Original Article

Primary and Secondary Hematolymphoid Neoplasms of the Gastrointestinal Tract: A Single Institute Experience

Gastrointestinal Sistemin Primer ve Sekonder Hematolenfoid Neoplazileri: Tek Merkez Deneyimi

Beril Güler
Department of Medical Pathology, Bezmialem Vakıf University, Istanbul, Turkey

ABSTRACT

Introduction: The gastrointestinal tract is the most common extranodal region for hematolymphoid neoplasms. However, when compared to inflammatory lesions or epithelial tumors, this group of neoplasms is quite rare and some of them cause diagnostic difficulties. In this study, the clinicopathological features of common hematolymphoid neoplasms of the gastrointestinal tract were aimed to be represented and observed rare entities were highlighted.

Materials and methods: Forty-six patients who were diagnosed of hematolymphoid neoplasia with gastrointestinal system infiltration between the years 2014 and 2021 were selected retrospectively from the archives of pathology department. Pathology reports, demographic and clinical data, endoscopic and imaging findings were collected from the hospital information system.

Results: Thirty-six of the patients were diagnosed of primary neoplasms of the gastrointestinal tract. Nine patients were accepted as secondary spread of systemic disease to the gastrointestinal tract. For one patient, differential diagnosis regarding primary or secondary disease could not be made with available data. The mean age was 56. Approximately three-quarters (73.9%) of the cases were diagnosed by endoscopic biopsy. Patients frequently (73.9%) presented with nonspecific gastrointestinal symptoms. However, ileus was described in cases with bowel localization. The most common diagnosis was diffuse large B-cell lymphoma (n:26) followed by MALT lymphoma (n:6). We had four patients diagnosed as duodenal-type follicular lymphoma. Rare cases were IRF4-associated large B-cell lymphoma (n:1), EBV positive large B cell lymphoma (n:1), extracavitary/solid variant primary effusion lymphoma (n:1), myeloid sarcoma (n:1).

Discussion: An unexpected difference was that the number of patients with diffuse large B-cell lymphoma was more than four times of MALT lymphoma. Possibility of confusion with poorly differentiated carcinomas is an important handicap especially in rare high grade lymphomas and myeloid neoplasms. Duodenal lymphoid follicles should be carefully evaluated and immunohistochemical evaluation should be performed.

Keywords: Gastrointestinal Neoplasms, Lymphoma, Hematologic Neoplasms

ÖZET

Giriş: Gastrointestinal sistem, hematolenfoid neoplazilerin en sık görüldüğü ekstranodal bölgedir. Bununla birlikte inflamatuar lezyonlar ve epiteliyal neoplazilere kıyasla oldukça nadir gözlenen bu grup neoplazilerde tanı zorlukları yaşanabilmektedir. Bu çalışmada gastrointestinal sistemin sık görülen hematolenfoid neoplazilerinin klinikopatolojik özelliklerini sunmayı, nadir görülen antitelere ise dikkat çekmeyi amaçladık.

Gereç ve yöntemler: Patoloji arşivimizden, 2014-2021 yılları arasında, gastrointestinal sistem infiltrasyonu ile hematolenfoid neoplazi tanısı alan 46 hasta retrospektif olarak tespit edilmiştir. Patoloji raporları yanı sıra demografik ve klinik verilere, endoskopi ve görüntüleme bulgularına hastane bilgi sisteminden ulaşılmıştır.

Bulgular: Otuzaltı hastada primer odak gastrointestinal sistemdi. Dokuz hastada, gastrointestinal infiltrasyon sistemik hastalığın sekonder yayılımı olarak kabul edildi. Hastalardan birinde, mevcut verilerle primer veya sekonder hastalık ayrımı yapılamadı. Ortalama yaş 56 idi. Olguların yaklaşık dörtte

First Received: 06.05.2022, Accepted: 25.07.2022 doi: 10.5505/aot.2023.68916

üçü (%73,9) endoskopik biyopsi ile tanı aldı. Hastaların sıklıkla başvuru sebebi nonspesifik gastrointestinal semptomlardı (%73,9). Barsak yerleşimli orgularda ise ileus tablosu ile karşılaşıldı. En sık tanı diffüz büyük B hücreli lenfoma (n:26), ardından MALT lenfomaydı (n:6). Duodenal tip foliküler lenfoma tanısı alan dört hastamız mevcuttu. Nadir vakalarımız; IRF4 ile ilişkili büyük B hücreli lenfoma (n:1), EBV pozitif büyük B hücreli lenfoma (n:1), ekstrakaviter/solid varyant primer efüzyon lenfoma (n:1), myeloid sarkomdu (n:1).,

Tartışma: Difüz büyük B hücreli lenfoma hasta sayısının MALT lenfomanın dört katından fazla olması beklenmeyen bir farktır. Özellikle nadir görülen yüksek dereceli lenfomalar ve myeloid neoplazilerin, az diferansiye karsinomlarla karıştırılabilme olasılığı önemli bir handikaptır. Duodenal lenfoid foliküller dikkatlice değerlendirilmeli ve immünhistokimyasal değerlendirme yapılmalıdır.

Anahtar kelimeler: Gastrointestinal Neoplaziler, Lenfoma, Hematolojik Neoplaziler.

