Chapter

MALT Stomach Lymphomas: Aspects of Diagnosis and Treatment

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Abstract

Marginal zone lymphoma (LMZ) accounts for 5–15% of all NHL in Europe. This option includes splenic (0.7%), nodal (2.4%) and extranodal (MALT-Mucosa-Associated Limphoid-Tissue) LMZ –5%. Extranodal variants of MALT lymphomas can occur in any organ due to chronic antigenic stimulation. The most frequent localization associated with *Helicobacter pylori* (*Hp*) infection is the stomach - 30%. The gastrobiopsy material of 115 patients with lymphoid cell infiltrates in the gastric mucosa was studied, a complex of morphological diagnostic criteria for MALT gastric lymphoma for gastrobiopsy was developed based on a combination of histological and immunohistochemical characteristics of tumor cells, the nature of their growth. It is known that the mandatory initial therapy for local stages of *Hp*-positive MALT lymphoma of the stomach is the eradication of *Hp*. 68 patients with stages I – II of gastric MALT lymphomas were observed. Anti *Hp* therapy resulted in 87.8% of complete remissions, with a median duration of 51 months. The median time to the onset of *Hp*-eradication was 3 months, and the median time to the implementation of the antitumor process was 5.5 months. With a median follow-up of 58 months, the median overall and relapse-free survival was not achieved: 10-year OS - 100%, 10-year RFS - 92. 3%.

Keywords: MALT lymphoma, stomach, gastrobiopsy, morphology, immunohistochemistry, anti-*Helicobacter pylori* therapy

1. Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma is an indolent extranodal marginal zone B-cell lymphoma, originating in acquired MALT that is induced in mucosal barriers as part of a normal adaptive immune response to a chronic immunoinflammatory stimulus, most notably chronic infection by *Hp* [1].

MALT lymphomas can show a wide morphologic spectrum. MALT gastric lymphoma is characterized by mature cellular elements, the presence of lymphoid follicles and lymphoepithelial lesions (LELs) [2]. Histological diagnosis of MALT lymphoma of the stomach is rather difficult and is made basing on a combination

of morphological features because none of them is exclusively pathognomic for this lymphoma type [3, 4]. Immunohistochemical analysis is much importance in the diagnosis of MALT-lymphoma, especially in controversial cases [5–7].

In recent years, the principles of MALT lymphoma treatment have been defined. According to the recommendations of the European Society of Medical Oncologists (ESMO), at the first stage of treatment of patients with *Hp* + MALT gastric lymphoma, regardless of the stage, it is recommended to prescribe anti-*Hp* eradication therapy. However, there is an addition in the guidelines of the general cancer network. According to the addition Eradication Antibiotic Therapy is preferable for patients with stages I and II1 according to Lugano, in the absence of translocation t(11; 18), which is found in 15-40% of patients with gastric MALT lymphoma and is a predictor of refractoriness to antibiotic therapy. These patients with translocation t(11, 18) should in any case receive additional treatment. Alternatively, rituximab alone or radiation therapy can be used.

As an antibacterial anti-*Hp* therapy, a 3-component regimen is usually used: a proton pump inhibitor with clarithromycin, in combination with amoxicillin or metronidazole for 10-14 days. The effect should be confirmed morphologically 6 weeks after eradication therapy and at least 2 weeks after discontinuation of the proton pump inhibitor.

Patients with a widespread tumor process - more than stage IIe require a systematic approach in the presence of indications for therapy.

2. Part 1. Morphoimmunological aspects of the diagnosis of MALT gastric lymphomas

2.1 Materials and methods

The study was performed on gastrobiopsies from 115 patients with lymphoid cell infiltration of gastric mucosa including 71 patients with MALT lymphoma of the stomach, 23 patients with reactive (nontumor) lymphoid infiltrations, 21 patients with non MALT type peripheral small B-cell gastric lymphomas (cytological grade I or I–II FL, MCL), Burkitt's lymphoma (BL). There were 48 males and 67 females in the study group. The study was carried out using histological and immunohistochemical methods. Immunohistochemical study was performed on cryostatic and paraffin sections. The reaction was assessed using fluorescent microscopy. **Table 1** shows the antibodies that were used to stain the preparations.

