REPUPLIC OF IRAQ
MINISTRY OF HIGHER EDUCATION
AND SCIENTIFIC RESEARCH
UNIVERSITY OF BABYLON
COLLEGE OF MEDICINE
DEPARTMENT OF PATHOLOGY

Immunohistochemical study using CD5, CD23 ,and CD79α markers in sample of Iraqi patients with gastrointestinal lymphoma

A thesis

Submitted to the Council of the College of Medicine and the Committee of Postgraduate Studies of University of Babylon in Partial Fulfillment of the Requirements for the Degree of Master in Medicin/Pathology

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جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة بابل
كلية الطب
فرع الامراض

(دراسة هستوكيميائية مناعية باستخدام علامات CD5وCD23و CD79αفي عينة من المرضى العراقيين المصابين بسرطان الغدد الليمفاوية المعدية المعوية)

رسالة

مقدمه الى مجلس كلية الطب في جامعة بابل كجزء من متطلبات نيل درجة الماجستير في الطب /علم الامراض

من قبل

هدى محمد عبد الواحد طليفح

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2023

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سورة فاطر الاية (28) **صدق الله العلي العظيم**

Certification of supervision

We certify that this thesis (**Immunohistochemical study using CD5, CD23 ,and CD79α markers in sample of Iraqi patients with gastrointestinal lymphoma)** was prepared by Huda Mohmmed Abdul Wahid under our supervision at department of pathology, College of Medicine / University of Babylon as a partial requirement for the master degree in pathology.

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Abbreviations	**KEY**
BCL	**B cell lymphoma**
BCLU	**B cell lymphoma unclassified**
BL	**Burkitts lymphoma**
CBC	**Complete blood count**
CCND3	**Cyclin D3**
DLBCL	**Diffuse large B cell lymphoma**
EATL	**Enteropathy associated T cell lymphoma**
EGD	**Esophagogastroduodenoscopy**
ENL	**EXTRANODAL lymphoma**
EPV	**E pstein Barr virus**
EUS	**Endoscopicultrasound**
FL	**Follicular lymphoma**
GC	**Germinal center**
GIT	**Gastrointestinal lymphoma**
HCD	**Heavy chain disease**
HCV	**Hepatitis c virus**
HG	**High grade**
HL	Hodgkin lymphoma
LDL	**Lactate dehydrogenase**
LG	**Low grade**
LN	**Lymph nodes**
MALT	**Mucosa associated lymphoid tissue**
MCL	**Mantle cell lymphoma**
MPL	**Multiple lymphomatous polyposis**
MZL	**Marginal zone lymphoma**
NHL	**Non Hodgkin lymphoma**
PGIL	**Primary gastrointestinal lymphoma**
PGL	**Primary gastric lymphoma**
REAL	**Revised European and American lymphoma**
TCF3	**Transcription factors 3**
TCL	**T cell lymphoma**
WBC	**White blood cell**
WHO	**World Health organization**

Abstract

Background: Primary gastrointestinal lymphoma(PGIL) is a rare tumor, accounting for less than 5% of all GIT lymphoma, 10-15 % of all non Hodgkin lymphoma and encompasses 30-40 % of total extranodal lymphoma, its incidence is increasing. Approximately 60-75% of all cases occur in the stomach followed by small bowel and large bowel. The majority of all gastrointestinal lymphoma are B cell which responsed to chemotherapy and have better prognosis while T cell lymphoma is less common accounting only 6%. Many efforts focus on finding reliable indicators that can help to predict the outcome or explain GIT lymphoma clinical variability. Markers such as CD5, CD23 and CD79 has been emerged and used in the evaluation of GIT lymphoma.

Aim **of the study:** To assess CD5,CD23 and CD79 expression in Iraqi patients with GIT lymphoma and their association with different indices (age, sex, , and histopathological subtypes).

Patients and methods: Samples included in this study represented as 30 formalin-fixed paraffin embedded biopsy tissue blocks of patients with GIT lymphoma who had undergone endoscopic and excisional biopsy. They are collected from the histopathology laboratories of Baghdad medical city, Alhussainy teaching hospital in Karbalaa as well as many private histopathology laboratories in Baghdad, Karbala and Hilla cities. Patients comprising (22 males and 8 females) ranging in age from (3-78) years. The collected pathological blocks were related to the period between 2016 to 2023, while the collection of blocks of this study was carried out during the period from October 2022 till April 2023.These blocks were stained Immunohistochemically for expression of CD5, CD23 and CD79 and evaluation of results using Histoscore (H score), H score was calculated by semi-quantitative

assessment of both the intensity of staining(grade) and percentage of positive cell per total number of malignant cells.

Results: The results revealed that the most frequent age of patients with GIT lymphoma ≥60years and more common in male 73.3% than female 26.7% and demonstrated that diffuse large B cell lymphoma(DLBCL) is the most common subtype 53,4%. In the present study the CD23 expression was negative in all patient with GIT lymphoma and CD5expression positive in 33.3% while negative in 66.7%. CD79 expression positive in 96.7%and negative in 3.3%, the result revealed no significant association between CD5 results and study variable (P-value > 0.05), and there was no significant association between CD5 results and CD79 results (P –value > 0.05).

Conclusion

1.CD23 have no role in the evaluation of GIT lymphoma. Negative results for CD23 can be used to isolate cases of non-Hodgkin lymphoma from benign lesions.

2.CD5 expression was negative in two third of patients with GIT lymphoma

3.CD79 highly expressed in patient with GIT lymphoma. H score of CD79 expression have negative correlation with age, gender and histopathological subtypes. There is no correlation between CD79 expression and CD 5 expression.

Chapter one

1:1 Introduction:

Lymphoma: is the most common form of hematological malignancy or blood cancer in the developed world represent about 5.3 % of all cancer[1] there are two types Hodgkin(HL) and non Hodgkin lymphoma(NHL), lymphoma is commonly originated in lymph nodes(nodal lymphoma), invasion of malignant lymphocytes in organs other than lymph nodes is called extranodal lymphoma (ENL) therefore any organ inside the body can be affected [2] .The gastroinstestinal tract is the most frequently affected followed by waldeyers ring (where the tonsil is consider as extranodal site),lung ,liver, spleen, bone and skin [3] .

Gastrointestinal lymphoma account for 30-40%of all extranodal lymphoma and majority being non Hodgkin type constitute 10-15%of all NHL [4] .

Its usually secondary to the hematogenous spread of nodal disease to extranodal tissue and primary gastrointestinal tract lymphoma(PGIL) is relatively rare and always non Hodgkin type [5] . They classify as B cell or T cell depended on type of lymphocyte become malignant, B cell is more common than T cell lymphoma [6].

Several subtype are included inside B cell NHL; mucosa associated lymphoid tissue (MALT) and Diffuse large B cell lymphoma (DLBCL) which is the most common histological types, others types Burkitts lymphoma (BL), Follicular lymphoma (FL), Mantle cell lymphoma (MCL) and others less common and often rare subtypes of NHL [7] .Although lymphoma can arise from any region of gastrointestinal tract (GIT), stomach is the most common involved organ follow by small intestine and large intestine[8] .

Helicobactor pylori infection has been implicated in the pathogenesis of gastric MALT lymphoma but its role in gastric DLBCL is uncertain[9].

Primary gastrointestinal lymphoma (PGIL) approximately 2-3 time more frequently seen in male compared to female and patient age with PGIT range (19 -90) years with median age of 55years , the ratio and age can be varied depending on the sites of PGIL and pathological subtype [10].The patient with T

cell lymphoma (TCL)is usually 10-14years younger compared to B cell lymphoma (BCL) [10] .

The introduction of the revised European and American lymphoma (REAL) classification and its successor, the world Health organization (WHO) classification of lymphoma its widely accepted that different lymphoma are not merely morphological variation of one disease but constitute individual disease with diverse clinical behavior [11].

The modern lymphoma classification is based on morphological, immunophenotype , genetic and clinical feature. Making the correct diagnosis according to WHO classification is critical because treatment can vary widely from simple "wait and watch" approach to local radiation or surgery to high dose chemotherapy with or without stem cell transplantation [12].

Most patient have overlapping symptoms of other gastrointestinal disease, without specific manifestation under endoscopy .Therefore, histological examination is prerequisite for determining diagnosis [13].However , the best way to obtain pathology is through endoscopic biopsy , its extremely important for diagnosis of GIT lymphoma [13].

Clinical staging is very important for the treatment of PGIL and the prognosis of patient. At present ,the common clinical staging method are Musshoff, Ann Arbor and Lugano [13]

1:2 Aim of study:

To assess CD5,CD23 and CD79 expression in Iraqi patients with GIT lymphoma and association with different indices (age, sex, , and histopathological subtypes).

Chapter two

Review of literature

2.1 GIT lymphoma

Primary gastrointestinal lymphoma (PGIL) is a malignant tumor originating from submucosal lymphoid tissue of gastrointestinal tract and is the most common extranodal lymphoma accounting for about 30-40% of all extra nodal lymphoma with majority being non Hodgkin type[4] .Although (PGIL) is a rare disease comprising only 1-4% of gastrointestinal (GI) malignant tumor ,its incidence is increasing[14] .Different regions of the GIT are involved in different subtype of PGIL with various frequency that reflects the diversity of the causative agents and the predisposing factors for each site and subtype of PGIL[7]the stomach is the most commonly involved site 60-75% in the gastrointestinal tract followed by small intestine 20-30% ,large intestine 5-10% and esophagus <1% [8] ·As in the figure :2.1

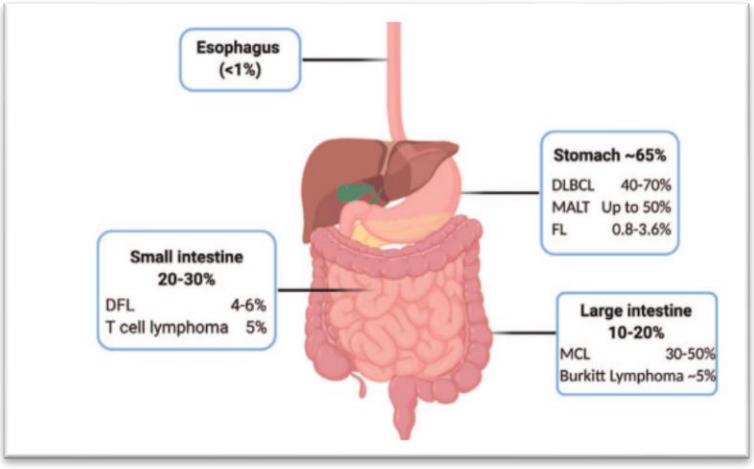

Figure 2-1. Prevalence of lymphoma and subtypes within the luminal gastrointestinal tract[15]

The majority of all gastrointestinal lymphoma are B cell lymphomas whereas more responsive to chemotherapy and have better prognosis, T cell lymphoma is less common accounting for only 6% and HL[16] .

Gastrointestinal tract lymphoma is usually secondary to the hematogenous widespread of nodal disease to extranodal tissue and PGIL is relatively rare [17] .

Dawson s criteria that were suggested 6 decades ago are used for the definition of PGIL, that include: 1-Abscent of peripheral lymphadenopathy at the time of presentation. 2-lack of enlarge mediastinal lymph nodes (LN) 3-normal total and differential white blood cell(WBC) 4- predominance of bowel lesion at the time of laparotomy with only LNs affected in immediate vicinity (LNs which are confined to the drainage area of the primary tumor site) and 5- no involvement of liver and spleen[18] .

High grade DLBCL and low grade MALT lymphoma are the most common histological subtypes, MALT lymphoma usually arises in background of chronic inflammation in particular, infection with Helicobacter pylori, but its role in gastric DLBCL is uncertain[9]

2.1.1Epidemiology:

GI lymphomas is about 1–4% of all GI malignancies, 10–15% of all non-Hodgkin's lymphomas (NHL), and 30–40% of all extranodal NHLs, making the GI tract the most common site for extranodal lymphoma[19]. Gastric lymphomas are common in patients aged more than 50 years , however it still has been reported in the second decade of life [20], the median age is 60-65 years and the incident rates in males are nearly twice as high as than females[21]. Recently, several studies have

shown an increase in the incidence among young age group with HIV infected patient [22].

2.1.2 ETIOLOGY:

The cause of PGIL is unclear, however several factor may contributed to GIT lymphoma .The potential risk factors associated with the pathogenesis of primary gastric lymphoma (PGL) included chronic gastritis by Helicobacter pylori (*H* pylori*)* considered the major risk factor for MALT lymphoma. , HIV, Epstein-Barr virus, hepatitis B virus, and human T-cell lymphotropic virus 1. Campylobacter jejuni *(*C jejuni*)* has also been described as an important organism implicated in the pathogenesis of MALT lymphoma, specifically of immunoproliferative small intestinal disease [23]. Long-term infection with the hepatitis C virus (HCV) seems to be a risk factor for certain types of lymphoma, such as splenic marginal zone lymphoma [24]. Other pathological conditions, such as celiac disease, inflammatory bowel disease, and immunosuppression, have also been associated with primary gastric lymphoma (PGL) [25].

2.1.3 CLINICAL PRESENTATION:

The initial symptoms of PGIL may be vague and nonspecific, leading to a delayed establishment of diagnosis up to several years [26]. Sign and symptoms mimicking other abdominal pathology such as gastritis, peptic ulcer disease, pancreatic disorders, or functional disorder of the stomach as well as other gastric neoplasm . The physical examination could be normal in 55 to 60 % of cases [27]. Other common symptoms included weight loss, nausea, vomiting, abdominal fullness and indigestion [28].Weakness, night sweat, jaundice, fever and dysphagia occur less frequently [28]. About 20 to 30% of patients with gastric DLBCL report gastrointestinal bleeding in the form of hematemesis or melena .while gastric

obstruction and perforation ,hepatomegaly, splenomegaly and lymphadenopathy are less common ,Common signs include epigastric tenderness and palpable mass. The tenderness is encountered in 20-35 % and masses in 17-25 % [29].

2.1.4 DIFFERIANTIAL DIOGNOSIS[6]

1. Crohn disease

2. Adenocarcinoma and other solid tumors

3. Benign lymphoid hyperplasia

4. Peptic ulcer disease

5. Celiac disease

6. Bacterial and fungal infections of GI tract

2.1.5 CLASSIFICATION:

Evidence –based classification of disease is essential for the treatment of individual patients, monitoring of global disease incidence, and investigation all aspect of disease causation ,prevention and therapy[30] .The WHO world health organization known as WHO blue book. classification of lymphoid tumor has provided a global reference for the diagnosis of lymphoid neoplasm since its 3rd edition in 2001[11]. Which has based on the R.E.A.L classification developed by the international lymphoma study group (ILSC) in the early 1990[31] .The WHO-HAEMS is a systemic evolution of the prior classification .In 2022 the WHO is set to release an update to it pivotal 2017 publication on the classification of hematolymphoid tumor lymphoid neoplasm. This revised 5th edition (WHO-HAEMS) will include a restructuring of entities into a hierarchical system, update

to nomenclature, revision of diagnosis criteria or subtypes, deletion of certain entities and introduction of new entities[32] .

