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Research Article

GASTROINTESTINAL MANIFESTATIONS OF MATURE B CELL NEOPLASMS: SINGLE CENTER EXPERIENCES FROM THE COLLECTIVE PERSPECTIVE OF HEMATOLOGY AND PATHOLOGY

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ABSTRACT

Objective: Hematological malignancies frequently affect the gastrointestinal (GI) tract, either by secondary extranodal or extramedullary extension to the GI tract or as the primary process, developing in the GI tract. Compared to other solid organ tumors of the GI tract, gastrointestinal non-Hodgkin's lymphomas (gNHL) are less common. Therefore, in the absence of nodal or extranodal involvement in imaging methods, difficulties may be encountered in diagnosis.

Materials and Methods: We retrospectively screened all B-cell lymphoma patients. Then, patients, who had been diagnosed without gastrointestinal system biopsy, were excluded from the study. Demographic data for these patients was obtained from the hospital information system and outpatient clinic files. Slides of these patients were obtained from pathology archive and re-evaluated under light microscope by two pathologists.

Results: Fifty-five patients were diagnosed with B-cell lymphoma via endoscopic or colonoscopic biopsies. Forty of these patients were diagnosed with Diffuse Large B-Cell Lymphoma (DLBCL), ten with Marginal Zone Lymphoma (MZL), two with Mantle Cell Lymphoma (MCL), two with Burkitt Lymphoma (BL) and one patient with Lymphoplasmacytic Lymphoma (LPL).

Conclusion: In line with the literature, in our study, the patients with GI tract diagnosis had the highest frequency of DLBCL. The second most common B-cell lymphoma was MALToma. Although the frequency of GI involvement is high in MCL, the number of patients, diagnosed with GI involvement was small. The reason for this was that the patients had been diagnosed on the basis of nodal involvement rather than GI biopsy.

Keywords: non-Hodgkin's lymphomas; B-cell neoplasm; Gastrointestinal lymphomas; Pathology

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INTRODUCTION

Hematological malignancies consist of a wide range of disorders and comprise lymphoproliferative and myeloproliferative malignancies. In lymphoproliferative diseases, gastrointestinal (GI) system involvement is more common. Lesions in the GI system may be of direct GI origin or may be accompanied by extramedullary or extranodal involvement. In addition, it is observed as extranodal involvement, which is frequently seen in patients with Non-Hodgkin's Lymphoma (NHL) and is difficult to manage. Although primary GI NHL are rare, compared to other GI malignancies (1-4%), it accounts for about 10-15% of all NHL and 30-40% of extranodal involvement (1,2). However, GI involvement is detected in around 50% of autopsy cases (3).

Gastrointestinal non-Hodgkin's lymphomas (gNHL) are less prevalent compared to other solid organ tumours of the GI tract. Therefore, in the absence of nodal or extranodal involvement in imaging methods, there may be difficulties in diagnosis. In terms of diagnosis, hematologists receive a more important support from pathologists compared to from imaging methods. Therefore, providing detailed information to the pathologists about the patient's clinical findings and imaging results is of great importance for diagnosis. The clinician must properly establish this information network.

For pathologists, it is important to evaluate GI biopsies in combination with clinical, endoscopic and radiological findings (Computed tomography (CT), Endoscopy-Colonoscopy, Endoscopic Ultrasonography (EUS), etc.). If B symptoms (fever, night sweats and weight loss) are present, possibility of lymphoma must be considered. However, typical site-related gastrointestinal symptoms, such as dyspepsia, abdominal pain, nausea and vomiting, may be the only manifestation. In some patients, GI lymphoma may be incidentally present. Symptomatic patients may not have typical corresponding endoscopic features (4). Although exophytic, ulcerative or hypertrophic lesions are common, the only endoscopic findings may consist of inflammation-like patterns such as petechia or normal/hyperaemic mucosa (5,6). After gathering the information, distinguishing-especially low grade-lymphomas from inflammatory lesions, is the initial approach of a pathologist to avoid any delays in diagnosis. Dense lymphoid infiltrates with numerous lymphoepithelial lesions, moderate cytological atypia or Dutcher bodies, alongside with features such as muscularis mucosae invasion or ulceration, are considered as alarming for lymphoma diagnosis (7). After the initial diagnosis, subtyping is essential for determination of treatment decision and prognosis (8).