Antibody	Application	Manufacturer
CD19, CD20, CD37	antibodies to linear antigens of B-lymphocytes	DAKO
CD3, CD4, CD5, CD7, CD8	antibodies to linear antigens of T-lymphocytes	DAKO
CD38	determination of plasma cells	DAKO
CD21 и CD23	determination of follicular dendritic cells	DAKO
HLADR, CD10	lymphoid progenitor cells, granulocytes	DAKO
immunoglobulin classes D, G, M	Ig expression	DAKO
light chains of immunoglobulins λ и κ.	determination of clonality	DAKO

Table 1.
List of antibodies used.

2.2 Morphoimmunological characteristics of MALT lymphoma

The study was performed in 71 patients aged 14 to 83 years, mean age 54.32 years. MALT lymphoma is always accompanied by active chronic inflammation which in half of cases is associated with H. p. infection; mucosal defects are found in two thirds of cases. MALT lymphoma has a very polymorphous morphological picture due to heterogeneous composition of the tumor component and a great interpatient variability of combinations. We assessed the following histological signs:

1. Cell composition with respect to nucleus shape;
2. The presence of monocytoid B-lymphocytes;
3. The presence of plasma cells;
4. The presence of tumor cell plasmocytoid differentiation;
5. LELs;
6. The presence of follicles (reactive, colonized);
7. The presence of blasts.

2.2.1 Cellular composition according to the shape of the nuclei of lymphoid cells

1. Cells with mainly round nuclei (morphologically closest to small lymphocytes: with clearcut nucleus outline, highly dispersed chromatin, non-visualized nucleoli, cytoplasm looking like a narrow, poorly outlined rim) — 5 cases (7.04%) (**Figure 1**).
2. Cells with centrocytoid morphology (small cells with cleaved or wedge-like nuclei, moderately dispersed or granulated chromatin, invisible nucleoli and a moderately wide cytoplasm rim) — 7 cases (9.86%).
3. Cells with mixed morphology (round and centrocytoid nuclei) — 53 cases (74.65%).
4. Cells with irregular nuclei — 6 cases (8.45%).

2.2.2 Tumor cell size

Tumor cell size ranged from small, similar to small lymphocytes to medium, similar to prolymphocyte and twofold greater than small lymphocytes. All MALT lymphomas were conventionally divided into 3 histological groups depending on the size of tumor cells (**Table 2**). The larger were the cells the greater were their degree of atypia and similarity to blasts.

2.2.3 Cell elements with a different morphology

Cell elements having a different morphology were present in the tumor infiltrations in parallel with the predominant type (**Table 3**).

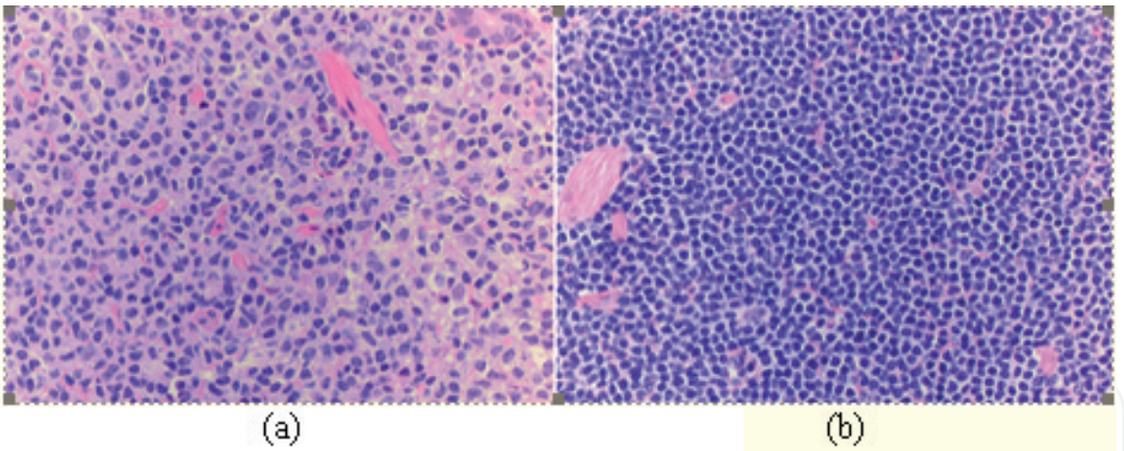

Figure 1.
Cytological features of MALT lymphoma can range from small lymphocytic (b) morphology to monocytoid (a, c) morphology (hematoxylin–eosin, original magnifications ×400 [2].