Introduction

Primary or secondary hematolymphoid neoplasms of the gastrointestinal system (GIS) have a wide spectrum of diagnosis and prognosis. Especially primary lymphoproliferative neoplasms have been better identified, subcategorized and some of them renamed in recent years [1, 2]. On the other hand, rarely, any systemic lymphoma or hematolymphoid neoplasia can also infiltrate GIS secondary.

The gastrointestinal system is the most common site of extranodal lymphomas. With geographic variations, primary gastrointestinal (GI) lymphomas account for approximately 4-20% of all non-Hodgkin lymphomas and 20-45% of extranodal NHLs [3-5]. Depending on the tumor location, they show non-specific GI symptoms such as nausea, vomiting, abdominal pain, or clinical presentations such as bleeding, ileus, perforation. Some subtypes are asymptomatic and can be diagnosed incidentally [2, 6].

It is reported that 44-81% of gastrointestinal lymphoproliferative neoplasms are observed in the stomach. The stomach is followed by the small intestine (often the ileum) and the ileocecal region. Similar to systemic lymphomas, the majority of GIS lymphomas have a B-cell immunophenotype. MALT lymphoma/ Extranodal marginal zone lymphoma and diffuse large B-cell lymphoma (DLBCL) are the most common diagnoses (50% and 30-40% of all gastric lymphomas, respectively). Helicobacter pylori (HP), known to be important in MALT lymphomagenesis, is thought to have a role in the pathogenesis of DLBCL as well. Enteropathy-associated T-cell lymphoma, defined as a complication of celiac disease, also supports the importance of inflammatory processes in the pathogenesis of GIS lymphoma [1-9].

There have been revisions in the current WHO Classification of Tumors of Hematopoietic and Lymphoid Tissue, and primary GIS lymphoid neoplasms. Duodenal-type follicular lymphoma, which is defined as a variant of systemic follicular lymphoma with differences in clinical and pathological features, is a new entity that has taken its place among B-cell lymphomas. Large B cell lymphoma with IRF4 rearrangement is reported as a provisional diagnosis. Indolent lymphoproliferative disorders (indolent T cell lymphoproliferative disorders of the gastrointestinal tract, NK-cell enteropaty) have been added to the new classification of T and NK cell lymphomas, which are known for their aggressive course. Entities such as extramedullary plasmacytoma, plasmablastic lymphoma, classical Hodgkin lymphoma, posttransplant lymphoproliferative disorders, which are mostly reported as case reports, are also rare lymphoid neoplasms of the GIS. Histiocytic, myeloid and dendritic cell neoplasms can be listed as rare hematopoietic tumors of the gastrointestinal tract [1-3].

This study has been aimed to present the single center experience about demographic, clinical and pathological characteristics of gastrointestinal hematolymphoid neoplasias with a wide diagnostic spectrum and to emphasize the points that should be considered in the histopathological evaluation of hematolymphoid neoplasia of the GIS.

Materials and Methods

A total of 46 patients with hematolymphoid neoplasia infiltrating the gastrointestinal tract between January 2014 and June 2021 were obtained retrospectively from archives of pathology department. In all cases, the histopathological diagnoses were made by a single pathologist via endoscopic biopsy, core biopsy, or surgical resection materials. Consultation cases were not included in the study group. Hematoxylin-eosin stained sections for all specimens were prepared in our department from routinely processed formalin-fixed paraffin blocks in a standard procedure, and additional immunohisto-chemical methods (and in situ hybridization-EBER for some cases) were also applied. All diagnoses were reviewed according to the current WHO classification. The number of patients in the diagnostic groups was determined. Cases presenting with GIS symptoms or predominant tumor mass in GIS were grouped primary [10]. Tumors that were first diagnosed from non-GIS locations but later recurred with GI involvement were considered secondary. None of the patients had a history of transplantation, HIV-seropositivity or immunosuppression.

Demographic and clinical data, biopsy indications, biopsy methods, endoscopic findings of all patients were obtained from medical records. In addition, tumors were recorded according to the macroscopic features observed in the resection materials or endoscopy / imaging findings (erythema, ulceration, polyp, increased wall thickness, ulcerovegetative mass, polypoid mass, bulky mass).

Histochemically Giemsa stain was applied to gastric biopsies as a standard procedure, and the presence of HP was evaluated histologically in all cases. The pathology reports of the pre-treatment bone marrow biopsies evaluated in our department were also accessed. Slides of diffuse large B-cell lymphoma cases were re-evaluated to investigate the presence of accompanying MALT lymphoma component. Similarly, MALT lymphoma cases were also reviewed in terms of high grade transformation.

Statistical analyses were performed using the SPSS for Windows (28.0 version, Armonk, NY: IBM Corp). The patient and tumor characteristics were defined as numbers and percentages. Categorical variables were tested with chi-square. The p-value <0.05 was considered as statistically significant difference.

Compliance with Ethical Standards:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the non-interventional research ethics committee of Bezmialem Foundation University with the document number 23352 dated 09/07/2021.

