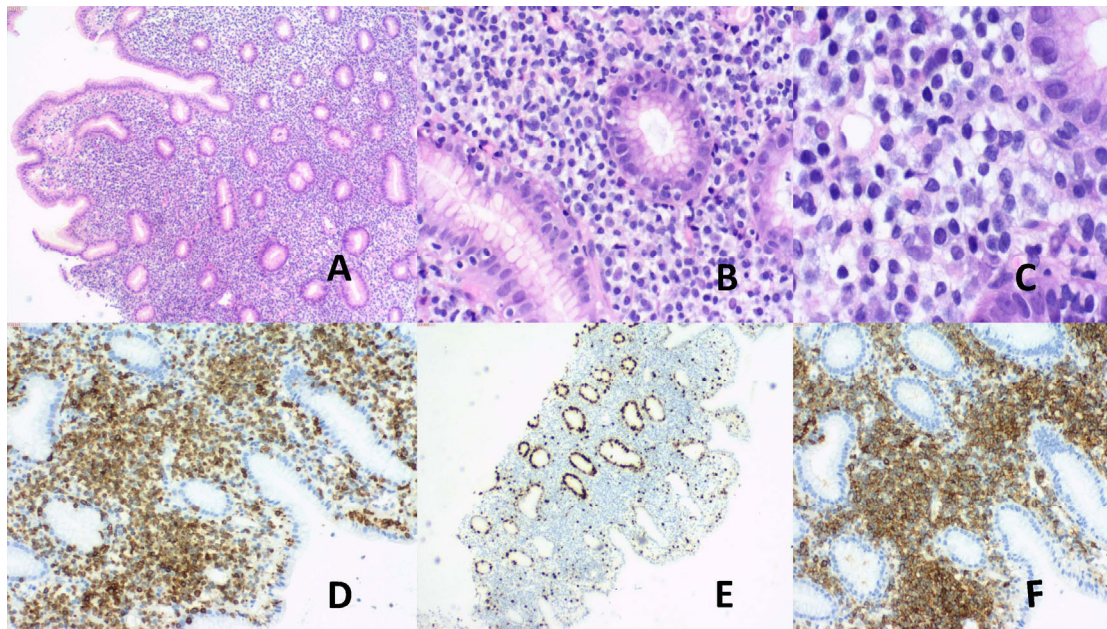


Figure 1. (A) Male, 46 years, vague abdominal symptoms. Multifocal GI involvement. Colonic biopsy. (A) Non-destructive mucosal atypical lymphoid infiltrates. H&E, X50. (B) & (C) Mucosal small atypical lymphoid cells infiltrate. Focal intraepithelial involvement present. H&E, (B) X200, (C) X400. (D) CD3+, X100. (E) Ki67 low, X100. (F) Aberrant CD20+, X100.

2.1.3. Immunophenotype

The atypical lymphoid cells exhibit T-cell phenotype and are positive for T-cell receptor (TCR, mostly beta and uncommonly gamma), CD3, CD2, CD4, CD5, CD7 and CD8. There are more CD4+ than CD8+ iITCL. According to the pattern of expression of CD4 and CD8, iITCL can be categorized as CD4+/CD8-, CD4-/CD8+, CD4+/CD8+ and CD4-/CD8- [2,4–32]. This immunophenotypic categorization appears to correlate well with non-neoplastic T cells. CD8+ iITCL more frequently express TIA1 (but not granzyme B or perforin)[14,22,23,25–30]. These different immunophenotypes of iITCL show different genetic features (see subsection 2.1.4), and may have bearing on pathogenetic mechanisms. Though there had been reports of CD4+ iITCL running higher risks of disease progression[8,13,16,19,20], this association is no longer documented in the 5th edition of the WHO Classification [2]. Ki67 proliferation index is low and mostly <10%.

2.1.4. Genetic Alterations

(a) TCR rearrangement

Clonal TCR rearrangement is present in all iITCL, more commonly TCR *beta* and less commonly TCR *gamma* [1,2,4–17,19–32].

(b) JAK/STAT and NF-KB pathway related genes

This is more frequent in CD4+/CD8-, CD4+/CD8+ and CD4-/CD8- iITCL [20,23,26–29,31]. Using Next Generation Sequencing (NGS), alterations in *STAT3* and *JAK2*, resulting in *JAK2::STAT3* fusion have been demonstrated [20,23,26–29,31]. Other genes with demonstrated alterations include *STAT3 SH2* mutation, *STAT5* alteration and *SOC51* deletion. Mutations in epigenetic modifier genes *DNMT3A*, *EZH2*, *KMT2D*, *TET2* and *TNFAIP3* that contribute to JAK/STAT pathway activation are also identified, more commonly in CD4+/CD8- and CD4-/CD8- iITCL [2,28,29,31]. Activation of the NF-KB pathway through histone modification of *KMT2D* and methylation of *TET2* may also contribute to pathogenesis.