Cell nucleus shape	Small cells (n = 26)	Small and medium cells (n = 40)	Medium cells (n = 5)
round	4 (15,4%)	1 (2,5%)	0
round /centrocyt-like	17 (65,4%)	35 (87,5%)	1
centrocyt-like	5 (19,2%)	1 (2,5%)	1
irregular	0	3 (7,5%)	3

Table 2.
MAL lymphoma: Cell element morphology of lymphoid infiltration with respect to three groups.

Morphological sign	small cells (n = 26)	small and medium cells (n = 40)	medium cells (n = 5)
Monocytoid B-lymphocytes	n – 22 (84,6%) e –4 (15,4%)	n – 24 (60%) y – 16 (40%)	n – 1 y – 4
Plasma cells	n-1 (3,9%) s – 7 (26,9%) m – 18 (69,2%)	n-7 (17,5%) s – 16 (40%) m-17 (42,5%)	n-0 s – 4 m – 1
Cells with plasmocytoid differentiation	32%	18,2%	20%
Lymphoepithelial lesions	n – 12 (46,2%) y – 14 (53,8%)	n – 23 (57,5%) y - 17 (42,5%)	n - 1 y - 4
Reactive follicles-colonized	n-18 (69,2%) y – 7 (30,8%) c – 18 (37,5%)	n – 29 (72,5%) y – 11 (27,5%) c - 7 (63,6%)	n – 4 y - 1 c – 1
Blasts	n – 15 (57,7%) y – 11 (42,3%) s – 81,8%	n – 4 (10%) y – 36 (90%) s – 38,9% l – 36,1%	n – 0 y - 5

Note: n - no, y- yes, s- single, m-multiple, c-colonized, l- layers of blast more than 20.

Table 3.
MALT-lymphoma: Morphological characteristics of lymphoid cell infiltration with respect to three groups.

Monocytoid B-lymphocytes (35,2%). They were with a bean-shaped or irregular nuclei, wide and poorly stained cytoplasm.

Plasma cells (85,9%). In most cases plasma cells were located immediately under covering epithelium as a massive sheet (46.47%), or less frequently were dispersed in small portions in surface layers of gastric proper mucous plate among leukocytes

(39.43%). The plasma cells had typical appearance: nuclei, more frequently of a round or slightly irregular shape, wide cytoplasm in the form of a rim or a tongue of flame of intense pink color after Brachet staining.

Cells with plasmocytoid differentiation (21,13%). They resembled plasma cells, that was better observed after Brachet staining.

Lymphoepithelial lesions (LELs) as aggregations of 3 or more marginal zone cells destroying glandular epithelium were found in 50,7%. 6 cases (17.14%) presented with 'blast' LELs formed by large blasts (**Figure 2**).

Follicles or follicle-like structures with light-color proliferation centers consisting of centrocytes and centroblasts, a small number of mitotic figures and individual macrophages with cellular detrite in their cytoplasm were present in 14,09% cases. Proliferation centers could be surrounded by a partially preserved, thin mantle zone. Lymphoid follicle colonization when preexisting lymphoid follicle was replaced by small neoplastic cells was found practically in half the cases with follicles (15,49%).

Blasts. They were with either roundIoval/slightly irregular nuclei and 1 to 3 nucleoli, or with round bottle-shape nuclei and 1 compact, centrally located nucleolus. Amount of large blast cells varies from single cells to small group of cells (not more than 20 cells in one group).

2.3 Immunophenotyping of MALT- lymphoma

49 cases were analyzed. MALTI-ymphoma neoplastic elements were free from characteristic pathognomic immunological signs.

