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Review

Indolent T- and NK-cell lymphoproliferative disorders of the gastrointestinal tract: a review and update

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Abstract

Primary gastrointestinal (GI) T- and NK-cell lymphomas are usually aggressive neoplasms associated with high morbidity and mortality. Over the past two decades, however, cases of primary GI lymphoproliferative disorders (LPDs) or lymphomas of T- or NK-cell derivation with indolent behavior have been reported. These LPDs are rare and they can be challenging to diagnose as they share clinical and pathological features with both, inflammatory disorders and aggressive T- and NK-cell lymphomas. Primary, indolent clonal T-cell proliferations of the GI tract, which can be CD4+, CD8+ or CD4− CD8−, have been included as a provisional entity in the newly revised World Health Organization (WHO) classification of lymphoid neoplasms and designated 'indolent T-cell LPD of the GI tract'. It is currently unclear whether the indolent NK-cell LPDs represent reactive or neoplastic proliferations. In this review, we describe the clinical, morphologic, immunophenotypic and genetic features of indolent GI T- and NK-cell LPDs and provide guidance in differentiating them from other inflammatory and neoplastic diseases. We believe that greater awareness of these LPDs amongst physicians and the research community will lead to timely and accurate diagnoses, stimulate investigations into the pathogenetic mechanisms underlying different entities thereby enhancing our understanding of disease biology and enable the development of effective therapeutic regimens. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: indolent; T-cell; NK-cell; lymphoproliferative disorder; lymphoma; gastrointestinal tract

Introduction

The gastrointestinal (GI) tract is the most common extranodal site of occurrence of non-Hodgkin lymphomas [1]. Most GI lymphomas are of B-cell lineage, and T-cell lymphomas account for up to 15% of all cases [2,3]. Primary intestinal T-cell lymphomas are usually aggressive neoplasms. The revised World Health Organization (WHO) classification of lymphoid neoplasms recognizes two distinct entities, *enteropathy-associated T-cell lymphoma* (EATL), formerly known as EATL type I, which is associated with celiac disease and occurs predominantly in the Western hemisphere and *monomorphic epitheliotropic intestinal T-cell lymphoma* (MEITL), formerly known as EATL type II, which has a wide geographic distribution and is the most frequent subtype encountered in Asia [4–6]. Extranodal NK/T-cell lymphoma, nasal type and other types of peripheral T-cell lymphomas may also occasionally occur in the GI tract [7,8].

Over the past couple of decades, sporadic case reports and limited series have described primary gastrointestinal T- and NK-cell proliferations, variably termed indolent lymphomas or lymphoproliferative disorders (LPDs) [9–24]. Recent, well-characterized case series from the United States, Europe and Japan have provided greater insight into the clinical, histopathologic and phenotypic spectrum of these LPDs [25–29]. This has led to the inclusion of indolent GI T-cell LPD as a provisional entity in the forthcoming, revised WHO classification, where it will be designated '*indolent T-cell lymphoproliferative disorder of the GI tract*' [5]. In the current review, we provide a comprehensive description of the clinical features, imaging findings, histopathology, immunophenotype and genetic alterations of indolent T- and NK-cell LPDs of the GI tract based on our appraisal of the reported cases. Clinicopathologic features helpful in differentiating these LPDs from inflammatory diseases and aggressive T/NK-cell lymphomas involving the GI tract are also discussed.

Indolent CD4+ T-cell LPDs of the GI tract

Epidemiology

Carbonnel et al. described the first case of indolent CD4+ T cell LPD of the GI tract in 1994 [10]. Since then, a total of 23 cases have been described [9–12,18,19,24,25,27,28]. The median age of patients at diagnosis was 51.5 years (range 22–68 years) and a male predominance was noted (M:F—1.9:1) (Table 1). The patients included 18 of Western European descent, 2 Asians (Japanese) and 1 each of Northern African and Afro-Caribbean ancestry; the race or ethnicity of one individual was not reported.

Clinical presentation

The most common symptoms included chronic diarrhea (21/23, 91.3%), noted in all cases where the LPD primarily involved the small bowel, and weight loss (19/23, 83%) (Table 1), which often led to the erroneous diagnosis of refractory celiac disease and a consequent delay in diagnosis [9–12,18,19,24,25,27,28]. Of note, diarrhea was not reported in individuals lacking significant small intestinal involvement by the LPD [11,12]. Egawa et al. described a patient with relapsing oral and colorectal ulcers and occult blood loss [11], while only polypoid stomach and duodenal bulb lesions were observed by Hirakawa et al. at presentation, with colonic and rectal involvement detected later [12]. Three (13%) patients had night sweats without fever [9,27,28]. Abdominal distension because of subacute bowel obstruction or bile acid malabsorption were rarely reported [18,19]. Concomitant celiac disease and autoimmune enteropathy were described in one case each [25]. At the time of diagnosis, most patients lacked extra-GI involvement, and disease was localized to the GI tract for a long duration; however, dissemination to other organs, e.g. liver, bone marrow, tonsil and peripheral blood, was observed with disease progression [9,19,24,25,27].

Endoscopic findings and imaging

The extent and pattern of involvement of the GI tract were quite variable on endoscopy, ranging from localized disease to extensive infiltration of multiple organs. Some cases displayed normal mucosa, but many showed mucosal abnormalities, characterized by nodules, polypoid lesions, fissures, superficial ulcers, erosions, diverticula and rarely tumor like masses or discrete, punched-out deep ulcers (Figure 1A–C) [9–12,18,19,24,25,27,28].

Endoscopic ultrasonography, performed in one case, revealed hypoechoic gastric nodules [12], while abdominal X-ray imaging demonstrated dilatation of intestinal loops and thickening of intestinal folds in some patients [9]. Enlarged mesenteric lymph nodes were frequently observed on computed tomography (CT) scans [18,19,24,25,27], which at times were mildly hypermetabolic on positron-emission tomography (PET) imaging [18,25,27]. PET-CT scans were useful in detecting disease transformation [27].

Histopathology

The small intestinal biopsies demonstrated normal mucosal architecture in some cases, while others showed crypt hyperplasia, either with preserved villous architecture (Figure 2A) or accompanied by variable degrees of villous atrophy. The lamina propria was expanded by a diffuse or patchy infiltrate of predominantly small-sized lymphocytes (Figure 2B). The lymphocytes displayed round, ovoid or angulated nuclei, fine chromatin, indistinct nucleoli and scant to moderate clear cytoplasm (Figure 2C). Infiltration through the muscularis mucosa into submucosa was observed in some cases. Scattered plasma cells and eosinophils were mostly seen in the superficial lamina propria. Scattered lymphoid follicles or aggregates were present. Most LPDs affecting the small intestine did not show a significant increase in intra-epithelial lymphocytes (IELs). However, a mild patchy increase in IELs was noted occasionally, and clusters of IELs (lymphoepithelial lesions) were seen at the villous base and/or in the crypts in a proportion of cases. Necrosis or lympho-vascular invasion was not observed. Granulomas were occasionally reported in the small bowel mucosa (or at extra-intestinal sites) in the absence of clinical or histopathologic evidence of inflammatory bowel disease (IBD) [10,19]. A granulomatous response to tissue or epithelial injury, as illustrated (Figure 4A–B), could be a possible explanation for this finding in some instances. The density of lamina propria lymphocytic infiltration at other GI sites such as the colon (Figure 4C) and stomach (Figure 4D–F) varied, and it could be subtle, requiring immunophenotypic or molecular analysis for confirmation. Mitotic activity was low in all cases. In the rare instance of disease transformation, an infiltrate of large pleomorphic lymphocytes, including multinucleated and bizarre forms, was observed, which was morphologically indistinguishable from EATL or anaplastic large cell lymphoma [27]. One case each with concomitant celiac disease, autoimmune enteropathy and IBD was reported [25,28]. However, no unusual or distinguishing morphologic features of the associated diseases were described in these cases.

