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REVIEW AND PERSPECTIVES

Update on lymphoproliferative disorders of the gastrointestinal tract: disease spectrum from indolent lymphoproliferations to aggressive lymphomas

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Abstract

This paper summarizes two sessions of the workshop during the XIX meeting of the European Association for Haematopathology (EAHP) held in Edinburgh in September 2018 dedicated to lymphomas of the gastrointestinal tract. The first session focused on the clinical and pathological features of primary gastrointestinal T cell and NK-cell lymphoproliferative disorders. The distinction between precursor lesions (RCD type 2) and enteropathy-associated T cell lymphoma were stressed, including the discussion of new diagnostic markers for the identification of aberrant phenotypes. Indolent T cell lymphoproliferative disorders of the gastrointestinal tract cases showed phenotypic heterogeneity with novel molecular alterations in few cases, such as *STAT3-JAK2* fusion. In addition, novel clonal markers of disease, such as *AXL* and *JAK3* somatic variants support the neoplastic nature of NK-cell enteropathy. The session on gastrointestinal tract B cell lymphoproliferations was dedicated to B cell lymphoproliferative disorders that arise primarily in the gastrointestinal tract (i.e., duodenal-type follicular lymphoma) or preferentially involve the digestive tract, such as large B cell lymphoma with *IRF4* translocation and mantle cell lymphoma (MCL), including diverse molecular subtypes (i.e., *CCND3*-positive MCL mimicking MALT lymphoma). Challenging cases of high-grade B cell lymphomas with complex genetic profiles demonstrated the usefulness of novel molecular diagnostic methods such as targeted NGS to identify high-risk genetic features with potential clinical impact.

Keywords Indolent lymphoproliferative disorders · Primary gastrointestinal · T cell lymphomas

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Part 1. Primary gastrointestinal T cell lymphoproliferative disorders

Introduction

Primary gastrointestinal (GI) T cell lymphomas are rare and aggressive neoplasms frequently associated with challenging differential diagnoses. Extranodal, NK-T cell lymphoma, nasal type, peripheral T cell lymphoma (PTCL), and ALK-negative ALCL can also involve the GI tract but will not be part of this review which will focus on primary GI T cell neoplasms.

The revised WHO (2017) classification recognizes two main distinct entities:

a) Enteropathy-associated T cell lymphoma (EATL), formerly EATL type I, associated with celiac disease (CD), including specifically refractory CD type 2 (RCD2), predominantly occurring in the Western countries.
b) Monomorphic epitheliotropic intestinal T cell lymphoma (MEITL), formerly EATL type II, not associated with celiac disease, with a wider geographic distribution, representing the most frequent subtype in Asia [1].

In addition, during the past decade, sporadic case reports and small better characterized case series have described primary gastrointestinal T- and NK-cell proliferations, variably referred to as "indolent lymphomas" or "lymphoproliferative disorders" (LPDs) providing greater insight into the clinicopathological and phenotypical spectrum of these entities [2, 3]. A more comprehensive knowledge has led to the inclusion of "Indolent T Cell Lymphoproliferative Disorder of the GI Tract" as a provisional entity in the 2017 WHO classification. Several of such cases submitted to the EAHP workshop have contributed to elucidate the pathological features, immunohistochemical, and molecular profiling of this provisional category.

NK-cell lymphoproliferative disorders (LPDs) of the GI tract, variably referred to as "NK-cell enteropathy" or "lymphomatoid gastropathy of NK-cell type," are poorly understood entities described in short series [3, 4], not included as such in the current WHO classification and only briefly referred to in differential diagnosis with "chronic LPD of NK-cells" [1]. Three cases included in the Workshop have provided a better understanding of this entity.

EATL and precursor lesions (RCD type2)

Eleven of such cases were submitted to the workshop including seven diagnosed as EATL, two diagnosed as RCD type 2, and two as RCD type 2 progressing into EATL.

RCD, defined by persistence of clinical symptoms and histological abnormality in the form of villous atrophy and increased number of intraepithelial lymphocytes (IELs), despite strict gluten-free diet for > 12 months [5], is a biologically diverse disease currently classified as follows:

a) Type 1: more frequent (up to 80% of cases) with normal phenotype, polyclonal IELs, high 5-year survival rate, and low risk of developing EATL.
b) Type 2: characterized by a clonal proliferation of aberrant IELs and considered a precursor of EATL [6, 7]. Definition of aberrant immunophenotype is critical in the identification of clonal intraepithelial lymphoid populations with a greater risk of progression to overt EATL. Reduced or absent surface CD3, absent CD8, and absent TCRbF1 receptor expression are considered aberrant immunophenotype in the IELs. Flow cytometry is considered the gold standard for the identification of these aberrant populations with IHC having adequate sensitivity in cases with high numbers of IELs [8].

Case LYWS276 (Dr. Basha & Dr. Macon), an interesting case of RCD2, showed pleomorphic medium to large-sized lymphoid cells mostly within the epithelium with occasional forms seen in the lamina propria. These showed an aberrant T cell phenotype (immunoreactivity for CD3, CD7, CD103, granzyme B partial, and TIA1, partial/weak) including strong CD30 expression. T cell receptor gene rearrangement was equivocal. CD30 positivity in intraepithelial T cells in patients with refractory celiac disease has been associated with transformation to EATL [9] and in this case suggests evolution of refractory celiac disease into EATL (Fig. 1).

Case LYWS447 (Dr. Molina et al.), a case of RCD type 2 evolving into EATL, highlighted the utility of NKP46 staining in this condition as potential diagnostic marker. NKP46 is significantly more expressed by malignant RCDII IEL than by normal IEL in CD and RCDI. Overexpression of the protein is also found in MEITL and EATL, but not in cases of indolent T cell LPD of the gastrointestinal tract [10].

Recent studies have reported the derivation of RCD2 from innate T/NK-like IELs, with frequent *JAK1* and *STAT3* mutations [11]. Case LYWS545 (Dr. Soderquist et al.) is a case of RCD2 in which the biopsy showed only mild villous atrophy and flow cytometry showed a large fraction of phenotypically aberrant IELs but TCRβ and TCRγ clonality studies showed polyclonal products. NGS revealed a *STAT3* S614R hotspot mutation. RCD2 generally (~ 75%) shows clonal, but non-functional, TCR gene rearrangements, with 50% demonstrating TCRβ, and the remainder TCRγ and/or TCRδ rearrangements. It has been suggested that cases lacking TCRβ gene rearrangement (immature T/NK phenotype) may be at lower risk of progression to EATL [12]. This case highlights how through NGS a diagnosis of RCD2 may be confirmed in the absence of clonal TCR gene rearrangement.