Results

The distribution of histopathological subtypes was shown in the graph (Figure 1). The average age of the patients was 56 (10-88). The female/male ratio was 1/1.3. However, the number of female and male patients was equal for each one of the most common diagnoses including the DLBCL, MALT lymphoma and Duodenal type follicular lymphoma groups. About three-quarters of the

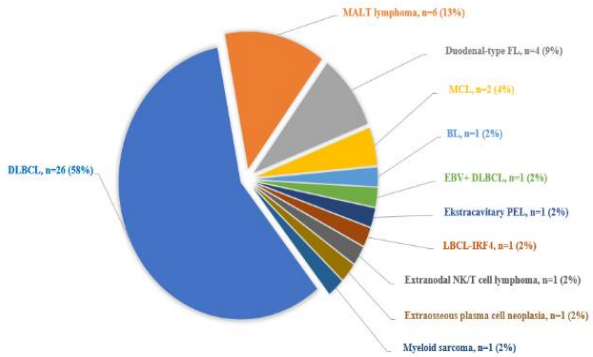

Figure 1: Histopathological subtypes.
DLBCL: Diffuse large B-cell lymphoma, FL: Follicular lymphoma, MCL: Mantle cell lymphoma, BL: Burkitt lymphoma, EBV+ DLBCL: EBV positive large B cell lymphoma, PEL: Primary effusion lymphoma, LBCL-IRF4: IRF4-associated large B-cell lymphoma.

Table1: Patient characteristics

	n	%
Age		
-<60	24	52.2
- ≥60	22	47.8
Gender		
-Female	20	43.5
-Male	26	56.5
Symptom of presentation		
-Gastrointestinal symptoms	34	73.9
-Urgent surgery indication	9	19.6
-Nonspecific	3	6.5
Biopsy method		
-Endoscopic biopsy	34	73.9
-Resection	11	23.9
-Percutaneous core needle biopsy	1	2.2
Macroscopic features		
-Ulcerovegetative mass	19	41.3
-Polypoid mass	11	23.9
-Ulceration	8	17.4
-Other*	8	17.4
Origin		
-Primary	36	78.2
-Secondary	9	19.6
-Undetermined	1	2.2

* Polyp, increased wall thickness, erythema, bulky mass etc.

biopsy specimens were endoscopic biopsy. The main complaints of the patients were GIS symptoms such as nausea, vomiting, dyspepsia, abdominal pain and etc. The patient and tumor characteristics were summarized in Table 1. Approximately half of the lymphoid neoplasms were detected in the stomach (52.2%). Tumors were grouped in terms of anatomical regions in Table 2.

With the assistance of imaging data, thirty-six (78.3%) of the cases were classified as primary GIS lymphoma. Nine cases (19.6%) were considered secondary involvement of the GIS. The most common location of secondary infiltration was the stomach (7/9) (Table 2). Five of the cases had a known history of systemic lymphoma (three DLBCL, one Extranodal NK/T-cell lymphoma, one nodal marginal zone lymphoma). In two DLBCL and two mantle cell lymphoma cases with diffuse lymph node involvement as well as gastric infiltration on imaging, there was not any known history of lymphoma. In the patient diagnosed with myeloid sarcoma presenting with a polypoid mass located in the ileum, primary or secondary differentiation could not be made with the available data.

In diffuse large B-cell lymphoma (26/46), which was the most common diagnostic group, the mean age was 60.69 (39-78). Most of them presented with an ulcerovegetative mass (17/26). Of the cases, 16 (61.5%) were located in the stomach, 5 (19.2%) in the small intestine, four (15.4%) in the colon, and one (3.8%) in the pancreatic head. One case of primary terminal ileum origin had a clinical history of Crohn disease. However, detailed information about the follow-up period and treatment status of Crohn's disease could not be obtained. Sixteen had GCB and nine had ABC immunophenotypes. One DLBCL case could not be classified according to the classical Hans algorithm [11]. A total of five DLBCL cases, three of which had activated B cell immunophenotype, were accepted as secondary infiltration of the gastrointestinal tract. Of the primary GIS DLBCLs, 66.7% were in the GCB phenotype and 28.6% were in the ABC phenotype (p=0.75). In two DLBCL cases, one primary and one secondary,

Table 2: Histopathological tumor subtypes according to anatomical regions

	Anatomic Sites												Total (%)
Histopathology	**Gastric – n:24**					**Small intestine – n:14**			**Large intestine – n:6**			**Pancreas n:1**	
Primary	*Cardia*	*Fundus*	*Corpus*	*Antrum*	*UD*	*Duodenum*	*Jejunum*	*İleum*	*Cecum*	*Colon*	*Rectum*		
DLBCL	3	-	7	3	-	2	1	2	1	2	-	-	21 (45.65)
MALT lymphoma	-	-	1	2	1	1	-	-	-	-	1	-	6 (13.04)
Duodenal-type FL	-	-	-	-	-	4	-	-	-	-	-	-	4 (8.69)
BL	-	-	-	-	-	-	-	1	-	-	-	-	1 (2.17)
EBV+ DLBCL	-	-	-	-	-	-	-	1	-	-	-	-	1 (2.17)
Extracavitary PEL	-	-	-	-	-	1	-	-	-	-	-	-	1 (2.17)
LBCL-IRF4	-	-	-	-	-	-	-	-	1	-	-	-	1 (2.17)
EPCN	-	-	-	-	-	-	-	1	-	-	-	-	1 (2.17)
Seconder													
DLBCL	-	1	2	-	-	-	-	-	-	-	1	1	5 (10.87)
MCL	-	-	1	1	-	-	-	-	-	-	-	-	2 (4.35)
Nodal MZL	-	-	-	1	-	-	-	-	-	-	-	-	1 (2.17)
Ekstranodal NK/T	-	-	1	-	-	-	-	-	-	-	-	-	1 (2.17)
Undetermined													
Myeloid sarcoma	-	-	-	-	-	-	-	1	-	-	-	-	1 (2.17)
Total	3	1	12	7	1	8	1	6	2	2	2	1	46 (100)

DLBCL: Diffuse large B-cell lymphoma, FL: Follicular lymphoma, BL: Burkitt lymphoma, EBV+ DLBCL: EBV positive large B cell lymphoma, PEL: Primary effusion lymphoma, LBCL-IRF4: IRF4-associated large B-cell lymphoma, EPCN: Extraosseous plasma cell neoplasia, MCL: Mantle cell lymphoma, MZL: Marginal zone lymphoma, UD: Undetermined.