Under the light of our experiences in our clinic, we aimed to examine our B-cell gNHL patients and to share the approaches by hematologists and pathologists to these patients. In addition, we intended to discuss the management process of these patients from diagnosis to treatment under the light of current literature.

MATERIALS AND METHODS

We retrospectively screened all B-cell lymphoma patients, who had been diagnosed in our clinic between 01.01.2015 and 01.01.2021. Subsequently, patients, who had not been diagnosed via gastrointestinal system biopsy, were excluded from the study. Demographic data for these patients was obtained from the hospital information system and outpatient clinic files. Also, we examined the response rates of the patients to treatment and their follow-up progress with respect to the gastrointestinal system.

Slides of these patients were obtained from pathology archive and re-evaluated under light microscope by two pathologists. All cases were diagnosed in line with revised World Health Organization (WHO) 2017 classification. Immunohistochemical results were obtained from the pathology reports and verified through examination of previously stained slides. Cell of origin (COO) was assessed according to the Hans criteria. According to the Hans criteria, cases were considered positive if 30% or more of the tumor cells were stained by the antibody. The Hans algorithm consisted of three markers (CD10 antibody for Germinal Center (GC) origin, BCL6 antibody for GC and non-GC origin, MUM1 antibody for post-GC origin). Based on combination of these three markers, DLBCL could be classified under two subtypes using the Hans algorithm, namely GC and non-GC.

The Helsinki Declaration of Ethical Principles of Medical Research was followed. Patients signed informed consent. Study approved by Trakya University ethics committee (TÜTF-BAEK 2021/234). Statistical analyses were performed using SPSS PC Ver.26 (IBM © SPSS Inc. USA). Descriptive statistics were given as number, percentage, and arithmetic mean ± standard deviation. A two-sided p value, smaller than 0.05, was considered significant. Overall survival (OS) was defined as time from diagnosis of lymphoma until death. To evaluate OS, Kaplan-Meier estimates were calculated. Log-rank test

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and Cox regression analysis were performed to estimate hazard ratios (HR) and 95% Confidence Intervals (CI).

RESULTS

Fifty-five patients were diagnosed with B-cell lymphoma via endoscopic or colonoscopic biopsies . Forty patients had been diagnosed with Diffuse Large B-Cell Lymphoma (DLBCL), ten patients with Marginal Zone Lymphoma (MZL), two patients with Mantle Cell Lymphoma (MCL), two patients with Burkitt Lymphoma (BL) and one patient with Lymphoplasmacytic Lymphoma (LPL) (Figure 1) / (Table 1).

Table 1: Demographic characteristics of GI Non-Hodgkin lymphoma patients

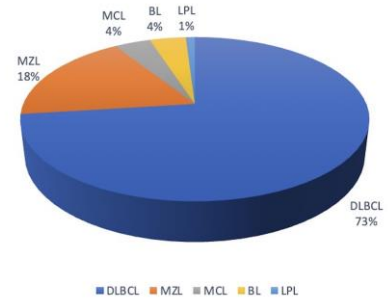
Demographic characteristics of GI Non-Hodgkin lymphoma patients	No. of cases N: 55 (%)
Gender Male/Female	37 / 18 (67/33)
Age	64 years (21-92)
Localization	
Oropharyngeal Area	3 (5,4)
Esophagus	1 (1,8)
Gastric	40 (72,7)
Ileum	3 (5,4)
Colon	8 (14,5)
Histological Type	
DLBCL	40 (72,7)
MZL	10 (18)
MCL	2 (3,6)
BL	2 (3,6)
LPL	1 (1,8)
Isolated GI Involvement	
DLBCL	20/55 (36,3)
MZL	15/40 (37,5)
MCL	5/10 (50)
BL	-
LPL	-
Clinical Symptoms or Signs of Patients Before Diagnosis	
Abdominal Pain	24 (43,6)
Weight loss	19 (34,5)
Vomiting	11 (20)
Dysphagia	2 (3,6)
Perforation	1 (1,8)
Asymptomatic	12 (21,8)