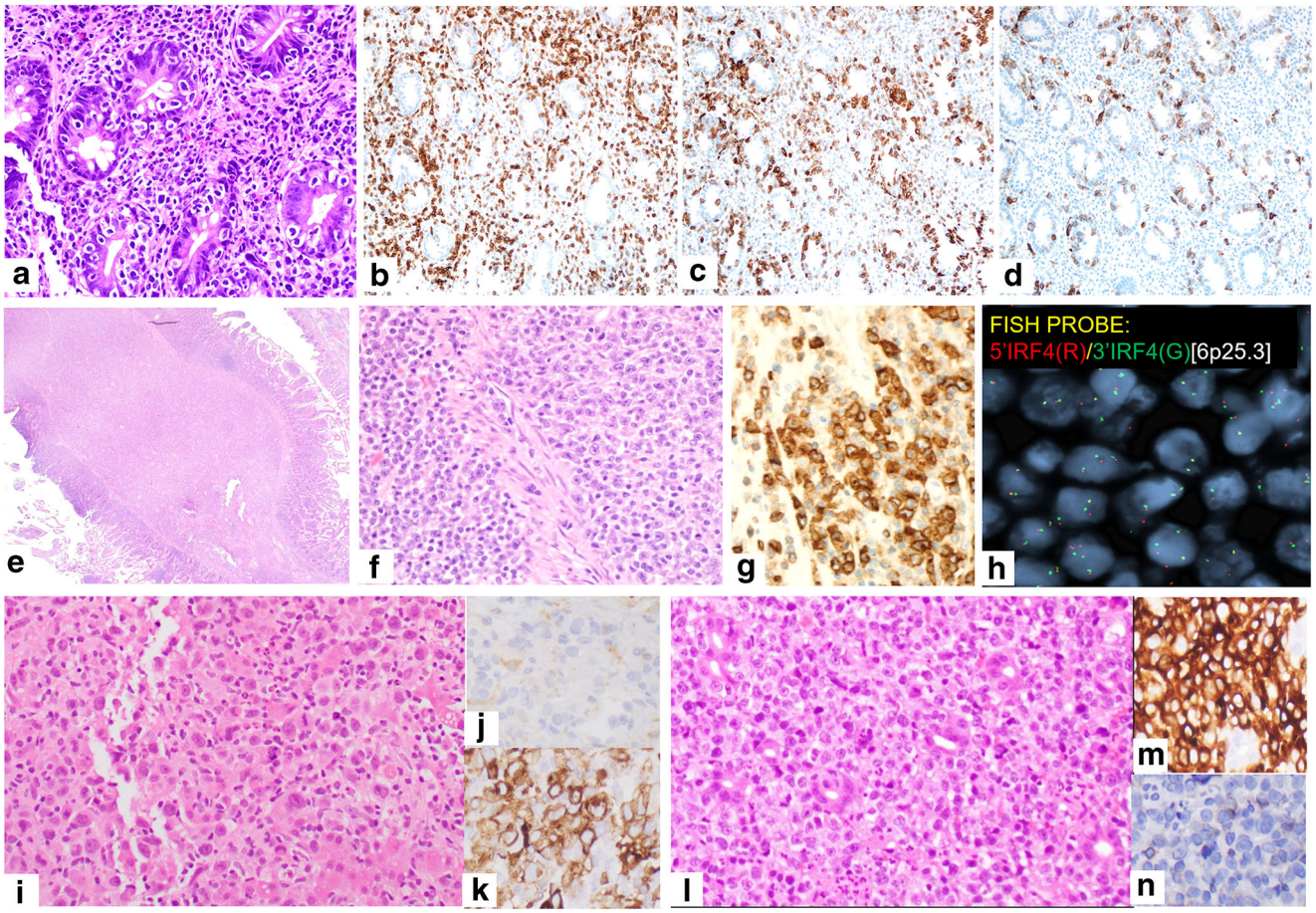

Fig. 1 EATL and Precursor lesions (RCD type2). **a** RCD2 evolving into EATL, high-power H&E of case LYWS276 (Dr. Basha et al.) pleomorphic medium- to large-sized lymphoid cells mostly within the epithelium. Atypical lymphoid cells are positive for CD3 (**b**) and CD7 (**c**). **d** CD30 shows atypical lymphoid cells in the epithelium and focally in the lamina propria. **e** and **f** EATL low- and medium-power H&E of case LYWS281 (Dr. Macon et al.): biphasic pattern with intermediate cells in the mucosa and large cells in the submucosa in a patient with known history of CD. **g** CD30 positivity. **h** Break apart FISH for *IRF4/DUSP22* translocation shows a pattern consistent with rearrangement. **I** and **j** Case LYWS571 (Dr. Soderquist et al.): EATL presenting as liver masses (**i**) 8 months before developing small intestine obstruction (**l**). The two sites show different morphology and immunoprofile (CD103 negative in the liver (**j**), and positive in jejunum (**m**) and CD30 positivity in the liver (**k**) and negativity in the jejunum (**n**). The patient had a previous diagnosis of RCD1

Enteropathy-associated T cell lymphoma is an aggressive disease with problematic differential diagnosis in some cases. Seven cases of EATL were submitted summarizing various aspects of the disease. Case LYWS451 (Dr. Swenson et al.) illustrates well the natural history of the disease arising from untreated celiac disease in an *HLA-DQ2*-positive patient. The initial duodenal biopsy showed features of RCD2 with aberrant immunophenotype and T cell receptor gene rearrangement. The immunophenotype (CD8+/CD30+/CD43+) was typical with the exception of CD8 positivity (described in up to 30% of cases [13]), which was also noted on the initial duodenal biopsy. Identical monoclonal T cell receptor gene rearrangement was present in all biopsies indicating a clonal relationship among them with overt lymphoma showing anaplastic morphology, prominent angiocentricity, angioinvasion, and perineural invasion. Aberrant phenotype with CD8/CD56 expression described in case LYWS456 (Dr. Hollander et al.) can cause problems of differential diagnosis with MEITL. The histopathological recognition of CD in the residual, distant mucosa observed at resection margins in this case was the clue for diagnosis. Nevertheless, cases with intermediate features of both EATL and MEITL might exist and then should be reported as intestinal T cell lymphoma NOS.

The challenging differential diagnosis with gastrointestinal location of ALK-negative ALCL was highlighted by case LYWS455 (Dr. Sanders et al.) and also emerged in case LYWS571 (Dr. Soderquist et al.) in which the first manifestation of the lymphoma was extraintestinal (liver) followed by discovery of jejunal disease a few months later in a patient with RCD1 (polyclonal IELs with normal phenotype). The lymphomas at the two locations were clonally related but showed different phenotype (CD103 negative in the liver and positive in the intestine). The liver lymphoma exhibited anaplastic-like morphology and phenotypically resembled

ALK−/ALCL. This could have led to such diagnosis if the history of celiac disease was not known.

An exceptional association with *DUSP22/IRF4* (6p25.3) rearrangement was described and presented in case LYWS281 (Dr. Macon et al.). Again, in this case, a diagnosis of EATL was strongly supported by the presence of CD in previous duodenal biopsies with identical clonal TCR gene rearrangement and *DUSP22/IRF4* (6p25.3) rearrangement.

Monomorphic epitheliotropic intestinal T cell lymphoma

Previously known as EATL type 2, monomorphic epitheliotropic intestinal T cell lymphoma (MEITL) is a primary intestinal T cell lymphoma derived from intraepithelial lymphocytes, accounting for most cases in Asia, affecting males more often than females and showing no clear association with celiac disease [14–16]. Ten cases were reviewed in the workshop. Case LYWS427 (Dr. Goodlad et al.) highlighted the aggressiveness of the disease with early dissemination to extranodal sites and the worldwide distribution describing a case in an indigenous Scottish male patient with no previous history or evidence of celiac disease. Microscopically, the neoplasm was composed of monomorphic medium-sized lymphoid cells with prominent epitheliotropism [1] Fig. 2. Gastrointestinal and multivisceral dissemination were also described in case LYWS311 (Dr. de Leval et al.) in which the stomach showed a degree of epitheliotropism identical to the intestinal mucosa and also seen in the lung, prostate, and kidney at autopsy. The liver showed a mass lesion and sinusoidal infiltration, also seen in the spleen, mimicking hepatosplenic T cell lymphoma, another neoplasm of gamma-delta derivation. Neoplastic cells of MEITL are generally positive for CD3, CD8 and CD56, lack CD5 and EBV, and express TCR gamma in most cases [17]. Unusual immunoprofile with lack of CD8 expression and challenging differential diagnosis with NK/T extranodal and other gamma-delta T cell lymphomas were described in case LYWS180 (Dr. Harahap et al.) and case 181 (Dr. Hultquist et al.). CD56 is expressed in the majority of the cases described. However, as emphasized in case LYWS432 (Dr. Quintanilla-Fend et al.) up to 13% of cases are CD56 negative. Lack of CD8 and CD56 should not preclude the diagnosis. The presence of *STAT5B* mutation was confirmed in this case. Around 60% of MEITL carry this mutation [18] and are of TCR-gamma-delta derivation. The most commonly mutated genes are *SETD2*, reported in up to 93% of cases [18], *STAT5B*, *JAK3*, and *SH2B3* [18]. *SETD2* and *STAT5B* gene mutations seem to be characteristic of MEITL and are only rarely present in EATL [19, 20].

Indolent T cell lymphoproliferative disorders of the gastrointestinal tract

These are defined as clonal lymphoproliferative disorders affecting any site of the GI tract, but more common in the small intestine and colon, that are characterized by an indolent and protracted clinical course and are currently included in the WHO classification as provisional entity [1]. Since the first description by Carbonnel et al. in 1994 [21], several small published series have highlighted the heterogeneity of this condition in terms of pathological and molecular features [2, 21–23]. A specific treatment for these patients has not yet been determined and despite the generally indolent clinical course, most patients have limited or no response to treatment. Occasional cases of disease progression to aggressive T cell lymphomas have recently been described [24, 25].