1. CD45 - common leukocyte antigen. There was a positive monomorphic reaction with diffuse growth of infiltrate. Cells, less frequently expressing this antigen, formed large clusters among the glands

2. B-cell markers (CD19, CD20). The infiltration cells expressed pan-B-cell markers as diffused, dense positive staining in most cases or, less frequently, as follicle-like areas on positive cell groups.

3. CD5 – antigen. Tumor cells were CD5-negative in all cases.

4. T-cell markers (CD8, CD4). T-cell component was present in most cases as single diffused cells, with CDI8 cytotoxic lymphocytes slightly predominating over CD4-helpers.

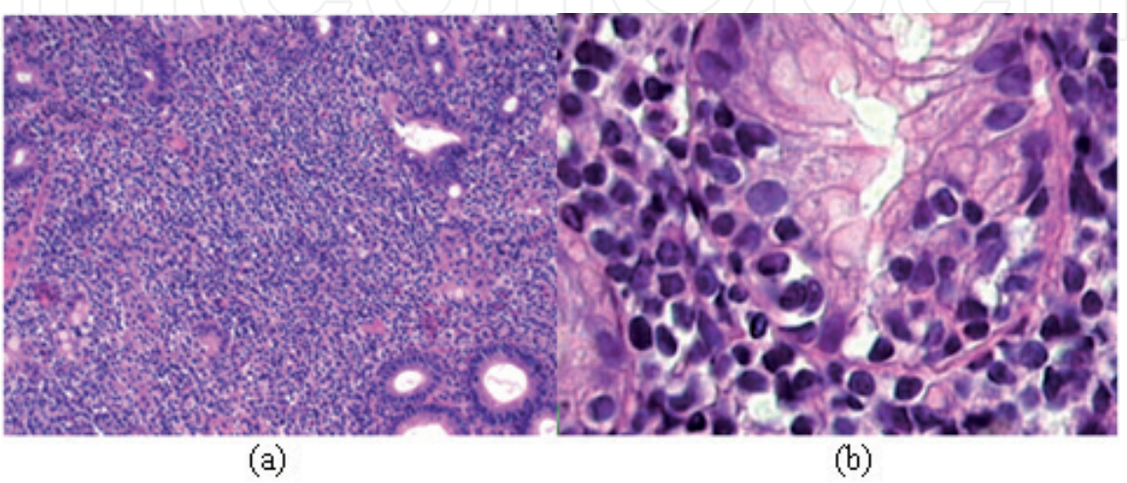

Figure 2.
Lymphoepithelial lesions (LELs) as aggregations of 3 or more marginal zone cells destroying glandular epithelium.

5. CD23 marker. Tumor cell reaction with CD23 was negative in more than 90% of cases.

6. CD21 and CD23 markers. FDCs were found in 19 cases. They formed a network among CD23-negative cells of tumor infiltration, though more frequently (17 cases, 89.47%) looked as loose clusters in CD21-positive infiltration (5 cases) or in CD21-negative infiltration (12 cases).

7. CD38 marker was assessed on both tumor cells and plasma cells. The tumor cell reactivity was negative; CD38- positive plasma cells were located in surface mucosa as foci or layers.

8. CD10 marker. All cases were CD10-negative.

Expression of CD20, CD3, IgD, IgG, IgM, and Ig λ and κ light chains was studied in 35 paraffin sections:

- clear-cut CD20 expression on tumor infiltration cells was found in all cases.
- CD3 was expressed on single diffuse cells among B-cells.
- Ig of all three classes were expressed on plasma cells.
- tumor cells demonstrated no Ig expression.
- Ig λ and κ light chains were expressed on plasma cells and very weakly on lymphoid neoplastic cells, though restriction of one of the chains was not found.

Therefore, all paraffin sections demonstrated plasma cell polyclonality, i.e. expression of different classes of Ig without restriction of one of the chains.

2.4 Differentiation criteria in the diagnosis of MALT-lymphoma of the stomach and morphologically similar lesions

2.4.1 Reactive lymphoid infiltrations of the stomach

The study was performed in gastrobiopsies from 23 cases aged 18 to 85 years, mean age was 53.47 years. More than half (56.52%) of the gastrobiopsies demonstrated mucosal defects of different severity: from surface erosion to ulcer. All 23 cases had signs of active chronic inflammation, mainly of moderate or severe degree (39.13 and 56.52% respectively). Twenty two (95.65%) cases presented with *Helicobacter pylori* in mucosa or in gland lumens on epithelial surface, the degree of contamination correlating with inflammation activity.

