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GASTROINTESTINAL LYMPHOMA IN TERTIARY GASTROENTEROLOGY CENTER: EPIDEMIOLOGICAL, CLINICAL AND ENDOSCOPIC FEATURES

ГАСТРОИНТЕСТИНАЛНИ ЛИМФОМИ ВО ТЕРЦИЕРЕН ГАСТРОЕНТЕРОЛОШКИ ЦЕНТАР: ЕПИДЕМИОЛОШКИ, КЛИНИЧКИ И ЕНДОСКОПСКИ КАРАКТЕРИСТИКИ

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Abstract

Introduction. Within the heterogeneous group of extranodal lymphoma, the gastrointestinal tract is the most frequently involved extranodal site accounting for 30-50% of all extranodal cases. Gastrointestinal involvement most oftenoccurs secondarily, while the primary gastrointestinal lymphomasare relatively rare accounting for 30%-45% of all extranodal lymphomas and 0.9% of all gastrointestinal tumors. Within the gastrointestinal tract, lymphoma can arise in any region but the stomach is the most commonly involved organ being affected in 50-70% of all the gastrointestinal lymphomas, followed by the small intestine and ileocecal region. The aim of the study was to analyze and present data regarding the endoscopic aspects and clinical presentation of patients with gastrointestinal lymphoma.
Methods. We retrospectively reviewed the medical records of patients with primary or secondary gastrointestinal lymphoma diagnosed at our Clinic over a fifteen-year period (January 1, 1999 to December 31, 2013). We analyzed the demographic data, clinical presentation, anatomic distribution, endoscopic aspect of the lesion, extension of the neoplastic process and occurrence of different histological subtypes.
Results. We discovered 18 patients with gastrointestinal lymphoma (7 males and 11 females). Fourteen patients (77.7%) were considered primary, while 4 patients (22.2%) were considered secondary gastrointestinal lymphoma. The stomach was affected in 14 cases (11 primary and 3 secondary), there were 2 duodenal lymphomas, 1 lymphoma of the terminal ileum and 1 peritoneal lymphoma. In most patients (10) massive and diffuse gastrointestinal infiltration was diagnosed, 5 patients had ulcerated lesions in the stomach and 3 patients presented with polyploid mass. Six patients presented with upper gastrointestinal bleeding, 1 patient with biliary tract obstruction, one patient with protein losing enteropathy, malabsorptionand consecutive bowel perforation and one patient presented only with ascites and pleural effusion. All the malignant lymphomas were Non-Hodgkin type and among them we registered only one T-cell lymphoma. Being diagnosed in 6 patients (33.33%), diffuse large B-cell lymphoma was the most prevalent histological type. The lymphoma was limited to the gastrointestinal tract in 6 patients, 7 patients had regional nodal involvement, in 2 patients there was an intra-abdominal spread and in 3 patients there was an extra-abdominal dissemination. Most patients received chemotherapy and only 2 patients were treated surgically. Two patients had rapidly progressive clinical course and lethal outcome shortly after the diagnosis was established and before chemotherapy was administered.
Conclusion. The gastrointestinal lymphoma has a variable clinical presentation and endoscopic aspect that often makes the diagnosis challenging. Substantial level of diagnostic awareness and comprehensive clinical approach are necessary in order to establish the correct diagnosis, provide appropriate treatment and prolong survival.

Keywords: gastrointestinal lymphoma, extranodal lymphoma, primary gastrointestinal lymphoma

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Апстракт

Вовед. Гастроинтестиналниот тракт е најчестата екстранодална локализација, застапена кај околу 30-50% од сите екстранодални лимфоми. Гастроинтестиналната засегнатост, најчесто настанува секундарно, додека примарните гастроинтестинални лимфоми се релативно ретки и на нив отпаѓаат 30-45% од сите екстранодални лимфоми и 0.9% од сите гастроинтестинални тумори. Во рамки на гастроинтестиналниот тракт, лимфомите може да потекнуваат од која било локализација, но 50-70% од нив се локализирани во желудникот, по што следат тенкото црево и илеоцекалната регија. Цел на студијата беше да

