

# Extranodal lymphomas of the gastrointestinal tract

## Pozawęzłowe chłoniaki przewodu pokarmowego

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### Abstract

*Extranodal lymphomas commonly involve the gastrointestinal tract (GI) and often present a diagnostic challenge for both clinicians and pathologists. Extranodal GI lymphomas (EGIL) have varied aetiology and may present as an acute emergency or chronically with vague abdominal symptoms in every age group. Morphologically they are as varied as any nodal lymphoma. The optimal diagnosis subclassification of these lesions requires a high index of suspicion on the part of the clinician, skilled endoscopist, or surgeon and a pathologist familiar with a range of presentations and diagnostic criteria. This review paper focuses on EGIL from the pathologist's perspective.*

**Key words:** non-Hodgkin lymphoma, extranodal, gastrointestinal tract

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### Streszczenie

*Pozawęzłowe chłoniaki często zajmują przewód pokarmowy (GI) i są wtedy dużym wyzwaniem diagnostycznym dla klinicystów i patologów. Pozawęzłowe chłoniaki przewodu pokarmowego (EGIL) cechują różną etiologią i prezentacje kliniczne, obejmujące ostre lub przewlekłe objawy brzuszne. Mogą wystąpić w każdym przedziale wieku i mieć zróżnicowany obraz morfologiczny, podobnie jak w przypadku chłoniaków o lokalizacji węzłowej. Prawidłowego rozpoznania EGIL powinno się dokonywać na podstawie danych klinicznych, wyników badań uzyskanych metodami endoskopowymi i chirurgicznymi oraz oceny histopatologicznej, dokonanej przez doświadczonego patologa. Niniejsza praca jest omówieniem tych zagadnień z perspektywy lekarza patologa.*

**Słowa kluczowe:** chłoniaki nieziarnicze, pozawęzłowe, przewód pokarmowy

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### Introduction

Extranodal lymphomas (EL), the neoplastic lymphoproliferative lesions arising outside lymph nodes, bone marrow, or spleen, can develop in nearly every organ; however, the gastrointestinal (GI) tract represents the most common site of EL presentation [1]. While secondary involvement of

the GI tract by a nodal non-Hodgkin lymphoma (NHL) is common, *de novo* extranodal GI lymphoma (EGIL) tracts are less common. These lesions may affect any site along the GI tract and are thought to arise from primary/innate or acquired lymphoid elements distributed within the lamina propria and submucosa, including intra-epithelial lymphocytes.

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**Table 1.** Incidence of primary extranodal gastrointestinal lymphoma incidence rates from various studies worldwide**Tabela 1.** Częstość występowania pierwotnych pozawęzłowych chłoniaków przewodu pokarmowego

Country	Study period	Incidence (10 <sup>5</sup> )	Reference
Denmark	1983–1991	1.19	[2]
Finland	1975–1993	1.25	[3]
United States	1978–1987	0.69 (whites)	[4]
England & Wales	1986–1993	0.58	[5]
France	1976–1990	0.9	[6]
Canada	1999–2003	1.73	[7]
Canada	1999–2009	2.10 (in 2009)	Howell et al. (manuscript submitted)

The difficulties in studying EGIL include the relative rarity of these malignancies in relation to their nodal counterparts, the wide range of clinical presentations, varying locations within tissues, the scarcity and often suboptimal preservation of the diagnostic material, and difficulties in histopathologic classification. Determination of a genuine *de novo* EGIL is challenging since disseminated extranodal cases and nodal cases with contiguous spread to the GI tract are much more common in clinical practice. Moreover, frequencies and GI tract distribution of EL differ among various countries (Table 1) [1–7].

The gross appearance of EGIL within the GI tract is variable and can range from polypoid lesions to diffuse infiltration with or without ulceration or necrosis, to exophytic masses, some of which may endoscopically, radiologically, and grossly mimic the appearance of a carcinoma. Too often, however, the diagnoses of *de novo* EGIL is made on minute and suboptimal biopsy material obtained endoscopically, highlighting the need for both clinicians and pathologists alike to be ever vigilant for this entity.