Immunophenotype

As shown in Table 1, all cases expressed CD4 (Figure 2D) and CD3 (Figure 2E) [9–12,18,19,24,25,27,28]. While detailed immunophenotypic information was not available for all, downregulation or loss of CD5 and CD7 was described in 33% (3/9) and 50% (5/10) of cases, respectively [9,18,19,27,28]. All cases analyzed expressed surface T-cell receptor (TCR) αβ by flow cytometry or

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Table 1. Clinical and pathological characteristics of indolent CD4+ T-cell lymphoproliferative disorders of the GI tract

	Carbonnel et al. 1994, 1999 Ref. #9,10	Egawa et al. 1995 Ref. #11	Hirakawa et al. 1996 Ref. # 12	Zivny et al. 2004 Ref. # 24	Svrcek et. al 2007 Ref. # 19	Margolskee et al. 2013 Ref. # 27	Perry et al. 2013 Ref. # 28	Malamut et al. 2014 Ref. # 25	Mendes et al. 2014 Ref. # 18
Age (years)	28 to 59	51	47	60	23	37 to 53	50	22 to 68	59
Gender	3 Males: 1 Female	1 Male	1 Male	1 Male	1 Male	2 Males: 1 Female	1 Male	5 males: 5 Females	1 Female
Predominant Symptoms/ Signs	Diarrhea, weight loss	Relapsing oral and colorectal ulcers	None	Diarrhea, weight loss	Diarrhea, weight loss	Diarrhea, weight loss	Diarrhea, dyspepsia, night sweats	Diarrhea, weight loss	Diarrhea, weight loss
Endoscopy	Normal or nodular mucosa	Punched out mucosal ulcers	Polypoid gastric and small bowel mucosa	Gastric and duodenal erythema	Not reported	Nodular mucosa	Not reported	Not reported	Not reported
Imaging	Not reported	Normal	Hypoechoic gastric nodules	Enlarged mesenteric LN	Enlarged mesenteric and retoperitoneal LN	Enlarged mesenteric LN	Not reported	Enlarged mesenteric LN	Enlarged mesenteric LN
Sites involved at presentation or follow-up	Small bowel, stomach, liver, LN, blood	Oral cavity, colon, rectum	Stomach, small bowel, colon, rectum	Stomach, small bowel, LN	Small bowel, BM	Small bowel, colon, stomach, Liver[#]	Small bowel	Small bowel, stomach, colon, LN, tonsil, BM	Small bowel, stomach, colon.
Histopathology	Normal/total villous atrophy. Small lymphocytes in LP.	Ulceration. Small lymphocytes in LP.	Normal mucosa. Small lymphocytes in LP	Villous blunting. Small lymphocytes in LP.	Normal/ shortened villi. Small/ medium lymphocytes in LP.	Partial/total villous atrophy. Small lymphocytes in LP.	Small lymphocytes in LP.	Partial/total villous atrophy. Small lymphocytes in LP.	Partial villous atrophy. Small lymphocytes in LP.
IEL	Increased (80/100) in 1 of 4 cases	Increased	Not increased	Not increased	Not increased	Not increased	Not increased	Not increased	Increased (50/100)
Immunophenotype	CD4+,CD8− CD2+,CD3+ CD5+, CD7+/−, CD103−	CD4+/−, CD8−, CD3+	CD4+/−, CD8−/+, CD2+, CD3+, CD103+	CD4+, CD8−, CD3+, CD103−	CD4+,CD8−, CD2+,CD3+, CD5+,CD7−, CD103−	CD4+,CD8−, CD2+, CD3+, CD5+/−, CD7+/−, CD103−	CD4+,CD8−, CD2+,CD3+, CD5−, CD7−	CD4+,CD3+, CD103+ (in 2 of 10 cases)	CD4+,CD8− CD2+,CD3+, CD7+, CD103−

(Continues)

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Table 1. (Continued)

	Carbonnel et al. 1994, 1999 Ref. #9,10	Egawa et al. 1995 Ref. #11	Hirakawa et al. 1996 Ref. # 12	Zivny et al. 2004 Ref. # 24	Svrcek et. al 2007 Ref. # 19	Margolskee et al. 2013 Ref. # 27	Perry et al. 2013 Ref. # 28	Malamut et al. 2014 Ref. # 25	Mendes et al. 2014 Ref. # 18
Genetic alterations	t(4;16) (q26;p13), trisomy 5	Not reported	Not reported	Not reported	Not reported	Heterogeneous; nonrecurrent (SNP array)	Not reported	Heterogeneous; nonrecurrent (array CGH)	Not reported
Treatment	MACOP-B, holoxane, etoposide, teneposide, doxorubicin, chlorambucil	Prednisone, salicylazosulfapyridine	Cyclophosphamide, vindesine, pirarubicin, prednisone	Cyclophosphamide vincristine prednisone	Doxorubicin, cyclophos phamide, vindesine, bleomycin anti-CD52, prednisone	Budesonide azathioprine, prednisone	Multiple bowel resections	Anti-CD52, vinblastine	Gemcitabine, prednisone
Outcome (Follow-up)	2 of 4: AWPD (2.1 years and 5.5 years) 2 Died (4.8 years and 14.6 years)	AWPD (17 years)	AWPD (1 year)	AWPD (7 years)	AWPD (3 years)	2 of 3: AWPD (2.5 years and 4.6 years), 1 Died (11 years)	Alive (7 years)	10 of 10: AWPD (1.4 years to 11.7 years)	AWPD (2.3 years)

AWPD: alive with persistent disease, BM: bone marrow, CGH: comparative genomic hybridization, IEL: intra-epithelial lymphocytes, LN: lymph node, LP: lamina propria, MACOP-B: methotrexate, cytarabine, cyclophosphamide, vincristine, prednisone, bleomycin, SNP: single nucleotide polymorphism.
[#]In one case, liver lesions were detected at the time of large cell transformation.