(c) *IL2* gene

IL2 gene alterations occur more commonly in CD8+ than CD4+ cases [2,23,29,31]. Implication of the *IL2* gene in iITCL was first demonstrated by traditional G-banding cytogenetic study [4], and later also by NGS. NGS uncovered *IL2::RHOH* (Ras homolog family member H) fusion due to inversion of chromosome 4 and *IL2::TNIP3* (TNFAIP3 interacting protein 3) fusion [23,29]. *RHOH* deficiency has been shown to be associated with T helper 17 cell polarization and T-cell defects [72,73]. In CD4-/CD8+ iITCL, deletion of 3' untranslated regions of *IL2* and mutation of *MCM5* (minichromosomal maintenance complex 5) have been demonstrated [23].

(d) Other genetic alterations

Alterations in *DIS3*, *MAPK1*, *TP53*, *POLE*, *SMAD4*, *SFB1* and *CDKN2A* have also been reported in some cases of CD4+ iITCL [23].

The number of studies and reported cases, however, are hitherto small and it is immature for definitive conclusion on distinctive pathogenetic and genetic differences among the different immunophenotypic categories of iITCL to be made. Furthermore, the number of genes, gene panels so far studied were limited and the technological methods used vary from study to study. With future evolution in molecular methodology, discovery of more genetic alterations in these indolent T-cell lymphomas may be made. It remains to be seen with more future work for better correlation of immunophenotype, genetics, pathogenesis and prognosis in iITCL.

2.1.4 Etiology and Role of EBV

The etiology of iITCL has remained nebulous. It has been etiologically associated with persistent antigenic stimulation [23], Crohn's disease [11,74], autoimmune enteropathy [15] and coeliac disease [8]. None of these postulations, however, has been substantiated by further evidence. It is widely accepted that iITCL is not associated with EBV and is typically EBV-negative. However, among the 81 cases identified by this review, only 22 cases were reported to have been tested for EBV (22/81, 27%). Among those tested for EBV, 19 cases were EBV-negative (19/22, 86%) and three were EBV-positive (3/22,13%) [8,27,30]. It is notable that the status of EBV infection in the remaining reported iITCL represented the majority of those reported cases (59/81,73%). The methodology of EBV detection was not mentioned in a significant number of reports, but in-situ hybridization on tissue sections for EBV-encoded small RNA (EBER) was the most frequently used in reports where the methodology of EBV detection was mentioned, including the 3 EBV-positive cases [8,27,30]. Though EBER is regarded as the preferred method for detecting latent EBV infection in tissue sections [75–78], there are alternative methods of EBV detection [54,55,57,75,76]. By using these alternative methods, reclassification of the so far reported EBV-negative cases to EBV-positive remains possible. Testing the remaining EBV-unknown status cases may also skew the hitherto reported EBV-status in iITCL. Since there were documented cases of EBV+ iITCL (3 cases, 13% among tested cases) [8,27,30], the role of EBV in iITCL remains to be explored. Furthermore, in one case of CD8+EBV+ iITCL, there was a high Ki67 proliferation index (90%) [30], which may potentially portend more aggressive behavior. The possibility of 2 groups of iITCL, namely EBV- and EBV+, therefore stays to be further studied. The possible groups may be different in immunophenotype, genetics and clinical behavior.

2.1.5 Neoplastic Nature of iTCL

The true biologic nature of indolent intestinal T-cell proliferations had been enigmatic, as reflected by the plethora of names ranging from “proliferative disorders, diseases to lymphomas” given to these entities by multiple researchers and authors in the literature in the past 3 decades. [4–32]. The body of cumulative information and evidence hitherto on this entity is in favor of its neoplastic nature, as follows:

1. *Ability to disseminate.* There have been multiple reports of dissemination to various non-intestinal distant sites including mesenteric lymph nodes, liver, lungs, skin, tonsils, epiglottis, peripheral blood and bone marrow, as described in Section 2.1 above [4,8,13–16,19,23,27–32]. More importantly, dissemination to inguinal lymph nodes had also been reported in 2020 in 2 cases [23]. This is in striking contrast to the former belief that lymph nodes spread from iTCL should be limited within the abdomen.

2. *Disease Progression.* Progression or transformation to higher grade lymphoma was documented in 5 of 81 cases (6%) [20,21,23]. Three cases transformed to overt T-cell lymphoma [20,21], with one demonstrated to share the same *STAT3::JAK2* fusion as the pre-existing iTCL.