### *De novo* EGIL

#### Epidemiology and incidence

*De novo* EGIL represent 4–12% (depending on the geographic location) of all NHL. As is the case for nodal lymphomas, EGIL have been reported with increasing frequency worldwide [8] with resulting increase in morbidity and mortality [9]. This trend is also noted in Canada, where the rates of NHL in general have doubled since the 1970s, and a similar trend is seen with *de novo* EGIL [9]. A recent study of an adult Canadian population between 1999 and 2003 demonstrated population-based incidence rates of primary EGIL of 1.73 per 100,000, higher than in other parts of the western

world [7]. Similarly, a rising incidence of EGIL has been documented in a comparable population between 1999 and 2009, with incidence for primary colonic EGIL being nearly 5-fold greater than USA rates documented in the 1990s [4, 10]. European studies report the incidence varying between 0.58 and 1.25 per 100 000 (Table 1).

There is no clearly defined explanation for the increases in EGIL occurrence, although it may be explained in part by enhanced detection methods increasing the awareness of this entity amongst internists and gastroenterologists with common use of endoscopy and colonoscopy in patients presenting with vague abdominal symptoms, as well as improved reporting and documentation of these lesions. Various reports indicate that the majority of all EGIL are seen in the stomach (50–70%), less commonly these are present in the small bowel (25%) and least commonly in the colon (10–15%). Only small case numbers have been reported within the oesophagus [11, 12], vermiform appendix [11, 13, 14], and anus. Approximately 10% of cases will present with multiple sites of involvement along the GI tract [15].

The majority of EGIL are diagnosed after age 55 (70–75%) and show slight male predominance (M:F ratio of 1.5:1). This tendency is seen among most of the NHL types with the exception of follicular lymphoma (FL), which has a female preponderance [15]. In the paediatric population, EGIL most commonly occurs in the cecum [16–18] with a proportion of cases localized to the vermiform appendix [13]. The prognosis of these rare paediatric cases appears to be excellent.

#### Predisposing factors

Several factors implicated in the development of EGIL are well recognized and differ depending on clinico-pathological entity. Gastric MALT (mucosa-

**Table 2.** World Health Organization (2008) histological classification of extranodal gastrointestinal non-Hodgkin' lymphoma (source [15])

**Tabela 2.** Histologiczna klasyfikacja pozawęzłowych chłoniaków nieziarnicznych przewodu pokarmowego według Światowej Organizacji Zdrowia (2008) (źródło [15])

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Mature B-cell neoplasms
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Follicular lymphoma including primary intestinal follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Burkitt lymphoma
Mature T-cell and NK-cell neoplasms
Enteropathy-associated T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Post-transplant lymphoproliferative disorders

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-associated lymphoid tissue) lymphomas have been attributed to chronic antigenic stimulation related to infection with *Helicobacter pylori* (*H. pylori*), with remission achieved following antibiotic treatment [19].

Immunoproliferative small intestinal disease (IPSID), also known as an alpha chain disease, a rare form of an extranodal marginal B cell lymphoma (MZL), which arises in the small intestine (MALT) causing diarrhoea and malabsorption, may respond to antibiotic therapy and is believed to be related to chronic infection with *Campylobacter jejuni* [20]. Celiac disease and certain serologic and genetic factors (*i.e.* HLA-DQ2/DQ8) have been implicated in the development of type I enteropathy-associated T-cell lymphoma (EATL). Immunocompromise in the form of chronic human immunodeficiency virus (HIV) infection, post-transplant immunosuppression, chemotherapy, or inflammatory bowel disease have also been attributed to rises in EGIL [21, 22]. Interestingly, HIV-associated EGIL shows a continued decrease in incidence over time, a finding presumably related to restored immune system defences with antiretroviral therapy [7]. The latter supports the notion that the increased incidence of EGIL is generally related to altered systemic immunocompetence.

### Clinical presentation

In general, patients with EGIL suffer less B-symptoms than their nodal counterparts. Clinical presentation is dependent on the location of the extranodal primary, and in the GI tract, symptoms depend on

lesion localization, *i.e.* stomach, small intestine, colon, or rectum. The clinical presentations range from discomfort, abdominal pain, and diarrhoea to surgical presentation of an abdominal mass, bowel obstruction, and acute abdomen with symptoms and signs of perforation and/or haemorrhage.

Diagnostic imaging findings also vary depending on the lesion localization. Bone marrow involvement is rare unless the extranodal disease has become widely disseminated [1, 18, 23]. Other rare endoscopic findings include case reports of a colonic MALT lymphoma detected endoscopically as a simple mucosal discoloration [24] or single or multiple polypoid lesions in mantle cell lymphoma (MCL) and primary intestinal FL, respectively. A case of atypical MALT in the transverse colon with a secondary macroglobulinaemia has been reported [25]. Presentations of EGIL mimicking dermatomyositis or Crohn's colitis are documented in the literature [26–30]. Finally, EGIL has been associated with localized amyloidosis [31, 32].