Comparesim between WHO Classification of Haematolymphoid Tumours, 5th edition: B-cell lymphoid proliferations and lymphomas and revised 4th edition[31] (appendix 1)

Table 2.1 : WHO classification of hematolymphoid tumors of the digestive system[33]. First provided in the Digestive System Tumors, 5th edition, published in 2019
WHO (2019)

Site specific hematolymphoid tumors	ICD-O codes
MALTa lymphoma	9699/3
Immunoproliferative small intestinal disease	9764/3
Follicular lymphoma, duodenal type	9695/3
Enteropathy associated T cell lymphoma	9717/3
Monomorphic epitheliotropic intestinal T cell lymphoma	9717/3
Intestinal T cell lymphoma	9717/3
Indolent T cell lymphoproliferative disorder of the gastrointestinal tract	9702/1
Hepatosplenic T cell lymphoma	9716/3
Follicular dendritic cell sarcoma	9758/3
Hematolymphoid tumors occurring with some frequency in the digestive system	ICD-O codes
Diffuse large B cell lymphoma, NOS	9680/3
Follicular lymphoma, NOS	9690/3
Follicular lymphoma, grade 1	9695/3
Follicular lymphoma, grade2	9691/3
Follicular lymphoma, grade 3A	9698/3

Follicular lymphoma, grade 3B 9698/3
Mantle cell lymphoma 9673/3
Conventional mantle cell lymphoma
Leukemic nonnodal mantle cell lymphoma
Burkitt lymphoma, NOS 9687/3
Endemic Burkitt lymphoma
Sporadic Burkitt lymphoma
Immunodeficiency associated Burkitt lymphoma
Plasmablastic lymphoma 9735/3
Posttransplant lymphoproliferative disorder, NOS 9971/1
Nondestructive posttransplant lymphoproliferative disorder
Polymorphic posttransplant lymphoproliferative disorder
Monomorphic posttransplant lymphoproliferative disorder
Classic Hodgkin lymphoma posttransplant lymphoproliferative disorder
Mucocutaneous ulcer posttransplant lymphoproliferative disorder
Extranodal NK / T cell lymphoma, nasal type 9719/3
Mast cell sarcoma 9740/3
Indolent systemic mastocytosis 9741/1
Aggressive systemic mastocytosis 9741/3
Systemic mastocytosis with associated hematological clonal non mast cell disorder 9741/3
Mast cell leukemia 9742/3
Langerhans cell histiocytosis, NOS 9751/1
Langerhans cell histiocytosis, disseminated 9751/3
Follicular dendritic cell sarcoma 9758/3
Histiocytic sarcoma 9755/3

2.1.5.1 Mucosa-associated lymphoid tissue (MALT)-type

(Extranodal marginal-zone lymphoma);

Marginal zone lymphomas (MZLs) are a group of indolent (slow-growing) B-cell non-Hodgkin lymphomas (NHLs), beginning in a part of lymph tissue called the marginal zone, which account for approximately 5 to 10 percent of all NHL cases[34].

MALT is the most common form of MZL (61% of all MZL cases) occur in organ devoid of lymphoid tissue, its commonly found in stomach (called gastric MALT lymphoma) that more affected antrum [35]. Other organ can also affected (called non gastric MALT lymphoma) like small intestine (less in large bowel), salivary gland and breast. It usually affects patients over 50 years of age with peak in second decade of life and slight male prevalence 1.5:1[36]

MALT lymphoma arise secondary to chronic infection by Helicobacter pylori of stomach causing gastritis or autoimmune condition (such as Hashimotos thyroiditis or Sjogren syndrome)[37].MALT lymphoma divided into H pylori positive malt lymphoma and H pylori negative malt lymphoma depended on association with Helicobacter pylori infection, Additionaly H pylori negative MALT lymphomas have higher positive rate for [11;18] [q21;q21] translocation than H pylori positive MALT lymphomas [38]As in the figure 2-2

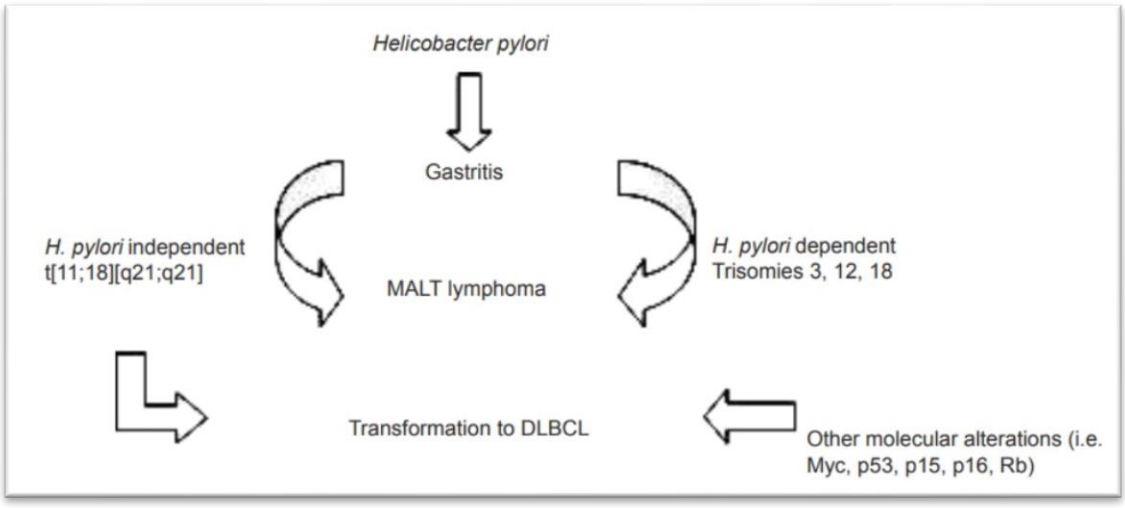

Figure2-2: Hypothesized pathways of mucosa-associated lymphoid tissue (MALT) lymphomagenesis with possible transformation to diffuse large B-cell lymphoma (DLBCL) [39]

Typically, gastric MALT lymphoma is a low-grade (LG) neoplasm, but it can be transformed into a high-grade (HG) lymphoma as well [40] characterize by dense lymphoid infilteration that invade and destroys gastric gland that so called lymphoepithelial lesion which is pathognomonic for lymphoma [41]. It has been postulated that MALT lymphoma arises from postgerminal center memory B cells with the capacity to differentiate into marginal zone cells and plasma cells [42]. As in the figure2-3

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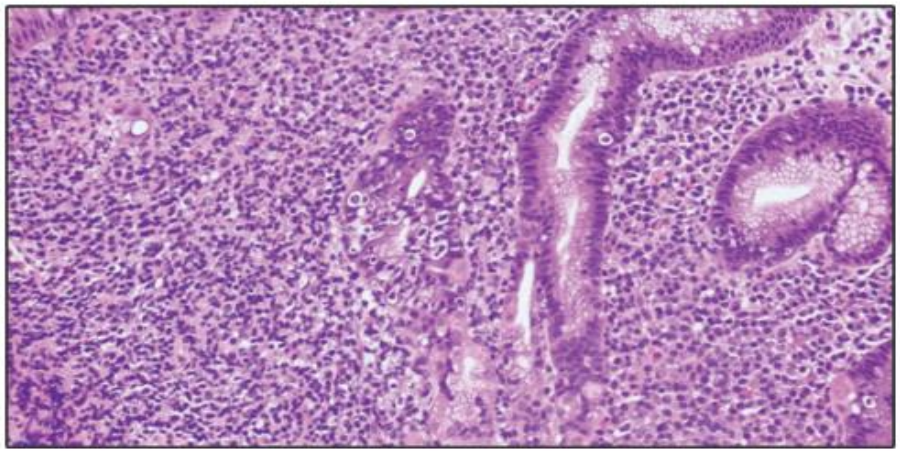


Figure2-3: gastricmucosa associated lymphoid tissue (MALT). Gastric mucosa showing a diffuse lymphoplasmacytic infiltrate, which is composed of small and mature lymphocytes with mild cytologic atypia and numerous background small plasma cells. Note the prominent lymphoepithelial lesions leading to glandular destruction[15]

MALT lymphomas do not have a specific antigenic profile, the B-cells share the immunophenotype with marginal zone B-cells present in the spleen, Peyer's patches and LN [43].

B lymphocytes of the marginal zone are the origin of MALT lymphoma and are characterized by a cellular population that is heterogeneous with a predominant presence of small lymphocytes or monocytoid appearing lymphocytes and large cells (immunoblasts and centroblast)[44]. The increase in the number of large cells in MALT lymphoma can create diagnostic challenges, suggesting a histological transformation into a DLBCL (characterized by the presence of compact aggregates or a large cell sheet-like proliferation) [45]. it is important to remember that gastric MALT lymphomas frequently have cytogenetic alterations that are different from those of typical primary DLBCL of the stomach. Therefore,

cytogenetics can differentiate the two variants in some cases [46]. MALT lymphomas have a nonspecific antigenic profile that can differentiate them from primary DLBCL which is characterized by different immunophenotypes, especially about CD45, CD5, and CD10 expression [47] .

Four recurrent chromosomal translocations have been found:as in table 2.2

Table2.2:

Cytogenetic abnormalities in gastric MALT lymphomas[39].

Abnormality	**%GastricMALT**	**Clinical implications**
t[11;18][q21;q21]	25%	Antibiotic resistance
t[14;18][q32;q21]	5%	Unknown
t[1;14][p22;q32]	Rare	Antibiotic resistance
t[3;14][q27;q32]	Rare	Reported in DLBCL with concurrent MALT
Trisomies	5-65%	3q27 most common; associated with high-stage disease

2.1.5.2 DIFFUSE LARGE B –CELL IYMPHOMA:

Primary GI diffuse large B-cell lymphoma, is the most histological subtype (up to 58%) of all PGILs. similarly to MALT, is most typically located in the stomach with a prevalence estimated at 30–40% of gastric lymphomas [48].

Gastric DLBCL is sometimes called high-grade gastric lymphoma. Compared to low-grade MALT lymphoma, high-grade gastric lymphoma is reported to be associated with a lower complete remission rate and shorter survival. However, recent studies showed no survival differences between MALT lymphoma and DLBCL, likely because of improved treatment modalities [(49).] High-grade PGL is practically always of the B-cell phenotype and are associated with an aggressive clinical presentation. An unsolved remaining question is whether all primary gastric DLBCL are derived from previous low-grade MALT lymphomas or if they appear de novo [(50).] De novo DLBCLs are bcl2 and CD10 positive whereas transformed MALT are bcl2 and CD10 negative [(51)]. Most DLBCLs occur in patients more than 60 years old and more common in male, Some evidence suggests the role of atrophic gastritis, especially among immunocompromised patients [(48).]

It originates from germinal center (GC) B-cells or post-germinal B-cells [(51).] DLBCL is characterized by large lymphoid cells with nuclei greater than twice the size of a small lymphocyte, and frequently larger than nuclei of tissue macrophage. The tumor cells contain round, oval, or slightly irregular nuclei with vesicular nuclear chromatin, prominent nucleoli, and ample amount of basophilic cytoplasm and have a diffuse growth pattern [(52).] In most cases, the predominant cells resemble either large centroblasts or immunoblasts.As in the figure 2-4

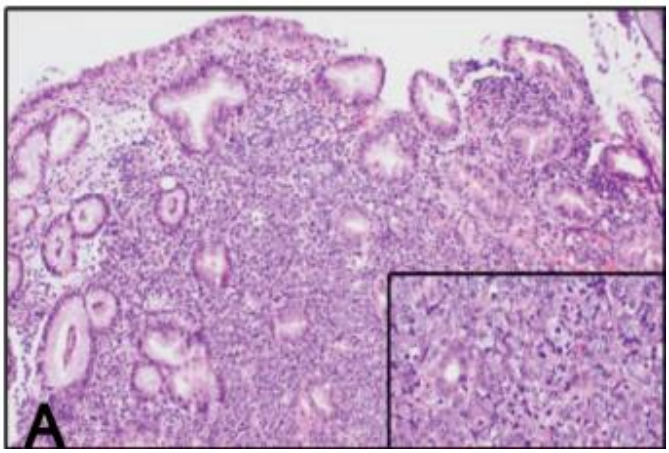


Figure2-4: Gastric diffuse large B-cell lymphoma (DLBCL). A, Gastric mucosa showing a diffuse infiltrate of large neoplastic lymphoid cells with open vesicular nuclei and prominent nucleoli[15] .

DLBCL, a heterogeneous group of tumors which are clinically, histologically, immunophenotypically, cytogenetically variable, can be divided into 3 subgroups, namely germinal-center B-cell-like, activated B-cell-like, and primary mediastinal DLBCL according to the gene expression patterns with each having a different prognostication. The most commonly seen translocations include t (14;18) (q32;q21) with BCL2-reaarrgment t (3;14) (p27;q32) with BCL6-rearrangement and t (8;14) (q24;q32) with MYC rearrangement, respectively. Variability has been observed in CD45, CD5 and CD10 expression, with the CD10 expression in particular referred as a prognostic indicator [47].

Oncogene Bcl-6 (located on chromosome 3q27) is often present in the most of extranodal high-grade lymphomas. An overexpression of this gene could descripted the occurance of both gastric DLBCL and DLBCL developing in other sites. Bcl-6 promoter region could be change due translocations, somatic

hypermutations, or deregulating mutations. These genetic rearrangements cause an overexpression of the gene, which seems to predict a better prognosis [53].

Bcl-2 oncogene expression was reported to be importantly less in gastric than non gastric primary extranodal high grade B-cell lymphomas, while nuclear p53 protein expression did not differ significantly between DLBCL are derived from previous low-grade MALT lymphomas or if they appear de novo [54]. In large cell gastric lymphomas, there have been no significant differences in either Bcl-2 or p53 expression profiles, independent of the evidence of an MALT component. However, in cases of large B-cell lymphomas with a low-grade MALT component, it has been reported an important downregulation of Bcl-2 and upregulation of p53 protein of uncertain clinical significance [55].

2.1.5.3 BURKITTS LYMPHOMA:

Its a B-cell uncommon form non Hodgkin lymphoma in adult, with short doubling time and high tumor burden [56] . BL is responsible for 1–2 % of lymphomas in adults and up to 40 % in children in the US and Western Europe [57].BL has three recognized clinical variant; endemic form, sporadic variant and immunodefiency – associated BL[58].The endemic form of BL is commonly seen in equatorial Africa with jaw and fascial bone involvement [59].Sporadic form seen as abdominal mass with bone marrow involvement[60]. Immunodefiency-associated BL appear with nodal or extranodal with most bone marrow involvement [61].Extranodal BL seen frequently in the stomach followed by small and large intestines mostly at ileocecal area [56].

Ileocecal BL occur in children as acute appendicitis [62].Complication such as intestinal obstruction and intussusception that require emergency surgical intervention occur in ileocecal lymphoma [63].

Risk factor for BL include Epstein Barr virus [EPV] malaria, HIV, low socioeconomic level[59] Chemotherapy and radiotherapy for rectum adenocarcinoma may be increase risk of secondary ileocecal BL[64].