3. *Frequent Genetic Mutations.* Alterations in *TCR* genes, genes of the JAK/STAT signaling pathway and epigenetic modifier genes that contribute to JAK/STAT activation, *IL2* gene and *DIS3*, *MAPK1*, *TP53*, *POLE*, *SMAD4*, *SFB1* and *CDKN2A* gene alterations in many cases as discussed in Subsection 2.1.3 [2,4,17,19–32].

In the Fifth edition of the WHO Classification of Haematolymphoid Tumours [1,2], the neoplastic nature of iTCL is recognized due to the significant morbidities related to the disease and its ability to disseminate. This entity is redesignated to “Indolent T-cell Lymphoma of the Gastrointestinal Tract” from the former revised Fourth edition designation of “Indolent T-cell Lymphoproliferative Disorder of the Gastrointestinal Tract”.

2.1.6. Treatment

Among the 81 reported cases, 19 cases did not receive any specific treatment, 1 was treated with surgery, 17 with chemotherapy, 4 with steroids, 7 with gluten free diet, 1 with mogamulizumab, and whether treatment was instituted was not mentioned in the remaining 32 patients. Though the initial response was favorable in a handful of cases where it was reported, the clinical course of iTCL was indolent with persistent or relapsing disease, irrespective of the treatment modality or whether treatment was instituted or not. [4–32].

2.2. Indolent Intestinal NK-cell Lymphoproliferative Disease (iINKLPD)

iINKLPD is a more recently recognized entity than iTCL [2,33–49], and was initially designated lymphomatoid gastropathy

(in the stomach) and NK-cell enteropathy (in the remaining intestine tract). It behaves in indolent fashion as persistent or relapsing disease over long durations. The common presentations include vague abdominal symptoms

or may be asymptomatic, only to be discovered incidentally on endoscopy. This review uncovered 56 cases of iINKLPD from 17 case reports or case series. There were 22 males, 32 females, and 2 cases with unidentified sex. The age ranged from 14 to 76 years (median 52 years). One case showed also concomitant involvement of the glans penis [47], while all the remaining 55 cases showed only involvement of the GI tract. [33–46,48,49].

2.2.1. Sites of Involvement and Gross Findings

The stomach and small/large intestines are more commonly involved. The gall bladder was also rarely implicated [31,44,46,49]. The disease may present as single or multiple elevated lesions or ulcers with hemorrhage and edema, measuring 1-2 cm in size [33–49].

2.2.2. Histology

The disease is usually limited to the lamina propria featuring expansion by confluent generally non-destructive infiltrates of mostly medium-sized atypical lymphoid cells with irregular nuclei and pale granular cytoplasm. This contrasts with iTCL where small atypical lymphoid cells are more common and the cytoplasm is agranular. Epithelial invasion with destruction and displacement of intestinal glands can occur. Mucosal ulceration and focal necrosis are occasionally present. The muscularis mucosae is usually intact, but may be involved. There is no angiocentricity or angioinvasion. Admixture with other inflammatory cells is usually present (Figure 2) [3,33–49].