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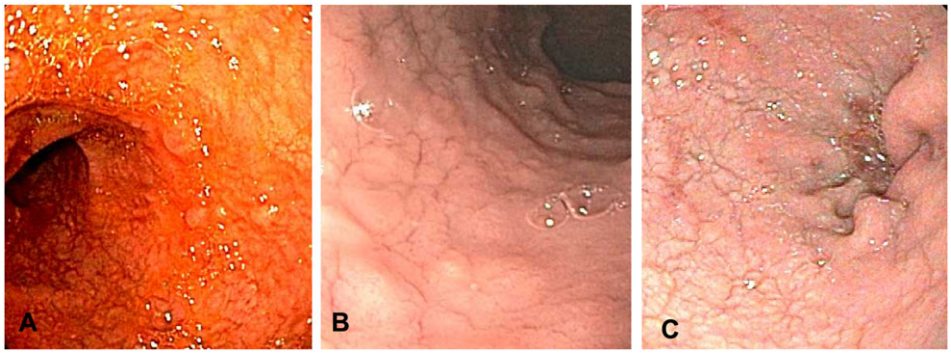

Figure 1. Endoscopic appearance of indolent T-cell LPDs of the GI tract: representative images of CD4+ cases are shown. Diffuse mucosal nodularity (A). Flattening of mucosal folds, vague nodularity and fissures (B). Cobblestone appearance with extensive scalloping and fissures; erythema and erosions are also present (C)

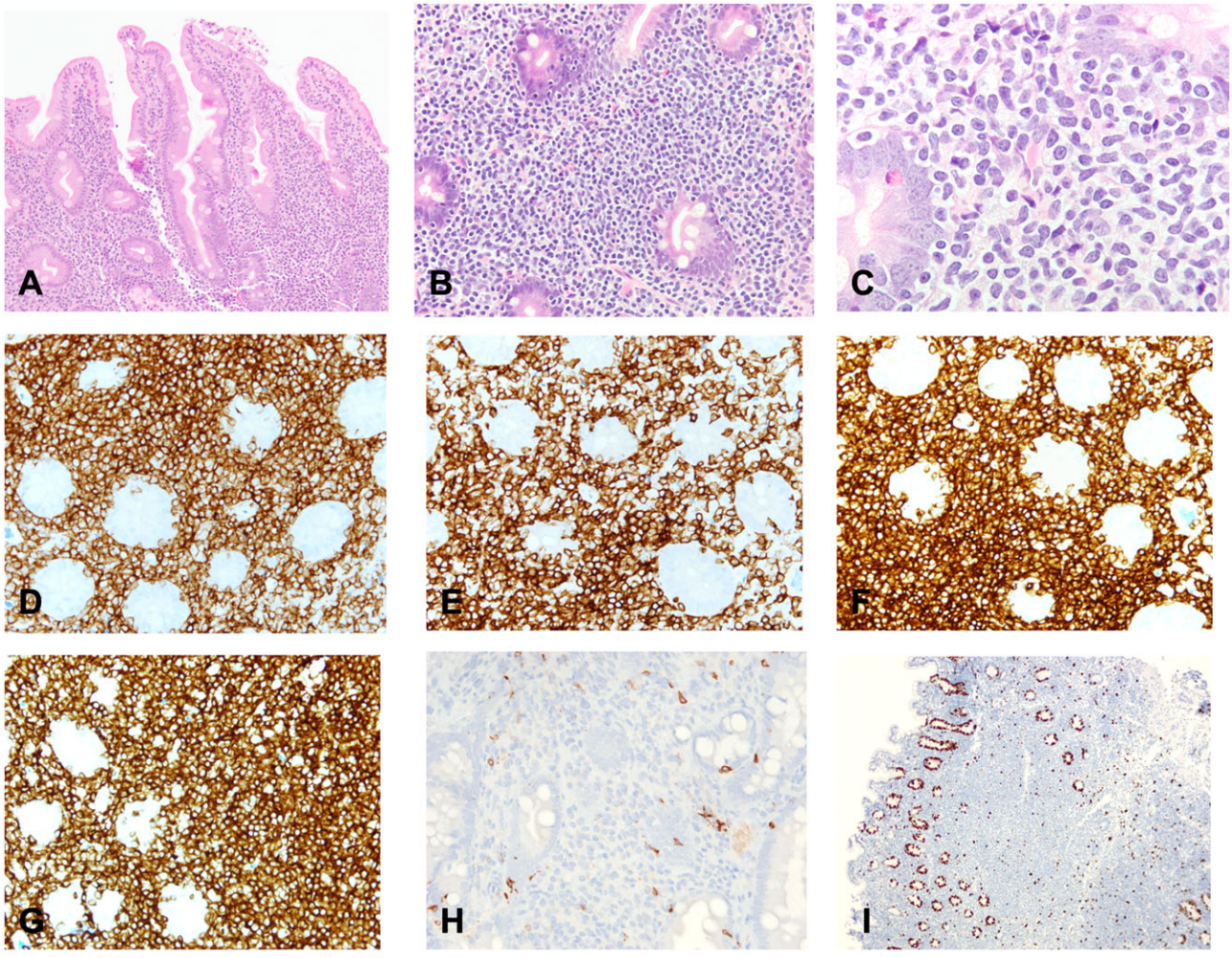

Figure 2. Morphologic and immunophenotypic features of indolent CD4+ T-cell LPD of the GI tract. The duodenal biopsy shows normal villous architecture, crypt hyperplasia and a dense lymphocytic infiltrate in the lamina propria (A). The lymphocytes, which are small to occasionally intermediate in size, focally infiltrate crypt epithelium (B). The lymphocytes have oval or irregular nuclei, fine chromatin, indistinct or small nucleoli and moderate clear cytoplasm; lymphoepithelial lesions are seen (C). The lymphocytes express CD4 (D), CD3 (E), CD5 (F) and CD7 (G). No CD103 expression is noted (H). The Ki-67 proliferation index is low (<5%) (I).

βF1 by immunohistochemistry. FOXP3 and PD-1 expression was not observed [18,27], and all assessed cases were CD30 and CD56 negative. However, CD30 and cytotoxic granule proteins (granzyme-B, perforin) were expressed in one case at the time of large cell transformation [27]. CD103 was negative (Figure 2H) in all except

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three cases [12,25]. The Ki-67 proliferation index was low (<10%) in all reported cases (Figure 2I). *In-situ* hybridization for EBER, when performed, was negative in the T-cells. A few EBER+ cells were observed in the lamina propria in one case, which may have represented an expansion of EBV infected B-cells [9]. The lymphoid follicles were composed of B-cells.

Genetic and molecular alterations

Virtually all reported cases showed clonal TCR β or γ gene rearrangement by PCR or Southern blot analysis. In the series of Carbonnel et al., conventional cytogenetic analysis, performed in two cases, demonstrated trisomy 5 in one case and t(4;16)(q26;p13) in the other [9]. The latter represented a rearrangement between the *interleukin-2* (*IL-2*) gene on 4q26 and the *B-cell maturation antigen* (*BCMA*) or *tumor necrosis factor receptor superfamily member 17* (*TNFRSF17*) gene on 16p13 [30]. Single nucleotide polymorphism (SNP) and comparative genomic hybridization (CGH) analyses revealed heterogeneous, non-recurrent copy number changes (ranging from 1 to 18 per sample) [25,27]. Interestingly, one case showed losses at 4q26 and 16p13, which were also the breakpoints in the previously described case with translocation t(4;16)(q26;p13) (Table 1) [9,25]. Complex copy number changes were observed during large cell transformation in one case [27], including gain of a region on Xp encompassing *STAT3*, an oncogene that is deregulated via different mechanisms in a variety of T-cell lymphomas [31]. The observed genetic abnormalities differed from those described in EATL and MEITL [4,32] except for one case that demonstrated an 8q gain [27], a known recurrent abnormality in MEITL [4].