Nine cases were submitted and reviewed in the workshop: four CD8-positive (LYWS124 by Dr. Green A. et al.; LYWS263 by Dr. Mehta J. et al.; LYWS288 by Dr. Aggarwal N. et al.; LYWS530 by Dr. Gonzalez-Farre B. et al.), three CD4-positive (LYWS421 by Dr. Madrid-Valero G. et al.; LYWS163 by Dr. Muppa P. et al.; LYWS174 by Dr. Betman S. et al.), and two CD4/CD8-negative cases (LYWS420 by Dr. Matthews P. et al.; LYWS558 by Dr. Poullot E. et al.).

In all cases, despite different phenotypes and in agreement with previous literature [26], the clinical presentation was similar and included chronic diarrhea, abdominal pain, nausea/vomiting, and weight loss. Some patients were diagnosed as inflammatory bowel disease, and others as irritable bowel syndrome or celiac disease, but all of them received treatments varying from azathioprine, to antibiotics, steroids, and CHOP chemotherapy. Interestingly, they all recurred over the years with no evidence of transformation to high-grade disease. Lymph node involvement was confirmed in three cases (LYWS530 by Dr. Gonzalez-Farre et al., LYWS421 by Dr. Madrid-Valero et al., and LYWS558 by Dr. Poullot et al.). As previously described, regardless of different immunoprofiles, the histological features were similar with infiltration of the lamina propria by monotonous small lymphocytes focally extending to the muscularis mucosa and exhibiting a mature phenotype with CD3 positivity associated either with CD8 and cytotoxic granules (TIA1+) [2] or with CD4 [25], and low (< 10%) Ki67 (Fig. 3). Two cases (LYWS420 by Dr. Matthews et al.; LYWS558 by Dr. Poullot et al.) were CD4− and CD8−, the latter also showing coexistence of TFH markers (CD10+/CXCL13+) with cytotoxic markers (perforin+; TIA1+/−), aberrant expression of CD20, also described in LYWS421 (Dr. Madrid-Valero et al.) and absence of *STAT3*, *STAT5B*, and *SETD2* mutations. Most cases confirmed TCR rearrangement, beta or gamma.

Recently, Sharma et al. demonstrated *STAT3-JAK2* fusion detected by FISH in a series of ITCLPDGIT which

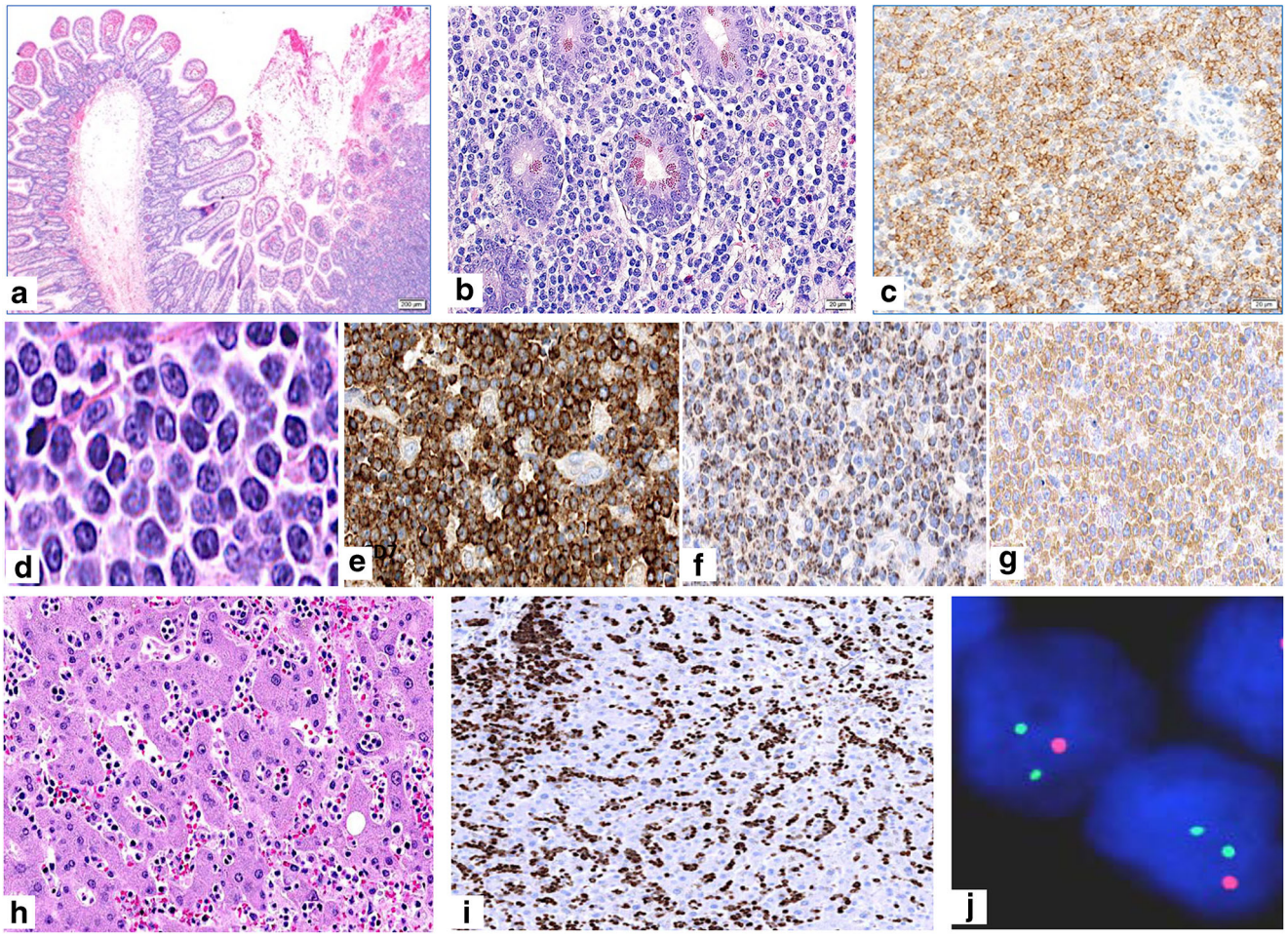

Fig. 2 MEITL. **a** Low-power H&E from case LYWS427 (Dr. Goodlad et al.) showing the lymphoma next to unaffected bowel mucosa with no changes of coeliac disease. **b** Medium-power H&E showing epitheliotropism. **c** Most cases are CD56+. **d** Case LYWS311 (Dr. de Leval et al.): H&E neoplastic cells are monomorphic and express, in addition to CD3, CD7, and TIA1 (**e** and **f**) with TCR gamma (**g**) in most cases. This case was a good example of multivisceral dissemination with involvement of the stomach, lung, kidney, spleen, and liver (**h** and **i**). **j** Heterozygous deletion of *SETD2* locus in most nuclei by FISH was demonstrated

seemed to be restricted to the CD4+ cases [22]. Three of their cases showed *STAT3-JAK2* fusion with identical breakpoint, suggesting a possible role in pathogenesis of this disorder. Dr. Feldman kindly tested the cases submitted to the workshop for the same translocation. The results, summarized in the Table 1, show that one out of three CD4+ cases (case LYWS174 by Dr. Betman et al.) demonstrated *JAK2* breaks and *STAT3-JAK2* fusion. Interestingly, in this case, staging bone marrow biopsy performed 17 months after the initial diagnosis did not show morphologic evidence of disease but cytogenetic analysis indicated minimal marrow involvement by the same LPD diagnosed in the gut suggesting early dissemination of a potentially more aggressive disease.

Therefore, despite similar indolent clinical course, the cases presented in the workshop and the data currently available in the few published series, albeit limited, seem to suggest different pathogenesis and higher risk of progression for the CD4+ cases.

NK-cell enteropathy

This is a poorly defined entity of uncertain nature. A recent review [26] has given a comprehensive literature overview of the disorder first described by Vega et al. in 2006 as indolent "NK-cell LPD of the GI tract" [27]. Subsequently short series from the USA have defined it as "NK-cell Enteropathy" [3] while similar cases from Japan were referred to as "lymphomatoid gastropathy of NK-cell type."[4] All cases of "lymphomatoid gastropathy" were mostly asymptomatic, discovered incidentally at endoscopy for gastric carcinoma surveillance, localized to the stomach, and often associated with *H. pylori* infection. Similar features were summarized in case LYWS347 (Dr. Lee et al.) where a gastric polyp contained the proliferation of NK-cells associated with *H. pylori* gastritis and the patient responded to helicobacter treatment.