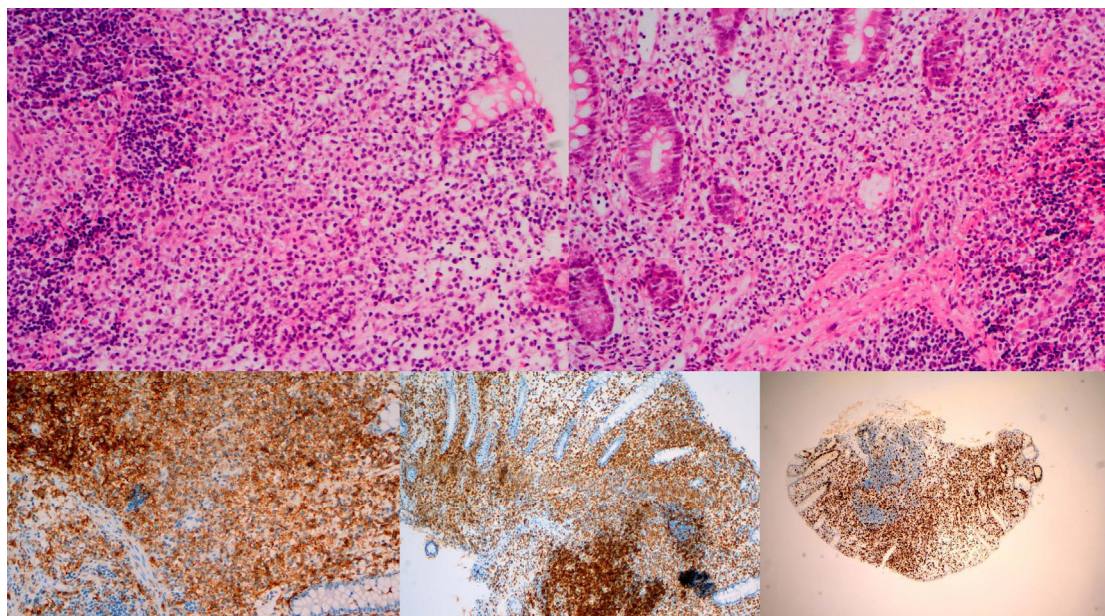


Figure 2. Male, 48 years, abdominal pain. Jejunal biopsy. (A) & (B) Non-destructive mucosal medium-sized atypical lymphoid cell infiltrate with pale granular cytoplasm. Involvement of muscularis mucosae in (B). H&E, X200. (C) CD56+, X100. (D) CD3+, X100. (E) Ki67 high (about 60%), X100.

2.2.3. Immunophenotype

By definition, the atypical lymphoid cells do not express TCR antigens and surface CD3. They frequently express CD56 and cytotoxic effector proteins TIA1 and granzyme B. CD2, CD7, CD8 and cytoplasmic CD3 may be expressed. The Ki67 positivity rate is usually low (<10%) but may be higher and up to 80% [3,33,35–37,41,43,45,48,49]. The significance of this difference in Ki67 positivity rate from iTCL, which is mostly low in the latter, is unknown.

2.2.4. Etiology and EBV Status

The etiology of iINKLPD is unknown, though *Helicobacter pylori* (HP) infection has been suggested to play a role, as response of iINKLPD to anti-HP treatment has been reported [3,29,34,39,43]. This, however, was not universally observed in the reported cases. In the 56 reported cases, all were EBV-negative. Though the number of cases reported was small for a definitive conclusion on the role of EBV in iINKLPD to be made, it appears that EBV is probably not etiologically or pathogenetically related to iINKLPD.

2.2.5. Neoplastic or Non-Neoplastic?

Unlike iTCL, the biologic nature of iINKLPD has not been clearly defined. Among the 56 reported cases, there was no observation of distant dissemination, progression or transformation of

the disease. However, genetic alterations including mutations in *JAK3*, *RUNX1*, *CIC*, *ERBB4* and *SETD5* had been reported in iNKLPD [3,29,48,49]. Phosphorylated STAT3 [2,49] and STAT5 [9] proteins had also been demonstrated in some cases of iNKLPD. These genetic and epigenetic anomalies point to a possible neoplastic nature of iNKLPD. The involvement of the glans penis in one case [47] also suggests dissemination of the disease outside of the intestine. However, the small number of reported cases with these changes preclude making definitive conclusions. The biologic nature of iNKLPD requires further study on a larger number of cases for clarification.

2.2.6. Treatment

Among the 56 reported cases, 34 were not given any specific treatment, 4 received surgery, 7 chemotherapy (with 2 given concomitant bone marrow transplant), 1 anti-HP therapy, and 10 cases without reported treatment modality. Despite the treatment modality, the indolent course of persistent or relapsing disease appeared unaffected [33–49]. More work is required on a greater number of cases for better understanding of the clinical outcome and optimal management of iNKLPD.

2.3. Differential Diagnoses of iTCL and iNKLPD from Other Intestinal NK- or T-Cell Lymphomas

The major differential diagnoses (DDX) are monomorphic epitheliotropic intestinal T-cell lymphoma (MEITCL), enteropathy-associated T-cell lymphoma (EATCL) and primary GI extranodal NK/T-cell lymphoma (ENNKTL) of the intestine. Intestinal metastasis from primary non-GI ENNKTL may also cause diagnostic confusion, but can be distinguished by presence of a primary (nasal or other non-nasal sites) in another location. MEITCL, EATCL and GI ENNKTL can be distinguished by their distinctive clinical manifestations, aggressive behavior, high grade morphology, immunophenotypic and genetic differences. In EATCL, there is often histologic evidence of residual coeliac disease. Primary GI ENNKTL may be distinguished by characteristic histological evidence of frequent angiocentricity, angioinvasion, and extensive geographic necrosis. Further, EBV is always positive in ENNKTL, in contrast to the usual EBV-negativity in iTCL and almost always EBV-negativity in iNKLPD [50–53]. A summary of the differences among these entities is depicted in Table 1.