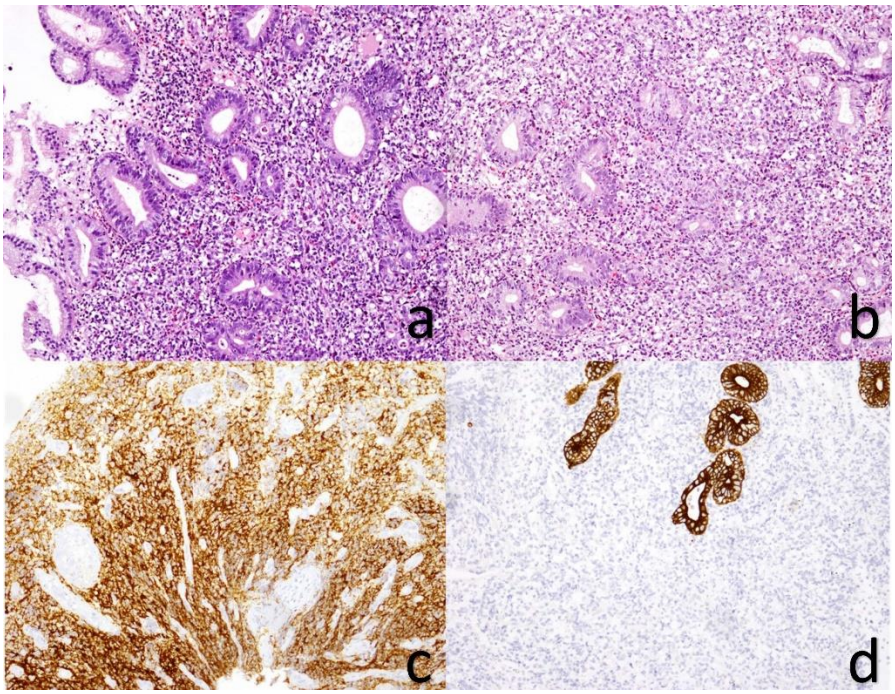

Figure 2: a-b) A case of gastric localized diffuse large B-cell lymphoma. Atypical lymphocytes with moderate amounts of clear cytoplasm resembling signet ring cells with infiltrating between glands, HEx100. c) Diffuse positive reaction with CD20, x100. d) Pancytokeratin positivity in residual glands, x100.

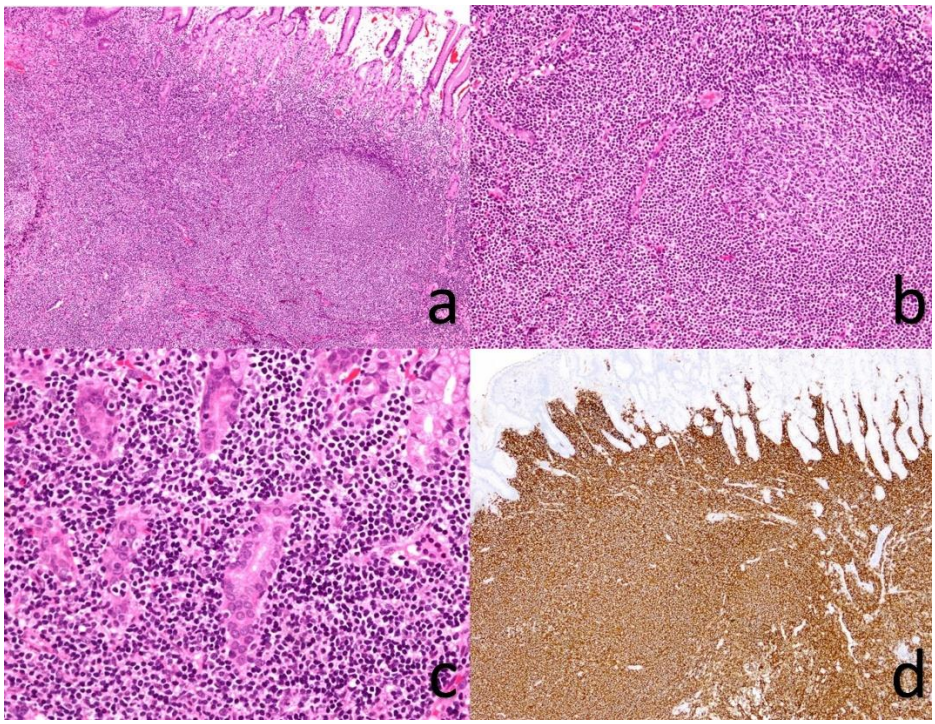

Figure 3: a) A case of MALT lymphoma with polypoid swelling of the mucosa, HEx40. b) Atypical lymphoid proliferation with small size, coarse chromatin, clear cytoplasm infiltrating residual germinal centers, HEx100. c) Lymphoepithelial lesion formation, HEx200. d) Immunohistochemical diffuse CD20 positivity, x20.

immunohistochemically strong and diffuse (>40%) c-myc expression and BCL2-BCL6 co-expression were detected. Concomitant low grade lymphoma (MALT lymphoma) was not found in any of the cases. The mean Ki67 proliferative index was 80.24% (45-98%) in our DLBCL cases known for their aggressive course. Helicobacter pylori was found in only one of thirteen patients with primary gastric DLBCL (Figure 2).