се анализираат и презентираат податоци, во врска со ендоскопскиот аспект и клиничка презентација на пациентите со гастроинтестинални лимфоми.
Методи. Ретроспективно беа ревидирани медицинските истории на пациентите со примарен или со секундарен гастроинтестинален лимфом, дијагностицирани на нашата клиника, во рамки на временски период од 15 години (од јануари 1999 до декември 2013). Беа анализирани демографските податоци, клиничката презентација, анатомската дистрибуција, ендоскопскиот аспект на лезијата, екстензивноста на неопластичниот процес и застапеноста на различни хистолошки подвидови.
Резултати. Во рамки на овој временски период беа детектирани 18 пациенти со гастроинтестинален лимфом (7 мажи и 11 жени). Примарен гастроинтестинален лимфом беше утврден кај 14 пациенти (77.7%), додека кај 4 пациенти (22.2%) беше утврдено присуство на секундарен гастроинтестинален лимфом. Лимфомите беа локализирани во желудникот кај 14 пациенти (11 примарни и 3 секундарни), беа нотирани 2 дуоденални лимфоми, 1 лимфом на терминален илеум и 1 перитонеален лимфом. Кај повеќето пациенти (10) беше утврдено присуство на масивна и дифузна гастроинтестинална инфилтрација, 5 пациенти имаа улцеративна лезија во желудникот и кај 3 пациенти беше утврдено присуство на полипоидна маса. Шест пациенти клинички се презентираа со горнодигестивно крварење, 1 пациент со билијарна опструкција, 1 пациент со енеропатија асоцирана со губење протеини, малапсорпција и цревна перфорација и 1 пациент се презентираше само со асцит и со плеврални изливи. Сите лимфоми беа Нон-Хоџкин тип, и меѓу нив регистриравме само еден Т клеточен лимфом. Дијагностициран кај 6 пациенти (33.33%), Дифузниот лимфом на големи Б клетки, беше најчестиот хистолошки тип. Лимфомот беше лимитиран на гастроинтестиналниот тракт кај 6 пациенти, кај 7 пациенти беше нотирано присуство на зголемени лимфни јазли, кај 2 пациенти беше утврдена интраабдоминална дисеминација и кај 3 пациенти беше регистрирана екстраабдоминална дисеминација. Повеќето пациенти беа третирани со хемотерапија и само 2 пациенти беа третирани хируршки. Двајца пациенти се презентираа со рапидно прогресивен клинички тек и летален исход, набргу по поставување на дијагнозата и пред третман со хемотерапија.
Заклучок. Гастроинтестиналните лимфоми имаат варијабилна клиничка презентација и ендоскопски аспект, што честопати го отежнува дијагностичкиот процес. Оттука, присуството на високо ниво дијагностичка свест и сеопфатен клинички пристап се неопходни за да се обезбеди точна дијагноза, соодветно лекување и продолжено преживување

Клучни зборови: гастроинтестинални лимфоми, екстранодални лимфоми, примарни гастроинтестинални лимфоми

Introduction

Although lymphoma as an entity refers to malignant proliferation of lymphoid cells within the lymphoid organs, it is well known that lymphoma can arise from any other organ or tissue comprising a large heterogeneous group of extranodal lymphomas (EL). EL refers to a lymphoma arising primarily from a site other than a lymph node, spleen, bone marrow or mediastinum (lymph node and thymus) [1]. Apart from the lymphoid organs, the extranodal lymphoid proliferation can occur in organs that contain associated lymphatic tissue such as small intestine, or even in organs that do not contain their own lymphoid tissue such as stomach [2]. EL can arise in every anatomic site of the body and it has been reported in almost every organ and tissue such as the gastrointestinal tract (GIT), Waldeyer's ring, nasopharynx and paranasal sinuses, salivary glands, skin, central nervous system, bone, testis, thyroid, breast, orbit, and rarely in adrenal glands, pancreas, and the genitourinary tract [3-16]. The extranodal involvement most commonly occurs secondaryas a consequence of an extension from the nodal site, while the primary extranodal lymphoma (PEL) are less frequent and are defined by a presence of a dominant lymphoid tumor mass and/or related symptoms in an extranodal organ with no or minor nodal involvement [17]. Most of the EL were Non-Hodgkin type (NHL) and in the literature there are only several extranodal Hodgkin lymphoma cases described. The GITis the most common extranodal site involved by lymphoma,being affected in up to 30-50% of all EL [18,19], in around 5%-20% of all lymphoma cases [20,21] and GIT lymphoma accounts for 0.9-6.5% of all gastrointestinal malignancies [22,23]. As other extranodal sites, the GIT is also mainly involved seconddarily, as a result of a spread from the mesenteric and retroperitoneal lymph nodes that are frequently involved in patients with generalized lymphomas [24]. Although primary gastrointestinal lymphomas (PGL) are relatively rare (approximately 0.9% of all GIT tumors [23]), they are still the most common type of PEL accounting for30%-45% of all extranodal NHL [25]. The primary sites of origin in decreasing order of frequency include the stomach (50-70%), small bowel (20-35%), colon (especially cecum) (5-10%), and esophagus (<1%) [26-28]. The diffuse large B-cell lymphoma (DLBCL) and the marginal zone B-cell lymphoma (MALT type) are the most frequent histological types among the PEL[2].
The aim of the study was to analyze and present data regarding the age and sex distribution, clinical presentation, endoscopic aspect, anatomic localization and occu-