The remaining two cases submitted (case LYWS252 by. Dr. Xiao et al.; case LYWS227 by Dr. Bertuzzi et al.) showed clinical presentation and endoscopic findings more similar to the

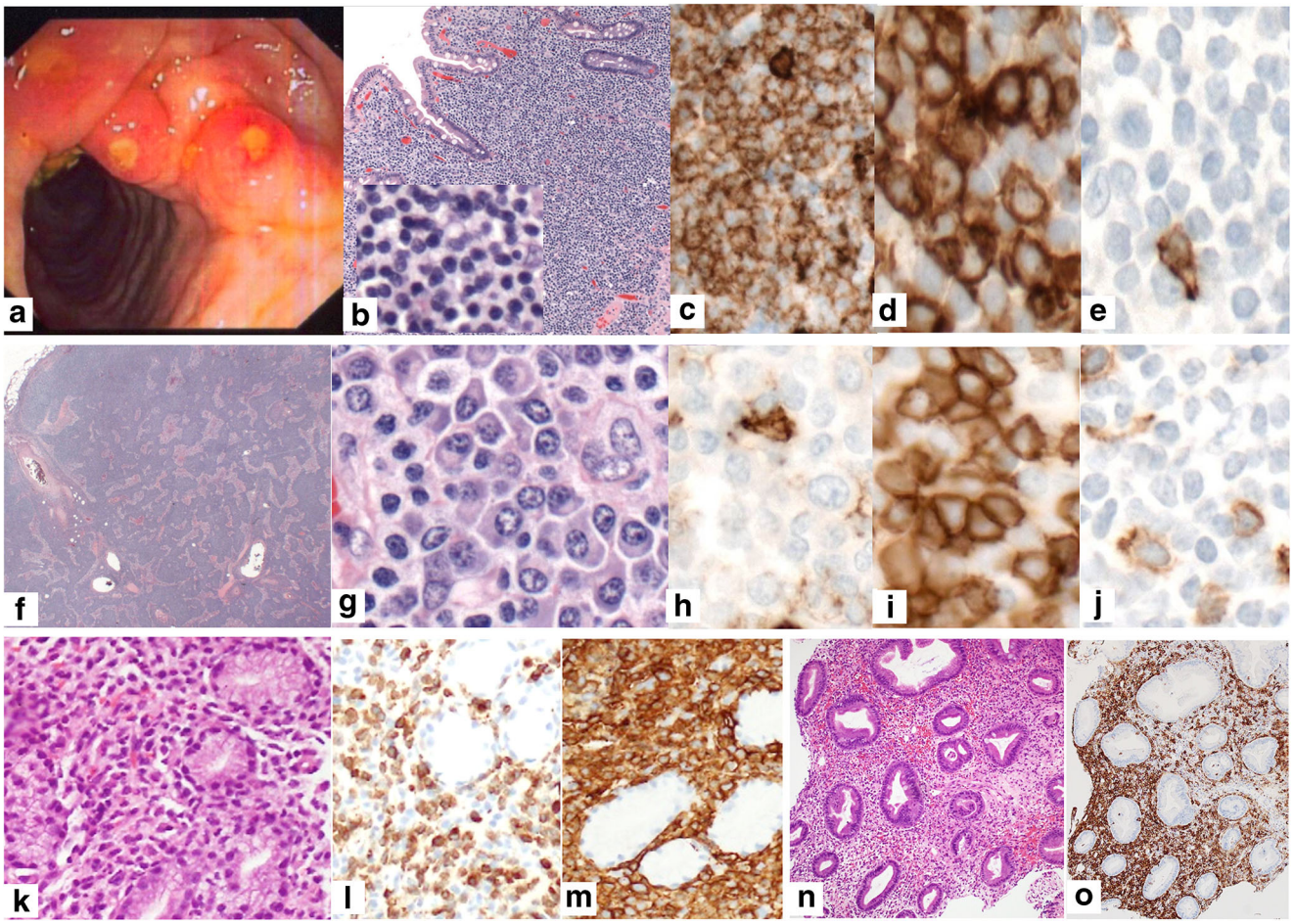

Fig. 3 Indolent T cell lymphoproliferative disorders of the gastrointestinal tract and NK-cell enteropathy. **a** Case LYWS263 (Dr. Mehta et al.), endoscopy showed polypoid lesions in the small intestine and rectum. Case LYWS421 (Dr. Madrid-Valero et al.). **b** The lymphoid infiltrate in the jejunal biopsy does not affect the epithelium and displaces rather than destroys the glandular elements. The lymphocytes are small with mature chromatin and scant clear cytoplasm. In this case, neoplastic lymphoid cells were CD20+ (**c**), CD4+ (**d**), CD8− (**e**). **f** The lymph node shows a partially preserved architecture with open sinuses but slight paracortical expansion. **g** Numerous small lymphocytes admixed to plasma cells are present in the paracortex expressing similar immunoprofile to the lymphoid proliferation in the small intestine with weaker expression of CD20 (**h**), CD4 positivity (**i**), and CD8 negativity (**j**). Case LYWS252 (Dr. Xiao et al.) NK-cell enteropathy. **k** Neoplastic cells infiltrating the gastric mucosa are small to medium sized, mildly atypical, located in the lamina propria, without evidence of epitheliotropism and positive for CD3 (**l**) and CD56 (**m**). These cells also infiltrate the mucosa of the small intestine in a similar fashion (**n**) with the same immunoprofile (CD56 is shown in **o**)

American series [3]: dyspepsia, reflux, long-standing diarrhea, and weight loss with involvement of multiple GI sites at endoscopy in the form of erythematous mucosa and superficial ulcers.

All cases, in agreement with previously published series, showed similar histological and molecular features: neoplastic cells were small to medium sized, mildly atypical, located in the lamina propria, without evidence of epitheliotropism, positive for CD3, CD56, and TIA1 (cytotoxic granules), negative for EBV with Ki67 up to 40% and no clonal TCR gamma gene rearrangement detected (Fig. 3).

An interesting and previously unreported finding emerged in case LYWS252 (Dr. Xiao et al.) where targeted mutational analysis performed with MSK IMPACT (400 genes) showed *AXL* and *JAK3* somatic variants (*AXL* (NM_021913) exon18 p.L721I (c.2161C>A), VAF 7%; *JAK3* (NM_000215) exon12 p.K563_C565del (c.1688_1696delAGAACTGCA), VAF 8%) [28].

The presence of such mutations would support a neoplastic rather than a reactive nature. *JAK3* mutations have often been described in NK/T cell lymphoproliferative disorders/lymphomas. *AXL* is a member of the TAM receptor family essential in NK-cell development and function in mouse models [29, 30]. This finding suggests that mutational analysis in NK LPDs might help to clarify the pathogenesis and the nature of these disorders.

Conclusions

Primary gastrointestinal T cell lymphoproliferative disorders represent a heterogeneous group encompassing aggressive