Table 1. Comparative Features of Gastrointestinal NK-/T-cell Lymphomas and LPD.

	iTCL	iNKLPD	ENNKTL	MEITL	EATL
Age (years)	CD4+: Median 51 CD8+: Median 45	30-90	35-58	Median 54-67	Median 61
Sex	M>F	M>F	M>F	M>F	M>F
Predominant sites involved	Small intestine, colon	Stomach, small intestine, colon, gall bladder	GI tract	Small intestine	Small intestine (mostly jejunum)
Multifocality	Common	Yes	27%	20-35%	32-54%
Enteropathy association	No	No	No	No	80%
Metastasis	BM, PB, tonsil, mesenteric LN	Rarely mesenteric LN	Multiple extraintestinal sites, frequently Stage IV	LN, lung, liver, brain, skin	LN, BM, lung, liver

Transformation	Reported	NR	NA	NA	NA
Depth involved	Mucosa, sometimes also MM and SM	Mucosa	Full thickness	Full thickness	Often full thgickness
Histology	Small /medium atypical cells, non-destructive dense infiltrate, no/rare epithelial invasion, no angioinvasion	Medium atypical cells, small nucleoli, pale granular cytoplasm, circumscribed confluent infiltrate, glands displaced, epithelial invasion +/-, necrosis +/-	Range of atypical cells, geographic necrosis, epithelial invasion, angiocentricity, angioinvasion, angiodestruction	Monotonous atypical cell infiltrates, necrosis, epithelial invasion, severe inflammatory backdrop, “starry sky” appearance	Range of atypical cells, epithelial invasion, angioinvasion, angiodestruction, features of CD
Molecular/genetic alterations	<i>STAT3, JAK2,, JAK2::STAT3 fusion, STAT5, SOCS1, KMT2D, TET2, DNMT3A, EZH2, TNFAIP3, IL2, RHOH, TNIP3, TCR</i>	<i>JAK3, RUNX1T1, CIC, ERB4, SETD5</i>	<i>PRDM1, PTPRK, HACE1, FOXO3, STAT3, JAK3, STAT5B, BCOR, KMT2D, ARID1A, EP300, TCR (in T-cell type)</i>	<i>Myc, SETD2, STAT3, STAT5, JAK1, KAK3, TCR</i>	<i>JAK1, STAT3, TET2, KMT2D, DOX3X, TNFAIP3, TNIP3, POT1, TP53, CD58, FAS, B2M, TCR</i>
Immunophenotype	CD3+, CD4+CD8-, CD4- CD8+,CD4+CD8 +, CD4-CD8-, TCR+, Ki67 low*	CD56+, CD2+, cCD3+, CD7+, TIA1+, GZB+, TCR-, Ki67 high	CD56+ (NK-cell type), cCD3+, sCD3+ (T-cell type), CD2+, TIA1+, GZB+, perforin+, TCR- (in NK-cell type), TCR+ (in T-cell type), Ki 67 high	CD2+, sCD3+, CD7+, CD8+, CD56+/-, TIA1+, TCR+, Ki67 high	CD3+, CD7+, TIA1+, GZB+, perforin+, Ki67>50%, CD30+/EMA+ (in anaplastic cases)
EBV	Negative@	Negative	Positive	Negative	Negative

Footnote: *Some cases reported Ki67 high, @Some cases reported EBV+, +: positive, -: negative, +/-: weak or focal positive, cCD3: cytoplasmic CD3, CD: Coeliac disease, BM: bone marrow, EATL: enteropathy associated T-cell lymphoma, ENNKTL: extranodal NK-/T-cell lymphoma, F: female, GZB: granzyme B, iINKLPD: indolent intestinal NK-cell lymphoproliferative disorder, iTCL: indolent intestinal T-cell lymphoma, LN: lymph node,

M: male, MEITL: monomorphic epitheliotropic intestinal T-cell lymphoma, MM: muscularis mucosae, NA: not applicable, NR: not reported, PB: peripheral blood, sCD3: surface CD3, SM: submucosa, TCR: T-cell receptor.

3. Indolent Non-Intestinal NK- or T-Cell LPD

This review uncovered 11 cases of indolent NK- or T-cell LPD that arose from non-intestinal sites. Four cases occurred in the nose, 1 in the nasopharynx (NP), 3 in the skin, 1 in lymph nodes, 1 in the pericardium and 1 in the vagina [49,54–63]. All cases were characterized by indolent clinical behavior of persistent or relapsing disease over long periods. Four cases were of T-cell lineage (2 nose, 1 pericardium, 1 lymph node) and 7 were of NK-cell lineage (2 nose, 3 skin, 1 NP and 1 vagina) [49,54–63]. Apart from the EBV-status unreported NK-cell NP case [49] and EBV-negative vaginal [63] case, the remaining 4 T-cell (1 lymph node, 2 nose and 1 pericardium) and 5 NK-cell (2 nose and 3 skin) were all EBV-positive, including an indolent NKLPD of the skin which was not initially tested for EBV but progressed to an EBV+ ENNKTL after a prolonged relapsing disease [56]. The rate of EBV-positivity among indolent non-intestinal NK- or T-cell LPD was therefore 82% (9/11).