Clinical outcome

Treatment comprised a variety of chemotherapy regimens (summarized in Table 1). However, despite aggressive treatment, 19 (83%) patients demonstrated persistent disease at a median follow-up of 4.8 years (range 1.0 to 14.6 years), including 5 (22%) with documented disease for more than a decade (Table 1). Interestingly, two patients in morphologic and clinical remission, 5 and 7 years post anti-CD52 antibody (Campath) therapy, showed persistent disease at the molecular level [25]. Only one patient (4%) reported by Perry et al. was alive without evidence of LPD after multiple small bowel resections and brief anti-TNFα antibody (Adalimumab and Certolizumab) therapy for IBD [28]. Disease progression or extra-GI involvement was observed in 10 (43%) patients [9,19,24,25,27], including one post publication [27], and transformation to large cell lymphoma was reported in one case [27]. Three patients (13%) died, either because of disease transformation (one patient) or other disease-related complications (two patients) [25,27].

Pathogenesis

The etiology of indolent CD4+ T-cell LPDs is unclear; however, immune or inflammatory processes have been speculated to play a role in disease pathogenesis [25,27]. Coexistent autoimmune or inflammatory diseases, including rheumatoid arthritis, celiac disease, autoimmune enteropathy and Crohn's disease, were reported in some individuals [25,28]. Human herpes virus 6 (HHV6) was identified in the small intestinal biopsy of one patient by PCR analysis, one patient was receiving acyclovir for herpetic keratitis and two patients had positive serology for human T-lymphotropic virus type 1 (HTLV1), but there was no evidence of viral infection or integration in intestinal biopsies by PCR or western blot analysis [25]. As mentioned above, recurrent chromosome or genetic alterations have not yet been identified.

The cell of origin of indolent CD4+ T-cell LPDs is not known. Although these LPDs bear morphologic and immunophenotypic resemblance to primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphomas, they do not show evidence of T-follicular helper (TFH) cell differentiation [18,27] and where assessed, they have lacked phenotypic features of FOXP3+ regulatory T-cells [27]. Only a minority of cases have shown CD103 expression. An origin from a mucosal T-helper subset is likely, even for the CD103 negative cases, but further characterization awaits transcriptional and cytokine profiling.

Indolent CD8+ T-cell LPDs of the GI tract

Epidemiology

Ranheim et al. described a case of indolent CD8+ T-cell LPD of the GI tract in 2000 [17]. A recent series reported seven new cases of CD8+ indolent T-cell LPDs besides the prior case [17,28] and a review of the literature yielded two additional cases that had clinicopathological features compatible with indolent CD8+ T-cell LPD of the GI tract [15,22]. The median age at diagnosis of the 10 reported patients was 45 years (range 15–77 years), and a slight male predilection was observed (M:F—1.5:1) (Table 2) [15,17,22,28]. Data regarding ethnicity were limited; however, the published cases included individuals of western European, Asian and African descent [15,17,22,28].

Clinical presentation

Diarrhea was the most common symptom (7/10, 70%), which was severe enough to cause an electrolyte imbalance (hypocalcemia and hypokalemia) in two patients (Table 2) [22,28]. Abdominal pain or bloating was also commonly observed (6/10, 60%) [22,28]. Two patients (20%) presented with oral cavity ulcers [28]. One patient initially presented with *Helicobacter pylori* associated gastritis and had positive serology for Hepatitis B at the time of diagnosis of the LPD

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Table 2. Clinical and pathological characteristics of indolent CD8+ T-cell lymphoproliferative disorders of the GI tract

	Tsutsumi et al. 1996 Ref. # 22	Ranheim et al. 2000 Ref. # 17	Leventaki et al. 2013 Ref. # 15	Perry et al. 2013 (only CD8+ cases and excluding case by Ranheim et al.) Ref. # 28
Age (years)	48	35	42	15 to 77
Gender	Male	Male	Male	3 Males: 4 Females
Predominant symptoms/signs	Abdominal distension, diarrhea, weight loss, leg edema	Recurrent oropharyngeal ulcer, rectal bleeding	Peptic ulcer	Abdominal pain, diarrhea
Endoscopy	Irregular granular mucosa	Small erosions in colonic mucosa	Nodular gastric and duodenal mucosa	Small polyps, erosions/erythema, irregular duodenal mucosa
Imaging	Mild, diffuse thickening of small bowel	Diffuse thickening of small bowel, enlarged mesenteric lymph nodes, splenomegaly	Mild thickening of small bowel wall, enlarged mesenteric lymph nodes, splenomegaly	Enlarged mesenteric lymph nodes (1 case)
Sites involved at presentation or follow-up	Small bowel	Palate, small bowel, colon, rectum	Esophagus, stomach, small bowel, colon, bone marrow	Oral cavity, esophagus, stomach, small bowel, colon
Histopathology	Small lymphocytes in lamina propria	Small lymphocytes in lamina propria	Small/intermediate lymphocytes in lamina propria	Small lymphocytes in lamina propria
Intra-epithelial lymphocytes (IEL)	Unclear if increased	Not increased	Not increased	Increased in 1 of 7 cases
Immunophenotype	CD4−,CD8+ CD2+,CD3+,CD5+	CD4−,CD8+, CD3+,CD5+, CD56−, TIA1−	CD4−,CD8+, CD3+,CD5−, CD56−, TIA1+/−, granzyme B(subset)+	CD4−,CD8+, CD3+, CD5+, CD7+/−, CD56−, TIA1+, granzyme B−/+[#]
Genetic alterations	Not reported	Not reported	Not reported	Negative for STAT3 mutations
Treatment	None	None	Interferon Isotretinoic acid, steroids	Cyclophosphamide, doxorubicin, vincristine, dexamethasone, aracytine, oxaliplatin, romidepsin
Outcome (follow-up)	Alive with persistent disease (1 year)	Alive with persistent disease (9 years)	Alive with persistent disease (19.8 years)	Alive with persistent disease (1.1 years to 14.6 years)

[#]only 1 of 7 cases was granzyme B+

[15]. This patient was the only one reported to have bone marrow and peripheral blood involvement at the time of diagnosis of LPD [15]. One individual had an unconfirmed history of Crohn's disease [28].

Endoscopic findings and imaging

On endoscopy, multifocal GI involvement was noted in 6/10 (60%) cases, with the small intestine and colon being the most common sites (Table 2) [15,17,22,28].

The duodenal mucosa was granular or showed thickened folds or nodules and the gastric mucosa either appeared normal or had a nodular appearance [15,22,28]. The colonic mucosa was either erythematous and friable or displayed numerous small polyps or erosions [28].

Imaging findings were similar to those reported for CD4+ T-cell LPDs. On abdominal CT scans, mesenteric lymphadenopathy was observed in three (30%) cases, mild to moderate splenomegaly in two (20%) cases and mild thickening of small bowel loops in two (20%) cases [15,22,28]. A small intestinal barium study performed in one case demonstrated diffuse granular mucosa [22].