Table 1 Summary of features in ITCLPDGIT

EAHP#	Clinical features	Phenotype/molecular	JAK2 BAP FISH/STAT3-JAK2 D-FISH
LYWS124	68 years old female. IBD/IBS. Upper GI endoscopy and colonoscopy normal.	CD2, CD3, CD5, CD7, **CD8**, TIA1, TCRbF1, GZB (subset), CD103 (subset) positive. Ki67< 10%. EBV-EBER positive in occasional cells. Clonal TCR.	Normal/normal
LYWS163	50 years old male. 20-year history of abdominal discomfort and several incomplete bowel obstruction episodes. CT enterography showed diffuse small bowel distention and mild small bowel wall thickening with mild mesenteric lymphadenopathies.	CD2, CD3, **CD4**, CD5, CD7, TCRbF1 positive. TCR delta, TIA1, GZB, CD56, and EBV-EBER negative. Clonal TCR. NGS: *ATM* (pY1248C) VAF 46.8%; *EZH2* (pA622P) VAF 26.5%.	Normal/normal
LYWS174	50 years old female with 3 years of diarrhea, bloating, and weight loss suggestive of seronegative celiac disease. Endoscopy showed diffuse congestion, friability, nodularity, and scalloping of the duodenum. Mild mesenteric lymphadenopathy was noted on CT scan.	CD2, CD3, CD5, CD7+/−, **CD4**, TCRbF1 positive. KI67 5%. CD8, CD30, CD103, FOXP3, BCL6, PD1, TIA1, GZB, perforin negative. 46,XX,t(9;17)(p22-23;q12) [1]/45,idem,-X [19] Loss of one X chromosome in 66% of cells by FISH. Clonal TCR. Targeted NGS of 465 cancer-associated genes revealed no somatic mutations.	*JAK2* breaks/*STAT3-JAK2* fusion
LYWS421	56 years old male. 4-year history of intermittent bouts of diarrhea and weight loss. CT scan reveals thickening of the initial segment of the jejunum wall and mesenteric lymphadenopathies. Biopsies confirm intestinal and lymph node involvement.	CD3, **CD4**, CD20 positive. Ki67 < 5%. CD8, CD56, EBV-EBER negative. CD3+CD4-CD8- (subset) Clonal TCR.	Normal/normal
LYWS530	36 years old male with malabsorption symptoms for 8 years, with subocclusive episodes and weight loss. Biopsies confirm intestinal and lymph node involvement.	CD3, CD5, CD7, **CD8**, TIA1 positive. Ki67 < 5%. CD4, CD56, EBV-EBER negative. Clonal TCR.	Normal/normal
LYWS420	51 years old male with a history of upper gastrointestinal symptoms.	CD2, CD3, CD5 (subset), CD7 (subset) positive. **CD4, CD8 negative**. Clonal TCR.	Normal/normal

lymphomas, entities with indolent clinical course but refractory to therapy and poorly characterized NK disorders requiring conservative management.

The cases reviewed have summarized salient clinical and pathological features but also added important information related to the pathogenesis and molecular profiles.

In RCD2, the importance of the CD30 positivity in atypical IELs has been highlighted as marker of progression into EATL as well as the expression of NKP46 staining as potential diagnostic and prognostic biomarker. In addition, NGS analysis can disclose mutations (*STAT3* S614R) in rare cases of RCD2 lacking clonal TCR gene rearrangement. In patients with previous history of CD and biopsy proven RCD2, progression into established EATL is a frequent event. However, when EATL is the first presentation, detailed clinical history and review of all previous biopsies for CD-type changes are mandatory. Aberrant immunoprofiles and extraintestinal involvement as first manifestation of EATL do occur and represent challenging differential diagnoses with MEITL and ALK-ALCL respectively.

MEITL, on the other hand, can also present at extraintestinal sites and rarely lacks expression of CD8 and/or CD56. Aberrant phenotypes should not alter the diagnosis in the absence of EBV. *STAT5B* and *SETD2* mutations seem to be rather specific for this type of GI LPD.

"Indolent T cell lymphoproliferative disorders of the gastrointestinal tract" as a provisional entity includes at present various disorders having in common indolent clinical course, lack of response to therapy, and some histological features. However, it appears that the different phenotypes (CD8+ vs CD4+) might imply different pathogenesis and prognosis. The presence of *STAT3-JAK2* fusion in CD4+ cases could represent a potential explanation but the number of published cases is still too small for further speculations.

A similar scenario emerges for NK-cell GI LPDs. While cases limited to the stomach (lymphomatoid gastropathy) seem to be "incidental," frequently related to *H. pylori* infection and as such responding to antimicrobial treatments, other cases involving multiple GI sites are associated with overt symptomatology and are consistently negative for microorganism stains. One of such cases presented at the workshop showed *AXL* and *JAK3* mutations suggesting a neoplastic rather than a reactive nature.

Part 2. Gastrointestinal B cell lymphomas: site-specific B cell lymphomas of the gastrointestinal tract and B cell lymphomas occurring typically in the digestive tract

Introduction

The 19th meeting of the EAHP Lymphoma workshop session on gastrointestinal tract B cell lymphoproliferations was dedicated to B cell lymphoproliferative disorders that arise primarily in the gastrointestinal tract (i.e., duodenal-type follicular lymphoma), or preferentially or typically involve the digestive tract. Although submission guidelines aimed to exclude MALT lymphoma, a few marginal zone lymphoma (MZL) cases were also received. In total, fourteen cases were reviewed that spanned both small B cell lymphomas and large B cell lymphoma entities. Among the small B cell lymphoma group, the majority of cases fell within the duodenal-type follicular lymphoma category (5 cases: LYWS199 by Dr. Buehler et al.; LYWS236 by Dr. Tousseyn et al.; LYWS251 by Dr. Basha et al.; LYWS378 by Dr. Nomani and Dr. Hsi; LYWS433 by Dr. Quintanilla de Fend et al.). Three cases of mantle cell lymphoma (LYWS304, Dr. Davis et al.; LYWS320, Dr. Fong et al.; LYWS329 Dr. Sadigh et al) and 3 cases of marginal zone B cell lymphoproliferations (LYWS121 by Dr. Soma et al.; LYWS186 by Dr. Rech et al., associated with monoclonal immunoglobulin deposition disease (IgM lambda) in the small bowel mucosa; LYWS37 by Dr. Shet et al.) were also reviewed. Among the large B cell lymphomas, 1 case of large B cell lymphoma with IRF4 rearrangement was received (case LYWS204 by Dr. McPhail et al.). Other non-site-specific B cell lymphoproliferations in this group included 1 case of high-grade B cell lymphoma (composite BL/DLBCL, case LYWS362 by Dr. Huettl et al.) and 1 case of monomorphic immunodeficiency-associated lymphoproliferative disorder (DLBCL type, case LYWS445 by Dr. Somja et al.).

Based on this selection of cases, three topics were addressed during the session discussion:

- Salient clinical and pathological features of duodenal-type follicular lymphoma, along with its genetic features, staging procedures, and natural history.
- Features of mantle cell lymphoma in the gastrointestinal tract and its differential diagnosis with other more common small B cell lymphomas occurring in these anatomical sites (i.e., MZL, MALT type).
- The possible occurrence of extranodal large B cell lymphomas with *IRF4* rearrangement at different levels of the gastrointestinal tract and the possible diagnostic approach for this novel genetically defined entity in routine practice.

Duodenal-type follicular lymphoma

Duodenal-type FL has been incorporated in the most recent WHO classification revision as a variant of FL [1]. It is usually discovered incidentally and involves the mucosal surface of the gastrointestinal wall, mainly the second portion of the duodenum. Other segments of the small intestine and colorectum (28% in some series) or stomach (8%) have also been described to be affected by this variant of FL, as nicely shown in case LYWS236 (Dr. Tousseyn et al.) with multifocal involvement of the colon presenting as a polyposis coli. Endoscopic findings are characteristic, showing a multifocal involvement of the gut by polypoid and nodular lesions (Fig. 3). The infiltrate usually involves the mucosa and submucosa, sparing the muscularis propria. The lack of invasion of deeper layers could be a useful criterion in the differential diagnosis with conventional FL involving the gastrointestinal tract. The histopathology of the cases usually discloses a nodular small B cell centrocytoid population of cells with germinal center B cell phenotype and strong expression of BCL2. The pattern of follicular dendritic cells is characteristic, showing follicular colonization with FDC displacement and preservation or reduced mantle zone (Fig. 1). AID expression has been found to be reduced in these cases in comparison with conventional FL [31], as nicely shown in case LYWS378 (Dr. Nomani and Dr. Hsi). The genetics of these cases is relatively simple, with almost constant presence of *BCL2* translocation and a mutational profile similar to conventional FL with presence of *CREBBP*, *KMT2D*, *TNFRSF14*, and *EZH2* somatic mutations but with a lower rate of *KMT2D* inactivation [32]. The BCL2 pseudonegativity using some commercial IHC clones, as nicely shown in case LYWS433 (Dr. Quintanilla de Fend et al.), may be explained by a process of aberrant somatic hypermutation leading to an increased rate of somatic mutations in the exon 1 of *BCL2*. This is relevant for diagnostic purposes since only alternative clones to clone 124 (clone E17 and SP66) would identify BCL2 overexpression, as has been already described in conventional FL [33]. Additional genetic insights have shown fewer aCGH alterations in duodenal-type FL in comparison with conventional FL with recurrent 1p36 deletion [34]. Gene expression profiling data have shown that the immune microenvironment of duodenal-type FL is distinct from nodal FL and characterized by a chronic inflammation signature [32] with some shared features with MALT lymphoma [35].