rrence of different histological subtypes in patients with gastrointestinal lymphoma.

Material and methods

The study was carried out at the University Clinic of Gastroenterohepatology, a tertiary care hospital in Skopje, Macedonia. After searching our computer database, we retrospectively analyzed the medical files of all the patients with histologically proven primary or secondary NHL of the GIT (esophagus, stomach, large and small bowel) diagnosed at our institution over a fifteen-year period (January 1, 1999 to December 31, 2013). Patients with abdominal nodal disease or liver and spleen involvement, but without evidence of gastrointestinal involvement were not included in the study. After careful review of the medical records and taking into account the Lewin's diagnostic criteria [29], all cases were categorized as PGL or secondary gastrointestinal lymphoma (SGL). Lymphoma in patients who presented with morphologically and clinically dominant lesion in the GIT with/without nodal affection in the regional lymph nodes were considered PGL. The gastrointestinal lymphoma (GL) with distant GIT involvement from the dominant nodal disease/tumor mass and the GL in patients who were previously diagnosed with nodal disease, which later recurred in the GIT were considered SGL.The diagnosis was established by histopathological analysis of the material provided by endoscopic biopsy or surgical resection and the specific lymphoma type was confirmed by using an immunohistochemical study for B and T-cell markers. Patients were analyzed regarding the demographic data, immunological status, clinical presentation, histopathological features, endoscopic appearanceand distribution of different localization within the GIT and the results were compared with the data from the recent literature.We attempted to determine the clinical stage by using the Ann Arbor classification [30], but we were not able to conduct a complete clinical staging in all patients because of lack of informationin the available medical records. The HIV status for most of the patients was not known.

Results

During the last fifteen year, we discovered 18 patients with GL diagnosed in our institution; 16 patients were hospitalized at our Clinic and 2 patients were diagnosed through the outpatient endoscopy unit. Seven patients (39%) were male and 11 patients (61%) were female (Figure 1), male to female ratio 1:1.6. The average age of presentation of the GL was 53.12 years (range 32-80), while the average age of the initial lymphoma occurrence was 52.76 years (four patients were previously diagnosed with generalized nodal disease which latter reoccurred in the GIT). The peak incidence of the GL was in the 6th decade (6 patients, 33.33%). At the time of presentation, most of the patients were immunocompetent. One patient had diabetes, one patient had

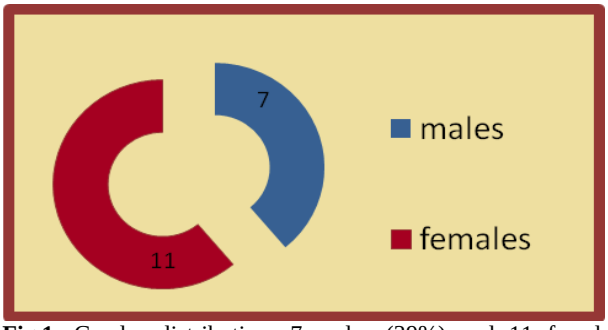

Fig.1. Gender distribution: 7 males (39%) and 11 females (61%)

liver cirrhosis, one patient had coronary artery disease, one patient was previously diagnosed with cervical cancer, one patient had chronic hepatitis B and one patient had chronic hepatitis C. Fourteen patients (77.77%) presented with a dominant gastrointestinal mass and were considered PGL, while 4 patients (22.22%) besides