Histopathology

The small intestinal biopsies showed distorted and occasionally hyperplastic crypts, while the villi were near normal in the majority of cases. The lamina propria showed diffuse infiltrates of mostly small lymphocytes that had round, oval or mildly irregular nuclei, fine chromatin, inconspicuous nucleoli and scant cytoplasm (Figure 3A–C) [15,22,28]. Infiltration into the submucosa was observed in some cases. A generalized increase in IELs was uncommon, reported in only one (10%) case [28]. The cytomorphologic appearance of the lymphocytic infiltrate in the oral cavity, stomach and colon was similar to that in the small bowel

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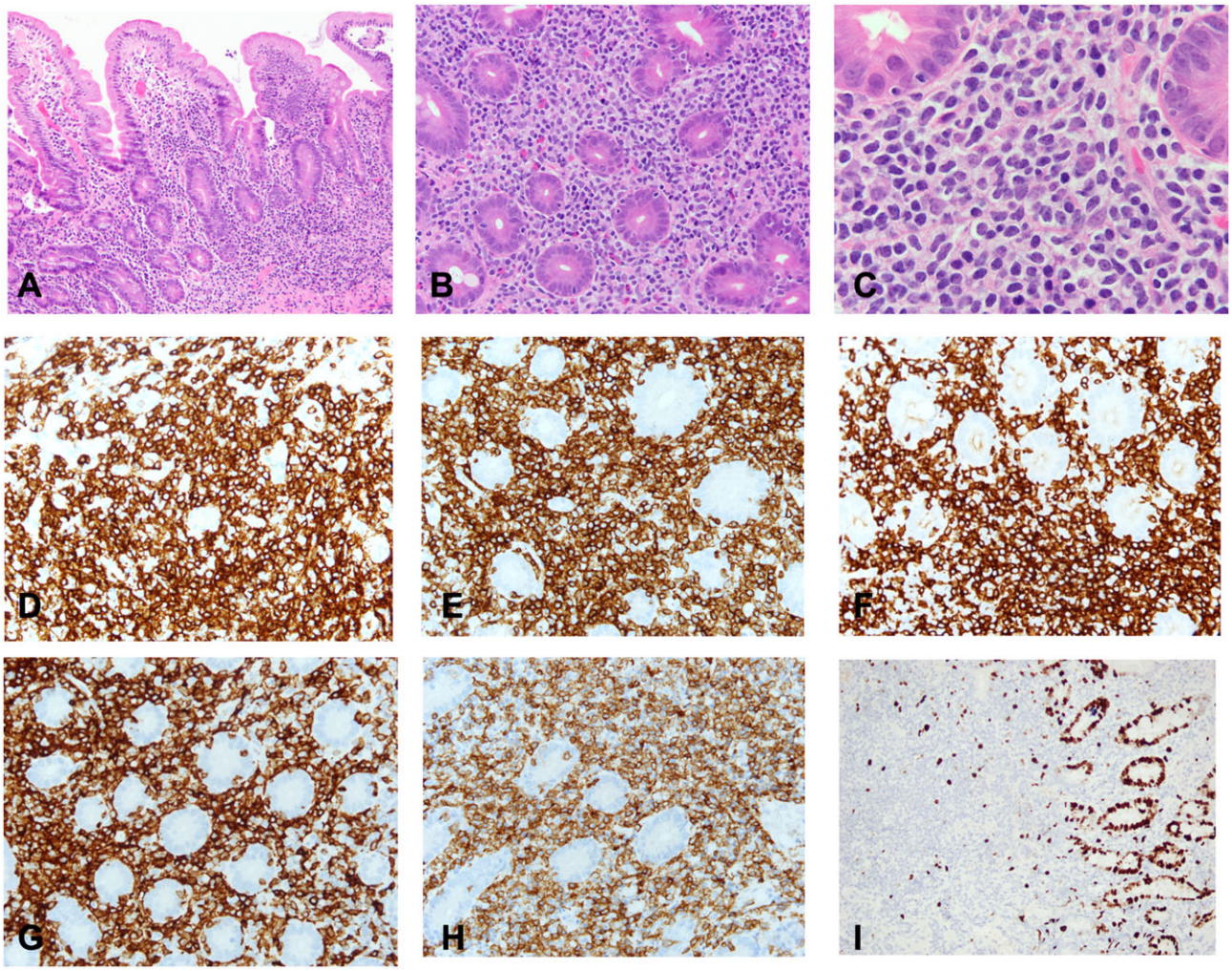

Figure 3. Morphologic and immunophenotypic features of indolent CD8+ T-cell LPD of the GI tract. The duodenal biopsy shows near-normal villi as well as an artefactually distorted villous (giving the false impression of atrophy), crypt hyperplasia and a patchy, dense lymphocytic infiltrate in the lamina propria (A). The lymphocytes are mostly small in size; focal infiltration into crypt epithelium is seen (B). The lymphocytes have round or oval nuclei, fine chromatin, indistinct nucleoli, and scant or moderate clear cytoplasm (C). The lymphocytes express CD8 (D), CD3 (E), CD5 (F) and CD7 (G) and the majority are CD103+ (H). The Ki-67 proliferation index is low (<5%) (I).

[15,28]. Mitotic activity was low in all cases. Scattered lymphoid follicles were present. None of the reported cases showed evidence of large cell transformation.

Immunophenotype

As shown in Table 2, the lymphocytes expressed CD8 (Figure 3D) and CD3 (Figure 3E) in all cases. Downregulation of CD5 or CD7 was infrequent, described in 10% (1/10) and 29% (2/7) of cases, respectively [15,17,22,28]. TCRαβ (or βF1) expression was observed in all cases analyzed [15,17,22,28]. TIA-1 was expressed by 87% (7/8) of LPDs but only 25% (2/8) were granzyme-B+ [15,17,28]. All assessed cases lacked CD30 and CD56 expression. The Ki-67 labeling index was <10% (Figure 3I) [15,22,28]. *In-situ* hybridization for EBER was negative in all cases assessed [15,17,22,28].

Genetic and molecular alterations

Clonal TCR β or γ gene rearrangements were detected in all cases by PCR or Southern blot analysis [15,22,28]. No cytogenetic data were reported for any case. Activating *STAT3* SH2 domain mutations, as described in T-large granular lymphocytic leukemia [33], were not identified by Perry et al., and no phospho-STAT3 expression was observed in a subset of cases analyzed [28].

Clinical outcome

All patients were alive and had persistent disease at a median follow-up of 2.0 years (range 1.0 to 19.8 years), despite the use of different chemotherapy regimens in 4 (40%) patients (Table 2). Disease progression or transformation was not reported in any case.

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Pathogenesis

The etiology of indolent CD8+ T-cell LPDs of the GI tract is unknown at present. Similar to indolent CD4+ T-cell LPDs, a role for persistent antigenic stimulation or immune dysregulation has been considered in some cases, especially those with a history of an inflammatory GI disorder [28]. No specific disease-associated chromosomal or genetic alterations have been uncovered so far.