Duodenal-type FL usually behaves in an indolent manner and the chance to progression is largely dependent on the clinical staging at diagnosis. The Lugano staging system is recommended to evaluate the potential of progression. Nodal involvement (stage II) is associated with a higher rate of progression [36]. Overall, the prognosis is excellent with 5-year OS rates of 100% and 5-year PFS rates of 93% in some series [37]. Thus, late relapses or progression to high-stage FL can

happen in the long term, as shown with case LYWS298 (Dr. Nomani and Dr. Hsi). Taken together, these data support a watch and wait therapeutic approach [38, 39] (Fig. 4).

Progression from duodenal-type FL to systemic disease seems to be characterized by a pattern of divergent clonal evolution from a putative precursor *BCL2* translocated B cell [33]. Few reports have shown cases of transformation from duodenal-type FL to diffuse large B cell lymphoma [40–43].

Mantle cell lymphoma

Mantle cell lymphoma is a mature B cell neoplasm usually composed of monomorphic small-medium-sized lymphoid cells with irregular nuclear contours [1]. Most cases are characterized by *CCND1* translocation but cases with translocations involving *CCND2* and rarely *CCND3* are well defined as well [43–45]. SOX11 and p27 immunohistochemical expression are useful to identify these CCND1-negative cases [43, 46]. Most cases of mantle cell lymphoma involve lymph nodes and present with high-stage disease usually with hepatosplenomegaly and bone marrow involvement. A non-nodal, leukemic, and frequently indolent disease has recently been well characterized [47, 48]. Gastrointestinal tract involvement by mantle cell lymphoma may show the typical (but uncommon and not entirely specific) clinical presentation of lymphomatous polyposis, usually involving the colon, as nicely shown in case LYWS320 (Dr. Fong et al.). Thus, together with marginal zone lymphomas, mantle cell lymphoma may explain cases of multiple lymphomatous polyposis in the colon, while duodenal-type follicular lymphoma usually produces lymphomatous polyposis in the small intestines. Other gastrointestinal tract manifestations include superficial ulcers, tumor masses, and diffuse infiltration of the GI wall. Sometimes, MCL presents with subclinical involvement of the GI tract or anecdotally may present with an appendicitis-like picture, as shown in case LYWS304 (Dr. Davis et al.). Importantly, the differential diagnosis with other small B cell neoplasms involving the gastrointestinal tract includes marginal zone lymphoma and CLL/SLL. Again, SOX11 immunohistochemical expression can be very useful in this setting as nicely shown in case LYWS329 (Dr. Sadigh et al.; Fig. 5). This case was a CCND3-positive mantle cell lymphoma with gastric, peripheral blood, and bone marrow involvement initially diagnosed as MALT lymphoma. Due to the concurrence of *H. pylori* infection, the patient was treated with antibiotics and performed well. Five years after the initial diagnosis, the patient suffered rectal bleeding, a 3.1-cm mucosal rectosigmoid polyp was found by endoscopy, biopsied, and considered as recurrent MZL disease. However, 3 years later, after the development of systemic peripheral blood, nodal, and extranodal disease progression, a t(6;14)(p21.1;q32) was discovered by conventional karyotyping in the peripheral blood (karyotype46,XY,add(5)(p15),t(6;14)(p21.1;q32),del(8)(p12),del(12)(p12),der(15)?t(3;15)(q11.2;q22) [5]/46,XY[15]). Retrospectively, SOX11 and CCDN3 immunohistochemical assays confirmed a case of CCND3-positive mantle cell lymphoma with clinically indolent systemic disease mimicking MALT lymphoma. Interestingly, after the last diagnosis, the patient was treated with Rituxan and Ibrutinib and achieved remission but 5 years later developed a frank leukemic picture. Interestingly enough this case had some overlapping clinical features with the recently recognized entity of indolent non-nodal mantle cell lymphoma, i.e., indolent clinical course with leukemic involvement. However, the case showed absence of splenomegaly, involvement of lymph nodes, and strong expression of SOX11 by IHC, features that are not typical for that specific new entity.

In summary, conventional mantle cell lymphoma may show a particular tropism for the gastrointestinal tract. This tropism is common to CCND1-positive MCL and other molecular subtypes. In contrast to MALT lymphoma, that is usually an antigen-dependent and localized disease with only exceptional bone marrow involvement, mantle cell lymphoma usually involves lymph nodes and bone marrow, and it is relatively common to identify a peripheral blood component. This is particularly true, but not restricted to the recently recognized entity of leukemic non-nodal mantle cell lymphoma, characterized by an indolent clinical course. The availability of novel markers, such as SOX11, is key to identify the different mantle cell lymphoma molecular subtypes.

Large B cell lymphoma with *IRF4* rearrangement

Large B cell lymphoma with *IRF4* rearrangement is a provisional tumor entity in the updated WHO classification [1]. It accounts for 5% of DLBCLs [49]. It is a lymphoma type composed of germinal center B cells with frequent follicular growth pattern, combined or not with diffuse areas, and characterized by *IRF4-IG* rearrangement, coupled with MUM1 overexpression by IHC [49, 50]. This lymphoma type is particularly frequent in young individuals and the distinction with pediatric-type follicular lymphoma is required [50]. Median age at diagnosis is 12 years (range 4–79 years old) [1]. Usual sites of involvement include the head and neck lymph nodes and Waldeyer's ring, accounting for 8% of DLBCL arising in Waldeyer's ring (2 out of 26 cases evaluated in a cohort of 126 cases) [51]. Other portions of the digestive tract can be involved and in the original case series, four cases (2 male, 2 female, aged 6–15 years old) showed involvement of the bowel. A new case of large B cell lymphoma with *IRF4* rearrangement was presented in the lymphoma workshop (case LYWS204 by Dr. Ellen McPhail et al.). The patient was a 40-year-old female with non-specific gastrointestinal symptoms and a significant thickening of the cecum by CT scan. At surgery, a cecal mass was removed; the histopathology and phenotype were consistent with this entity (Fig. 5). FISH was confirmatory of *IRF4* translocation and additional *BCL6* translocation, as found in a variable proportion of cases (14–67% of cases, according to age) [49]. These cases typically