2.4.1.1 Tumor cell size

Lymphoid cells of the studied infiltrates were predominantly small (86.96%). There were no infiltrations consisting of medium-sized cells among the cases studied.

2.4.1.2 Cellular composition according to the shape of the nuclei of lymphoid cells

Morphological signs of reactive lymphoid cell infiltrates were as follows: cells with centrocytoid morphology of nuclei, without signs of cytological atypia, or with mild cytological atypia, predominated.

2.4.1.3 Cell elements with a different morphology

1. Monocytoid B-lymphocytes were not detected in any of the investigated infiltrates.

2. Plasma cells in all 23 cases were found in large numbers in the form of layers under the surface integumentary epithelium.

3. Cells with plasmacytoid differentiation were not found.

4. Lymphoepithelial lesions were present in about 1/5 of cases. LELs consisted of more than 3 small lymphoid cells, and the glands were distorted. Infiltration of the epithelium of the glands with segmented leukocytes or so called crypts of abscesses were mainly observed.

5. Follicles were found in 34,78% of samples as round or slightly irregular, light-color centers of proliferation with a typical centrocyte or centroblast composition and single macrophages with wide cytoplasm and phagocyted bodies. Germinal centers were surrounded by a narrow, denser and darker (after hematoxylin and eosin staining) mantle zone of small lymphoid cells with round nuclei. There were no cases with follicle colonization.

6. Two (8.7%) cases presented with single large (blast) cells. These cells looked like centroblasts or immunoblasts and were diffused in small cell infiltration.

2.4.1.4 Immunophenotyping of reactive lymphoid infiltrates

1. CD45 marker. A positive reaction was detected on all cells of the infiltrate, which were mainly in the form of small groups or loose diffuse clusters.

2. T, B-cell markers (CD19, CD20, CD8, CD4). There was a mixed cell infiltrate, where T-lymphocytes predominated over B-lymphocytes, or less often were in equal proportions, while CD8-positive T-lymphocytes predominated.

3. CD21, CD23, CD5, CD10. There was a negative reaction of infiltrate cells.

4. When reacting with CD21 and CD23, the presence of a positive, well-expressed, arranged network of FDC reactive follicles was noted.

5. CD38 - marker. Expression on plasma cells was noted.

To sum up, majority cases of reactive infiltrates have mild cytology atypia, severe atypia cases were not found at all, monocytoid B-cells were absent, and lymphoid cells did not undergo plasmocytoid differentiation.

Thereby, lymphoid infiltrate of MALT-lymphoma, in contrast to reactive infiltrate, has tendency to be more destructive and expansive. One third of all the MALT-lymphoma cases has mild cytology atypia. As cytological atypia grows, monocytoid cells appear more frequently, amount of plasma cells progressively decrease, moreover, the frequency of follicle appearance decrease, while the majority of cases have follicle colonization.

2.4.2 Peripheral small B-cell lymphoma of the stomach

The study was performed in 21 cases aged 14 to 83 years, mean age was 48 years. The cases were represented by follicular lymphoma of I, I – II, II cytological degree (n = 10), lymphoma from cells of the mantle zone (n = 6), Burkitt's lymphoma (n = 5). Defects of the mucous membrane from surface erosion to ulcer were noted in two-thirds of the material examined. Inflammation was mild or moderate in all variants of lymphomas. *Helicobacter pylori* infection was observed in 8 cases (38.1%). Infiltration growth was focal diffuse in about a third of cases with mantle cell lymphoma and follicular lymphoma, and diffuse in 2/3 of cases. In Burkitt's lymphoma the infiltration growth was diffuse in all 5 cases. Burkitt's lymphoma consists of cells of medium size, but it can be misinterpreted as small cell lymphoma due to artificial deformation after the tissue fixation. Morphological characteristics of follicular lymphoma, lymphoma from cells of the mantle zone, Burkitt's lymphoma are compared in **Table 4**.