DLBCL: Diffuse large B-cell lymphoma, MCL: Mantle cell lymphoma, MZL: Marginal zone lymphoma, BL: Burkitt lymphoma, LPL: Lymphoplasmacytic lymphoma

Forty out of 55 patients, who had been diagnosed with B Cell NHL with gastrointestinal system involvement, had a diagnosis of Diffuse Large B-Cell Lymphoma. The mean age of DLBCL patients was 65 and 18 patients were female. The majority of DLBCL patients had been diagnosed on the basis stomach biopsy (75%).

Figure 1. Diagnosis and involvement distribution of B Lymphoma

1a



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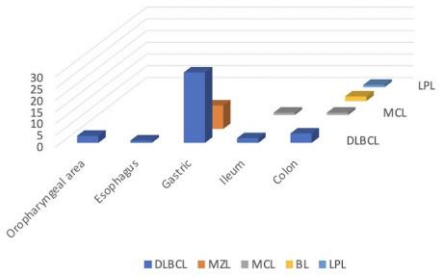

patients. 1a: Distribution of Patients with gastrointestinal (GI) involvement, 1b: Distribution of involvement regions

Four patients had been diagnosed on the basis of colon biopsy, three on the basis of biopsy of the oropharyngeal area, two on the basis of biopsy of the ileum and one on the basis of esophagus biopsy. Nine of the patients were asymptomatic at diagnosis, 19 patients had abdominal pain, 17 patients had weight loss, 11 patients had vomiting and two patients had dysphagia. One patient presented with perforation. Eighteen patients expressed CD10, BCL6 immunoreactivity and were diagnosed as germinal centre origin immunophenotype in line with the Hans algorithm. Eleven patients were double/triple expressor (c-MYC and BCL2 or c-MYC, BCL2 and BCL6 immunoexpression). When evaluated in terms of prognostic factors, we found that 21 patients had B symptom and 31 patients were diagnosed with high Lactate Dehydrogenase (LDH), 20 patients had R-IPI score> 2 and 26 patients had NCCN-IPI> 3. It was observed that 17 patients had died and seven of the deceased patients could not receive or did not want to receive treatment. Furthermore, ten patients had died in the first month. R-CHOP chemotherapy had been given to all treated patients. Mean survival of patients, who had received treatment, was 39.5 months. It was seen that only ten patients had undergone GI endoscopy after treatment.

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Involvement of a different area of the ileum was observed in one patient. GI involvement was not detected in any other patients in the post-treatment setting. Radiological involvement was not detected in other living patients.

Ten patients had been diagnosed with MZL (MALTOMA) and six of these patients were male. Mean age was 67.4 years. Five patients had received treatment for H. Pylori. Also, five patients had received systemic therapy (R-CHOP for four patients, Rituximab for one patient) in line with their stages. Control endoscopy had been performed for all patients during their follow-up. It was observed that 2 patients had relapsed following systemic therapy. Mean follow-up duration of all patients was 47.9 months. No relapsed cases had been found among patients, who had received treatment forH. Pylori. All patients are currently followed-up.

Two patients had been diagnosed with MCL. One patient had been diagnosed on ther basis of colon biopsy while another patient on the basis of biopsy of ileum. Both patients were male. Mean age of the patients was 63.5 years old. One of the patients had undergone autologous stem cell transplant (ASCT) following high dose treatment. Relapse disease had been detected in the patient during the first control after ASCT in the same location. Endoscopic control had not been performed in the other patient, instead, patient had been examined using PET / CT. No relapse had been detected. Both patients are currently alive, and the median survival was 21.5 months.

Two patients had been diagnosed with Burkitt's Lymphoma. All of them had been diagnosed on the basis of the colon biopsy. Mean age was 46 years and both patients were male. High-dose treatment had been administered and one patient had died after the first cycle due to sepsis and the other patient had been referred to ASCT due to complete response in control PET/CT. In one patient, LPL diagnosis had been made on the basis of colonoscopy. The 74-year-old male patient had been followed-up for 24 months..