The clinicopathological features of indolent CD8+ T-cell LPDs of the GI tract are similar to the indolent CD8+ lymphoid proliferations of the ear, now referred to as *primary cutaneous acral CD8+ T-cell lymphomas*, which predominantly occur in males [5,34,35]. The precise cell of origin of indolent CD8+ T-cell LPDs of the GI tract is not known; however, derivation from a mucosal CD8+ T-cell with a latent cytotoxic phenotype is favored in most cases. The expression of CD103 has not been systematically evaluated, but in the authors' experience it can be expressed in at least a subset of cases (Figure 3H), further suggesting an origin of such LPDs from a mucosal CD8+ T-cell precursor.

Indolent CD4− CD8− T-cell LPD of the GI tract

One case of CD4− CD8− (double negative) indolent T-cell LPD of the GI tract was included in the series of Perry et al. [28]. The patient presented with complaints of abdominal pain, and diarrhea and had a history of Crohn's disease. Oral cavity ulcers were noted on examination with no other sites of ulceration reported. However, upon biopsy, multiple GI sites including the oral cavity, small bowel and colon showed a diffuse lamina propria infiltrate of small lymphocytes with cytomorphologic features similar to the CD4+ and CD8+ T-cell LPDs.

The lymphocytes did not express cytotoxic granule proteins (TIA-1 and granzyme-B) and clonal TCR γ gene rearrangement was detected by PCR analysis [28]. The cell of origin of this LPD is not known. Downregulation of either CD4 or CD8 because of sustained activation or during neoplastic transformation is plausible. The patient received five cycles of CHOP chemotherapy and was alive with persistent disease 0.8 years post diagnosis.

Indolent NK-cell LPDs of the GI tract

Epidemiology

Vega et al. first described an indolent NK-cell LPD of the GI tract in 2006 [23]. Since then, two case series and sporadic reports have further characterized 24 cases of indolent NK-cell LPDs restricted to the GI tract, which have been variably designated 'lymphomatoid gastropathy' or 'NK-cell enteropathy' (Table 3) [13,14,16,20,21,23,26,29]. Cases of lymphomatoid gastropathy were described in middle aged or older Japanese individuals (median age—56 years, range 46–75 years) without significant gender predilection (M:F—0.9:1) [13,20,21,29]. Meanwhile, cases of NK-cell enteropathy were reported from the United States and Korea, the median age at diagnosis being 46 years (range 14–68 years), and a female predominance was observed (M:F—0.6–1) [14,16,23,26]. A case of CD56+ T-cell LPD reported by McElroy et al. has been included in this category as the described clinicopathological and molecular features were suggestive of NK-cell enteropathy [16].

Clinical presentation

Twelve of thirteen (92%) Japanese patients with lymphomatoid gastropathy were asymptomatic, the lesions being detected during upper endoscopy for gastric cancer surveillance, and epigastric discomfort was noted in one patient (Table 3) [13,20,21,29]. Three patients had a history of gastric cancer and had undergone partial gastrectomy or endoscopic mucosal resection previously [29]. In contrast, patients with NK-cell enteropathy reported from the US and Korea frequently presented with abdominal pain or discomfort (7/11, 64%) [14,16,23,26]. Other less common symptoms and signs included diarrhea, constipation, vomiting, rectal bleeding and weight loss. Only two patients with NK-cell enteropathy were asymptomatic, being diagnosed at screening colonoscopy [23,28].

Endoscopic findings and imaging

On endoscopic examination, all cases of lymphomatoid gastropathy were localized to the stomach. The lesions measured approximately 1.0 cm, and they were either elevated or flat, with or without erosions or ulcerations, and had a reddish color [13,20,21,29]. Involvement of either single or multiple GI sites (esophagus, stomach, small intestine and colon) was observed in individuals with NK-cell enteropathy [14,23,26]. The lesions measured 1.0 to 2.0 cm, and their appearance was quite variable; hyperemic foci, mucosal nodules, erythematous bulls-eye (target) lesions or superficial bleeding ulcers [14,23,26].

On CT imaging, there was no evidence of systemic disease, lymphadenopathy or organomegaly in all except two patients (Table 3). Koh et al. detected diffuse thickening of the esophagus, stomach and small bowel, as well as mesenteric lymphadenopathy and mildly increased metabolic activity in the lymph nodes on PET-CT scan [14]. McElroy et al. reported multiple enlarged abdominal lymph nodes 5 years after initial presentation of the LPD [16].

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Table 3. Clinical and pathological characteristics of indolent NK-cell lymphoproliferative disorders of the GI tract

	Vega et al. 2006 Ref.# 23	**Takeuchi et al. 2010 Ref. # 29**	**Mansoor et al. 2011 Ref. # 26**	**Tanaka et al. 2011 Ref. # 20**	**McElroy et al. 2011 Ref. # 16**	**Terai et al. 2012 Ref. # 21**	**Koh et al. 2013 Ref. # 14**	**Ishibashi et al. 2013 Ref. # 13**
Age (years)	32	46–75	27–68	50	52	57	14	71
Gender	1 Male	5 Males: 5 Female	2 Males: 6 Female	1 Male	1 Female	1 Female	1 Female	1 Female
Predominant symptoms/signs	Epigastric pain	None	Abdominal pain, rectal bleeding	None	Diarrhea, vomiting	Heartburn, nausea	Vomiting, diarrhea	Epigastric discomfort
Endoscopy	Bull's eye mucosal lesions	Elevated mucosal lesions	Erosion/ ulceration	Small red mucosal lesions	Mucosal nodules, ulceration	Elevated mucosal lesion	Nodular mucosa/ hyperemia	Elevated mucosal lesion/erosion
Imaging	Normal	Normal	Normal	Normal	Increased uptake in LN by PET	Normal	Enlarged mesenteric LN, spleen	Normal
Sites involved at presentation or follow-up	Small bowel, stomach, colon.	Stomach	Stomach, small bowel, colon,	Stomach	Stomach, small bowel, colon,	Stomach	Stomach, small bowel, esophagus	Stomach
Histopathology	Medium to large cells in LP.	Medium to large cells in LP.	Medium to large cells in LP.	Medium to large cells in LP.	Medium to large cells in LP.	Medium to large cells in LP.	Medium sized cells in LP.	Medium to large cells in LP.
Immunophenotype	CD4−,CD8−, cCD3+, CD7+, CD56+, TIA1+	CD4−CD8−, cCD3+, CD7+, CD56+, TIA1+, granzyme B+, perforin+	CD4−,CD8−, cCD3+, CD7+, CD56+, TIA1+, perforin+	CD4−,CD8−, cCD3+, CD7+, CD56+, TIA1+, perforin+	CD4−,CD8−, cCD3+, CD7+, CD56+, TIA1+,	CD4−,CD8−, cCD3+, CD7+, CD56+,	CD8+, βF1−, CD3+, CD56+,	CD4−CD8−, cCD3+, CD7+, CD56+, TIA1+, granzyme B+
Treatment	No chemotherapy	No chemotherapy	CHOP/CVAP.	No chemotherapy	CVAP	No chemotherapy	No chemotherapy	No chemotherapy
Outcome (follow-up)	AWPD (2 years)	Alive (1 to 12.1 years), 3 relapsed, 7 regressed	AWPD (1.8 to 10 years)	Alive (1.9 years), relapsed	AWPD (8 years)	Alive (2 years), relapsed	AWPD (3.3 years)	Alive (0.3 years) regressed

AWPD: alive with persistent disease; CHOP: cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone; CVAP: cyclophosphamide, vincristine, adriamycin, prednisone; IN: Lymph node; LP: lamina propria; PET: Positron emission tomography.