Thereby, morphological features, typical for MALT-lymphoma (atypical lymphoid small cells, reactive follicles, LELs) can be seen in other peripheral B-cell lymphomas, that is why ICH-research is decisive.

Among peripheral small-cell B-cell lymphomas, 7 cases of follicular lymphoma and 4 cases of mantle cell lymphoma were studied by immunohistochemistry. All studied lymphomas (lymphoma from cells of the mantle zone, follicular lymphoma) were B-cells and contained single or small groups of diffuse T-cells. In this case, the diagnosis of follicular lymphoma was made on the basis of the totality of CD23, CD38, CD10 occurring in various combinations. It should be noted that all 3 cases of gastric follicular lymphoma were CD10-negative, while the cells of the tumor infiltrate were either CD38-positive or CD23-positive. For lymphoma from cells of the mantle zone the reaction with CD5 was diagnostically significant: all cases were positive. Morphological characteristics of lymphoid cell infiltrations in gastric mucosa for lymphomas and reactive infiltrations are compared in **Table 5**.

Morphological sign	**Follicular lymphoma (n = 10)**	**Lymphoma from cells of the mantle zone (n = 6)**	**Burkitt's lymphoma (n = 5)**
Tumor cell size	small cells	small and medium	medium cells
Monocytoid B-lymphocytes	1	1	0
Plasma cells	7	2	0
Cells with plasmocytoid differentiation	1	0	0
Lymphoepithelial lesions	4	1	2
Reactive follicles-colonized	2	0	0
Blasts	9	4	5

Table 4.
Peripheral small B-cell lymphomas, Burkitt's lymphoma: Morphological characteristics of lymphoid cell infiltration in gastric mucosa.

Morphological sign	MALT lymphoma	Reactive lymphoid infiltrates	Other lymphomas (FL, MCL)
Monocytoid B-lymphocytes	35,2%	Absent	FL –10%, MCL – 16,6%
Plasma cells	85,9%	100%	FL –70%, MCL – 33,3%
Cells with plasmocytoid differentiation	21,1%	Absent	FL –10%, MCL – 0%
Lymphoepithelial lesions	50,7%	Single in 20%	FL –40%, MCL – single in 16,6%
Reactive follicles-colonized	30% (15% - signs of col.)	30%, no signs of col.	FL - 20% with col. MCL – 0%
Blasts	73,2%	10%	FL - 90%MCL – 66,6%

Note: FL- follicular lymphoma, MCL- lymphoma from cells of the mantle zone, col- colonization.

Table 5.
Diagnostically meaningful morphological characteristics.

3. Part 2. Clinical aspects of MALT gastric lymphomas

3.1 Materials and methods

Blokhin National Medical Research Center of Oncology analyzed the data of 68 patients with early stages of gastric MALT lymphoma who received initial treatment from 1973 to 2004 [8]. The median follow-up was 61 months. The prevalence of female patients was noted - 64.71% versus 35.29%, almost half of the patients - 48.7% were over 60 years old. In accordance with the criteria for dividing gastric MALT lymphomas into categories depending on the number and nature of growth of blast-transformed cells, the patients were distributed as follows: small cell subvariant - 31 (45.6%); intermediate - 22 (32.4%) and mixed - 15 (22.0%). *H. pylori* infection was found in 54 patients - 85.7%.

A comprehensive assessment of the effectiveness of therapy consisted in summarizing clinical, morphoimmunological, radiological, ultrasound and endoscopic data. To assess the long-term results, the indicators of the duration of the delaying time to relapse, event-free and overall survival were used. To determine the reliability of the results obtained, the X-2 criterion and the Student's test were used to plot the survival curves - according to the Kaplan and Meier method, the comparison of the curves was performed using the Lograng test.