DISCUSSION

Gastric NHLs, which constitute 1-4% of all GI malignancies, are seen most frequently in the stomach (60–75% of all cases) and less frequentlyin the small intestine and ileocecal area. Histopathological findings in GI tract reveal indolent as well as aggressive lymphomas, which may consist of mature B, T or NK cells. Intestinal B-cell lymphomas are more frequent (6:1) compared to T-cell lymphomas (3,9). DLBCL and MZL are the most frequently encountered subtypes by the clinician.

On observation of GI tract conditions with a top to bottom approach, it is seen that a wide range of symptoms are observed in these patients. In upper GI tract involvement, patients may present with symptoms such as dysphagia and hoarseness. Symptoms such as abdominal pain, weight loss, nausea and vomiting may be observed in gastric involvement, which is seen in 60-75% of patients with gNHL. Patients with small intestine (%20) and colon (%6-12) involvements may present with clinical symptoms secondary to obstruction, weight loss and bleeding (3,9).

CT and MRI are important in demonstrating not only GI involvement but also other accompanying involvement. Endoscopic ultrasonography is more valuable in GI tract, in particularin case of mucosal involvement. It may also be used in the follow-up of patients following treatment. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) is frequently used in diagnosis and follow-up. However, histopathological evaluation is recommended for mucosal evaluation after treatment, in particular in patients diagnosed on the basis of stomach biopsy (9).

Main histopathologic groups of gastrointestinal lymphomas consist of mature B-cell lymphomas, T cell lymphomas and NK/T cell lymphomas. Since the most common group is mature B-cell, MALT lymphoma and DLBCL substitutes most of the cases. Other B-cell lymphomas are follicular lymphoma, BL, MCL and rarely lymphomatoid granulomatosis, LPL, EBV-positive DLBCL, high-grade B-cell lymphoma, small lymphocytic lymphoma, ALK-positive large B-cell lymphoma, plasmablastic lymphoma and extramedullary plasmacytoma (10).

Diffuse Large B-Cell Lymphoma is the most common subtype of gNHL. It accounts for 38-57% of gNHL patients. When all GI lymphoma subtypes are considered, it is seen that 40-78% of cases are DLBCL. DLBCL presents as a mass-forming lesion or, less commonly, as an infiltrative lesion (11). There is a tendency to invade nearby structures, which may cause mucosal ulceration and perforation. GI obstruction is less common. However, in case of muscularis propria invasion in small intestine involvement, aneurysmal dilatation may be seen as a result of the destruction of the intramural autonomic nerve plexus. Accompanying intraabdominal lymph node involvement is frequently seen. In treatment, classical R-CHOP regimen has been being used for a long time (9-12).

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Consistent with the literature, most of our patients had been diagnosed with (73%) and with the diagnosis had been based on gastric biopsy. Most of the patients (77.5%) had had gastrointestinal system-related symptoms at the time of diagnosis, only nine patients had been asymptomatic. In the follow-ups, 42% of the patients had died. since a significant portion of these patients (58.8%) die within the first month after diagnosis, it must be emphasized that rapid and careful management is required after diagnosis.

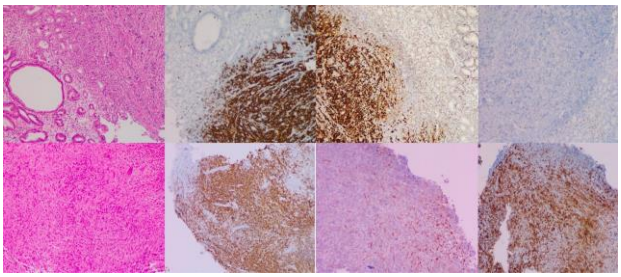

Figure 2. Diffuse large B cell lymphoma microphotographs (x100); Germinal center B cell. Atypical lymphocyte infiltration involving the lamina propria and submucosa of the stomach antrum, with dense crush artifact progressing between glands (A, H&E), CD20 (B) and bcl-6 positive (C), MUM1 negative (D). Activated B cell: Atypical lymphocytes with intense crush artifact infiltrated the submucosa of the antrum (E, H&E), CD20 diffuse positive (F), while CD10 is only positive in stromal cells (G) and MUM1 is strongly positive in atypical lymphocytes (H).