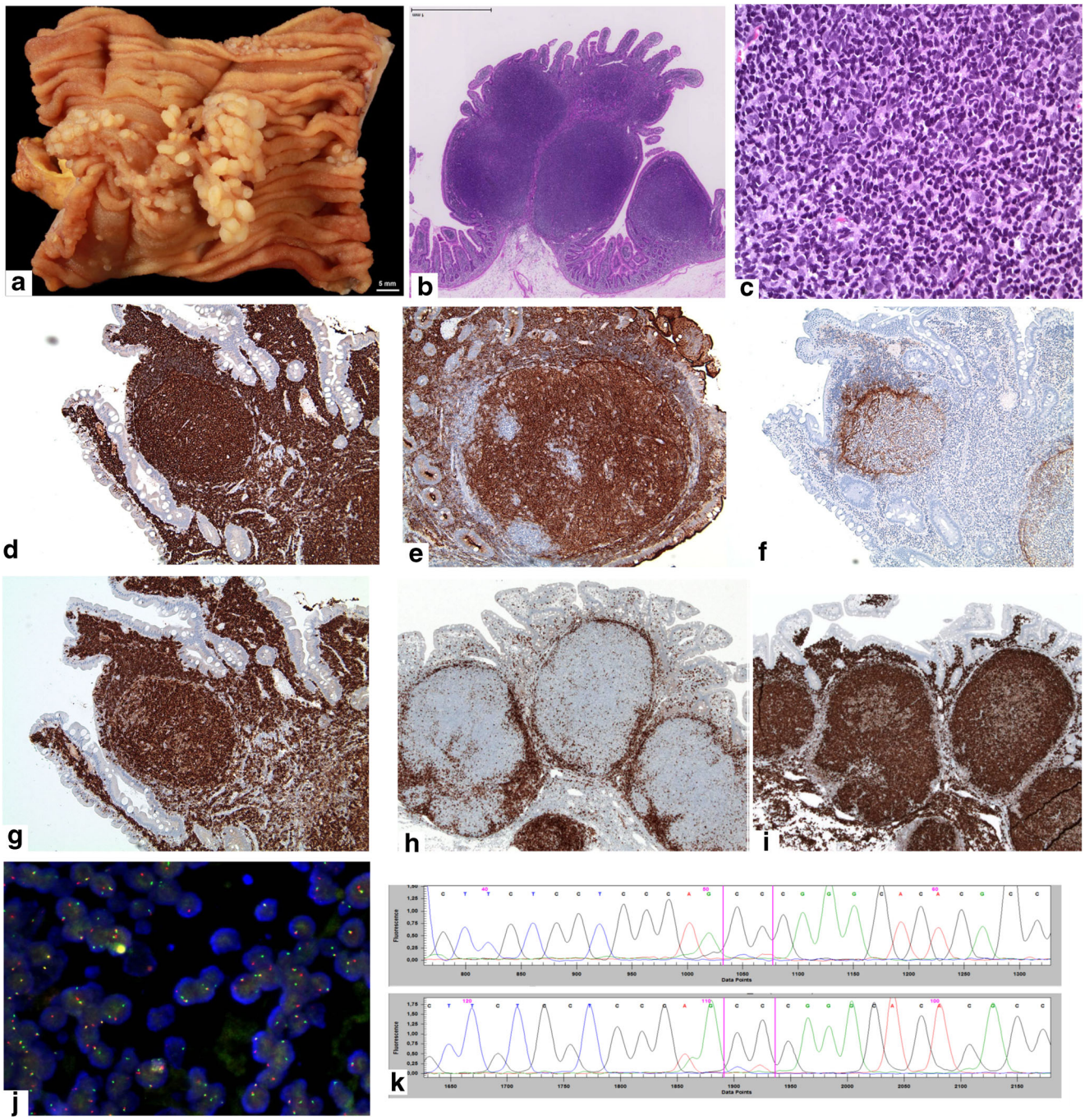

Fig. 4 Duodenal-type follicular lymphoma. **a** Macroscopic picture of case LYWS199 (Dr. Buhler et al.) with multifocal extensive involvement of jejunum and terminal ileum (not shown). **b** Low-power picture (H&E) showing the typical polypoid configuration due to involvement of the surface mucosa by nodular collections of small centrocytoid cells. Note the lack of polarization in the nodules. **c** High-power HE from case LYWS378 (Dr. Nomani and Dr. Hsi) showing a monomorphic G1 cytology. CD20 (**d**) is positive, as well as germinal center markers such as CD10 (**e**) and BCL6 (not shown). **f** CD21 immunostains demonstrate the characteristic displacement of follicular dendritic cells. BCL2 is typically overexpressed by immunohistochemistry (**g**) due to BCL2 translocation (**g** and **j**). Occasional cases (case LYWS433 by Dr. Quintanilla et al,) show BCL2 pseudonegativity with the conventional clone (124, in **h**) and alternative antibodies are required (BCL2 E17 clone is shown in the picture, **I**). **k** *BCL2* mutations in the flexible loop domain (p.P53Y, c.157_158delinsTA) are responsible of a conformational modification in the epitope that prevents BCL2 recognition by clone 124

lack *BCL2* and *MYC* translocations [49]. Besides the typical genetic features, these cases harbor a specific gene expression profile separate from other DLBCL NOS [49]. However, immunophenotypic cell of origin classifiers is difficult to apply for these cases as increased expression levels of MUM1 and BCL6 most probably arise due to the specific genetic

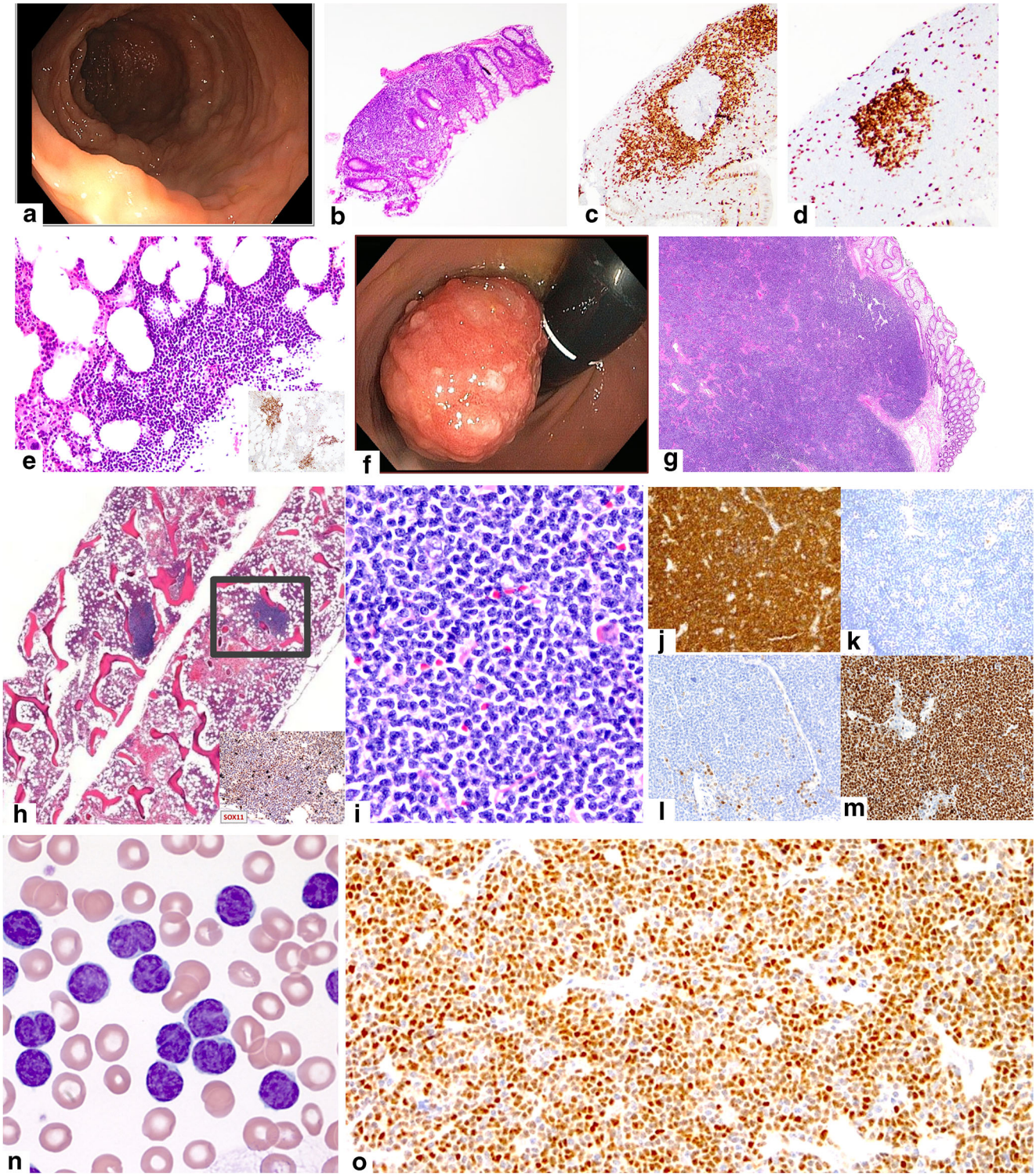

Fig. 5 Mantle cell lymphoma involvement of the gastrointestinal tract. **a** Endoscopic picture of a case of colon polyposis (case LYWS320 by Dr. Fong et al.). HE (**b**), CCND1, and Ki67 IHC staining (**c** and **d**). The case showed bone marrow involvement (HE in **e**). Endoscopic picture of case LYWS329 (Dr. Sadigh et al.) with a rectosigmoid mass. HE showing a submucosal infiltration by small centrocytoid cells (**g**), shown in greater detail in **i**. (**h**) Multifocal interstitial bone marrow infiltration by small cells with SOX11 expression (inset). The case shows expression of CD20 (**j**), negativity for CCND1 (**k**), CCND2 (**l**), and positivity for CCND3 (**m**). **n** Peripheral blood smear showing a small mature lymphoid cell population with cleaved nuclei. SOX11 was positive (**o**)

background. Screening methods to identify cases suitable for FISH testing might be based on the age of the patient, the location of the disease (head and neck, Waldeyer's ring, bowel), the peculiar histopathological pattern with typical