BL is rapidly growing tumor with poor prognosis, displays a diffuse, monotonous infiltrate of medium-sized neoplastic lymphoid cells with round nuclei and little cytoplasm showing finely clumped and dispersed, with multiple basophilic nucleoli, presenting pathologically with a "starry sky" pattern [64]As in the figure2-5

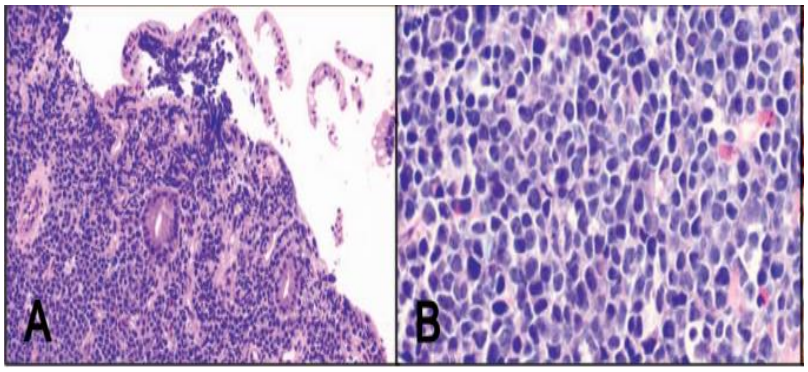


Figure2-5: Burkitt lymphoma. A, Colonic mucosa showing a diffuse lymphoid infiltrate comprised of medium sized neoplastic lymphocytes with blastoid-appearing nuclei and characteristic ''squared-off'' nuclear borders (B) [15].

The morphological distinction between BL and DLBCL has been problematic for pathologists [65]. Distinguishing between these two lymphomas, however, is critical, especially in adults (BL is rare in adults and rarely found in the stomach and colon), as the two diseases are treated differently [65].New studies have demonstrated that BL has a specific signature but there are cases that resemble DLBCL and aggressive BCLs, and have a molecular signature similar to BL, hence fall into an intermediate category. 2008 WHO classification recognized this issue

and added a provisional entity of BCL, unclassifiable, with characteristics intermediate between DLBCL and BL (BCLU) [64] .

Mutations in the transcription factor 3 gene, *TCF3* (19p13.3) or in its negative regulator *ID3* (1p36.12) take place in about 70% of sporadic and immunodeficiency-related BL and less frequently 40% in endemic cases. TCF3 supports the proliferation and survival of lymphoid cells by activating the B-cell receptor/phosphatidylinositol 3-kinase signaling pathways and modulating the expression of *CCND3* (*cyclin D3*, 6p21.1), which also undergoes mutation in 30% of BL cases [66].

Tumor cells express membrane immunoglobulins (IgM, Ig light chain), B-cell antigens (CD19, CD20, CD22), CD10, bcl-6, c-MYC , The most common cytogenetic change is t(8;14)(q24;q32) and t(8;22)(q24;q11) translocations that are characterized by overexpression of *c-MYC* oncogene and can be detected in 90% of cases by classical karyotyping or FISH. The proliferation index Ki-67 of BL is very high, usually over 95%, so it is not surprising because BL is the fastest growing human cancer [65]. Cytogenetic analysis is recommended to allow a clear distinction between BL and other *c-MYC*-driven B-cell NHL, especially DLBCL [64].

2.1.5.4 IMMINOPROLEFRATIVE SMALL INTESTINAL DISEASE;

IPSID, also known as alpha heavy chain disease[HCD] is rare variant of intestinal MALT it constitutes for 30% of all GI lymphoma in middle East [23].That involved proximal small intestine, characterize by ‘centrocyte like’ mucosal

infiltration with plasma cell produce truncated alpha heavy chain lacking of the light chain as well as the first constant domain[67].

IPSID mainly affect older children and young adults.

Recurrent c.jejuni infection role in pathogenesis is suspected .Moreover there is no evidence that c jejuni plays a role in cancer development [68].In some cases, antibiotic therapy may lead to remission, but in other patients transformation to DLBCL was observed [19].

Cytogenetic studies demonstrated clonal rearrangement including t[9,14][p13,q32] translocation with involvement of the PAXS gene [67].

2.1.5.5 FOLICULAR LYMPHOMA:

Primary extranodal FL is relatively uncommon , constituting less than 7% of GI tract lymphomas[69].The tumor typically arise in the duodenum with second part of duodenum is the most sit involvement following by ileum and colon.

It is most commonly occur in middle age adult with slight female predominance 2:1 [70] .

Microscopically, Duodenal Follicular lymphoma(DFL) shares many morphologic and immunophenotypic features with nodal FL. Neoplastic follicles expand intestinal villi and/or the lamina propria and are typically restricted to the mucosa but may extend into the submucosa. These follicles are predominantly composed of small mature cleaved lymphoid cells (centrocytes) with rare to infrequent centroblasts, consistent with low-grade morphology (grade 1-2). High-grade features including more than 15 centroblasts per high power field, infiltration into muscularis propria and/or peri-intestinal adipose tissue, and involvement of nearby mesenteric lymph nodes are not characteristic features of DFL and when

present should prompt one to consider secondary involvement by systemic FL [71]. As in the figure 2-6

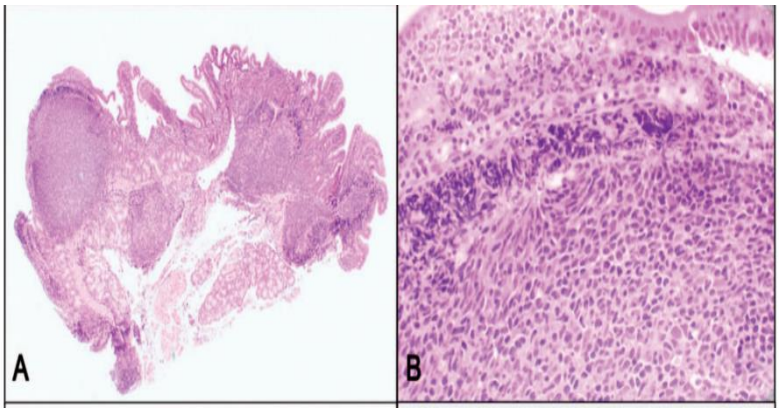


Figure 2-6: Duodenal follicular lymphoma. A, The lamina propria is expanded by neoplastic follicles. B, Follicles are predominantly composed of centrocytes and rare background centroblasts[15].

BCL2 and CD20 are nearly uniformly positive, CD10 positivity generally highlights both neoplastic follicles and interfollicular tumor cells in cases with a follicular, as well as mixed follicular and diffuse growth patterns [72].

CD21 immunohistochemistry highlights follicular dendritic cells within follicles, which are arranged in a peripheral pattern imparting a characteristic ‘‘hollowed out’’ appearance [73]. The Ki-67 proliferative index is low (20%). Histologic transformation to large-cell lymphoma has been reported, but this phenomenon is far less likely than in nodal FL [74]. The cytogenetic hallmark of FL is t[14;18] [q32;21], with rearrangement of the BCL2 gene seen in up to 90% of cases [74].

2.1.5.6 Mantle-cell lymphoma (MCL):

Its mature B-cell neoplasm with aggressive biological feature, MCL is represent less than 9%of GI non Hodgkin lymphoma [75]. It occurs in middle-aged

to older individuals, with a median age of diagnosis of around 68 years. MCL is much more common in men than women, with a ratio of ~2:1.

MCL in the GI tract may characteristically present as multiple mucosal polyps involving segment of luminal intestine known as multiple lymphomatous polyposis(MLP)[76],It most commonly occur in ascending colon and small intestine (mostly in the ileum and ileocecal region)and gastric involvement are next common ,it may be multifocal or diffuse[77]. As in the figure 2-7

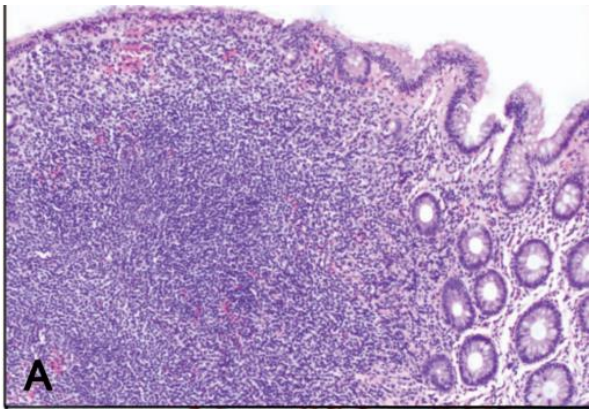


Figure 2-7: Mantle cell lymphoma. A, Colonic mucosa showing a diffuse infiltrate of small mature atypical lymphoid cells[15]

It is important to note that MLP may be present in other lymphoproliferative neoplasm such as FL and MALT lymphoma and its not specific for MCL [78].

MCL originates from small to medium size lymphocyte mantle zone (inner layer) of follicular tissue [77].MCL is characteristic by translocation t(11;14)(q13;q32) which joins the igh gene sequence with BCL1 locus, leading to CCND1gene up-regulation and cyclin D1 over expression [79].

Cyclin D1 over expression is highly characteristic and specific feature of MCL. It usually detected in CD20+ and CD5+ lymphoid infiltrates, but not in CD20+and CD5- lymphoid infiltrates. Therefore it most helpful in distinguish MCL from MALT or reactive B cell lymphocyte of chronic gastritis [(79).]

Neuronal transcription factor SOX11 nuclear expression is also characteristic for MCL and can help distinguish MCL from other BCLS [(80).]

2.1.5.7 Mature T cell, NK/T cell lymphomas:

NK/T cell neoplasm are invariably associated with EPV infection and are mostly aggressive thus differentiation from benign NK – cell enteropathy is paramount[(19)]

PGL with T cell phenotype is vary rare, comprising only 7% of PGL in endemic area of HTLV-1 infection .Primary gastric T cell lymphoma without HTLV-1 infection is extremely rare, and sporadic cases have been reported[(81)] Intestinal T –cell lymphoma account for 5% of all GI lymphoma and 1.4% of all lymphoma [(82)]

The revised WHO classification of hematolymphoid tumors has recognized the following 4 distinct entities; 1- Enteropathy- associated T cell lymphoma (EATL), 2- Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), 3- Indolent T- cell lymphoproliferative disorders of GI tract, and 4- intestinal T cell lymphoma ,not other wised specified[(83).]

2.1.5.7.1 Enteropathy –associated T cell lymphoma (EATL):

Its intestinal intraepithelial T cell malignancy most commonly occurring in the jejunum or ileum rarely it may present in the duodenum , .stomach or colon[(84)]EATL I is manifested in individual with underlying enteropathy (primary

celiac sprue) and occurs at higher frequency in northern Europe when the prevelance of celiac sprue is high[85] .Biopsy from patient suspected of celiac disease should be examined carefully to exclude development of lymphoma[86]

Microscopically , EATL I is seen in a diffuse distribution with associated surface mucosal ulceration ,the neoplastic lymphoid cell are composed of medium to large atypical lymphocytes displaying significant cytologic atypia and varing degrees nuclear membrance irregularities and prominent nucleoli with pale –to-clear cytoplasm. Numberous large cell with pleomorphic and anaplastic feature are also commonly encountred, the background spotty necrosis is usually present [87]..As in the figure 2-8

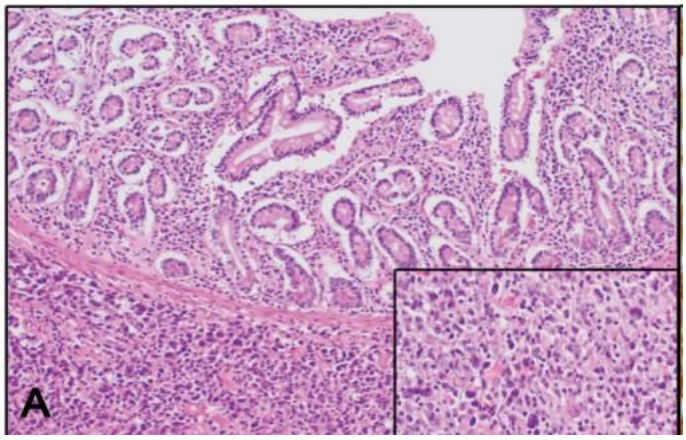


Figure2- 8: Enteropathy-associated T-cell lymphoma. A, Sheets of large cells with numerous scattered pleomorphic and anaplastic forms[15].

2.1.5.7.2 Monomorphic epitheliotropic intestinal T –cell lymphoma(MEITL);

Monomorphic epitheliotropic intestinal T –cell lymphoma is known as EATL II, its also derived from intraepithelial T cell. In contrast to EATL I its not associated with celiac disease, occure mostly in Asian and rare in white

peoples[84]Both types of EATL are highly aggressive, recur commonly despite intensive multimodal therapy and have poor outcome[84]

In EATL II it may be impossible to reach correct diagnosis because morphology resemble MCL and immunohistochemical stain should be used[88]

Microscopic examination show diffuse transmural lymphoid infiltrate with accopaning mucosal ulceration, the lymphoma cell are small to median in size with dark to finely dispersed chromatin , incorspicuous nucleoli, and moderate amount of clear cytoplasm imparting monomorphic appearance [89] .As in the figure2-9

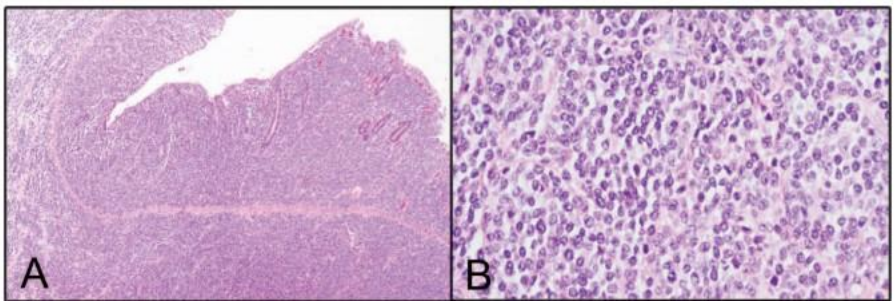


Figure2-9: Monomorphic epitheliotropic Tcell lymphoma. A, Diffuse transmural infiltrate composed of small mature lymphoid cells. B, Monotonous cells with clear cytoplasm[15]

2.1.5.7.3 Indolent T cell lymphoproliferative disorderes of GI tract:

The WHO classification defines indolent T cell lymphoproliferative disorders as indolent, nonepitheliotropic ,clonal T cell lymphoprolefirative disorders that involved the mucosa of any portion of GI tract but its more frequently occur in the small and large intestine[90] .Patient present with chronic nonspecific symptoms[91]

Microscopically; the lamina propria is expanded by small lymphocytes with monotonous appearance causing crypt displacement without overt architecture destruction[91]

2.1.5.7.4 Intestinal T cell lymphoma, not other wised specified;

As the name applies, its diagnosis of exclusion and refers to heterogenous group of T cell lymphomas that lack the morphologic and phenotypic criteria of above entities…..Thus owning to its heterogenety, its believed that nodal and extranodal peripheral T cell lymphomas some of which represent primary GI lymphoma are best classified within this group including aggressive primary intestinal T/NK cell lymphoma[92].