### Histological classification

Currently, the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissue [15] set the diagnostic standard for the morphological subclassification of NHL including EGIL. Within the GI tract, the various categories of *de novo* EGIL are subdivided into B- and T/NK-cell neoplasms and post-transplant lymphoproliferative disorders (PTLD) (Table 2).

This various morphologic subtypes of EGIL also show differences in anatomic distribution. In a recent study of a North American adult population, a diffuse large B cell lymphoma (DLBCL) made up the majority of lymphoma histologies along all areas of the GI tract including the stomach, small bowel, colon, and various other multiple sites [10]. This relative preponderance of DLBCL in *de novo* EGIL is supported by other studies worldwide, in which the histological subtype of EGIL was also a high grade/DLBCL regardless of the GI site [5, 7]. Others have shown a majority of *de novo* EGIL as being of the extranodal MZL [2], or instances in which the proportion of MZL/MALT and DLBCL classification were approximately equal [33].

### Staging

The consensus conference in Lugano in 1993 established staging of EGIL [34]. From this meeting came specific criteria for determining the pathologic staging of these lymphomas, with stage I tumours being confined to the GI tract, stage II demonstrating local nodal involvement, and stage III in-

**Table 3.** Clinical staging of primary extranodal gastrointestinal non-Hodgkin lymphoma\***Tabela 3.** Zaawansowanie kliniczne pierwotnie pozawęzłowych chłoniaków nieziarnicznych przewodu pokarmowego\*

Stage	Tumour extent <sup>a</sup>
<b>1993 Lugano Consensus Conference</b>	
I	Tumour confined to GI tract: <ul style="list-style-type: none"> <li>• single primary site</li> <li>• multiple non-contiguous lesions</li> </ul>
II	Tumour extending into abdomen from a GI primary:
II <sub>1</sub>	• local nodal involvement (para-gastric for gastric lymphomas; para-intestinal for intestinal lymphomas)
II <sub>2</sub>	• distant nodal involvement (mesenteric in cases of intestinal primary; para-aortic, para-caval, pelvic, inguinal)
II <sub>E</sub>	Penetration of serosa to involve adjacent organs/tissues — e.g. IIE (site of adjacent organs/tissues) Note: involvement of both nodal and adjacent organs/tissues, designate as IIE <sub>1</sub> or IIE <sub>2</sub>
IV <sup>b</sup>	Disseminated extranodal involvement or GI tract lesion with supra-diaphragmatic nodal involvement
<b>TNM classification of non-Hodgkin lymphomas<sup>a</sup></b>	
I <sub>E</sub>	Localized involvement of a single extralymphatic organ or site
II <sub>E</sub>	Localized involvement of single extralymphatic organ/site and regional lymph node(s) ± ± involvement of other lymph node regions on the same side of the diaphragm
III <sub>E</sub>	Localized single extra-lymphatic organ/site and node regions on both sides of the diaphragm:
III <sub>S</sub>	• or spleen
III <sub>E + S</sub>	• or both
IV	Disseminated (multifocal) involvement of one or more extralymphatic organs ± regional nodes or extralymphatic organ involvement with distant (non-regional) nodal involvement

\*Adapted from Rohatiner et al., 1994 and TNM Classification of Lymphomas (Sobin et al., 2010); <sup>E</sup>E indicates GI tract lesion extending to involve adjacent organs (1993 Lugano Conference) but <sub>E</sub> denotes involvement of extralymphatic organs or sites in the TNM system; <sup>b</sup>stage III has been combined with Stage IV in the 1993 Lugano Consensus Conference; GI — gastrointestinal tract

cluded with stage IV (bone marrow involved, any extranodal involvement or GI tract lesion with supra-diaphragmatic nodal involvement) (Table 3).

### Prognostic factors

Various conflicting reports in the literature exist as to prognostic factors in *de novo* EGIL, which is probably related to morphologic heterogeneity. Azab et al. [35] demonstrated by multivariate analysis that clinical stage, surgical resection, and histological grade all represent independent prognostic variables. For instance, in the stomach, MALT lymphomas behave indolently, presenting as stage I or II disease, whereas transformation of this lesion to a DLBCL, especially with bone marrow involvement, results in a 5-year survival of 10% [36].