Pathologist perspective (PP); Diffuse large B-cell lymphoma consists of three main morphological variants: centroblastic, immunoblastic and anaplastic. Centroblasts are medium to large-sized cells with vesicular chromatin and 2-4 nucleoli, based on nuclear membrane, whereas immunoblasts have centrally located nucleolus (10). Anaplastic morphology must be distinguished from poorly differentiated carcinoma or melanoma. Neoplastic cells express pan-B cell markers such as CD20, CD19, CD79a and PAX5. Ki67 proliferation index is commonly >40% (13). COO is another important consideration in terms of treatment decision. Germinal center B-cell subtype (GC) is originated from germinal cells, whereas activated B-cell subtype (ABC) is derived from germinal center exit/post germinal center. Hans, et al., have developed an immunohistochemistry-based algorithm, which had high concordance with gene expression profiling, in order to classify cell of origin (14). Accordingly, CD10, BCL6 and IRF/MUM1 are considered positive if $\geqslant$ 30% cells are stained. CD10+ or BCL6+ MUM1- refers to GC subtype, whereas BCL6- or BCL6+ MUM1+ refers to ABC subtype. Meyer, et al. (15), have included GCET1 and LMO2 as GC markers and FOXP1 as ABC marker. HGAL/GCET2 has also been considered as a GC marker (16). CD30 positivity has been observed in 10-20% patients with DLBCL (17). DLBCL lymphoma could also express MYC and BCL2 by immunohistochemistry, in which case, it is called double expressor (18) (Figure 2).

Marginal zone lymphoma is the second most common gNHL, with a frequency of 23-48%. Half of the patients had gastric involvement. H. pylori is an important risk factor and 90% of the patients with MALT lymphoma were positive and antibacterial therapy was sufficient in the majority of cases. Immunoproliferative small intestinal disease (IPSID) is seen in young patients with duodenum involvement and is common in the Middle East. This disease, also called Mediterranean lymphoma, is caused by C. jejuni. FDG-PET or CT may prove inadequate in MZL patients with an indolent lymphoma. Endoscopic methods with histopathological diagnosis are more valuable. In addition to wait and see approach, regimens such as Rituximab single, R-CVP, R-CHOP are used in treatment for patients in need of treatment (1,9, 11, 19).

In line with literature, MALT lymphoma (18%) was the second most common B lymphoma group in our patients. Our patients were also followed-up endoscopically due to the ability of diagnostic biopsy in MALT lymphoma patients with indolent course and since endoscopic methods were better for post-treatment evaluation. Relapse was detected in 20% of the patients at endoscopic follow-up.

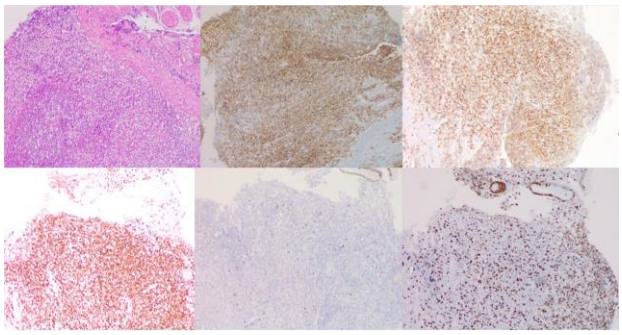

Figure 3. Extranodal marginal zone lymphoma of mucosa, associated lymphoid tissue (MALT lymphoma) microphotographs (x100). Lymphoid proliferation with gland destruction, passing through the muscularis mucosa and spreading to the submucosal area. Secondary follicles accompany this proliferation (A, H&E), atypical lymphocytes are CD20 positive (B), CD5 (C) and CD3 negative (D), CyclinD1 is also negative (E) while Ki67 proliferation index (F) is %20-30.