These neoplasm follow aggressive clinical course, including widespeard disease at presentation[91]

2.1.6 DIAGNOSIS:

Blood tests: A complete blood count (CBC)—which measures how many red blood cells, white blood cells and platelets are present in the blood—is often helpful in diagnosing lymphoma, as the cancer can affect blood cell levels. Blood samples may also be tested for specific proteins, such as lactate dehydrogenase (LDH), which can indicate whether the cancer is fast- or slow- growing , and the presence of viruses and bacteria, including H. pylori, hepatitis B and hepatitis C.

Clinical presentation and radiological features are often nonspecific. Esophagogastroduodenoscopy (EGD) and biopsy are primary methods for diagnosis [93]. During diagnostics, the clinician verifies the lymphoma, determines its site and stage, and detects possible relationship of some lymphoma subtypes with some infections and disorders, and inherited conditions. Comprehensive history taking and physical examination may provide a very important clues for reaching the goal promptly [94]. The first objective examination tool depends on the patient's complaints and the result of the physical examination. Endoscopy is the

firstly used diagnostic modality for visualization of the lesion and for getting biopsy samples depending on the involved site. The histological examination of biopsy samples taken during endoscopy is the "gold standard" for the diagnosis of PGIL. The endoscopy by itself cannot identify lymphoma or differ it from the more common GI carcinomas [(94).]

Multiple and step biopsies are required because endoscopic findings may vary from subtle mucosal changes to gross lesions. These may include mucosal edema, friability, patchy redness, irregular patchy gray or whitish granularity, contact bleeding, superficial irregular erosions and ulcerations [(95).]

Radiological examinations can help establish diagnosis and determine the extent of the lesions. Gastric wall thickening, atypical ulcer deformities, obstruction and mass effect are enhanced features suggestive, but not specific for gastric lymphoma [(96).]

Chest and abdomen CT scan should be done to exclude systemic disease, lymph node extension, and/or to evaluate for infiltration of the adjacent structures. Gastric wall thickening or mass lesion can be identified in 85% of cases by imaging, while lymphadenopathy is reported in only 50% of them [(97).] On CT scan, three quarters of cases of low grade MALT lymphomas may present with infiltrative form and polyploid form in the remainder [(97).]

Comparing MR and CT, they show a similar diagnostic capability and overlapping radiological features but due to high costs, long time required for each examination, and possible artifacts, MR is used just when the patient cannot be submitted to CT. [(98).] The EUS is an accurate technique in the evaluation of the extent and invasion of the lesion. The depth of lymphomatous infiltration and the presence of perigastric lymph nodes can be detected by EUS

and are important for treatment planning. The problem of EUS is that in follow-up and restaging after treatment (chemotherapy or radiotherapy), EUS tends to over stage residual disease and cannot always differentiate between tumor infiltration and inflammatory response to therapy [99].

It can differentiate between lymphomas and carcinomas in early stages, but in advanced stages both have similar appearances. With the development of the above diagnostic methods, open surgery is rarely needed to confirm the diagnosis [99]

2.1.7 STAGING:

Once the diagnosis of PGIL is established, accurate staging is important for planning treatment and prognosis ,it is essential to exclude systemic lymphoma with secondary involvement of the stomach [100].

Different subtypes of PGIL have different dissemination pattern from their nodal counterparts, which limits the use of conventional Ann Arbor staging system [101] .

The Ann Arbor staging system routinely used in nodal NHL , is not optimal for specific relevant features of primary extranodal lymphoma in GIT [102].

To aid staging of PGIT, various modification have been proposed including Musshoff, Blackledge and the modified Lugano has been accepted as standard in patient with PGIT[101] As in the table 2.3

Table 2.3 Staging classification according to Musshoff's criteria[103]

Stage Definition
IE Lymphoma limited to the stomach
IIE1 Involvement of stomach and contiguous lymph nodes

IIE2 Involvement of stomach and noncontiguous subdiaphragmatic lymph nodes
III Involvement of stomach and lymph nodes on both sides of diaphragm
IV Hematogenous spread (stomach and one or more extralymphatic organs or tissues)

The Following subscripts may be added E=extranodal, S=splenic, A=asymptomatic, B=symptomatic.

Table 2.4 Modified Blackledge staging system for gastrointestinal lymphomas[103]

Stage I Tumor confined to gastrointestinal tract without serosal penetration: Single primary site Multiple, non-contiguous lesions
Stage II Tumor extending into abdomen from primary site: Nodal involvement
II1 Local (gastric/mesenteric)
II2 Distant (paraaortic/paracaval)
Stage IIE Penetration of serosa to involve adjacent 'structures':
Enumerate actual site of involvement, e.g. stage IIE (pancreas), stage IIE (large intestine), stage IIE (post-abdominal wall) Perforation/peritonitis Stage IV Disseminated extranodal involvement or a gastrointestinal-tract lesion with supradiaphragmatic nodal involvement Various staging systems have been used.

Several authors have suggested that such modification may be of prognostic significance [104].

The staging include endoscopy with step biopsy in order to identify microscopic infiltration of nearly structure including the duodenum .Total body CT scan permits assessment of nodal involvement above and below the diaghram and extention of the lumen outside the stomach .The EUS is superior to CT scan in detection of false-negative cases and may be employed for accurate estimation of

both the depth and invasion and involvement of regional lymph nodes .Bone marrow examination helps determine the present or absence of tumor spread [105].

TNM staging for tumors of epithetial origin has also proposed as an alternative in PGIT to describe to what extent the disease is localized or spread. The European Gastro-intestinal lymphoma study (EGILS) group proposed modified TNM staging system named after the first venue of the group in Paris [102]

The modified staging system adjusted to the PGIL consider histopathological characteristic of the extranodal B and T cell lymphomas and accordingly enroll:(1) depth of tumor infiltration along with the thickness of GIT,(2)extent of nodal involvement,(3) lymphoma spreading [102] .

Paris staging system is valid for lymphomas originating from the gastroesophageal junction to the anus and has increasingly gained its significance[105].

Paris staging system classifies PGIL as follows[105] .

Table 2.5:

TX—lymphoma extent not specified
T0—no evidence of lymphoma
T1—lymphoma confined to the mucosa/submucosa
T1m—lymphoma confined to mucosa
T1sm—lymphoma confined to submucosa
T2—lymphoma infiltrates muscularis propria or subserosa

T3—lymphoma penetrates serosa (visceral peritoneum) without invasion of adjacent structures

T4—lymphoma invades adjacent structures or organs

NX—involvement of LNs not assessed

N0—no evidence of LN involvement

N1—involvement of regional LNs

N2—involvement of intra-abdominal LNs beyond the regional area

N3—spread to extra-abdominal LNs

MX—dissemination of lymphoma not assessed

M0—no evidence of extranodal dissemination

M1—non-continuous involvement of separate site in GIT (e.g., stomach and rectum)

M2—non-continuous involvement of other tissues (e.g., peritoneum, pleura) or organs (e.g., tonsils, ocular adnexa, lung, liver, spleen, breast, etc.)

BX—involvement of bone marrow not assessed

B0—no evidence of bone marrow involvement

B1—lymphomatous infiltration of bone marrow

TNM—clinical staging: status of tumor, node, metastasis, bone marrow

pTNMB—histopathological staging: status of the tumor, node metastasis, bone marrow

pN—the histological examination will ordinarily include six or more LNs

According to the site of the PGIL "regional" LNs implies: (a) stomach: perigastric LNs and those located along the branches of the coeliac artery (left gastric artery, common hepatic artery, and splenic artery); (b) duodenum: pancreatoduodenal, suprapyloric and infrapyloric, hepatic LNs, and those located along superior mesenteric artery; (c) small intestine: mesenteric LNs; the ileocolic as well as the posterior caecal LNs for the terminal ileum only; (d) colorectum: pericolic and perirectal LNs and those located along the ileocolic, right middle, and left colic, inferior mesenteric, superior rectal, and internal iliac arteries[102].

2.1.8 PROGNOSIS:

Several risk factors have been studied that may contribute to survival in patients with PGL. In previous studies, female gender, low-grade histology, good PS, and surgical resection have been reported to be associated with good overall survival. The international prognosis index (IPI) developed for DLBCL (age >60 years, advanced stage, poor PS, and elevated LDH) is commonly used and is predictive of survival in PGL. Although these clinical factors have been identified, many patients with PGL still have varying prognoses, and other factors may also contribute to prognostication in these patients. Five-year survival rates were reported to be 91% for low-grade, 73% for secondary high-grade and 56% for primary high-grade tumors [106].

The clinical course and prognosis of PGİL are dependent on histopathological subtype and stage at the time of initial diagnosis [107]. The best overall survival (OS) and progression-free survival (PFS) were observed in MALT lymphoma and FL, followed by DLBCL, and the poorest in EATL and other lymphomas of T-cell lineage [108]. Overall survival rates remain poor also in MCL [109].

The response of low grade MALT lymphoma to H .pylori eradication is predicted by stage .Low grade , early stage MALT lymphoma following successful H.pylori eradication has complete regression in about 75-80%of cases [110]. Gastric MALT lymphoma is commonly an indolent, multifocal disease and because of that, it has a high rate of relapse after surgery. In 10% of cases, it can have synchronous involvement of intestinal and extraintestinal sites [111].

Where the disease is limited to the gastric mucosa or submucosa.Studies shown that comlete response has been achieved in nearly all patient. Where is complete response have decreased in patient when disease extended to the muscularis propria or serosa [112], it has also shown that patient with nodal disease achieved no complete response with H .pylori eradication alone [113] .About 10% of gastric MALT lymphoma with t(11,18)(q21.q21)translocation are resistant to H .pylori antibiotic therapy that require strict follow up ,and if clinically indicated ,trial of chemotherapy , immunotherapy and/or radiotherapy for localized disease may be pursued[114].

Gastrointestinal DLBCL prognosis influenced by several factors: age, stage of disease, lactate dehydrogenase (LDH) level, and use of chemotherapy are independently and significantly associated with survival. The International Prognostic Index (IPI) is the most valuable and main clinical tool widely employed [115].

Table 2.6..:International prognostic index[105]

Adverse risk factor
Age >60 years
≥2 extranodal site
Ann-arbor stage III-IV
high LDH

perforated status ≥ 2(ECOG) RISK: Iow (n=0-1) low- intermediate(n=2) high-intermediate(n=3) high(n=4-5)

A more aggressive clinical course has been reported in patient with more aggressive disease, such as present of systemic symptoms, bulky lymphadenopathy and elevated LDH level. Gene expression profile (GEP) is a new evolving approach to diagnose, classify and prognosticate DLBCL. According to GEP two prognosticaly significant types of DLBCL have been identified [(115).] The molecular subgroups include GCB and ABC, which are associated with different chromosomal aberrations. GCB group has a better prognosis than the ABC group [(115).] GEP is considered the "gold standard" to identify the molecular subtypes of DLBCL, however, is not available in routine diagnostics due to its cost-ineffectiveness.

Patients have higher survival rate with CD10 positive disease in compared to patient with CD10 negative lymphomas [(116).]

Patient with IPSID in early phases of disease may completely resolved following antibiotic therapy and transformation to DLBCL is not uncommon [(117)]

Primary GI MCL is more aggressive and survival is poor compared to nodal MCL involving the GIT and compared to MALT lymphoma patient with GI tract MCL confers worse prognosis. Patients respond poorly to chemotherapy [(118).] Despite the improved response rate of Chemotherapy for MCL, current overall survival rates remain poor because of the advanced stage in most of the cases and the early

relapse. Median survival with standard treatment for MCL patients remains between 1.5 and 4 years [109].

Poor clinical outcome have reported in both type I and type II EATL with 5 years survival of 8-20% [119], death often results from malabsorption and other abdominal or clinical complication.

GI FL has poorer outcomes than previously suggested [120]. Anatomical location within the GIT may have prognostic implications, with primary duodenal and small intestinal disease having a significantly higher progression-free survival rate than non-duodenal presentations [120].

2.2TUMOR MARKER:

Tumor markers are biochemical indicators of present of tumor,Its refers to a molecule that can be detected in plasma and body fluids [121]. Tumor marker are measurable biochemical that are associated with malignancy, these markers are either produced by tumor cell (tumor –derived) or by the body in response to tumor cell (tumor –associated), they are released into circulation and measured in the blood[122]

Tumor markers are not the primary way for tumor diagnosis rather they can be used as a test to support the diagnosis [121] . Although they are ordinarily imperfect as screening test for detection of occult (hidden) cancer once particular tumor has been found using a marker, the marker may be a modality of monitoring the success or failure of treatment [123]. The tumor marker level may also reflect the extent (the stage) of the disease ,indicating how quickly the cancer is possibly to progress and helping to determine the prognosis [123].

Advantages of using tumor markers: 1-its screening and early detection of cancer, screening refers to looking for cancer among people who do not have any symptoms of disease .While early detection is finding cancer at early stage. 2-Aid in diagnosis of cancer; however tumor markers are usually not used to diagnosis cancer, its can help determine if a cancer is likely in some patient after diagnosed by biopsy[124] ,3-Determine response to treatment are of the most important utilize for tumor markers is to monitor patient being treated for cancer, if the initially raised tumor marker level goes down with treatment it indicate that treatment having beneficial effect [123]. 4- prognostic indicator of disease progression and 5-indicate relapse during follow- up period, marker used to detect cancers that recur after initial treatment[125]

2.2.1 CD23

CD23 was defined as the low-affinity receptor for immunoglobulin (Ig) E and also known as FCER II plays important roles in regulation of IgE responses [126]. CD23 is a type II transmembrane glycoprotein of approximately 45kDa molecular weight comprising a large C-terminal globular extracellular domain that is strikingly similar to C-type lectins , followed by a stalk region bearing several repeats that serve asputative leucine zipper that are important in CD23 oligomerization [127] its found on mature B cell, activated macrophages, esonophile , follicular dentric cells, platelets and megakaryocyte and intestinal epithelial cells[128] its expression to subject to regulation by a number of stimuli. In humans, CD23 is encoded by an 11-exon gene, FCER2, located at chromosome 19p13.3 [129] CD23 differs dramatically from the high affinity receptor in terms of structure. FCERI has multiple subunits whereas FCERII is comprised solely of CD23 polypeptid.