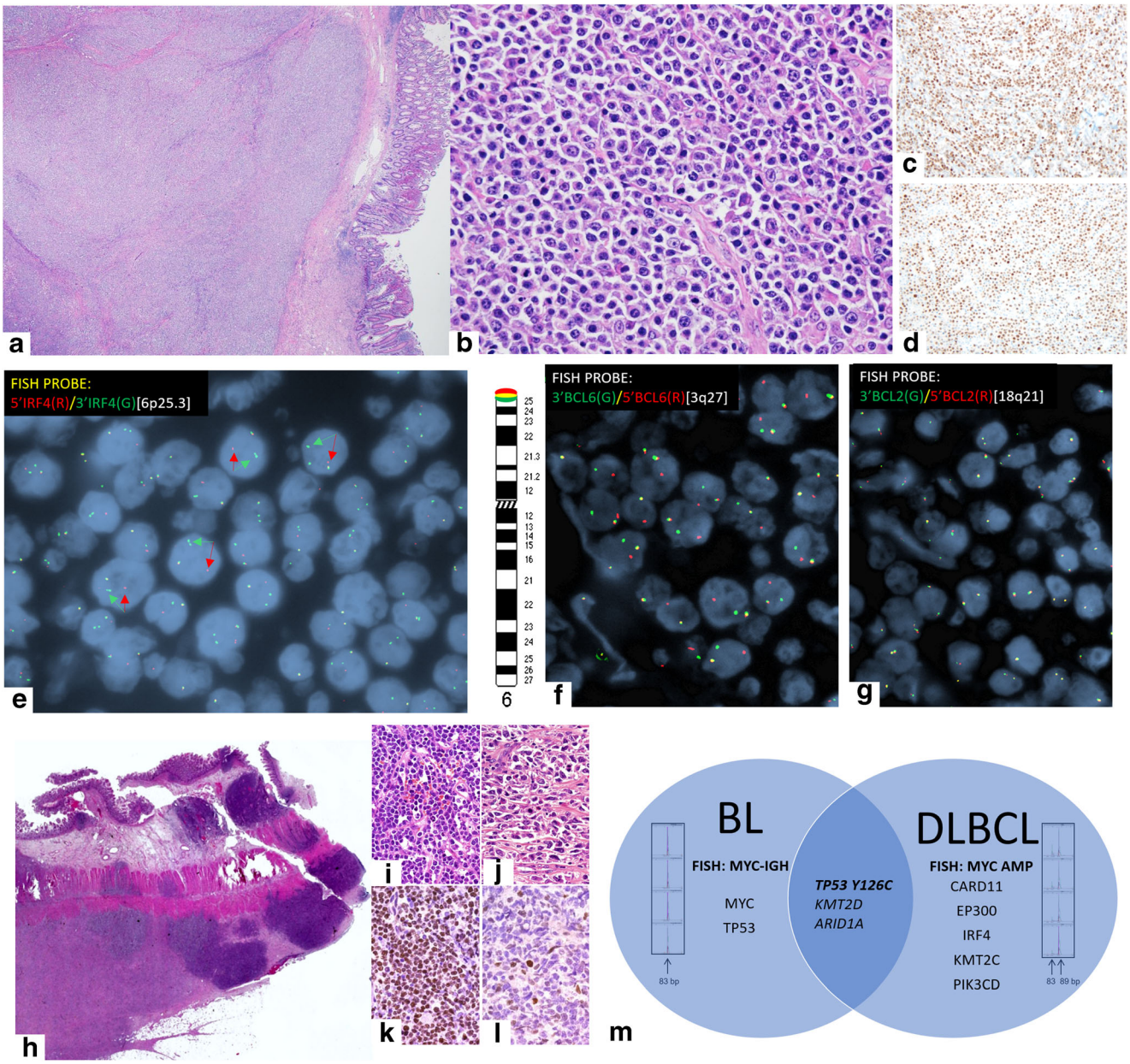

Fig. 6 Large B cell lymphomas in the gastrointestinal tract. Large B cell lymphoma with *IRF4* rearrangement may involve the bowel and typically discloses a partially nodular architecture (case LYWS204 by Dr. McPhail et al. is shown) (**a**). High power shows a relatively monomorphic population of large centroblastic-type cells (**b**). Immunohistochemistry shows co-expression of BCL6 and MUM1/IRF4 (**c** and **d**, respectively). The cases are defined by the presence of *IRF4* translocations by FISH and a substantial number of cases may show *BCL6* breaks (**f**), *BCL2* translocations are absent (**g**). High-grade B cell lymphoma with composite features of BL and DLBCL may occur in the ileocecal region (case LYWS362 by Dr. Huttl et al. is shown). This particular case disclosed areas with BL-type morphology and DLBCL morphology (**h** to **j**). Interestingly, MYC IHC overexpression was found in the BL-type component (**k**) but not in the DLBCL areas (**l**). Comprehensive genetic analysis showed a biclonal population (different *IGH* rearrangements) with different types of *MYC* rearrangements by FISH and disease-related divergent mutational pattern with few common mutations including *TP53*Y126C

centroblasts in follicular (FL3B) and diffuse (DLBCL) growth, and MUM1 overexpression along with strong BCL6 positivity. The prognosis of patients with large B cell lymphoma with *IRF4* rearrangement is favorable after treatment with conventional chemoimmunotherapy, with or without radiation [49]. Limited data are available to suggest an alternative, more conservative, treatment approach for these patients. However, its precise identification may lead to studies testing the true clinical impact of this provisional molecular subtype.

High-grade B cell lymphoma

Extranodal presentation in the ileocecal region is one of the preferred locations for Burkitt lymphoma (BL) including both

endemic and sporadic variants [1]. A unique case with composite Burkitt lymphoma and DLBCL in the ileocecal region of a 72-year-old male was presented in the LYWS (case LYWS362 by Dr. Huettl et al.). The case showed a biphasic lesion with clear cut BL and DLBCL regions. Further molecular workup demonstrated a biclonal population with different *IGH* rearrangements and *MYC* rearrangements pattern (*IGH-MYC* translocated in the BL are and *MYC* amplified in the DLBCL tumor). NGS analysis disclosed also significant genetic heterogeneity with disease-related mutations in each compartment. Interestingly, a common pathogenic somatic missense mutation in *TP53* gene was found (*TP53*Y126C) (Fig. 5). The clinical impact of specific *TP53* somatic mutations in DLBCL has been precisely defined in the literature [52, 53], alone or in combination with other genetic hits, such as *MYC* translocations [54]. This particular combination of genetic findings (*MYC* translocation and *TP53* somatic mutation) challenges the current definition of DH lymphoma and demonstrates the added value of NGS approaches to identify additional high-risk molecular features in large B cell lymphoma cases (Fig. 6).

Conclusions

Duodenal-type FL is usually a localized but multifocal disease involving the surface of the gastrointestinal wall with polypoid and nodular lesions. It may involve different portions of the gut and the histopathological features are characteristic, together with a GC B cell phenotype with reduced AID expression and a pattern of follicular colonization with FDC displacement. Staging according to Lugano system provides prognostic information, regarding risk of clinical progression. Genetic features are overlapping with conventional FL but a lower rate of genetic inactivation of *KMT2D* and immune microenvironment signatures might be distinct relevant features.

Conventional mantle cell lymphoma shows a particular tropism for the gastrointestinal tract. This tropism is common to CCND1-positive MCL and other molecular subtypes and may mimic MALT lymphoma. The availability of novel markers, such as SOX11 and the use of cytogenetics, is key to identify the different mantle cell lymphoma molecular subtypes and solve the differential diagnosis with other small B cell lymphoma types.

IRF4 translocated large B cell lymphomas are uncommon (5% of all DLBCL) and arise in young patients preferentially in Waldeyer's ring, cervical lymph nodes, and bowel. A partially follicular pattern of growth, intense expression of MUM1 and BCL6, and absence of *BCL2* translocation are clues for a diagnosis of suspicion. Demonstration of *IRF4* rearrangement is usually required for the diagnosis and may help in the differential diagnosis with pediatric-type FL. However, some rare cases with otherwise typical features of this disease do not show an *IRF4* break by commercially available DNA probes. Nevertheless, confirmation of the diagnosis by FISH should be sought in all cases.

Gastrointestinal tract involvement by both Burkitt lymphoma and DLBCL occurs. Unrestricted use of targeted NGS mutational analysis of high-grade BCL may uncover clinically relevant genetic events in addition to well-defined high-risk features (i.e., *MYC* translocation) that may challenge the current definition of high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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