The mean age was younger (48.16, 28-73) in MALT lymphoma cases (6/46), the second most common diagnosis of the study group. All of the cases were diagnosed by endoscopic biopsy. GIS symptoms were described in five cases. The complaint of the patient who presented with a polypoid mass located in the rectum was bloody diarrhea. The other four cases were located in the stomach (two antrum, one corpus, one unknown), and one case was located in the duodenum. Accompanying helicobacter pylori enfection was detected in three gastric and one duodenal neoplasia. Vaguely nodular or diffuse patterned atypical lymphoid proliferation was predominantly consisted of cells with small round nuclei and clear cytoplasm. In all of the biopsies, the presence of lymphoepithelial lesion could be demonstrated, at least by immunohistochemical pancytokeratin. In some of the cases, the dendritic cell network was irregularly expanded. Centroblast or immunoblast-like large cell aggregation, which could be evaluated in favor of transformation into high-grade lymphoma, was not observed. All neoplasms had kappa/lambda monotypic plasmacytoid differentiation supporting the diagnosis. The mean Ki67 proliferation index was 16.60% (5-30%) (Figure 3).

The mean age of the patients with duodenal-type follicular lymphoma was 57.5 (40-69). In the endoscopy of the cases presenting with non-specific GI symptoms, polyp was described in three and erythema in one. Bacilli were observed in favor of Helicobacter pylori in one of the biopsies. The extent of the atypical lymphoid infiltration with nodular features in the mucosa and submucosa was more clearly demonstrated by immunohisto-chemical CD20 staining. Similar to systemic follicular lymphoma, strong positive reaction with CD10, BCL6 and BCL2 was detected in all cases. The CD21 and CD23 positive follicular dendritic network, which appeared to be trapped in the periphery of the atypical follicles, was a key finding observed in all cases. Ki67 proliferation index was 21.25% (15-30%) on average.

Patients who had rare diagnoses presented with acute abdomen symptoms. A ten-year-old male patient who presented with ileus due to intussusception was diagnosed with Burkitt lymphoma. Another case in the pediatric age group underwent ileocecal resection for a mass in the cecum and was diagnosed with IRF4-associated large B-cell lymphoma. The ulcerovegetant mass observed in the ileal resection material of the case who applied to the hospital with perforation was reported as EBV-positive large B cell lymphoma. The surprise diagnosis in the duodenal endoscopic biopsy of the patient who was examined clinically for icterus was extracavitary/solid variant primary effusion lymphoma. One of our rare diagnoses was lambda monotypic positive plasma cell neoplasia presenting with an ulcerovegetative mass in the ileum. Although it was easy to recognize the plasma cells histomorphologically in some of the biopsy sections, the morphology was quite anaplastic in some sections. Concomitant lymphoid cell component was not detected. As a result, infiltration was interpreted in favor of extraosseous plasmacytoma, accompanied by clinical data. Plasma cell myeloma infiltration was not detected in the patient's bone marrow biopsy. Another focus of involvement was not detected on imaging. One patient who underwent resection with ileus had myeloid sarcoma. Gross examination revealed three separate masses located in the ileum. The patient did not have any known history of myeloid neoplasia prior to this diagnosis. There was not any registered bone marrow biopsy in our department for this patient.

Bone marrow biopsies of thirty-three cases which were performed for staging were reviewed. Bone marrow infiltration was detected in only one of the cases grouped as primary gastrointestinal lymphoma. This case with ileus symptoms and an ulcerovegetating mass in the terminal ileum was diagnosed with diffuse large B-cell lymphoma. Gastro-intestinal infiltration was secondary in the other four cases with bone marrow involvement.

Discussion

In recent years, hematolymphoid neoplasms of the gastrointestinal tract have been one of the topics on which revisions have been reported and new entities have been defined. Although the boundaries of definitions about neoplasia have been detailed, lymphoid proliferations with aggressive morphology but indolent course, which are considered as disorders in the new classification, make the pathological diagnosis more stressful. For this tumor group, which may require multiple immunohistochemical examinations, sometimes adequate tissue cannot be obtained with commonly used endoscopic/ colon-oscopic biopsy methods. Ulceration and crush artifact are other problems which are frequently encountered in these biopsies and complicate morphological evaluation. On the other hand, differential diagnosis especially with poorly differentiated malignancies, is another histopathological challenge in GIS where the expectation of epithelial neoplasia

Table 3: Similar retrospective studies in our country [11-15].