CD23 has multiple ligands, including IgE, CD21 and members of two families of integrins. The principal ligand is IgE, which is bound by both membrane-bound and soluble trimeric CD23 species ,The next best characterized ligand for CD23 is CD21 [130].The interaction of CD23with CD21 involved both carbohydrate-dependent and independent interaction [131].CD23 can interact in cis and trans with major histocompatibility complex (MHC) class II protein, in carbohydrate-independent manner, using structure in the CD23 protein that are located in the stalk region of the molecule[132].This interaction is believed to facilitate antigen processing and presentation by antigen –IgE complexes captured by CD23 [133]

as in the figure 2.10

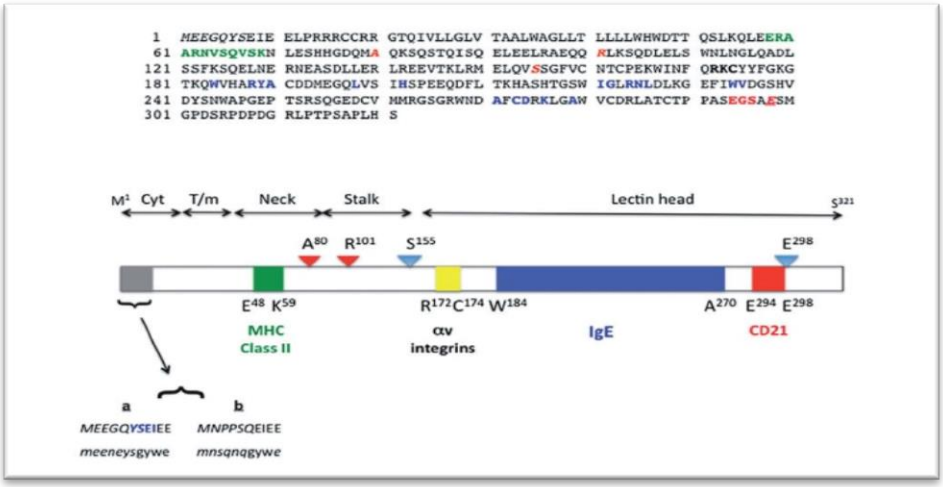


figure 2.10: Primary structural features of human CD23[134].

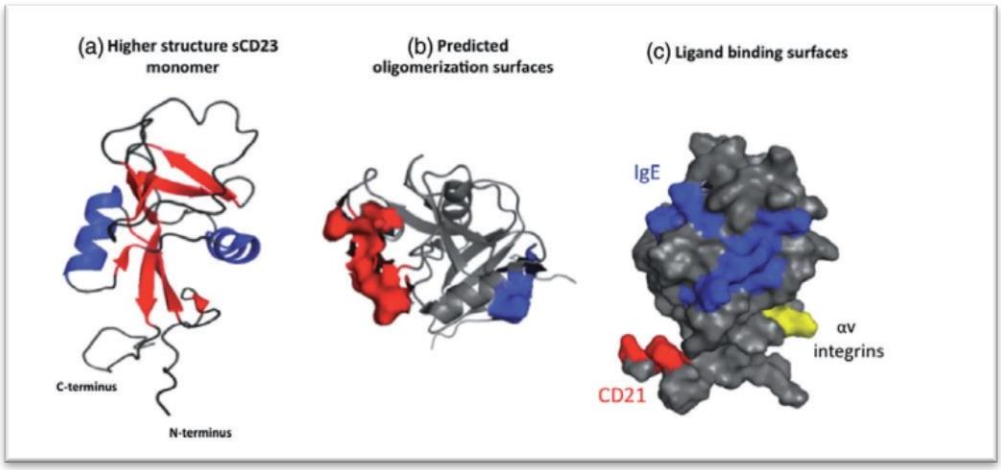


Figure 2.11Higher structural features of CD23[131].

There are many studies suggest that elevated CD23 , either on neoplastic cell surface or as a soluble form is a usefull marker in either diagnosis and prognosis of disease. Differentiates small lymphocytic lymphoma (SLL\chronic lymphocytic leukemia CLL)CD23positive(+) from mantle cell lymphoma or MALT lymphoma

CD23 negative(-).Distinguish nodal marginal zone lymphoma from follicular lymphoma by identify a disrupted follicular dendritic cell pattern [135] .EBV transformed cell express high level of CD23 [136] and CD23 is a usefull marker in delineating mediastinal diffuse large B cell lymphoma from classical Hodgkin lymphoma[137].Soluble CD23 levels are elevated in range of disease conditions with autoimmune or inflammatory component rheumatoid arthritis (RA), systemic lupus erythromatous (SLE) ,S jogrens syndrome(134)

2.2.2CD5 (Leu-1)its first described over 30 years ago that has been used as a surface marker to identify both human and murine cell population [138].

Its a67-kda type 1 monomeric glycoprotein belonging to ancient family of scavenger receptor cystein –rich protein(SRCR)characterized by cysteine –rich extracellular domin of approximately 100 aminoacid [139] .It play a conserved role

in both lymphocyte development and function among species [140].It expressed on most T lymphocyte and subset of mature B cell, previously termed B-1 cells. T cells express higher level of CD5 2-5 folds than B cells [141].Although physiological function is unknown , several lines of evidence suggest that CD5 may play a role in the regulation of T cell activation and in T cell-antigen presenting interaction[142].

Recent studies have suggested that function of CD5 may differ with respect to specific cell population, for example on peripheral T cell , CD5 appears to play co-stimulatory role[143].On jurkat cell,CD5 was recently shown to negatively regulated TCR signaling [144].CD5 may provide continual stimulation through B cell Ag receptor(BCR)via its interaction with V_H–framework region [145] as in the figure 2.12 .The gene is located on long arm of chromosome 11q13.there is no confirmed ligand for CD5but there is evidence that CD72 Ac type lectin ,may be a ligand or that CD5 may be homophiliic ,binding CD5 on the surface of other cell [146].CD5 is up-regulated on T cell upon strong activation .In thymus ,there is a correlation with CD5 expression and strength of the interaction of the T cell towards self-peptides[146],CD5 is a good immunohistochemical marker for T cell, although not as sensitive as CD3 .About 76%of T cell neoplasm are reported to express CD5 ,and it is also found in chronic lymphocytic leukemia and mantle cell lymphoma(both being B cell malignancies),that do not express CD3 . It is commonly lost in cutaneous T cell lymphoma, and its absent can be used as an indicator of malignancy in this condition .The absent of CD5 in T cell lymphoblastic leukemia ,While relatively rare, is associated with poor prognosis.[147].

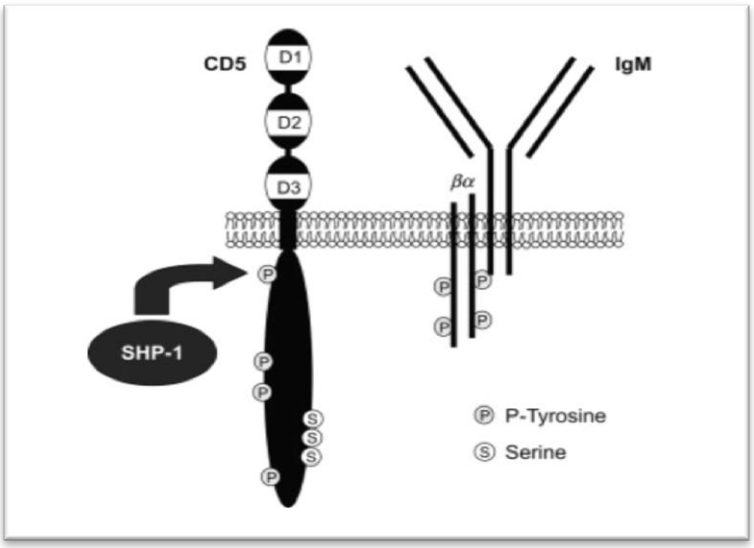


Figure 2.12 The B cell receptor (BCR) comprises membrane immunoglobulin (Ig) M, with Igα/Igβ as transducing molecules. CD5 is made up of three extra-cytoplasmic domains (D1–D3) and is associated with the BCR and brings about the src-homology 2 domain-containing phosphatase (SHP-1) to dampen the transducing cascade. The tyrosine residues are phorphorylated (P) by phosphorylases but not serine residues[148]

2.2.3CD79:

The mouse CD79A gene, then called mb-1,was cloned in the late 1980s,followed by the discovery of human CD79A in the early 1990s.It is short gene 4.3 kb in length, with 5exons encoding for 2 splice variant resulting in 2 isoform[149].

Is composed of CD79a and CD79b component expressed exclusively in all mature and immature B cell and majority of B cell neoplasm, including precursor B-acute lymphocytic leukemia (pre B –cell ALL), L and H lymphocyte predominance Hodgkin lymphoma, and many plasma cell tumor [149]The CD79a protein is present on the surface of B-cells throughout their life cycle, and is absent on all other healthy cells, making it a highly reliable marker for B-cells in immunohistochemistry. The protein remains present when B-cells transform into

active plasma cells, and is also present in virtually all B-cell neoplasm than that of CD79b[150]

Because even on B-cell precursors, it can be used to stain a wider range of cells than can the alternative B-cell marker CD20, but the latter is more commonly retained on mature B-cell lymphomas, so that the two are often used together in immunohistochemistry panels [150]

Loss of CD79b expression is characteristic feature of CLL/SLL and may be diagnostic use [151].

Table 2.7: Expression of CD79a and CD79b proteins in B cell[152]

	Early –B	COMMON –B	Pre B	Mature B
Cd79a	+	+	+	+
Cyt –CD79b	-	+/-	+	+
Mem CD79b	-	-	-	+

Cyt-CD79b, cytoplasmic CD79b; Mem-CD79b, membranous CD79b.

CD79molecule comprising two transmembrane protein,CD79a and CD79b,which form a disulfide- linked heteromer and are members of immunoglobulin(Ig)gene superfamily[153], thus forming the B-cell antigen receptor (BCR). This occurs in a similar manner to the association of CD3 with the T-cell receptor, and enables the cell to respond to the presence of antigens on its surface [150].

CD79a also called MB-1,Bcell antigen receptor complex associated protein alpha- chain .MB-1 gene located on chromosome 19,band q13.2-3,encodes CD79a. The human CD79a cDNA contains 1,068 base pair with the longest open reading

frame of 678 and encodes a226- amino acid membrane glycoprotein[154]CD79a is also known as cd79α, Igm-α and Igα[155]

CD79b called B29 receptor include Ig beta protein .The human B29 gene located on chromosome 17, band q23, encodes CD79b. The human B29 gene encodes 1,270- base pair(bp), c DNA and a 229 amino acid protein[156]The B29 gene is located between SCN4A gene and five genes of the human growth hormone gene cluster CD79b is also reffered to as cd79 B and IgB[157] .As in the figure2.13

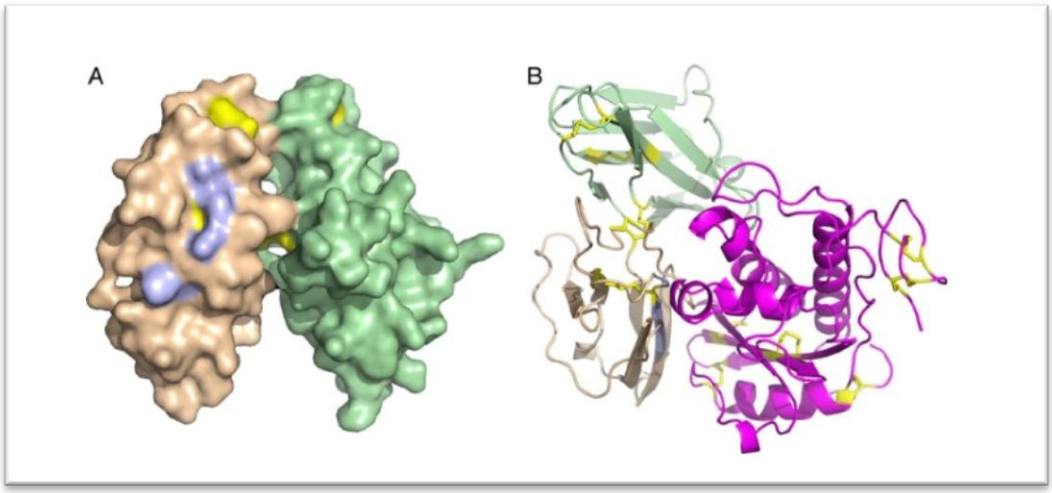


Figure2.13 Rigid body models of the CD79A/CD79B heterodimer (A) and the CD79A/CD79B:Na-ASP-2 complex (B). CD79A is colored wheat; CD79B, pale green; and Na-ASP-2, magenta. Cysteine residues and disulphide bonds are rendered as sticks in yellow. The CD79A peptide HFQCPH (residues 51–56) is colored blue. A, Surface representation of the CD79 heterodimer model. B, Cartoon rendering of the modeled ternary complex of Na-ASP-2 and CD79[158].

The transmembrane CD79a and CD79b protein couple at the extracellular end with any one of the five different types of transmembrane Ig molecule (IgM.IgD,IgG,IgE,or IgA),which are disulfide-linked protein composed of two Ig

heavy chain and two Ig light chain[155]..The intracellular domain is composed of 61 amino acid for CD79a and 48 amino acid for CD79b.The cytoplasmic portions of CD79a and CD79b provide the link required to transduce the extracellular signal, such as that produced by antigen binding to the Ig portion of BCR ,across the cell membrane and into the cytoplasm that will result in rapid increase in the level of protein tyrosine phosphorylation on a number of substrate and activation of multiple biochemical pathway[159]

Genetic deletion of the transmembrane exon of CD79A results in loss of CD79a protein and a complete block of B cell development at the pro to pre B cell transition[.160]Similarly, humans with homozygous splice variants in CD79A predicted to result in loss of the transmembrane region and a truncated or absent protein display agammaglobulinemia and no peripheral B cells[161]

Chapter three

Patient, Material and Method

3.1. Patients

A retrospective cross section study done in the laboratories of Baghdad medical city, 30 formalin fixed paraffin embedded biopsies tissue blocks were obtained from 30 patients who had undergone endoscopic and excisional biopsy and diagnosis were confirmed as gastrointestinal lymphoma by expert histopathologists. The pathological paraffin blocks were related to the period 2016 to 2023, that collected from Alhussainy teaching hospital in Karbala and many private histopathology laboratories in Baghdad and Hilla during the period from October 2022 till April 2023.The patients ages were ranging from 3-78 years and were comprising from 22 males and 8 females.

3.2. Antibody and Equipment:

The antibody that were used in this study are listed in **table (3-1).**

Table (3-1): The Antibody and kits used in the study.

No.	Antibody	Company	Origin
1	Monoclonal mouse Anti-Human CD5	Dako	Denmark
2	Monoclonal Mouse Anti-HumanCD23	Dako	Denmark
3	Monoclonal mouse Anti-Human	Dako	Denmark

	CD79α		
4	EnVision FLEX system EnVision FLEX Peroxidase – Blocking Reagent (RTU) Primary Antibody –FLEX RTU or diluted concentrated EnVision FLEX /HRP(RTU) EnVision FLEX Substrate Working Solution EnVision FLEX Hematoxylin (RTU)	Dako	Denmark

The equipment were used in this study are listed in table (3-2).

Table (3-2): The equipment and tools used in the study.