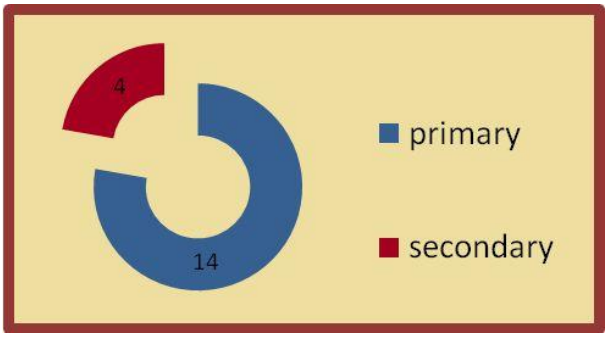

Fig.2. PGL vs SGL: 14 cases of PGL(77.7%) and 4 cases of SGL(22.2%)

the gastrointestinal involvement had a massive abdominal lymphadenopathy and/or splenic involvement and were considered SGL (Figure 2). The stomach was the most prevalent extranodal localization, being affected in 14 cases (11 PGL and 3 SGL); there were 2 duodenal lymphoma, 1 lymphoma of the terminal ileum and 1 peritoneal lymphoma (Figure 4) Six of the gastric lymphomas were infiltrating the corpus, in 5 cases there was infiltration of the corporal and proximal gastric segment, in 2 cases the gastric antrum and pyloric region were involved and one case was restricted to the subcardial region. In most patients (10) massive and diffuse gastrointestinal infiltration was diagnosed (7 gastric lymphomas, one duodenal, one ileal and one peritoneal lymphoma), 5 patients had ulcerated lesions in the stomach, and 3 patients presented with polyploid mass (two gastric and one duodenal tumor). In most patients (14) the gastrointestinal involvement was the initial manifestation of the lymphoma and 4 patients were previously diagnosed with generalized nodal disease additionally relapsing within the GIT. Six of the 14 ca-

ses of gastric lymphomas presented with upper gastrointestinal bleeding (Figure 3.). One patient who was previously diagnosed with abdominal nodal disease later presented with biliary tract obstruction as a consequence of secondary involvement of the duodenum.The lymphoma of the terminal ileum was initially discovered in a 35-year-old female during her early pregnancy. She presented with protein losing enteropathy, malabsorption and nutritive deficiency and later she developed bowel obstruction symptoms and bowel perforation discovered during surgery. The female patients with primary peritoneal lymphoma presented only with ascites and pleural effusion without lymph node enlargement, tumor formation or specific gastrointestinal symptoms.The remaining patients presented with abdominal pain and nonspecific constitutional symptoms (9 patients with abdominal pain and 10 patients with weight loss, Figure 3). In most patients (16) the diagnosis was established from the endoscopic biopsies while the patients with ileal and peritoneal lymphoma were diagnosed during surgery. All malignant lymphomas were Non-Hodgkin type and among them we registered only one T-cell lymphoma. There were 6 DLBCLs, 4 MALT lymphomas, 3 lymphocytic lymphomas, 1 anaplastic large cell lymphoma, 1 precursor B lymphoblastic leukemia/ lymphoma, 1 peripheral T-cell lymphoma, anaplastic type (the lymphoma of the terminal ileum) and 2 lymphomas were not classified at the time being (Figure 5). The lymphoma was limited to the GIT in 6 patients, 7 patients had regional nodal involvement, in 2 patients there was an intra-abdominal spread of the neoplastic process and in 3 patients there was an extra-abdominal dissemination. Most patients received chemotherapy and only 2 patients were treated surgically. Two patients (aggressive peritoneal DLBCL and peripheral T-cell lymphoma of the terminal ileum) had rapidly progressive clinical course and lethal outcome shortly after the diagnosis was established and before chemotherapy was administered.