Molecular genetics in gastric MALT lymphomas also aid in predicting the biological behaviour of these tumours and may help in guiding therapy. For instance, t(11;18)-positive cases have inferior response to *H. pylori* eradication therapy, but un-

dergo transformation to high grade histology at much lower rates than their t(11;18)-negative counterparts [37].

### Diagnosis and ancillary studies

Diagnosis and further subclassification of these neoplasms is based on comprehensive evaluation of good quality morphology, immunophenotypic features, and cytogenetic/molecular data, which together with clinical/endoscopic and radiological assessment are usually helpful in subsequent subclassification. These studies, however, may not be definitive in differentiating the neoplastic lesions from reactive or oligoclonal/clonal atypical lymphocytic infiltrate.

Differentiating early extranodal MZL of MALT type from exuberant chronic *H. pylori* gastritis with associated lymphoid hyperplasia can be problematic. The presence of oligoclonal/clonal B-cell expansion in this context has to be interpreted with caution since clonally expanded B lymphocytes have

been reported in flow cytometric studies and polymerase chain reactions (PCR) in both EGIL and biopsies harbouring chronic gastritis, as well as colon biopsies showing non-specific colitis [38]. It is generally accepted that clonal/oligo-clonal B-cell expansions are not limited to neoplastic lymphoproliferative disorders but may also be seen in reactive lesions. B-cell clonal bands are detected in cases of *H. pylori* gastritis with associated lymphoid hyperplasia; however, the reproducibility of these bands was limited and increased backgrounds were seen, in contrast to low-grade MALT lymphomas [39].

MALT lymphomas may be associated with four different types of mutations: the translocations t(11;18)(q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21), and t(3;14)(p13;q32). The genes affected by at least three of these mutations are involved in the same pathway leading to the activation of the NF $\kappa$ B. Of these, t(11;18) is the most specific and has known clinical significance [40]. The MALT lymphoma with this particular translocation is unlikely to respond to *H. pylori* eradication, which more commonly presents as a locally aggressive tumour which usually does not transform into a high-grade component [37].

### Special topics in EGIL

#### MCL

Mantle cell lymphoma commonly presents with stage III or IV with selected predilection for the GI tract. Clinically the GI involvement may be silent, but endoscopically widespread multiple lymphomatous polypoid lesions are scattered throughout the small and large intestine. A biopsy of these reveals dense, monotonous lymphocytic infiltrate of centrocyte-like cells characteristically co-expressing CD20/BCL-2/CD5 and cyclin D1.

#### Other CD5-positive low-grade lymphomas of the GI tract

Low-grade EGIL co-expressing CD5 and lacking cyclin D1 often presents considerable diagnostic difficulty, frequently magnified by the scarcity of diagnostic material. Morphologically, these lesions may represent GI tract involvement by chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL), to less commonly encountered cyclin D1/D3 negative variant of MCL, extranodal MZL resembling MALT type with atypical CD5 expression or CD5 positive lymphoplasmacytic lymphoma (LPL).

#### Primary intestinal FL

Nodal FL secondarily involving the GI tract is well recognized. However, following a number of case reports a distinct clinical presentation of *de novo* FL exclusively limited to the GI tract with no demonstrable clinical/radiological extension beyond the GI tract has been described and adopted by WHO classification as a novel clinico-pathological entity [41, 42]. The single or multiple exophytic or polypoid lesions usually affecting the upper GI tract (duodenum) but also described in other GI parts (colon) show morphologic and immunohistochemical features indistinguishable from the classic nodal counterpart. Immunophenotypically, these CD20 positive lesions show distinct and bright co-expression of BCL-2 protein and often demonstrate the presence of t(14;18). Whenever presenting in limited stage (I/IIe) they invariably have an excellent prognosis.

#### Burkitt lymphoma

Burkitt lymphoma (BL) is a highly aggressive mature B-cell lymphoma with heterogeneous presentation patterns. Four distinct epidemiological variants are recognized: sporadic, endemic, HIV infection related, and a type of PTLD. The latter two subtypes may present as EGIL, are related to altered immunocompetence of the host, and may be lacking *c-myc* mutations. The sporadic variant, which affects predominantly children and young adults, usually presents as an extranodal tumour of the ileocaecal region [43]. This subtype is variably associated with the Epstein-Barr virus (EBV) (10–85% of cases), and most cases show the sole *c-myc* mutation (90%).