The majority (5/6 tested cases, 83%) [57–62] of these cases were associated with a high Ki67 positivity rate with a reported rate of over 90% in one pericardial case [62]. Two NK-lineage EBV-positive cases of the skin where outcome information was available revealed high grade transformation to ENNKTL (2/2, 100%) after long durations of indolent disease [55,56]. This compares with the lower rate of transformation in iTCL (5/81, 6%), where the EBV status of all 5 cases were not reported [19,20,23], and that none of the 19 tested EBV-negative iTCL cases resulted in transformation [4–32]. There was also no disease progression or transformation in all 56 NK-cell EBV-negative iNKLPD [33–49].

It appears that EBV-positivity is more prevalent in indolent non-intestinal NK- or T-cell LPD, and may be associated with higher Ki67 proliferation index [57–62] and high grade transformation of disease [55,56]. It may be argued that indolent EBV-positive non-intestinal NK- or T-cell LPD should not be compared with other indolent EBV-negative intestine counterparts and should be grouped together with the high grade primary GI EBV-positive ENNKTL [50]. However, ENNKTL is clearly different from indolent EBV+ NK- or T-cell LPD in clinical behavior, histology, immunophenotype, genetics and outcome and should be separately categorized [50,53]. Despite easy distinction from those ENNKTL with a conspicuous large cell component, prominent geographic necrosis, angiocentricity and angioinvasion, indolent EBV+ NK- or T-cell LPD can mimic some ENNKTL with a predominant small cell component [50,53] morphologically and immunophenotypically, thus causing great diagnostic difficulty without clinical follow up. The indolent EBV+ NK- or T-cell LPD may also cause confusion with chronic active EBV disease (CAEBV), but could be distinguished by its lack of severe systemic symptoms and deranged liver functions at presentation which are characteristic of CAEBV [53]. It should also be mentioned that indolent EBV+ T-cell LPD of the skin may be confused with various other cutaneous lymphomas or LPD which are also often indolent but distinguishable by being always negative for EBV. Since the number of reported indolent EBV+ non-intestinal NK- or T-cell LPD is so far very small, it is not possible to define this as a distinctive biologic entity. Further work on many more cases is required for elucidation on the biologic nature and role of EBV in these entities. Table 2 summarizes the miscellaneous features of the 9 reported EBV+ indolent non-intestinal NK- or T-cell LPD.

Table 2. Summary of Reported EBV+ non-intestinal indolent T- and NK-cell LPD.

Series (reference, year)	Sex	Age	LPD Duration (years)	Site(s)	Disease progression	Px of progressed disease	Clinical outcome	Histology of LPD	Immunophenotype	Genotype	Lineage	EBV/EBER of LPD	Ki67
Rahemtullah et al[54] (2008)	M	71	4	neck LN	EBV+ BCL with plasmacytic differentiation	CT	DOD (66 m)	LG	CD2+, CD3+, CD5+, CD7+, CD4+, CD20+, CD30+(dim), CD56+(dim)	TCR: GL Ig: polyclonal	T	+	NR
Watabe et al[55] (2009)	F	39	10	skin (legs)	ENNKTL, nasal type (skin)	CT	DOD (128 m)	LG*	CD3+, CD56+, GZB+, CD8+/-, perforin +/-	TCR:GL	NK	+	NR
Seishima FM et al[56] (2010)	F	60	11.5	skin (lip and cheek)	EBV+ ENNKTL, nasal type (nose & multiple skin sites)	CT	DOD (146m)	LG*	CD56-, CD4+/-, CD8+/-, cytotoxic (ND)	NR	NK (CD56 turned + on progression)	NR	NR
Jiang QP et al[157] (2012)	F	78	10	nose	NP	NA	AWD	LG	CD3+, CD56+, Cytotoxic+, CD20+	TCR:GL Ig : GL	NK	+	60%
Zuriel D et al[58] (2012)	F	55	22	skin (recurrent, right upper arm)	NP	NA	AWD (recurrence 192 m & 264 m,	LG	CD2+, CD3+, cytotoxic+, CD56+ (at 264 m) Ki67 >90%	TCR: GL	NK	+	90%