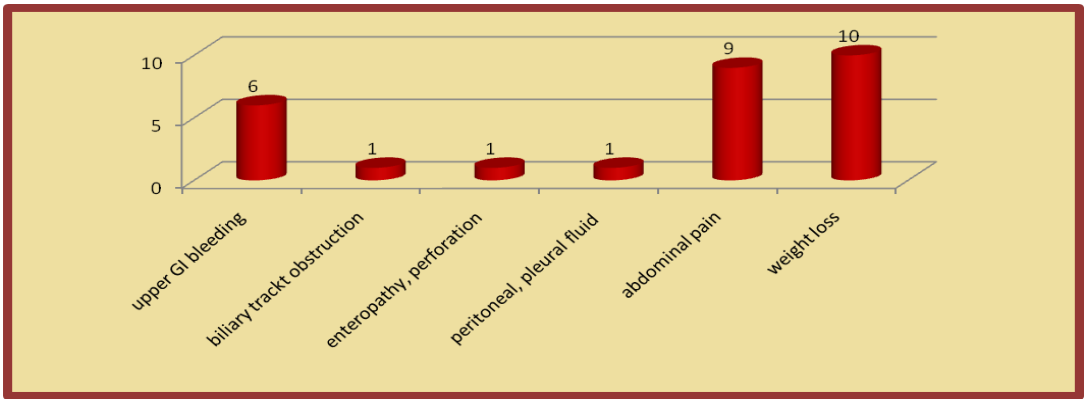

Fig. 3. Clinical presentation of patients with GL

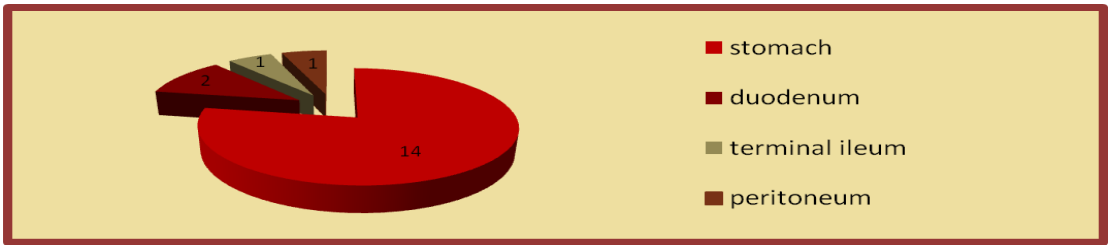

Fig. 4. Distribution of GL within the gastrointestinal tract: the stomach was the most prevalent extranodal localization, 14 cases (11 primary and 3 secondary)

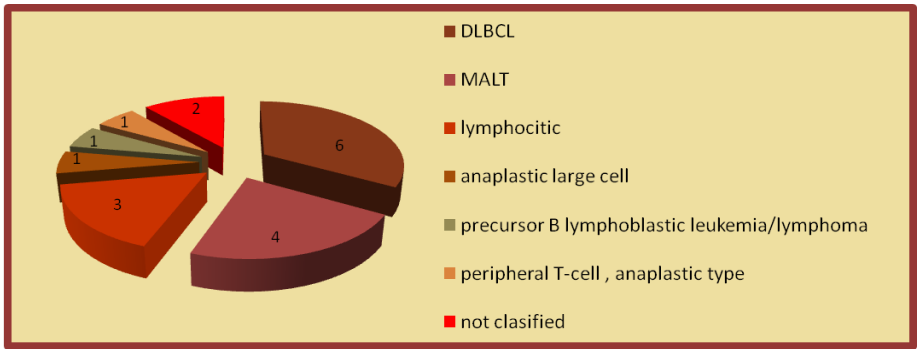

Fig. 5. Presence of different histological types: all malignant lymphoma were Non-Hodgkin type; there were 15 B-cell and only one T-cell lymphoma and DLBCL was the most prevalent subtype