PP; MALT lymphoma which most frequently exhibits t[11;18] [q21;q21] (20), consists of small lymphoid cells

MMDJ
MEANDROS MEDICAL AND DENTAL JOURNAL
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Meandros Medical and Dental Journal
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with irregular and hyperchromatic nucleus. Since there is no specific immunohistochemical profile and diagnosis is generally made by exclusion of other conditions, caution must be exercised to distinguish this tumor from benign reactive lymphoid tissue. Lymphoma cells proliferate in a marginal zone pattern and around reactive follicles, which then form confluent dense areas, leading to follicle replacement [10]. Lymphoepithelial lesions (aggregates of ⩾3 marginal zone cells with distortion or destruction of the epithelium) and deeper infiltration should be examined carefully. CD20-positive cells may have plasmacytic differentiation, which can be highlighted by kappa and lambda immunostaining (21). CD21 and CD23 may be helpful to highlight the dispersed dendritic cell network. CD5-positivity may be observed in rare cases (22) (Figure 3).

Mantle Cell Lymphoma accounts for 5-13% of gNHL cases. It is known that extranodal involvement is common in MCL and approximately 90% of patients have GI involvement. However, routine screening is not recommended (23). Most patients did not have GI tract involvement at the time of diagnosis. It is detected as small mucosal polyps, often in the small intestine or colon. We think that the number of patients, diagnosed with gastrointestinal biopsy is low, since we do not routinely take endoscopic samples from all MCL patients at the time of diagnosis.

PP; Mantle cell lymphoma consists of small to medium sized monomorphic cell population with different patterns, which may cause diagnostic difficulties: nodular, diffuse, mantle zone and follicular (10). Lymphoma may occur as multiple mucosal polyps, called multiple lymphomatous polyposis (24). MCL is characterized by the translocation t[11;14] [q13;q32] and leads to Cyclin D1 overexpression (25). Main immunohistochemical features are CD5 positivity and BCL6, CD10 and CD23 negativity (may be weakly positive). Cyclin D1 is expressed in most of the cases (including CD5-negative cases) and SOX 11 is highly sensitive even in Cyclin D1-negative cases (26). DLBCL cases, especially those who show CD5 positivity, must be distinguished from blastoid variant of MCL. Cyclin D1 and SOX11 are useful in this aspect (Figure 4).
Follicular Lymphoma (FL) is the most common lymphoma among indolent lymphomas. Among nodal lymphomas, FL is the second most common following DLBCL. Extranodal involvement is not common in patients. GI involvement is seen in 5-12% (11,18).

PP; Follicular lymphoma is a relatively rare extranodal lymphoma with gastrointestinal tract involvement, which generally affects duodenum as primary (27) and which presents as multiple small polyps and subtyped as duodenal type FL with a good prognosis (10). The translocation (14;18) which involves BCL2 locus is observed in most of these cases (28). Follicular lymphoma subtypes, including in situ follicular neoplasia, is characterized by CD10 and BCL2 positivity of the effected germinal centers. This panel is important to distinguish it from reactive follicles. Ki67 proliferation index is usually low and restricted peripheral dendritic cells of the follicle may be highlighted by CD21 (29).

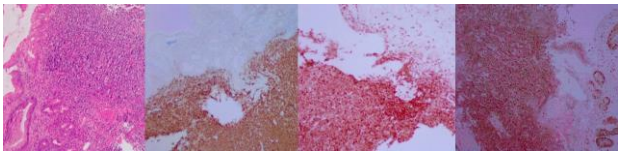

Figure 4. Mantle cell lymphoma microphotographs (x100). Infiltration of medium-sized monotone lymphocytes showing infiltration between antral mucosal glands and towards the submucosal area (A, H&E), CD20 (B) and CD5 (C) diffuse positive, strong immunoreaction of Cyclin D1 (D).

Burkitt's Lymphoma is an aggressive B lymphoma that is less common in adult lymphomas and constitutes 5% of gNHL cases. GI involvement is more common in this sporadic subtype. It is frequently encountered with bulky intraabdominal involvement. High lactate dehydrogenase and tumor lysis are the laboratory indicators, which may be encountered in diagnosis. The c-MYC rearrangement is non-specific, but is often found (11,30).