The immunophenotype of BL is that of a mature B-cell neoplasm with tumour cells expressing B-cell associated antigens (CD20, CD19, CD22, CD79a), and germinal centre markers (CD10/BCL-6 and CD43). Progenitor markers (Tdt/CD34) are typically absent, and most of the cells are in proliferative cycle as per high proliferative index Ki-67, which commonly approaches 100%.

On occasion, BL may be difficult to differentiate from DLBCL. Borderline cases, which present with morphologic features of BL but lack the characteristic high proliferative rate, immunohistochemical, and/or cytogenetic signature, may currently be classified as B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL. This distinction may not be important in a paediatric population, where BL and DLBCL cases are treated

in a similar fashion, but may alter the therapeutic approach in an adult patient, where a more aggressive regimen with central nervous system prophylaxis may be implemented in cases of BL/undetermined B-cell category, as opposed to R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) only commonly used in DLBCL patients.

### **PTLD**

In the era of bone marrow and solid organ transplantation, PTLT has emerged as a significant complication of the necessary immunosuppression. Most of these lesions are EBV-related and are of B-cell origin. The gastrointestinal tract is one of the most commonly affected systems. The incidence of PTLT is dependent upon the type of transplanted organ; small bowel transplants carry risk of 30%, heart, liver, lung, and pancreas 2–12%, while renal transplants have the lowest risk at 1%. Several comprehensive reviews on this subject are available [44, 45].

### **T-cell lymphomas and celiac disease**

Enteropathy-associated T-cell lymphoma (EATL) is rare form of an extranodal T-cell lymphoma arising from intraepithelial T cells and affecting mostly ileum and jejunum. Based on the morphology and genetic profile, these have been divided into two groups; type I EATL often has a background of refractory celiac disease, malabsorption, and ulcerative jejunitis. Most cases, however, develop in type II refractory celiac disease. These lymphomas represent the majority of EATL (80%) and commonly affect patients of North European ancestry [46]. Morphologically, they are composed of CD3- and CD103-positive T-cells which are polymorphous in size and shape, are often CD4/CD8/CD56-negative and may co-express CD30.

Much less common type II EATL, also known as a monomorphic variant, is composed of small to medium sized cytotoxic type CD8-positive T-cell lymphocytes co-expressing CD56. This variant of EATL often presents in the small bowel with symptoms of obstruction or perforation. It is not associated with celiac disease and may represent a sporadic clinico-pathologic entity unrelated to risk imposed by celiac disease [22]. All types of EATL have an overall poor prognosis [15].

### **Extranodal NK/T-cell lymphoma of the nasal type**

This distinct and EBV-encoded RNA (EBER)-positive T cell lymphoma affecting the upper aerodigestive tract also has an increased predilection for skin and GI tract involvement. Clinically, it may

present as a surgical emergency with signs and symptoms of acute abdomen and perforation. Surgical procedure may procure resected sections of bowel featuring necrotic and ulcerated lesions composed of polymorphous infiltrate of CD56-positive cytotoxic T/NK cells exhibiting a high degree of EBER positivity, as demonstrated by *in situ* hybridization. The CD30 expression present in some subsets of these cases may result in misdiagnosis with GI involvement by ALK-1 negative anaplastic large cell lymphoma or EATL. Neither of these latter two T-cell lymphoma types, however, show such a distinct EBER expression.

### **T-cell prolymphocytic leukaemia**

T-cell prolymphocytic leukaemia (T-PLL), known as T-cell CLL in the past, is a widely disseminated disease which may involve any portion of the GI tract in a fashion similar to any low-grade NHL. Morphologically, mature and variably convoluted lymphocytes permeate the tissue and characteristically co-express CD2/CD3/CD5/CD7 mature T-cell markers. In a considerable proportion of cases, co-expression of CD4/CD8 and TCL1 is diagnostic of this disease entity.

### **Benign NK-cell proliferations of the gut**

Benign NK-cell enteropathy may present as morphologically and immunophenotypically atypical NK-cell lymphocytosis of the superficial mucosa in a patient with endoscopic evidence of fold thickening, superficial ulcerations which may be accompanied by vague abdominal symptoms. An infiltrate of CD56/*c*CD3-positive NK-cells lacking surface expression of CD3 is present. Commonly, both EBER and PCR products indicating the presence of EBV DNA are negative. This presentation usually results in exhaustive investigation and has yet to have a determined significance, but its existence is important to avoid pitfalls in calling these cases overtly malignant [47].

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