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Histopathology

Cases of lymphomatoid gastropathy and NK-cell enteropathy showed similar cytomorphologic features. The lamina propria was expanded by a population of atypical lymphoid cells that were intermediate to large in size and had round, oval or irregular nuclei, fine chromatin, inconspicuous or rarely prominent nucleoli and moderate pale pink cytoplasm (histiocytoid appearance) [13,14,16,20,21,23,26,29]. Eosinophilic cytoplasmic granules were seen in some cells. No significant intraepithelial lymphocytosis was observed. In some cases, the atypical lymphocytic infiltrate was surrounded by a rim of mature lymphocytes, eosinophils, plasma cells and histiocytes [26]. Glandular destruction was seen in florid cases without evidence of angiocentricity or necrosis, but superficial hemorrhagic foci were occasionally noted [13,14,16,20,21,23,26,29].

Immunophenotype

The atypical lymphoid cells expressed cytoplasmic CD3, CD7, CD56 and cytotoxic granule constituents (TIA-1, granzyme-B, perforin), but lacked surface CD3, CD5, CD4 and B-lineage or myelo-monocytic antigens, findings consistent with NK-cell lineage (Table 3) [13,14,16,20,21,23,26,29]. All except one case also lacked CD8 expression [14]. Flow cytometry performed on a limited number of cases demonstrated bright CD7 and CD56 expression [23,26,29]. The Ki-67 labeling index ranged from 10% to 30% [26,29]. *In situ* hybridization for EBER was negative in all cases [13,14,16,20,21,23,26,29].

Genetic and molecular alterations

PCR analysis for TCR γ gene rearrangement did not demonstrate clonal products in any case [13,14,16,20,21,23,26,29]. Cytogenetic data were not reported and nor were any genetic alterations described. The clonal nature of NK-cell LPDs has not been established. Vega et al. suggested that indolent NK-cell LPD of the GI tract may be a polyclonal process, based on the heterogeneous expression pattern of CD158 or KIR (killer cell immunoglobulin-like receptor) antigens [23]. Aggressive NK-cell lymphomas have been reported to demonstrate specific gene methylation patterns, with *p73* being the most commonly hypermethylated gene followed by *hMLH1* and *CDKN2A/P16* [36]. Hypermethylation of these genes was not observed in the single case of lymphomatoid gastropathy analyzed [28].

Clinical outcome

The majority of patients with lymphomatoid gastropathy showed spontaneous regression of the LPD in the absence of chemotherapy, with only 38% experiencing a relapse at a median follow-up of 2.8 years (range 0.3 to 12.1 years) [13,20,21,29]. On the contrary, lesions persisted in all patients with NK-cell enteropathy at a median follow-up of 3.0 years (range 1.8 to 10.0 years), although disease remission for at least 3 years and diminution of lesions was reported in one patient each [14,16,23,26]. Aggressive chemotherapy was administered to 36% (4/11) of patients with limited benefit [16,26].

Pathogenesis

The etiology of indolent NK-cell LPDs of the GI tract is unclear. The GI tract contains a variety of tissue resident NK-cells or NK-like innate lymphoid cells [37,38]. It is not known at present whether the NK-cell LPDs represent neoplastic proliferations or a reaction to certain dietary antigens or infections, in the presence (or absence) of any immune alterations, resulting in an aberrant proliferation of tissue resident NK-cell subsets or homing of circulating NK-cells to the GI tract [37,38]. The role of host factors in the development of this type of LPD has not been systematically assessed. A relationship between lymphomatoid gastropathy and *H. pylori* infection has been considered, because *H. pylori* infection was observed in 92% (12/13) of cases and the lesions regressed following therapy for *H. pylori* eradication [13,20,21,29]. *H. pylori* infection was not detected in the single case of NK-cell enteropathy evaluated [16]. High anti-gliadin antibody titers were observed in one patient with NK-cell enteropathy in the absence of celiac disease [23]. Intriguingly, the GI lesions regressed after initiation of a gluten free diet, raising the possibility that the LPD represented an aberrant NK-cell response to a dietary antigen.

Differential diagnosis

Distinguishing indolent T- or NK-cell LPDs of the GI tract from inflammatory disorders as well as more aggressive lymphomas, either primary or those secondarily involving the GI organs, can be challenging. A high proportion of individuals with CD4+ indolent T-cell LPDs, but surprisingly none with CD8+ T-cell LPDs, were misdiagnosed as having celiac disease or refractory celiac disease as they did not respond to a gluten free diet [25,27,28]. Similar to celiac disease, indolent T-cell LPDs may display crypt hyperplasia and occasionally villous atrophy but a significant increase in IELs is usually not observed. Clusters of lymphocytes forming 'lymphoepithelial lesions' can, however, be seen in some CD4+ cases (Figure 2 B, C). Cases of CD8+ T-cell LPDs with proximal small intestinal involvement and a patchy increase in intraepithelial lymphocytes can be misinterpreted as celiac disease if attention is not paid to the extensive lamina propria lymphocytic infiltrate.

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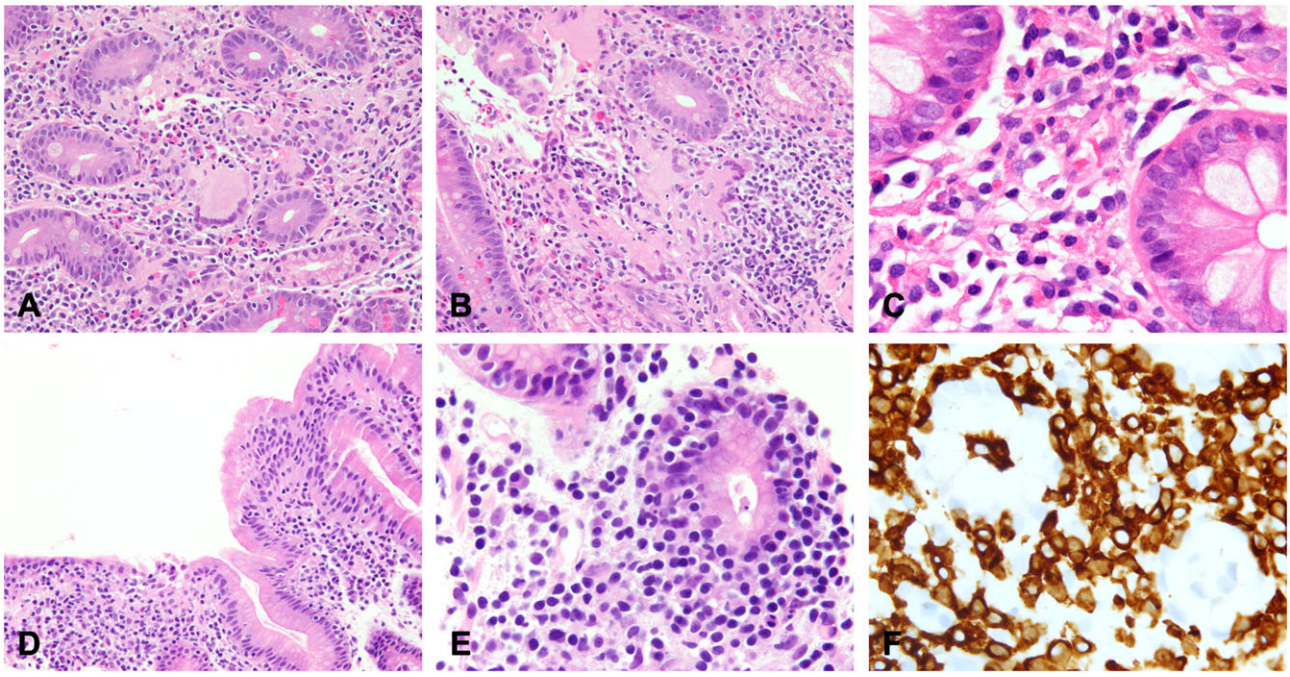