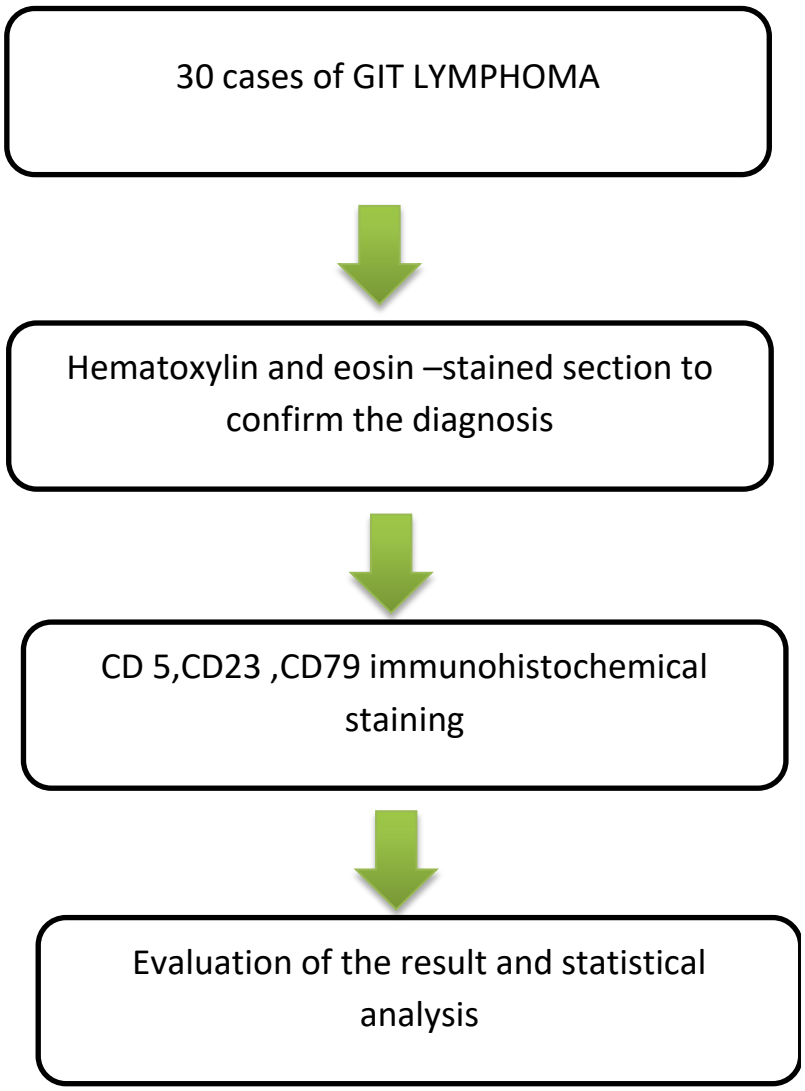
No.	Equipment and Tools	Company	Origin
1	Dako Pen	Dako Denmark A/S	Denmark
2	DPX(Disteren plasticizer Xylene)	Sigma	Germany
3	Eosin Yellowish stain solution	SyrBio	Syria

4	Ethanol (99%)	Scharlau	Spain
5	Hematotoxiline stain solutio	SyrBio	Syria
6	Callipered Cylinders	MBL.BORO	Italy
7	Cover Glass	CITOGLAS	China
8	Flask 250 ml	Oxford	U.K.
9	Floating water bath	Electro thermal	Germany
10	Gauze Roll	Huanggang Huangzhou Xianghui Textiles	China
11	Gloves	United Medical Indu-ries	KSA
12	Humidified chamber	Individually hand made	Iraq
13	light microscopy	Olympus	Japan
14	Micropipette 10-1000	Slamed	Germany
15	Micropipette 2- 20	Gilson	France
16	Microtome	Thermo	U.K.
17	Oven	Memmert	Germany
18	Plan tubes	Bio-Basic	Canada
19	Polysine slides	Thermo	U.K.
20	Refrigerator	Keriazi	Egypt
21	Slides	Sail Brand	China
22	staining jars	Memmert	Germany
23	Syringe(5and20)ml	Set. Inject	Turkey
24	Timer	Digital timer	China

25	Water bath flat plate	Electro thermal	Germany

3.3 Method:

3.3.1 Study design diagram



3.3.2. Collection and preparation:

During the period from October 2022 till April 2023, 30 case of GIT lymphoma include formalin-fixed paraffin embedded tissue blocks were obtained from the histopathology laboratories of previously mentioned centers .The practical part of this study was done in the postgraduate laboratory , Department of pathology/ Baghdad medical city.

3.3.3. Tissue sectioning and slide preparation:

Four tissue sections of (5µm) thickness were cut from each paraffin blocks; one section was mounted on ordinary slides and stained with Haematoxylin and Eosin stain for histopathological re-examination, while the other sections were mounted on charged slides for subsequent immunohistochemical study of CD5, CD23, and CD79 markers.

3.3.3.1. The protocol of Haematoxylin and Eosin staining (H. & E.):

This protocol was used for histopathological reexamination and as follows:

1-Deparaffinization of sections has been performed by incubating the sections in an oven at 60 C℃for 2 hours, followed by 2 changes in xylene each for 5 minutes.

2- Then tissue was rehydrated in decreasing grades of ethanol including 3 changes of 100 % ethanol each for 5 minutes; followed by 95 % ethanol for 5 minutes; 70 % ethanol for 5 minutes and washing in distilled water.

3- Subsequently sections were stained in Harris hematoxylin for 3-10 minutes.

4- After that slide were washed well in running tap water.

5- Followed by removing excess stain by differentiating the sections in 1% acid alcohol solution (1% hydrochloric acid + 70% ethanol) for 5-10 seconds.

6- Then slides were washed well in tap water until sections regain their blue color.

7.Later sections were stained in Eosin for 2-5 minutes.

8- Dehydration slowly through increasing grades of alcohols (i.e., 70%, 90%, 100% and 100%) each for 5 minutes.

9- Followed by clearing in 2 changes of xylene, each for 5 minutes.

10- Finally slides were mounted with DPX (Distyrene, plasticizer and xylene) and covered with coverslip.

3.3.3.2 Immunohistochemical staining protocol:

The immunostaining method used in the current study was DAKO detection system which applied for CD5, CA23 and CD79 staining and included the followings steps:

1-Five microns sections of formalin-fixed and paraffin-embedded tissue were mounted on positive charged slides.

2-Deparaffinization was done by incubating the sections in an oven at 60 C℃for 2 hours, followed by 3 changes in xylene each for 5 minutes, then rehydration in decreasing grades of ethanol (100%, 90% each for 10 minutes then 70% for 5 minutes).

3- Epitope retrieval was done by incubating the tissue section into EnVision FLEX Target retrieval Solution PH 9 (Tris –EDTA) was already placed in water bath rise its temperature 97c for 40 minutes cool down to 65c followed by incubating the section in wash buffer PH7.4 for 5 minutes.

4- Tissue was encircled with Pap Pen.

6- After those slides were placed in Polydetector Peroxidase Blocker for 5 minutes to block endogenous peroxidases.

7- Wash was done in 3 changes of IHC wash buffer each for 5 minutes.

8- Later sections were incubated with ready to use primary antibody (CD23 is 1:50. Dilute the antibody in DAKO antibody Diluent, CD5 used at dilution 1:50, CD79 used at dilution range 1:25 -1:50) for 30 minutes at room temperature.

9- Wash was done in 3 changes of IHC wash buffer each for 5 minutes.

10- Then sections were incubated with PolyDetector HRP Label for 15 minutes.

11- Wash was done in 3 changes of IHC wash buffer each for 5 minutes.

12- Later Hematoxylin counterstaining was done by 3 dips.

13- Followed by washing of slides in DI water.

14- Tissue was dehydrated and mounted with coverslip.

15- Slides were examined under light microscope.

3.3.4. Evaluation of immunostaining:

Under the light microscope, the criterion for detection of positive immunoreaction was dark brown stain that precipitates as protein expression (cytoplasmic and nuclear) The intensity of the staining was measured by counting the percentage of positive cells for immune reaction in 300 malignant cells on X40(400). The immunostaining was calculated as the percentage of immunoreactive cells per total number of malignant cells, the scoring for result by using H score .

H score calculated by multiply intensity × percentage

3.3.5 Statistical analysis

Statistical analysis was carried out using SPSS version 27. Categorical variables presented as frequencies and percentages, continuous variables presented as mean, standard deviation and range. Fisher's exact test was used to find the association between categorical variables. A *p*-value of ≤ 0.05 was considered as significant.

Chapter Four

Results

4.1. Distribution of patients according to age.

The patients age with GIT lymphoma were range from (3-78) years with mean age was (38.1± 27.14) and divided into four groups (<20, 20-40, 41-60, ≥ 60) to determine the more frequent ages. The result show that GIT lymphoma was more frequently diagnosed in older age group with higher incidence at age group (≥ 60) years which account for 11 cases(36.7)% and low incidence in ages of (20-40)years that show in 3 cases(10.0)% as in figure 4.1

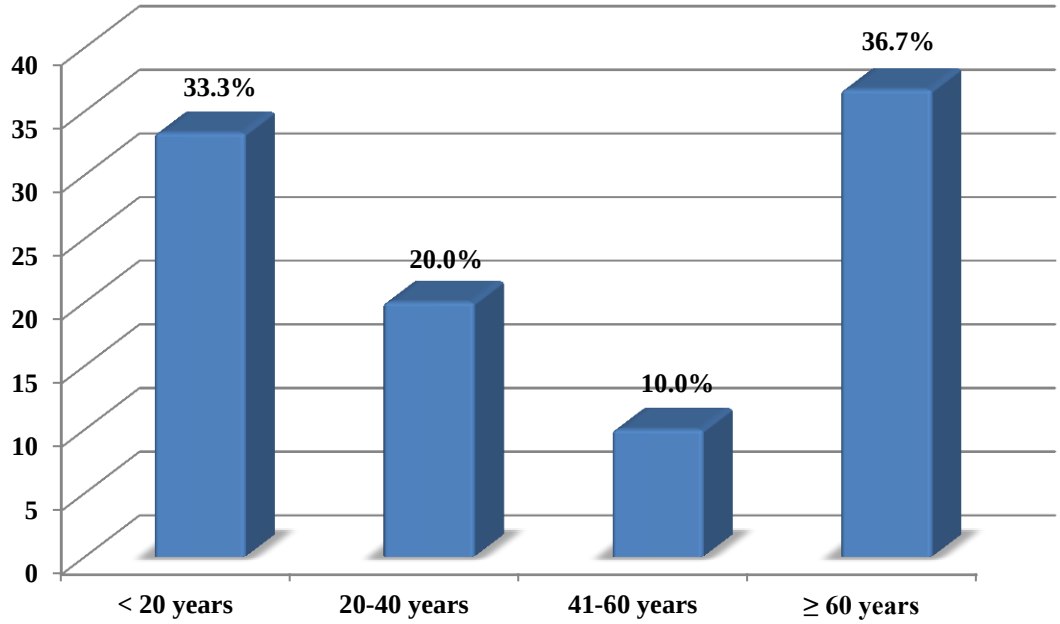


Figure 4.1: Distribution of patients with GIT lymphoma according to age (N=30)

4.2: Distribution of patients with GIT lymphoma according to gender:

The gender of patients group with GIT lymphoma includes 22 male (73.3%),8 female (26.7%).The present study demonstrated that the incidence of GIT lymphoma in males was higher than in female as in figure 4.2

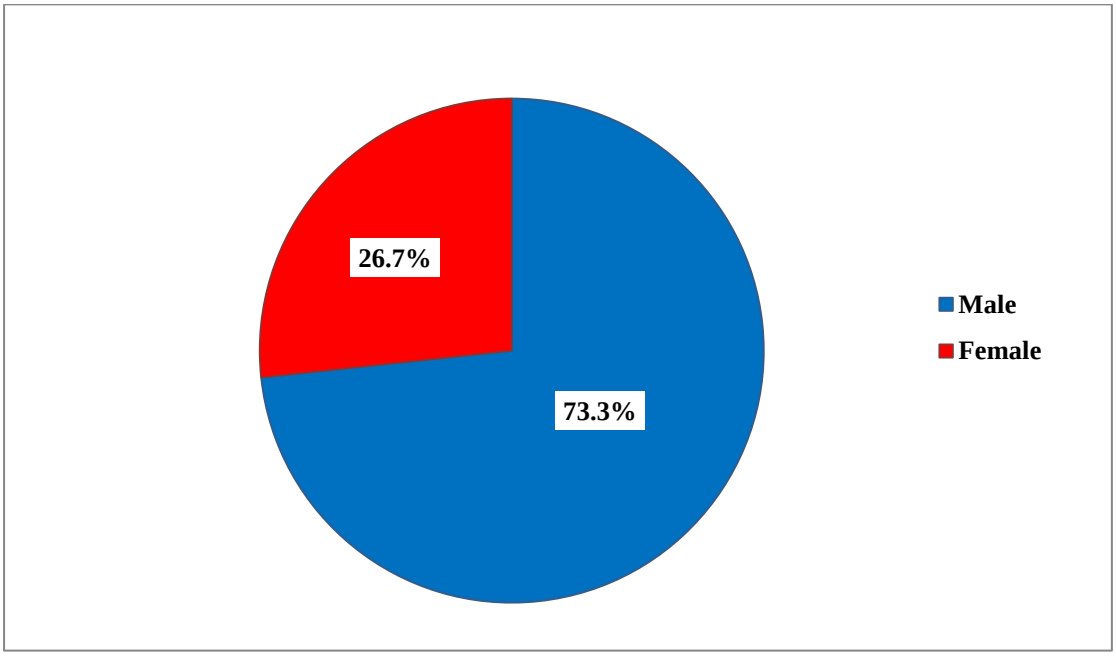


Figure 4.2 : Distribution of patients with GIT lymphoma according to gender (N=30)

4.3:Distribution of patients with GIT lymphoma according to its subtypes:

The present study demonstrated that DLBCL is more frequent type 16 cases (53.3)% while follicular lymphoma and T cell lymphoma are the least frequent types account one case each 3.3% as in table 4.1

Table4.1: Distribution of patients with GIT lymphoma according to its subtypes

Diagnosis	Frequency	%
Diffuse large B cell lymphoma	16	53.4%
Malt lymphoma	6	20.0%
Burkitts lymphoma	6	20.0%
Follicular lymphoma	1	3.3%
T-cell Non-Hodgkin's lymphoma	1	3.3%
Total	30	100.0%

4.4 Immunohistichemical study:

4.4.1Distribution of patient with GIT lymphoma according study marker:

CD23 immunohistichemical expression was reported to be negative in (30) cases of GIT lymphoma.

CD5 immunohistochemical expression was reported to be positive 33.3% (10 out of 30) cases of GIT lymphoma, while CD79 immunohistochemical expression was reported to be positive 96.7% (29 out of 30) cases of GIT lymphoma . As in table 4.2

Table4.2: Immunohistochemical expression of CD23 ,CD5 and CD79 in GIT lymphoma

Study markers	Number	%
H score CD 23 Negative (0)	30	100.0%

Positive	0	0.0%
Total	30	100.0%
H score CD 5		
Negative (0)	20	66.7%
+1	3	10.0%
+2	7	23.3%
Total	30	100.0%
H score CD 79		
Negative (0)	1	3.3%
+1	1	3.3%
+2	6	20.0%
+3	11	36.7%
+4	11	36.7%
Total	30	100.0%

4.4.2: Association between H score CD 5 results and study variables : The present study demonstrated that there is no significant association between H score CD5 results including (negative 0. +1, +2) and study variable including (age ,sex, subtypes) P- value > 0.05 . As in table 4.3.