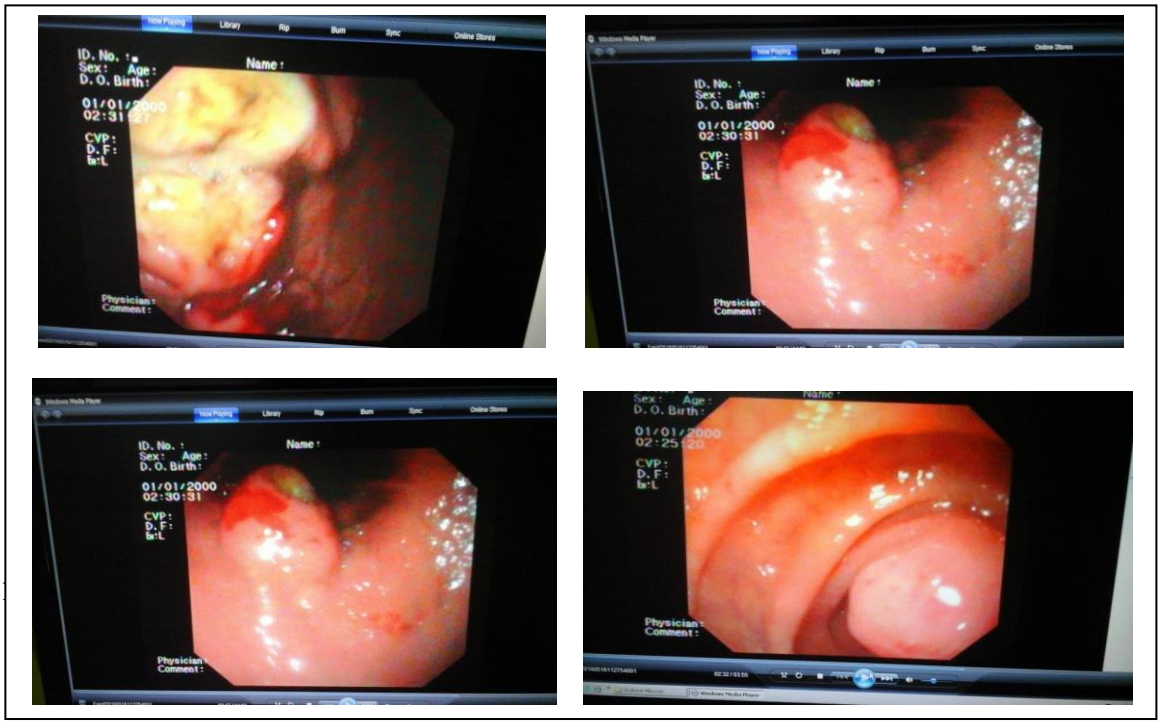

Fig. 6. Endoscopic appearance of gastric lymphoma (DLBCL)

Discussion

Epidemiological studies that deal with PEL and GL report that incidence and distribution of different lymphoma types vary in different geographic regions of the world, probably as a result of the geographic variations in the prevalence of viral or bacterial infection, celiac disease, diet or other environmental factors [25,31-34]. The incidence of PEL is around 15-25% of NHL in the United States and around 30-42% in parts of Europe [20,28,35], but it is higher in Middle East and Far East (Pakistan and Saudi Arabia up to 50%, 45% in Kuwait, 48.3% in Northern Iraq, 47.2% in Taiwan, 46.6% in Japan, 55% in Korea, 58.7% in Thailand, 44.9-61.4% in China, 22% in India) [4,9-11,14-16,36]. Primary small intestinal lymphoma is more prevalent in the Middle East and Mediterranean basin in comparison to the Western countries and the incidence of Burkitt lymphoma in Africa is approximately 50-fold higher than it is in the US [37,38]. There are some specifics related to some regions in Europe, suggesting that some lymphoma types, for example, the marginal zone lymphoma of MALT type occurred less frequently in South-East European countries (6.6%) than in West-European countries (10.5%), but it was still relatively common in Macedonia (7.6%) and Croatia (7.4%) [39]. Moreover, over the past two decades, many epidemiologic studies reported a rise in the incidence of NHL, extranodal lymphoma and GL in most parts of the world [12,13, 40-44]. Surprisingly, despite the thorough search through our database, within these 15 years we discovered only 18 cases of GL, a number much lower than we expected. This could possibly be explained by the fact that some patients diagnosed and managed at the Hematology Clinic could have had a gastrointestinal involvement that was not clinically dominant and remained unrecognized. Since we were only searching our gastroenterology database, it is possible that some of these patients were not detected and recruited within the study population. Moreover, the small number of patients prevented us from performing a more thorough analysis and making more reliable conclusions.

The distinction between PGL and SGL is complex and rather difficult. There were several previous attempts to create a suitable definition for EL, but the suggested diagnostic criteria are still not particularly precise. In the late 1961 Dawson and the coworkers set a diagnostic criteria for PEL, defining it by: 1) absence of palpable superficial lymph nodes on first physical examination; 2) absence of mediastinal lymphadenopathy detected on plain Chest X-ray; 3) dominant lesion at extranodal sites; 4) involvement of lymph nodes in the vicinity of the primary lesion; and 5) white blood cell count within normal range [27]. There was also a need to define the lymphoma with gastrointestinal involvement as PGL and to distinguish this entity from the lymphoma with secondary gastrointestinal involvement. Lewin *et al*. in a large series of 117 PGL patients defined the PGL as a lymphoma presenting with dominant lymphoid mass and/or associated symptoms within the GIT [29]. Later in 2003 Krol *et al*. suggested a liberal definition of PGL as a NHL that apparently originated at an extranodal site, even in the presence of disseminated disease, as long as the extranodal component was clinically dominant [45].