Figure 4. Unusual histopathologic features and patterns of colon and stomach infiltration. Occasionally, indolent T-cell LPDs of the GI tract may exhibit scattered multinucleated giant cells (A) or distinct granulomas (B), at times surrounding damaged crypts as illustrated, which can lead to an erroneous diagnosis of Crohn's disease. Lymphocytic infiltrates of indolent T-cell LPDs in the colon can be subtle at times, with only focal, loose clusters of small lymphocytes observed admixed with plasma cells and eosinophils, requiring phenotypic and molecular analyses for confirmation (C). The gastric mucosa can exhibit dense and diffuse or mild, patchy lymphocytic infiltration by indolent T-cell LPD, as illustrated in this case of a CD4+ LPD (D). Periglandular lymphocytic collections with focal infiltration of the epithelium can be observed (E). Presence of LPD can be confirmed by immunohistochemistry, as shown – CD4+ T-cells surrounding and infiltrating gastric glands (F), and molecular analysis

Other clues that help in ruling out celiac disease in such instances include, negative celiac serologies and an absence of celiac disease-associated HLA alleles. It should be noted that CD4+ indolent T-cell LPD might rarely occur in a celiac patient [25]. These cases require meticulous histopathologic and immunophenotypic evaluation, as well as molecular analysis to determine the presence of a clonal T-cell population.

A history of IBD, specifically Crohn's disease, was reported in some cases of indolent T-cell LPDs, although histopathologic features of IBD were not described in any of the biopsies at the time of diagnosis of LPD. Since granulomas may be present at mucosal sites involved by indolent T-cell LPDs (Figure 4A-B), pathognomonic histologic alterations and supportive clinical and endoscopic features are required for a definitive diagnosis of IBD. Due to insufficient data, the relationship between IBD and indolent T-cell LPD of the GI tract is unclear at present [25,28]. Indolent NK-cell LPDs of the GI tract may also mimic IBD on imaging, especially ulcerative colitis [26] and lesions in the stomach can be misdiagnosed as gastritis or gastric adenocarcinoma, because of the frequent presence *H. pylori* infection [13,20,21,29]. However, the distinct histopathologic and phenotypic features of these LPDs mentioned above are helpful in arriving at the correct diagnosis.

Discriminating indolent T- and NK-cell LPD from aggressive T- or NK-cell lymphomas that arise in or involve the GI tract requires comprehensive pathological and clinical evaluation. MEITL and EATL can be discerned by the presence of atypical, intermediate or large-sized intraepithelial lymphocytes and transmural infiltration by the atypical lymphocytes in many instances. These lymphomas have distinct immunophenotypic features, e.g. express CD56 and megakaryocyte-associated tyrosine kinase (MATK) or CD30 and they have a high proliferation index [4,6,39–41]. Furthermore, the clinical presentation of MEITL and EATL is generally more acute because of frequent intestinal obstruction or perforation [4,6,39]. MEITL and EATL also exhibit recurrent genomic changes that differ from those detected in indolent T-cell LPD of the GI tract [4,32]. Indolent NK-cell LPD of the GI tract can be mistaken for extranodal NK/T-cell lymphoma, nasal type either arising in the GI tract (a rare occurrence) or involving it secondarily [20,21,23,26,29]. This has led to erroneous and aggressive treatment in some cases, including chemotherapy, gastrectomy or bone marrow transplantation [26,29]. The lack of significant cytologic atypia, absence of angiocentricity and angiodestructive lesions or necrosis and an absence of EBV infection are helpful features in excluding NK/T-cell lymphomas in most instances [42,43].

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Other T-cell lymphomas that can rarely involve the GI tract and need to be considered in the differential diagnosis of indolent T-cell LPDs include, T-cell prolymphocytic leukemia, angioimmunoblastic T-cell lymphoma, Mycosis fungoides/Sezary syndrome, HTLV-1 associated adult T-cell leukemia/lymphoma and peripheral T-cell lymphoma, NOS [44–49]. Apart from the cytomorphologic appearance and unique phenotypic features, the pattern of organ involvement (e.g. cutaneous disease, hepatosplenomegaly, lymphadenopathy), clinical features (e.g. fever, erythroderma), serological studies (e.g. anti-HTLV-1 antibodies), other laboratory parameters (e.g. elevated WBC count, lymphocytosis, hypercalcemia, polyclonal hypergammaglobulinemia) and imaging studies can help in establishing the correct diagnosis.

Unanswered questions and future directions

Recent studies have led to a better appreciation of the clinical, histopathologic and phenotypic spectrum of indolent T- and NK-cell LPDs of the GI tract, which are currently considered to be rare. However, data regarding the incidence and prevalence of the different subtypes are lacking. Greater awareness of the unique clinicopathological features of these LPDs will undoubtedly lead to the identification of additional cases and perhaps re-categorization of some that might have previously been misclassified either as inflammatory disorders or more aggressive lymphomas. Because of the lack of adequate staging and limited follow-up for many cases, it remains to be determined whether the biology of CD4+ and CD8+ T-cell LPDs differs. The etiology of indolent T- and NK-cell LPDs is unknown at present and it is unclear whether specific pathogenetic mechanisms or molecular alterations underlie different entities (or subsets within a particular entity). The application of next generation sequencing techniques and transcriptional profiling may shed light into the molecular perturbations that trigger indolent T- and NK-cell LPDs of the GI tract and help determine if they represent relatively homogeneous entities or common morphologic and phenotypic endpoints of distinct disorders. An appropriate therapy for the indolent T-cell LPDs has not been established. A careful 'watch and wait' approach has been suggested, because, the risk for disease transformation appears low and the aggressive chemotherapy regimens employed thus far have high toxicity and are not curative. A better understanding of disease pathogenesis might also lead to the development of novel targeted and efficacious therapies for these rare disorders.

Consent

Not applicable

Ethical background to the study

Not applicable

Conflict of interest

The authors declare that there is no conflict of interest. No extramural funding was received.

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