							skin right upper arm)						
Tabeanelli V et al[59] (2014)	F	52	13	nose	NP	NA	AWD at 156 m	LG	CD2+, CD3+, CD5+, CD7+, CD56+, βF1+, TCR α/δ+, cytotoxic+, Ki67 (moderately high)	TCR: clonal	T	+	Moderate high
Zhang QF et al[60] (2016)	M	53	20	nose	NR	NA	AWD at 242 m	LG	CD3+, CD56+, cytotoxic+, Ki67(80%)	NR	NK	+	80%
Devins K et al[61] (2018)	F	71	long standing	nose	NR	NA	AWD (many years)	LG	CD2+, CD3+, CD3+/-, CD5+/-, CD7+/-, CD56- cytotoxic+, Ki67 (<1%)	TCR: clonal KIT mutation+	T	+	<1%
Wang Z et al [62] (2020)	M	64	19	Pericardium	NP	NA	AW	LG	CD3+,CD30+,CD43+, TIA1+, MUM1+, BCL2+	TCR:clonal	T	+	>90%

Footnote: AW: alive and well; AWD: alive with disease; BCL: B-cell lymphoma; CT: chemotherapy; DOD: died of disease; ENNKTL: extranodal NK/T-cell lymphoma; GZB: Granzyme B; IgG: immunoglobulin gene; LG: low grade; LN: lymph node; LPD: lymphoproliferative disease; MG*: medium grade histology with lymphoepithelial lesion; MG@: medium grade histology with angiocentricity and focal necrosis, NA: not applicable; NP: no progression of disease; NR: not reported; NED: no evidence of disease; Px: treatment modality; RT: radiotherapy; TCR: T-cell receptor gene; *: interpreted from published images; +: positive, +/-: weak or focal positive.

4. Indolent T-Lymphoblastic Proliferation (iTBLP)

iTBLP was first described in 1999 in the upper aerodigestive tract of a male subject which remained indolent and stable for over 16 years without treatment [32,64,65]. iTBLP is rare and about 50 cases have been reported in various nodal and non-nodal sites. The latter includes mandibular, cervical, supraclavicular, parotid, inguinal, abdominal, liver, adrenal, retroperitoneal, nasopharyngeal and mediastinal locations [32,64–66]. iTBLP may affect reactive lymph nodes [66], occurs in Castleman disease, myasthenia gravis, paraneoplastic autoimmune multiorgan syndrome, and may be associated with neoplasms (hepatocellular carcinoma, dendritic follicular cell sarcoma and acinic cell carcinoma) [32,64–66]. The clinical course is benign and indolent and does not require treatment. It is characterized histologically as non-destructive presenting as tumor-like, tumor infiltrating lymphocyte-like or focal cellular cluster (>50 cells) lesions [64]. The cells are small to medium-sized that lack significant atypia. Immunophenotypically, they are positive for Tdt and CD3, with variable positivity for CD1a, CD4, CD7, CD8, CD10, CD34 and CD99. This immunophenotype is in keeping with that of a common lymphoid precursor [64–66]. Genotypically, clonal *TCR* rearrangement is not present. The most important DDX is T-cell lymphoblastic lymphoma (TLBL). TLBL is distinguishable by tissue destruction, larger lymphoblastic cells with significant atypia, aberrant immunophenotypic features including expression of LMO2 and presence of clonal *TCR* rearrangement. The rarity of TLBL in adults should also be helpful in distinction from iTBLP in adult patients. It is important to recognize the association of iTBLP in a variety of malignant tumors, in order to avoid confusion and misinterpretation [64–66].

5. Indolent Cutaneous LPD

Many cutaneous T-cell lymphomas or LPD are clinically indolent and include primary cutaneous CD4-positive small or medium T-cell LPD (PcutCD4+TLPD), primary cutaneous acral CD8-positive T-cell LPD (PcutacCD8+TLPD), mycosis fungoides, lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. PcutCD4+TLPD was a provisional entity in the 2017 WHO Classification and PcutacCD8+TLPD was originally designated as a lymphoma. These are recently reclassified as LPD, due to the benign indolent clinical course. These 2 entities are highlighted below.