These definitions are still in wide use, especially as inclusion criteria in studies that deal with the PGL. But it is important to stress that in the routine clinical practice this distinction is sometimes very difficult to make. There is a significant number of patients that are diagnosed in an advanced stage where there is a large mesenteric mass along with a gastric infiltration. In these circumstances it is very difficult to define the dominant mass and to distinct the leading symptoms, which makes the definition of PGL rather challenging.

According to the two largest studies of GL of German and Greek population, being affected in 68-75%, stomach is the most prevalent GIT localization followed by small intestine including duodenum (9 %), ileo-cecal region (7%), more than one gastrointestinal localization (6-13%), rectum (2%) and diffuse colonic involvement (1%) [19,34]. Although there are studies in which most GL were located in the small bowel, [31,46,47] most studies report the gastric lymphoma as the most prevalent PEL [13,29,36,43,48,49]. In our report the stomach was also the most prevalent extranodal localization, being affected in 14 cases (11 PGL and 3 SGL), followed by small bowel (including duodenum and terminal ileum) in 3 cases. According to the literature, the primary gastric lymphoma is an uncommon tumor and accounts for about 2% of all lymphomas and for less than 15% all gastric malignancies [27]. However, primary gastric lymphoma is the most common EL, representing 30%-40% of all EL and 60%-75% of all GL [19,20,34,50]. Most of the primary gastric lymphomas (more than 90%) are either DLBCL or MALT lymphoma [51,52]. The primary gastric lymphoma was also the most prevalent entity in our group. We detected eleven cases of primary gastric lymphoma. Among them there were 4 DLBCL (Figure 6), 4 MALT lymphomas, 2 lymphocytic type lymphomas and one remained undetermined. Six of these patients presented with upper GI bleeding, which is not very common presentation of gastric lymphoma. DLBCL is the most prevalent GL and the most prevalent NHL in the western countries comprising 30-40% of all NHL cases [41,53]. Although the occurrence of DLBCL in our study was much lower than in most reports, DLBCL was still the most prevalent histopathological type being present in 6 cases (33%).

PGL is related to some risk factor such as Helicobacter pylori (H. pylori) infection, celiac disease and immunosuppression [23]. The relation between H. pylori and gastric MALT lymphoma is well established, but the role of H. pylori in gastric DLBCL is uncertain and still a matter of debate [54,55]. The H. Pylori infection has been involved in the pathogenesis of gastric MALT lymphoma and the bacteria can be identified in the gastric mucosa of more than 90% of these cases [56]. The H. pylori infection causes an immunological response leading to chronic gastritis with aggregation of T CD4+ and B lymphocytes and formation of lymphoid follicles in the gastric lamina propria [57]. The treatment of gastric MALT lymphoma involves eradication of H. pylori infection and the regression of the lymphoma in response to the eradication strengthens the causal theory between H. pylori and the entity [58]. Considering the retrospective nature of our research, we were not able to register and analyze the H. pylori status in most patients and to provide data and conclusion on this matter.

Despite the small number, we registered several interesting and unusual findings in our study. In most reports the GL was more prevalent in male than in female patients [1,13,43,48,49], which was not the case in our group, but taking into account the small number of patients, this deviation has no particular relevance. We registered a case of peripheral T-cell lymphoma that is very rarely found in the literature [58,59]. On the contrary, we did not detect a single case of colonic lymphoma which is rather unusual. It is also remarkable that there was a rare and unusual case of peritoneal lymphoma presented with ascites and pleural fluid accumulation without solid organ involvement or peripheral lymph node enlargement, which makes it a possible case of primary effusion lymphoma. Unfortunately, we were not able to confirm this with certainty because of the rapid clinical progression and the premature lethal outcome before the immunohistochemical and genetic analyzes were performed.

Conclusion

NHL is a heterogeneous group of lymphoproliferative malignant disorders with variable localization, presentation, natural course and malignant potential. The gastrointestinal involvement along withthe nonspecific clinical presentation and variable endoscopic appearance additionally contributes to the difficulty in the diagnostic process. Moreover, the new therapeutic protocols change the prognostic prospective of the lymphoma from potentially lethal to potentially curable disease. These are the reasons why a substantial level of diagnostic awareness and comprehensive clinical approach are necessary in order to establish the diagnosis correctly, provide appropriate treatment and prolong survival.

Conflict of interest statement. None declared.

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