PP; Burkitt lymphoma is an aggressive tumor, mostly seen in terminal ileum of the gastrointestinal tract (31). Cells of Burkitt lymphoma are usually basophilic and medium-sized with angular borders. Chromatin is usually clumped with multiple nuclei. Tumors are highly proliferative with numerous mitotic figures and apoptosis. Starry sky appearance is due to tingible body macrophages (10). CD20, CD19 and CD79a are positive as well as germinal center markers such as CD10 and BCL6. Ki67 proliferation index is nearly %100 and there is MYC overexpression. Aberrant BCL2 expression may be observed, however, high expressions should be distinguished from high grade B cell lymphomas (32). DLBCL is another differential diagnosis, in particular if it is characterized by medium sized cells. However, BL cells are more monomorphic and Ki67 proliferation index is higher than DLBCL while latter is approximately %40-60 (Figure 5). Radiological

MMDJ
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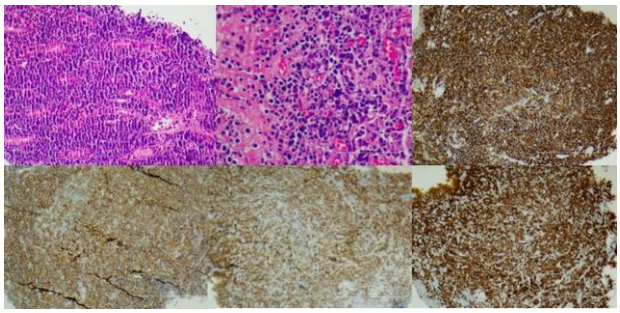

Figure 5. Burkitt lymphoma microphotographs: Dense atypical lymphoid proliferation in lamina propria of the stomach antrum (A, H&E, x100). Cells are monomorphic with coarse chromatin and mitotically active (B, H&E, x400). CD20 (C) and CD10 (D) are diffuse positive, c-myc %90 (E), ki67 proliferation index is %100 (F).

imaging also plays an important role in the diagnosis process. We are routinely using 18FDG PET/CT method for pre- and post-treatment evaluation in malignancies such as DLBCL, BL, MCL, whichmay show a progressive course and have a high proliferation index. However, similar benefit in indolent malignancies may not be achieved due to slow proliferation of the malignant tissues. Endoscopic methods and CT are more frequently used in the follow-up of these patients. In our study, relapses had been observed by endoscopic method in four patients during follow-up. Two of these patients had indolent disease. However, no relapses had been detected during follow-up by PET/CT and endoscopic imaging was not required for these patients. We think that follow-up can be done by PET/CT. Although we frequently use 18FDG PET/CT for follow-up, it is important to use endoscopic methods, as they can be used for diagnostic purposes as well as imaging.

CONCLUSION

Clinician and pathologist communication is the most important factor in the diagnostic process in gastrointestinal manifestations of mature B-cell neoplasms. Due to its prevalence, clinicians often consider solid malignancies as the initial differential diagnosis for masses in GI tract. In order to clarify the diagnosis and the stage of the disease, the clinical information of the patients must be fully described and transferred by the clinician to the pathologist. The presence of B symptoms, splenomegaly and lymph adenomegaly are important indicators in terms of differential diagnosis. If cytopenias are accompanied by laboratory findings, they must be emphasized and shared with pathologists for accurate diagnosis and clinical management.

Acknowledgments
None

Authorship contributions
UD and BBK planned and designed the study, gathered the data, and performed the statistics. UD and BBK wrote the paper. BBK and FÖP took the pathological pictures. EGU, TAK, HOK supervised. FÖPand AMD reviewed the paper and statistics.

Data availibity statement
The authors state that the data supporting the study's results can be found in the article. Additionally, the raw data can be obtained from the corresponding author upon a reasonable request.

Declaration of competing interest
Authors state that they have no conflict of interest.

Ethics
The study was conducted following the Declaration of Helsinki, Ethical Principles for Medical Research, and was approved by the Trakya University Faculty of Medicine Ethical Committee (TÜTF-BAEK2021/234). Consent forms were obtained from the patients for the study. No artificial intelligence-supported technology was used in our study.

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MMDJ
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