Table 4.3: Association between H score CD 5 results and study variables (N=30).

Study variables	H score CD 5 results			P-value
	Negative (0)	+1	+2	
Age (years)				
<20 years	6 (30.0)%	0 (0.0)%	4 (57.1)%	0.474
20-40 years	5 (25.0)%	1 (33.3)%	0 (0.0)%	

41-60 years	2 (10.0)%	0 (0.0)%	1 (14.3)%	
≥ 60 years	7 (35.0)%	2 (66.7)%	2 (28.6)%	
Total	20 (100.0)%	3 (100.0)%	7 (100.0)%	
Gender				
Male	13 (65.0) %	3 (100.0)%	6 (85.7)%	0.555
Female	7 (35.0)%	0 (0.0)%	1 (14.3)%	
Total	20 (100.0)%	3 (100.0)%	7 (100.0)%	
subtypes				
DLCBL	11 (55.0)%	1 (33.3)%	4 (57.1)%	
Malt lymphoma	4 (20.0)%	2 (66.7)%	0 (0.0)%	
Burkitts lymphoma	4 (20.0)%	0 (0.0)%	2 (28.6)%	0.316
Follicular lymphoma	1 (5.0)%	0 (0.0)%	0 (0.0)%	
T-cell NHL	0 (0.0)%	0 (0.0)%	1 (14.3)%	
Total	20 (100.0)%	3 (100.0)%	7 (100.0)%	

Fisher's exact test

4.4.3: The association between H score CD 79 results including and study variables: The association between CD79 results including (negative 0 ,+1, +2 ,+ 3 ,+ 4) and study variables including (age, sex, subtypes ,) demonstrated that there was no significant association between H score CD 79 results and variable study, as in table 4.4

Table 4.4: Association between H score CD 79 results and study variables (N=30)

Study variables	H score CD 79 results					P-value
	Negative (0)	+1	+2	+3	+4	
Age (years)						
<20 years	0 (0.0)	0 (0.0)	3 (50.0)	1 (9.1)	6 (54.5)	
20-40 years	1 (100.0)	0 (0.0)	0 (0.0)	3 (27.3)	2 (18.2)	0.216
40-60 years	0 (0.0)	0 (0.0)	1 (16.7)	2 (18.2)	0 (0.0)	
≥ 60 years	0 (0.0)	1 (100.0)	2 (33.3)	5 (45.4)	3 (27.3)	
Total	1 (100.0)	1 (100.0)	6 (100.0)	11(100.0)	11(100.0)	
Gender						
Male	0 (0.0)	1 (100.0)	6 (100.0)	8 (72.7)	7 (63.6)	0.272
Female	1 (100.0)	0 (0.0)	0 (0.0)	3 (27.3)	4 (36.4)	
Total	1 (100.0)	1 (100.0)	6 (100.0)	11(100.0)	11(100.0)	
Subtypes						
DLCBL	1 (100.0)	0 (0.0)	2 (33.3)	9 (81.8)	4 (36.4)	
Malt lymphoma	0 (0.0)	1 (100.0)	2 (33.3)	2 (18.2)	1 (9.1)	
Burkitts lymphoma	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	4 (36.4)	0.12
Follicular lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	
T-cell NHL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	
Total	1 (100.0)	1 (100.0)	6 (100.0)	11(100.0)	11(100.0)	

*P value ≤ 0.05 was significant(Fisher's exact test)

4.4.4: Association between H score CD 79 results and H score CD 5: The present study demonstrated there was no significant association between H score CD 79 results(negative 0 , +1 ,+2 ,+3 ,+4) and H score CD 5 results(negative 0 ,+1 ,+2) P-value >0,05 as in table 4.5.

Table4.5: Association between H score CD 79 results and H score CD 5 results (N=30)

H score CD 5 results	H score CD 79 results					P-value
	Negative (0)	+1	+2	+3	+4	
Negative (0)	1 (100.0)	1 (100.0)	3 (50.0)	7 (63.6)	8 (72.7)	0.986
+1	0 (0.0)	0 (0.0)	1 (16.7)	1 (9.1)	1 (9.1)	
+2	0 (0.0)	0 (0.0)	2 (33.3)	3 (27.3)	2 (18.2)	
Total	1 (100.0)	1 (100.0)	6 (100.0)	11 (100.0)	11 (100.0)	

*P value ≤ 0.05 was significant.(Fisher's exact test)

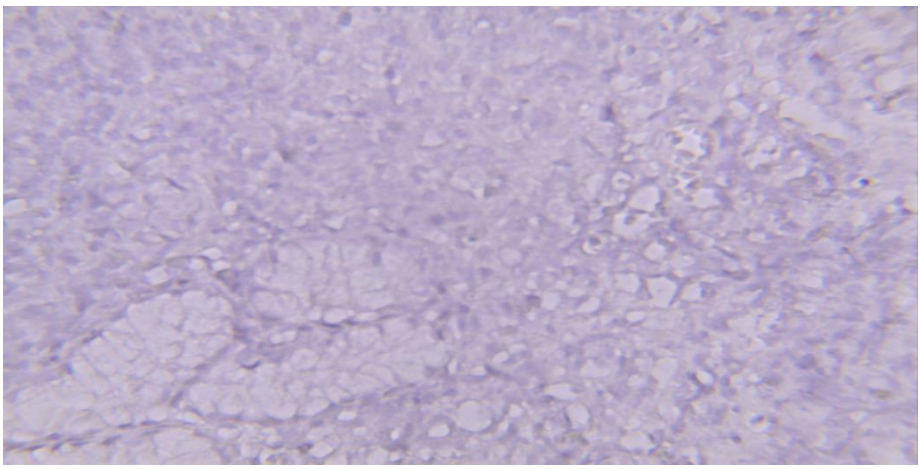


Figure 4.3 : IHC staining for CD23 show no nuclear and cytoplasmic staining (original magnification x40

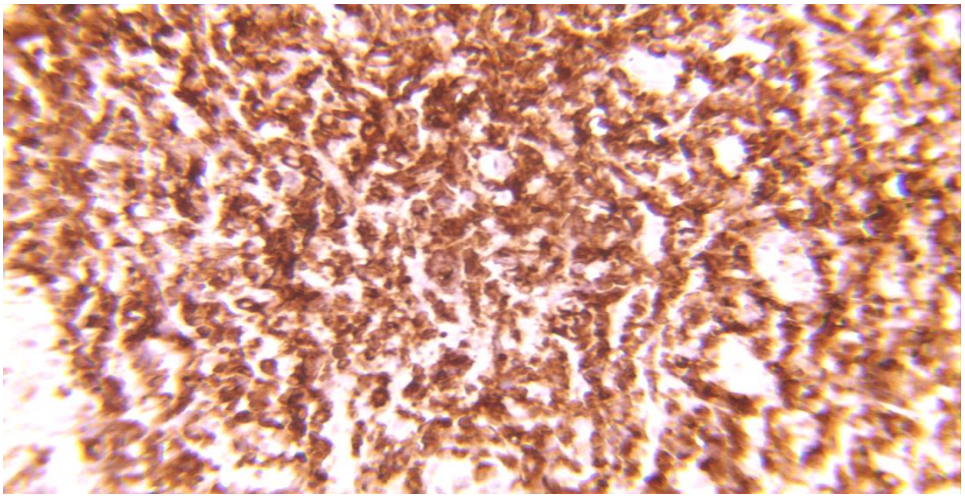


Figure 4.4 : diffuse ,strong nuclear and cytoplasmic staining for CD79 (original magnification(x40)

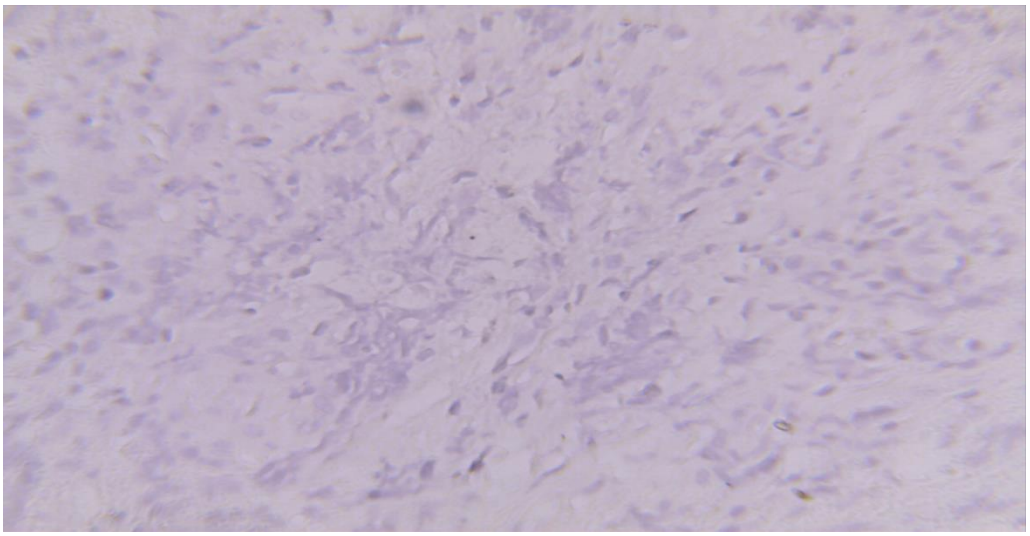


Figure 4.5 : IHC staining show no nuclear and cytoplasmic staining for CD5 (original magnification x40)

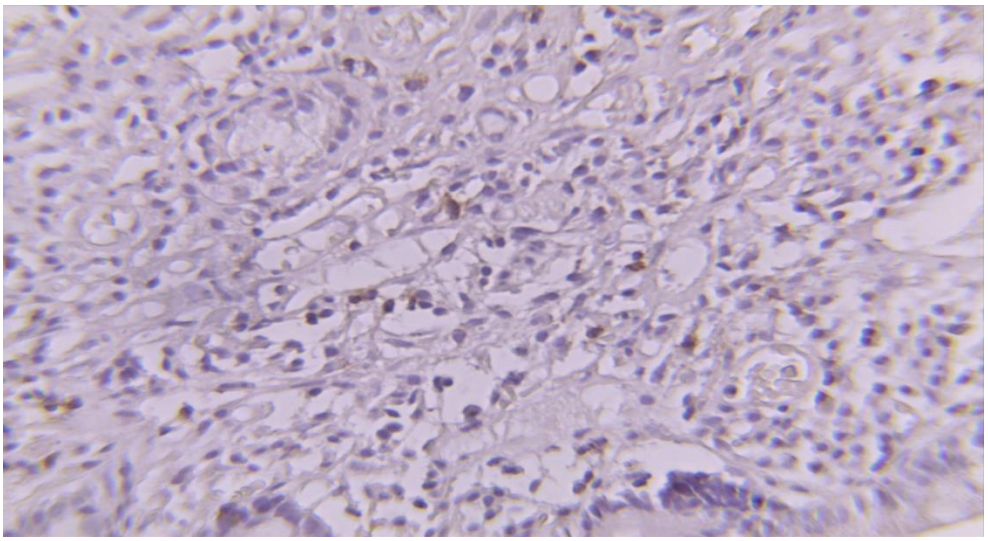


Figure 4.6 :low percentage of intense reaction for CD5 (original magnification x40)

Chapter Five

Discussion

5.1 Demographic distrubution of patients (age and gender)

In the present study, the patients age with GIT lymphoma were range from (3-78) years , with mean age was (38.1 ± 27.14) with maximum age was 78 and minimum age in child 3years.. GIT lymphoma more frequently diagnosed in older age groups with highest incidence in age group of ≥ 60 corresponding to 11 case (36.7)%.The results agree with other study carried out in **China by Yu Xiang eta , in 2022** [162]that found the median age is 63 years. While disagree with study carried out in **Iran by Farahnaz Bidarizereh poosh ,eta 2021**[163] that show the incidence of GIT lymphoma is more common in age group <60 years old these difference in age groups could be contributed to the difference in environmental risk factors and also smaller sample size.

Our patients group with GIT lymphoma involved in this study included 22 males 73.3 % and 8 females 26.7% the incidence of GIT lymphoma in males was higher than in females .Similar results by **Shirwaikar ThomasA, et 2019**[164] who found its more common in males, and by **Ahmed M.AL-Akwaa , et 2004 in Saudia Arabia**[165] that found males are 2-3 times more affected than females.

5.2 Distribution of patient according to its subtypes:

the present study demonstrated more than half of patients with GIT lymphoma (N=16, 53.4%) presented with Diffuse large B cell lymphoma, MALT lymphoma and Burkitts lymphoma represent only 6 patients (20.0%), only one patient presented with Follicular lymphoma (3.3%) and only one patient presented with T-cell Non-Hodgkin's lymphoma. The present results agree with another study done by **Luis Miguel Juarez, et 2018**[166]which also show that diffuse large B cell lymphoma is the highest one 59%, while low incidence in follicular and T cell lymphoma, and disagree with study done by **Dehyhran ,eta in IRAN 2013** [167] that

show Maltoma is the most common type 60% this difference may be due to ethnic variation and smaller sample size.

5.3 Immunohistochemical expression of study marker:

5.3.1 CD23:.

The staining results regarding this marker revealed that CD23 was reported to be negative in all types of GIT lymphoma included in this study (DLBCL, MALT ,Follicular lymphoma ,burkitts lymphoma and T cell lymphoma), and this result is agree with some difference with other study in **USA by SH Kroft eta in 1998** [168] that found lack of expression of CD23 in all cases of his study (49cases)of gastric lymphoma with rare exception that one case positive CD23 highlighted residual follicular denderic cell lymphoma and found This lack of CD23 expression might represent a useful feature in small or partially crushed biopsy specimens, particularly in the differential diagnosis with follicular small cleaved cell lymphoma presenting in the gastrointestinal tract.

And also other study done in **India by Mehta,eta in 2022** [169]that show CD23 was negative in all cases of his study (30 cases of PGL) that include MALT lymphoma and DLBCL which will rule out low grade lymphoma such as Follicular and small cell lymphoma that not found in subtypes in our study.

5.3.2 CD5:

It's a member of the the scavenger receptor cycteine –rich family of extracellular domain like structure and involved in signal transduction ,CD5 is weakly expressed on most immature T cell precursor and is more intensely expressed on mature T lymphocytes, Additionally is weakly expressed on a subset of normal B cells and in the B cell lymphoma.

In the present study CD5 was negative in 66.7% of cases and positive in 33.3% H score CD5 was negative (0) in two third of patients (N=20 , 66.7%), H score CD5 (+1) represent three patients (10.0%) and H score CD5 (+2) represent seven patients (23.3%) included (DLBCL ,MALT lymphoma, Burkitts lymphoma and T cell lymphoma)

These results have agreement with other study done by **Kazuhisa Hasui ,eta in 2003** [170] that involved 34 cases of gastric B cell lymphoma found CD5expression was negative in MALT lymphoma and DLBCL and positive in T cell lymphoma **,**but not explained the intensity or H score of CD5 expression.