Author / Year	Patients	Age *Min-Max (Median)*	Gender *F/M*	Anatomic sites of origin (%) *Stomach/Small intestine/Large intestine/Other*	Diagnostic procedure *Laparotomy/ Endoscopy/ Other*	Diagnoses (%) *DLBCL/ MALT/FL/ MCL/TCL*
Dincol et al. 1992	33	26-75 (ND)	18/15	39.3 / 48.4 / 12.1	21 / 12 / -	ND
Atalay et al. 2003	56	14-81 54.5	26/30	78.5 / 18 / 3.5	12 / 44 / -	ND
Alacacıoglu et al. 2007	24	34-80 64	12/12	83.3 / 8.3 / 8.4	ND	75/25/-/-/-
Erkurt et al. 2009	41	18-90 58	22/18	61 / 26.8 / 7.3	ND	58.5/26.9/2.4/2.4/9.8
Yildirim et al. 2019	22	25-77 47	8/14	31.8 / 50 / 18.2	ND	86.4/-/4.5/4.5/-
Current study	46	10-88 56	20/26	52.2/32.6/13.1	11/34/1	56.5/13/8.7/4.3/2.2

F: Female, M: Male, DLBCL: Diffuse large B-cell lymphoma, FL: Follicular lymphoma, MCL: Mantle cell lymphoma, TCL: T-cell lymphomas, ND: Not descripted.

is higher. Based on these considerations, we tried to collect the histopathological and clinical features of gastrointestinal lymphoma cases in our center. There are very few similar retrospective studies published in our country. Some of our data were compared with these studies in Table 3 [11-15]. To summarize the basic results of this study; i) Almost half of the patients were diagnosed with DLBCL. ii) MALT lymphoma, the first lymphoid neoplasia that comes to mind in the gastrointestinal tract, was only 13% of the cases. iii) Although classical FL immuno-profile was observed in duodenal follicular lymphoma cases with low grade histo-morphology, the dendritic meshwork organization which was pushed to the follicle periphery was distinctive from systemic forms, iiii) In pancytokeratin-negative undifferentiated neoplasms, if positivity can not be detected with common B or T cell immunomarkers, the differential diagnosis spectrum should be expanded and additional markers (plasmacytic, myeloid/ histiocytic/ dendritic, viral, etc.) should be added to the immune panel.

The stomach is prominent primary site of GI lymphomas. Although different rates are given for the incidence of intestinal lymphoma, it is reported to be high in Middle Eastern countries (49-81%) [5, 9]. Tumor location is important in terms of histo-pathological subgroup and therefore prognostic differences. The stomach is the region where mostly indolent lymphoma group is observed, especially MALT lymphoma. In the intestine, mainly high grade lymphomas are detected [5, 9]. However, the GI tract region where DLBCL is observed with the most frequency is the stomach and followed by the ileocecum, in current reviews [2]. Approximately half of our cases showed infiltration in the stomach, and the small intestine was the second most common location of tumors. DLBCL constituted more than half of all our cases and of tumors located in the stomach. Do to the fact that we have not made a clinical-prognostic comparison in our study, indolent or aggressive histological subtype differences depending on tumor location have not been observed.

Gastric DLBCL can transform from MALT lymphoma. It has been reported that a low-grade component accompanying high-grade

lymphoid neoplasia is detected in approximately one-third of the biopsies [9]. We did not have a case in which low-grade and high-grade neoplastic proliferation were detected together, which could be an example of this information.

In various published case series, B-cell non-Hodgkin lymphomas constitute the majority of GIS lymphoproliferative neoplasms, similar to systemic forms [9]. In the study of Nakamura et al. (5), T-cell lymphomas were reported at higher rates in both the gastric and intestinal groups compared to the other series, and this was attributed to the geographical incidence difference. Any subgroup of T-cell lymphoma/disorder of primary GI origin was not detected in our archive. Our patient with extranodal NK/T-cell lymphoma infiltrating secondary to the gastric corpus was the only case with T-cell immunophenotype. The patient, who had primary uveitis symptoms before endoscopy, lost vision three months after the biopsy.

Because of its prognostic importance, GI DLBCL should be classified in terms of GCB or ABC phenotypes, similar to systemic forms [2]. In the study of Lin et al (11), they found no significant difference with regard to numbers or survival between GCB and ABC subtypes in ninety cases grouped according to three algorithms. Similarly, Hwang et al. (12) did not observe prognostic difference between the two groups. Although the GCB immunophenotype was dominant in our DLBCL cases, no statistically significant difference was found. Assessment of prognosis was not performed within the scope of our study. For the differential diagnosis of high-grade B-cell lymphoma c-myc, BCL2 and BCL6 should be added to the immunopanel in gastrointestinal DLBCL cases. Double/triple expressor cases should be referred to FISH for evaluation of MYC, BCL2 and/or BCL6 gene rearrangements. These cases are characterized by a more aggressive course [2]. Contrary to this information, in the study of Choi et al. (11), it was reported that c-myc gene rearrangement is more common in GI DLBCL cases compared to nodal forms, but did not have a negative effect on overall survival. Two of our cases showing coexpression of c-myc, BCL2 and BCL6 relapsed with diffuse disease. However, gene rearrangement with FISH has not been confirmed. One patient with triple expressor DLBCL with primary terminal ileum localization, who also has Crohn's disease, may serve as an example for questioning the role of chronic inflammation in lymphomagenesis. In large population-based cohort studies investigating the risk of lymphoma in inflammatory bowel diseases, no statistically significant increase was found in ulcerative colitis patients. On the other hand, an increase in the risk of lymphoma development has been reported in Crohn patients by being associated with various variables such as disease duration, hospitalization, treatment protocols and etc. [16-18]. Refractory celiac disease can be considered the prototype entity for the relationship between non-infectious inflammatory processes and lymphoma [6]. In fact, the first infectious inflammatory factor which comes to mind as a risk factor, H. Pylori, was detected in only one primary DLBCL case. In MALT lymphomas, H. pylori was seen in two-thirds of the cases. However, the number of cases was insufficient for statistical comparison.