5.1. PcutCD4+TLPD

This was a provisional entity in the 2017 revised fourth edition of the WHO Classification [32,67]. It is currently designated an LPD because of the benign indolent clinical behavior, with spontaneous regression in about 30% of cases [32,67,68,70]. It is a clonal disease and *TCR* gene rearrangement is demonstrable in the majority of tested cases [68,69]. It affects a wide age range with a median of 59 years. Both sexes are affected almost equally. Clinically, it affects most commonly the neck and neck and presents as an asymptomatic erythematous solitary nodule and less frequently as a tumor, papule, macule or plaque with size ranging from 4-60 mm. Histologically, two patterns were reported. The entire dermis is involved in one pattern, sometimes with extension to the subcutis. The other pattern features a subepidermal band-like infiltrate of the superficial dermis. Epidermotropism and folliculotropism may be present, rendering mycosis fungoides a differential diagnosis. The infiltrate consists mostly of small to medium atypical lymphoid cells and contains no more than 40% large cells. Immunophenotypically, the lymphoid cells are CD3+, CD4+, CD8-, CD30-, follicular T-helper cell markers+ (mostly PD-1+) and low Ki67 proliferation index. Reactive B cells and CD8+ T cells may be present. The prognosis is excellent. Treatment with intralesional steroids, excision or radiotherapy are effective, and spontaneous remission without treatment occurs in 30% cases. The major DDX are mycosis fungoides, primary cutaneous marginal zone lymphoma and cutaneous lymphoid hyperplasia [32,68,70].

5.2. *PcutacCD8+TLPD*

It was designated as a lymphoma in the 2017 revised fourth edition of the WHO Classification and has been recently regarded as an LPD in view of the indolent benign clinical behavior. It is a slow growing solitary reddish purple skin nodule or plaque measuring up to several centimeters. It affects acral sites including the face, ear, nose, hands or feet. It is histologically characterized by a dermal dense monotonous atypical lymphoid infiltrate consisting of medium-sized cells. Extension into the subcutis is common. Immunophenotypically, the lymphoid cells are CD3+, CD4-, CD8+, CD30-, cytotoxic cell phenotype+ (TIA1+ mostly), CD56- and PD1-. CD68 is positive, showing the characteristic Golgi-dot-like positivity. Ki67 proliferation index is low. Clonal TCR rearrangement is present in nearly all cases. The prognosis is excellent, with complete remission after excision or local irradiation [32,69,71].

6. Conclusions

Indolent NK- or T-cell LPD are less recognized and characterized, compared to the B-cell counterparts. The latter including B-cell lymphocytic lymphoma/leukemia, marginal zone lymphoma of mucosa-associated lymphoid tissue, lymphoplasmacytic lymphoma, indolent mantle cell lymphoma (leukemic type) and follicular lymphoma are well delineated morphologically, immunophenotypically, genotypically and nosologically [79]. iTCL was first described 3 decades ago, followed almost a decade later by reports of iNKLPD. The indolent clinical behavior of these entities has been the major confounding factor in delineating their biologic nature. The significant morbidities, ability to disseminate, potential for disease progression and transformation and multiple genetic alterations identified in iTCL have led to its recent recognition as a lymphoma [2,28,31]. iNKLPD, on the other hand, appears less definitive. However, the frequent presence of *JAK3* and other genetic mutations, and expression of the phosphorylated STAT3 and STAT5 proteins point to the possible neoplastic nature of iNKLPD.

The role of EBV in these indolent NK- or T-cell lymphomas or LPD is also perplexing. Though it is commonly believed that EBV-negativity is a feature of iTCL and iNKLPD, the reports of EBV+ iTCL challenge this commonplace conviction [8,27,30]. The more frequent reports of EBV-positivity in indolent non-intestinal NK- or T-cell LPD, provides more conjectural aura to this belief [57–62]. The small number of tested reported cases of iTCL that were confirmed to be EBV-negative, amid an even larger number of cases with no reports of their EBV status (59/81,73%), raises the need for accumulation of further evidence and work before a firm dogma to be made on the role of EBV in these entities. Ki67 proliferation index is low in most iTCL. However, it is higher in iNKLPD and indolent non-intestinal EBV+ NK- or T-cell LPD. This finding is interesting, but the significance is unknown.

The recognition of iTBLP is eye-opening since the presence of lymphoblasts often conveys the notion of proliferation and neoplasia. The indolent behavior of iTBLP warrants greater awareness of the entity, in order to avoid unnecessary radical therapy. Though many cutaneous T-cell lymphomas are indolent in behavior, *PcutCD4+LPD* and *PcutacCD8+LPD* have recently been reclassified as LPD instead of lymphoma due to the uniformly excellent clinical behavior. Such redesignation is important for better recognition of their biological nature and avoidance of over-treatment.

Conflict of interest: The author declares no conflict of interest.

Funding: This work received no external funding.

Acknowledgment: The authors thank Dr. Xingen Wang, Department of Pathology, Peking University Shenzhen Hospital, for supplying images of Figures 1 and 2.

Ethics Committee Approval: This is not required for a Review Article.

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