CD5 negative in DFL shown by **Jessica Alvarez-lesres eta in 2021**[15] that similar with our studies results that found the neoplastic cell in DFL show the immunophenotype similar to nodal FL by lack expression of CD5. CD5 expression negative in in Burkitts lymphoma have agreement with study **in India by Swarapa Mitra eta in 2014**[171] that found CD5 negative in Burkitts lymphoma.

Other study **in Korea by Myung Hwan Kim 2014**[172] showed that CD5 positive in MALT lymphoma of sigmoid colon, this agree with our study that CD5 positive in MALT lymphoma of intestine

Study done **in japan by Eri Ishikwa eta in 2018** [173]that show CD5 positive in de nova DLBCL that has worse prognosis than CD5 negative DLBCL ,this agree with our study that CD5 positive in DLBCL with some difference .so non of above studies that show CD5 positive explain the intensity of marker staining.

5.3.3CD79α;

Its adisulphide –linked –transmembran heterodimer is not covalentily associated with surface Ig forming B cell receptor complex. The expression of CD79 is largely restricted to B linage cell but may be co expressed with CD3 in proportion of T lymphoblastic leukemia/lymphoma. In our study the CD79α expressed in 96.7% (29 cases) and negative in 3.3 % (0ne cases)

this results agreed with other studies done **in Japan by Shintaro Sugita, eta in 2007** [174] That show T cell lymphoma had aberrant expression of B cell marker such as CD79α (CD79α positive lymphoid cells were focally aggregated into small nodules in the area of massive infiltaration of T lymphocyte these lymphoid cell were negative for T cell marker and we concluded that B lymphocyte aggregation was reactive. And other study in **Austria by Karin Blakolmer eta in 2000** [175]. that revealed reactivity of CD79α in T cell lymphoma.

CD79α was positive in gastric Burkitts lymphoma shown by study **in Romania by Simona Gurzu ,eta in 2017** [176] that agree with our study that show positivity for B-cell markers CD79a,and others marker is required to differentiate BL from DLBCL in his study .

Other study in **Chines by Kazuhisa Hasui eta ,in 2003**[170] similar to present study that show gastric MALT lymphoma and DLBCL positive for CD79 α. And its also accordance with other study **in India by Ritu Mehta eta in 2022**[169] that found gastric MALT stain positive for CD79 and in case of the DLBCL diffuse proliferation of large lymphocyte cell stain positive for CD79 but not explain the intensity of expression.

CD79α positive in Follicular lymphoma similar to study done in **Thailand by Charoenlap C eta, in 2021**[177] that show neoplastic cell The neoplastic cells show an immunophenotype similar to that of a low-grade nodal FL by expressing CD79α.

Chapter Six

Conclusions and Recommendations

6.1 conclusion:

From current study we can conclude the following :

1. CD23 expression was negative in all patient with GIT lymphoma so have no role in the evaluation GIT lymphoma.

2.CD5 expression was negative in two third of patient with GIT lymphoma .

3.CD79 expression was the most commonly expression markers in patient with GIT lymphoma in this study.

4.H score of CD79 expression have negative correlation with age ,gender and subtypes.

5. no correlation between CD79 expression and CD 5 expression.

6.2 Recommendation

1. A prospective study with larger sample size and follow up of patients are recommended to substantiate our results .

2. Studying the correlation of CD5 and CD79 with international prognostic factors in GIT lymphoma such as ≥ extranodal site, high LDH and Ann –arbor stage III-IV.

3.Immunohistochemical studies of other markers useful in detection GIT lymphoma and to correlate these studies with CD79 marker expression in GIT lymphoma**.**

Reference

7. Reference

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Appendix 1

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Tumour-like lesions with B-cell predominance	
Reactive B-cell-rich lymphoid proliferations that can mimic lymphoma	Not previously included
IgG4-related disease	Not previously included
Unicentric Castleman disease	Not previously included
Idiopathic multicentric Castleman disease	Not previously included
KSHV/HHV8-associated multicentric Castleman disease	Multicentric Castleman disease
Precursor B-cell neoplasms	
B-cell lymphoblastic leukaemias/lymphomas	
B-lymphoblastic leukaemia/lymphoma, NOS	(Same)
B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy	B-lymphoblastic leukaemia/lymphoma with hyperdiploidy
B-lymphoblastic leukaemia/lymphoma with hypodiploidy	(Same)
B-lymphoblastic leukaemia/lymphoma with iAMP21	(Same)
B-lymphoblastic leukaemia/lymphoma with BCR::ABL1 fusion	B-lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL1
B-lymphoblastic leukaemia/lymphoma with BCR::ABL1-like features	B-lymphoblastic leukaemia/lymphoma, BCR-ABL1-like
B-lymphoblastic leukaemia/lymphoma with KMT2A rearrangement	B-lymphoblastic leukaemia/lymphoma with t(v;11q23.3); KMT2A-rearranged
B-lymphoblastic leukaemia/lymphoma with ETV6::RUNX1 fusion	B-lymphoblastic leukaemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-RUNX1
B-lymphoblastic	Not previously included

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leukaemia/lymphoma with ETV6::RUNX1-like features	
B-lymphoblastic leukaemia/lymphoma with TCF3::PBX1 fusion	B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); TCF3-PBX1
B-lymphoblastic leukaemia/lymphoma with IGH::IL3 fusion	B-lymphoblastic leukaemia/lymphoma with t(5;14)(q31.1;q32.1); IGH/IL3
B-lymphoblastic leukaemia/lymphoma with TCF3::HLF fusion	Not previously included
B-lymphoblastic leukaemia/lymphoma with other defined genetic abnormalities	(Same)
Mature B-cell neoplasms	
Pre-neoplastic and neoplastic small lymphocytic proliferations	
Monoclonal B-cell lymphocytosis	(Same)
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	(Same)
(Entity deleted)	B-cell prolymphocytic leukaemia
Splenic B-cell lymphomas and leukaemias	
Hairy cell leukaemia	(Same)
Splenic marginal zone lymphoma	(Same)
Splenic diffuse red pulp small B-cell lymphoma	(Same)
Splenic B-cell lymphoma/leukaemia with prominent nucleoli	Not previously included (encompassing hairy cell leukaemia variant and some cases of B-cell prolymphocytic leukaemia)
Lymphoplasmacytic lymphoma	
Lymphoplasmacytic lymphoma	(Same)
Marginal zone lymphoma	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	(Same)
Primary cutaneous marginal zone lymphoma	Not previously included (originally included under “extranodal marginal zone lymphoma of

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	mucosa-associated lymphoid tissue")
Nodal marginal zone lymphoma	(Same)
Paediatric marginal zone lymphoma	(Same)
Follicular lymphoma	
In situ follicular B-cell neoplasm	In situ follicular neoplasia
Follicular lymphoma	(Same)
Paediatric-type follicular lymphoma	(Same)
Duodenal-type follicular lymphoma	(Same)
Cutaneous follicle centre lymphoma	
Primary cutaneous follicle centre lymphoma	(Same)
Mantle cell lymphoma	
In situ mantle cell neoplasm	In situ mantle cell neoplasia
Mantle cell lymphoma	(Same)
Leukaemic non-nodal mantle cell lymphoma	(Same)
Transformations of indolent B-cell lymphomas	
Transformations of indolent B-cell lymphomas	Not previously included
Large B-cell lymphomas	
Diffuse large B-cell lymphoma, NOS	(Same)
T-cell/histiocyte-rich large B-cell lymphoma	(Same)
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with MYC and BCL2 rearrangements	High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements
ALK-positive large B-cell lymphoma	(Same)
Large B-cell lymphoma with IRF4 rearrangement	(Same)
High-grade B-cell lymphoma with 11q aberrations	Burkitt-like lymphoma with 11q aberration

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Lymphomatoid granulomatosis	(Same)
EBV-positive diffuse large B-cell lymphoma	EBV-positive diffuse large B-cell lymphoma, NOS
Diffuse large B-cell lymphoma associated with chronic inflammation	(Same)
Fibrin-associated large B-cell lymphoma	Not previously included (Previously considered a subtype of diffuse large B-cell lymphoma associated with chronic inflammation)
Fluid overload-associated large B-cell lymphoma	Not previously included
Plasmablastic lymphoma	(Same)
Primary large B-cell lymphoma of immune-privileged sites	Not previously included, encompassing primary diffuse large B-cell lymphoma of the CNS in revised 4th edition (plus primary large B-cell lymphoma of the vitreoretina and primary large B-cell lymphoma of the testis)
Primary cutaneous diffuse large B-cell lymphoma, leg type	(Same)
Intravascular large B-cell lymphoma	(Same)
Primary mediastinal large B-cell lymphoma	(Same)
Mediastinal grey zone lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma
High-grade B-cell lymphoma, NOS	(Same)
Burkitt lymphoma	
Burkitt lymphoma	(Same)
KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas	
Primary effusion lymphoma	(Same)
KSHV/HHV8-positive diffuse large B-cell lymphoma	HHV8-positive diffuse large B-cell lymphoma, NOS
KSHV/HHV8-positive germinotropic	HHV8-positive germinotropic lymphoproliferative disorder

Appendix 1

lymphoproliferative disorder	
Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation	
Hyperplasias arising in immune deficiency/dysregulation	Not previously included, encompassing non-destructive post-transplant lymphoproliferative disorders, among others
Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation	Not previously included, encompassing polymorphic posttransplant lymphoproliferative disorders, other iatrogenic immunodeficiency-associated lymphoproliferative disorders, among others
EBV-positive mucocutaneous ulcer	(Same)
Lymphomas arising in immune deficiency / dysregulation	Not previously included, encompassing monomorphic posttransplant lymphoproliferative disorders, classic Hodgkin lymphoma posttransplant lymphoproliferative disorders, lymphomas associated with HIV infection, among others
Inborn error of immunity-associated lymphoid proliferations and lymphomas	Lymphoproliferative diseases associated with primary immune disorders
Hodgkin lymphoma	
Classic Hodgkin lymphoma	(Same)
Nodular lymphocyte predominant Hodgkin lymphoma	(Same)
Plasma cell neoplasms and other diseases with paraproteins	
Monoclonal gammopathies	
Cold agglutinin disease	Not previously included
IgM monoclonal gammopathy of undetermined significance	(Same)
Non-IgM monoclonal gammopathy of undetermined significance	(Same)
Monoclonal gammopathy of renal significance	Not previously included

Appendix 1

Diseases with monoclonal immunoglobulin deposition	
Immunoglobulin-related (AL) amyloidosis	Primary amyloidosis
Monoclonal immunoglobulin deposition disease	Light chain and heavy chain deposition disease
Heavy chain diseases	
Mu heavy chain disease	(Same)
Gamma heavy chain disease	(Same)
Alpha heavy chain disease	(Same)
Plasma cell neoplasms	
Plasmacytoma	(Same)
Plasma cell myeloma	(Same)
Plasma cell neoplasms with associated paraneoplastic syndrome -POEMS syndrome -TEMPI syndrome -AESOP syndrome	(Same) Except AESOP syndrome not previously included

الخلاصة

الخلفية

سرطان الغدد الليمفاوية المعدي المعوي الأولي هو ورم نادر ، يمثل أقل من 5٪ من جميع الاورام المفاوية في الجهاز الهضمي ، (10-15)٪ من جميع ليمفوما الغيرهودجكين وتشمل (30-40)٪ من إجمالي سرطان الغدد الليمفاوية خارج الغدة. ما يقرب من (60-75)٪ من الحالات تحدث في المعدة ثم الأمعاء الدقيقة ،. غالبية الأورام اللمفاوية المعدية المعوية هي الخلايا البائية حيث الاستجابة للعلاج الكيميائي والتشخيص الأفضل ، والخلايا التائية أقل شيوعًا بنسبة 6 ٪ فقط. تركز العديد من الجهود على إيجاد مؤشرات موثوقة يمكن أن تساعد في التنبؤ بالنتيجة أو تفسير التباين السريري لورم الغدد الليمفاوية في الجهاز الهضمي. ظهرت علامات مثل CD23 و CD5 و CD79 واستخدمت في تقييم سرطان الغدد الليمفاوية في الجهاز الهضمي.

هدف الدراسة:

صممت دراستنا لتقييم التعبير CD5 و CD23 و CD79 في المرضى العراقيين المصابين بسرطان الغدد الليمفاوية في الجهاز الهضمي والارتباط بمؤشرات مختلفة (العمر والجنس والأنواع الفرعية المرضية النسيجية) .

المرضى والطرق:

تمثل العينات المتضمنة في هذه الدراسة 30 كتلة نسيج خزعة مثبتة بالفورمالين مضمنة بالبارافين لمرضى سرطان الغدد الليمفاوية في الجهاز الهضمي والذين خضعوا للخزعة بالمنظار والخزعة الاستئصالية. تم جمعها من مختبرات التشريح المرضي في مدينة بغداد الطبية وكذلك العديد من المختبرات التشريحية الخاصة في كربلاء وبغداد ومدينة الحلة ومستشفى الحسيني التعليمي في كربلاء. وكان عدد المرضى متألف من (22 ذكور و 8 اناث) تتراوح اعمارهم من (3-78) سنة. كانت الكتل المرضية المجمعة مرتبطة بالفترة من 2016 إلى 2023 ، بينما تم جمع الكتل من هذه الدراسة خلال الفترة من أكتوبر 2022 حتى أبريل 2023 ، وقد تلطخت هذه الكتل بكيميائيات مناعية للتعبير عن طريق CD5 و CD23و CD79 باستخدام طرق التلوين.

النتائج:

أوضحت النتائج أن أكثر المرضى الذين يعانون من سرطان الغدد الليمفاوية في الجهاز الهضمي (60) سنة بمتوسط العمر (38.1 ± 27.14) وأكثر شيوعًا عند الذكور 73.3٪ من الإناث 26.7٪ وأثبتت أن DLBCL هو النوع الأكثر شيوعًا 53.4٪ في الدراسة الحالية ، كانت النتيجة H CD23 سلبية في جميع المرضى المصابين بسرطان الغدد الليمفاوية في الجهاز الهضمي وتعبير CD5 موجبةفي 33.3٪ بينما

كانت سلبية في 66.7٪. تعبير CD79 موجب في 96.7٪ وسالب في 3.3٪ أظهرت النتيجة عدم وجود ارتباط معنوي بين نتائج اختبار CD5 لدرجة H ومتغير الدراسة -P القيمة> 0.05 ، ولم يكن هناك ارتباط معنوي بين نتائج CD5و CD79(P value> 0.05)

خاتمة:

1. CD23 ليس له أي دور في تقييم سرطان الغدد الليمفاوية المعوية. يمكن استخدام النتائج السلبية لـ CD23 لعزل حالات ليمفوما اللاهودجكين عن الآفات الحميدة.

2. كان تعبير CD5 سلبيا في ثلثي المرضى الذين يعانون من سرطان الغدد الليمفاوية في الجهاز الهضمي

CD79.3 يتم التعبير عنه بشكل كبير في مريض سرطان الغدد الليمفاوية المعوي. درجة H للتعبير CD79 ليس له علاقةمع العمر والجنس والأنواع الفرعية التشريحية المرضية. لا يوجد ارتباط بين تعبير CD79 وتعبير CD 5.