Our cases of duodenal-type follicular lymphoma with histologically low grade morphology and nodular pattern have been diagnosed in the last two years. Similar to those reported in the review of Auerbach et al. (2), atypical follicles without tingible body macrophages, whose mantle region could not be distinguished, consisted of cells with centrocyte morphology. Diagnosis is not difficult with the described histopathological features and immunohistochemical profile (CD10+, BCL6+, BCL2+). The dendritic meshwork of atypical follicles pushed and

trapped at the periphery is another sensitive feature of duodenal-type FL that should be emphasized. However, we think that awareness of this entity is important in differential diagnosis, since reactive lymphoid follicle development can be observed frequently in GIS.

GI lymphomas, especially DLBCL, are neoplasms that are usually diagnosed at an early stage without bone marrow infiltration [6, 19]. Similar to the literature, bone marrow invasion was detected in only one of primary GIS tumors. This was the triple expressor patient with the history of Crohn disease.

Another striking point was the variety of diagnosis in our case group, which also included secondary hematolymphoid neoplasms. Endoscopic biopsy specimens constitute the majority of the materials in most pathology laboratories currently. In these small biopsies, which sometimes show artificial features, aggressive lymphomas and poorly differentiated carcinomas such as signet ring cell carcinomas that do not form a definitive pattern can be confused (Figure 2). Similar to this situation, diagnostic difficulties can be experienced in hematolymphoid neoplasms with partial epithelial morphology. In particular, the diagnosis is even more challenging for hematolymphoid tumors that do not express common B or T cell antigens. It was not easy to finally reach the diagnosis due to the anaplastic component of our extracavitary/solid variant primary effusion lymphoma and extraosseous plasmacytoma cases.

Myeloid sarcoma, of which histopathological diagnosis is always challenging, presents as tumoral masses formed by immature myeloid cells in extramedullary regions. Skin, soft tissue, lymph nodes are the most common locations of these rare tumors. It has been reported that 6.5-10% of cases originate from the GIS, which is even rarer [20, 21]. Tumor can develop de novo, can be a presentation form of acute myeloid leukemia recurrence or can accompany other myeloid neoplasms. In the histopathological diagnosis process, it is important to first consider the entity. Inadequate immunophenotyping, especially in small biopsies, can lead to misdiagnosis (up to 25-47%) [22]. Non-Hodgkin lymphomas, poorly differentiated carcinomas or melanoma can be considered in the differential diagnosis [23]. We would like to remind another rare diagnosis that can be encountered in the evaluation of GIS biopsies through our case of myeloid sarcoma located in the ileum.

In this study, which consists of retrospectively collected cases, the diagnostic variety of gastrointestinal hematolymphoid neoplasms can be observed. However, it was an important limitation that the number of cases was not sufficient for statistical analysis. The lack of treatment/follow-up results and prognostic evaluation can be considered as another limitation.

Conclusion

In this study, we tried to review GI hematolymphoid neoplasma with demographic, clinical, macroscopic and histopathological characteristics in a single center. The most common location of tumors was the stomach and the most common macroscopic feature was an ulcerovegetative mass. The patients frequently described non-specific GI symptoms. Although DLBCL and MALT lymphoma are the two most common subtypes, a wide variety of subtypes should be kept in mind in the differential diagnosis, especially when the rarer secondary lymphoproliferative neoplasms are also considered. While it is difficult to distinguish low-grade lymphoproliferative neoplasms from inflammatory entities and/or benign conditions, high-grade neoplasms can be confused with epithelial tumors. For this reason, in addition to detailed histopathological examination, immunohistochemical evaluation is critical in the

diagnostic approach of hematolymphoid neoplasms. Although the limited number of cases in our single-center study did not allow statistical assessment, we thought that our heterogeneous diagnostic spectrum would contribute to the literature and be useful in the evaluation of this group of neoplasms.

.

REFERENCES

[1] R.S. Gonzalez, A. Raza, R. Propst, O. Adeyi, J. Bateman, S.C. Sopha, J. Shaw, A. Auerbach, Recent Advances in Digestive Tract Tumors: Updates From the 5th Edition of the World Health Organization "Blue Book", Archives of Pathology & Laboratory Medicine (2020).

[2] A. Auerbach, N.S. Aguilera, OVERVIEW OF GI LYMPHOPROLIFERATIVE DISORDERS, Seminars in Diagnostic Pathology, Elsevier, 2021.

[3] M.A. Bautista-Quach, C.D. Ake, M. Chen, J. Wang, Gastrointestinal lymphomas: Morphology, immunophenotype and molecular features, Journal of gastrointestinal oncology 2012; 3(3): 209.

[4] J. Krugmann, S. Dirnhofer, A. Gschwendtner, U. Berresheim, R. Greil, K. Krugmann, F. Fend, Primary gastrointestinal B-cell lymphoma-A clinicopathological and immunohistochemical study of 61 cases with an evaluation of prognostic parameters, Pathology-Research and Practice 2001: 197(6); 385-393.

[5] S. Nakamura, T. Matsumoto, M. Iida, T. Yao, M. Tsuneyoshi, Primary gastrointestinal lymphoma in Japan: a clinicopathologic analysis of 455 patients with special reference to its time trends, Cancer: Interdisciplinary International Journal of the American Cancer Society 2003; 97(10): 2462-2473.

[6] M. Olszewska-Szopa, T. Wróbel, Gastrointestinal non-Hodgkin lymphomas, Adv Clin Exp Med 2019; 28(8): 1119-24.

[7] P. Ghimire, G.-Y. Wu, L. Zhu, Primary gastrointestinal lymphoma, World journal of gastroenterology: WJG 2011; 17(6): 697.

[8] G. Martinelli, F. Gigli, L. Calabrese, P.F. Ferrucci, E. Zucca, C. Crosta, G. Pruneri, L. Preda, G. Piperno, M. Gospodarowicz, Early stage gastric diffuse large B-cell lymphomas: results of a randomised trial comparing chemotherapy alone versus chemotherapy+ involved field radiotherapy, Leukemia & lymphoma 2009; 50(6): 925-931.

[9] P. Koch, F. del Valle, W.E. Berdel, N.A. Willich, B. Reers, W. Hiddemann, B. Grothaus-Pinke, G. Reinartz, J. Brockmann, A. Temmesfeld, Primary gastrointestinal non-Hodgkin's lymphoma: I. Anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German Multicenter Study GIT NHL 01/92, Journal of clinical oncology 2001; 19(18): 3861-3873.

[10] K.J. Lewin, M. Ranchod, R.F. Dorfman, Lymphomas of the gastrointestinal tract. A study of 117 cases presenting with gastrointestinal disease, Cancer 1978; 42(2): 693-707.

[11] D. Dinçol, F. Içli, S. Erekul, N. Günel, H. Karaoğuz, A. Demirkazik, Primary gastrointestinal lymphomas in Turkey: a retrospective analysis of clinical features and results of treatment, Journal of surgical oncology 1992; 51(4): 270-273.

[12] C. Atalay, M. Kanlıöz, S. Demir, I. Pak, M. Altinok, Primary gastrointestinal tract lymphomas, Acta Chirurgica Belgica 2003; 103(6): 616-620.

[13] İ. Alacacioğlu, M.A. Özcan, M. Meral, Ö. Pişkin, F. Demirkan, G.H. Özsan, S. Özkal, B. Ündar, Primer Gastrointestinal Lenfoma Hastalarının Klinik Özellikleri ve Tedavi Sonuçlar›: Tek Merkez Deneyimi. UHOD 2007; 17(3): 143-150.

[14] M.A. Erkurt, I. Aydogdu, I. Kuku, E. Kaya, Y. Basaran, Clinicopathologic characteristics and therapeutic outcomes of primary gastrointestinal non-Hodgkin's lymphomas: 10 years of experience from a single center in eastern Anatolia, Medical Principles and Practice 2009; 18(5): 399-406.

[15] N. Yildirim, M. Turkeli, M.N. Akdemir, M. Simsek, S.B. Tekin, Evaluation of 22 primary gastrointestinal lymphoma patients, The Eurasian journal of medicine 2019; 51(1): 53.

[16] J. Askling, L. Brandt, A. Lapidus, P. Karlen, M. Björkholm, R. Löfberg, A. Ekbom, Risk of haematopoietic cancer in patients with inflammatory bowel disease, Gut 2005; 54(5): 617-622.

[17] C.N. Bernstein, J.F. Blanchard, E. Kliewer, A. Wajda, Cancer risk in patients with inflammatory bowel disease: a population-based study, Cancer 2001; 91(4): 854-862.

[18] J.D. Lewis, W.B. Bilker, C. Brensinger, J.J. Deren, D.J. Vaughn, B.L. Strom, Inflammatory bowel disease is not associated with an increased risk of lymphoma, Gastroenterology 2001; 121(5): 1080-1087.
[19] S.-Y. Choi, S.J. Kim, W.S. Kim, K. Kim, Y.-H. Ko, Aggressive B cell lymphomas of the gastrointestinal tract: clinicopathologic and genetic analysis, Virchows Archiv 2011; 459(5): 495-502.
[20] S. Pileri, S. Ascani, M. Cox, C. Campidelli, F. Bacci, M. Piccioli, P. Piccaluga, C. Agostinelli, S. Asioli, D. Novero, Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients, Leukemia 2007; 21(2): 340-350.
[21] M. Movassaghian, A.M. Brunner, T.M. Blonquist, H. Sadrzadeh, A. Bhatia, A.M. Perry, E.C. Attar, P.C. Amrein, K.K. Ballen, D.S. Neuberg, Presentation and outcomes among patients with isolated myeloid sarcoma: a Surveillance, Epidemiology, and End Results database analysis, Leukemia & lymphoma 2015; 56(6): 1698-1703.
[22] P. Phatharacharukul, N. Fayad, R. Siwiec, Colonic Myeloid Sarcoma as a Rare Presentation of Relapsed Acute Myeloid Leukemia, ACG Case Reports Journal 2020; 7(6): e00407.
[23] G. Kaygusuz, D. Kankaya, C. Ekinci, P. Topçuoğlu, I. Kuzu, Myeloid sarcomas: a clinicopathologic study of 20 cases, Turkish Journal of Hematology 2015; 32(1): 35

Corresponding author e-mail: berilgus@yahoo.com

Orcid ID:
Beril Güler 0000-0002-4948-0557

Doi: 10.5505/aot.2023.68916