3.2 Analysis of clinical characteristics

A comparative analysis of the clinical characteristics of 3 groups of patients was carried out according to morphological variants, which made it possible to identify the clinical features of each of them (**Table 6**):

- For small-cell gastric MALT lymphomas, the most characteristic was the predominance of women, elderly age (63 years), the presence of a long gastroenterological history, scant clinical symptoms, an isolated lesion of the stomach body with a predominance of ulcerative and gastritis-like macroscopic growth, stage I of the disease and the presence of *Helicobacter pylori* infection

- For the intermediate subvariant of gastric MALT lymphoma, the prevalence of women is also characteristic, the median age is 61 years, the rapid development of the disease (within 1 year), early onset of intense pain syndrome, a more pronounced tendency to the spread of the tumor in the stomach (larger lesion

Characteristics	Morphological variant of MALT lymphoma		
	Small cell	**Intermediate**	**Mixed cell**
Number of patients - 68	31 (45.6%)	22 (32.4%)	15 (22%)
Median age	63	61	41
Women (%)	67.7%	68.2%	53.3%
Duration of disease development up to 12 months	61.3%	100%	80%
Hp-infection	96.7%	90%	53.8%
Pain syndrome	80.7%	84.6%	100%
Growth form: Infiltrative ulcerative Gastritis-like Mixed	48.5% 29% 6.4%	72.7% - 9.1%	60% - 13.3%
Stage: I Stage: II	90.3% 9.7%	68.3% 40%	40% 60%

Table 6.
Characteristics of patients with stage I-II gastric MALT lymphomas.

volume) and on adjacent organs and lymph nodes, the presence of *Helicobacter pylori* infection is detected in the form of a moderate degree of bacterial content.

- Mixed-cell gastric MALT lymphomas develop in young people (median - 41 years), with intense permanent pain syndrome, with a predominance of infiltrative-ulcerative and ulcerative forms of growth, with a tendency to early spread to regional lymph nodes - by the time of diagnosis in 2 / 3 patients, stage II is detected, and *Helicobacter pylori* infection is observed in only half of the patients.

3.3 Treatment results depending on morphological subvariant

3.3.1 The immediate effectiveness of various therapies

Various approaches have been used in treating patients, including anti-*Helicobacter pylori* therapy, surgery, and systemic chemotherapy. When using eradication antimicrobial therapy in the general population, the overwhelming majority of patients achieved a complete response (CR) - 87.5%, the median duration of CR - 51 months (range: 5 months - 81 months). The effect was realized quickly: the mediana of *Hp* eradication was 3 months, and the mediana of the CR observance was 5.5 months. Surgical treatment was performed for 28 patients (41.12%).

The efficacy of the therapy, depending on the morphological subvariant was evaluated (**Table 7**).

The efficacy of treatment in the group of patients with small cell subvariant of gastric MALT lymphoma was evaluated in all 31 patients. The median follow-up in this group was 64 months. Eradication anti-*Hp* therapy, which was used as the only method of treatment only in stage I (Lugano classification, 1993) of small-cell gastric MALT lymphomas, was performed for 16 patients (51.6%).

This approach allowed achieving CR in the vast majority of patients - 14 (87.5%), and the median duration of complete remissions was 51 months (5 - 81 months). Thus, anti-*Helicobacter pylori* therapy is competent and effective in primary small-cell gastric MALT-lymphomas of stage I with *H. pylori*, i.e. positive tumors with limited tumor lesion of the stomach (stage I) (**Figure 3a**, **b**).

Treatment type	CR (%)	CR mediana/ months	Stabilization (%)	Progression (%)	Patients total (abs - %)
Small cell variant of gastric MALT lymphoma - 26 patients					
anti-H.pyloi -therapy	87.5	51	12.5	—	16 – 51.6
Surgical	100	73	—	—	12 – 38.7
Chemotherapy	—	—	100	—	3 – 9.7
Total	**26 – 83.9**		**5 – 16.1**	**—**	**31 – 100**
Intermediate variant of gastric MALT lymphoma - 22 patients					
Chemotherapy + anti-H.pyloi	71.4	37.5	7.1	—	14 – 63.7
Surgical	100	54	—	—	8 – 46.3
Total	**18 – 81.8**		**3 –13.6**	**—**	**1 – 4.6**
Mixed subvariant of gastric MALT lymphoma - 15 patients					
Surgical treatment + PCT	11	57	—	1 (7%)	12-80
Chemotherapy	1 (7%)	39	1(7%)	1(7%)	3-20
Total	**12- 80**	**—**	**1 (7%)**	**2 (13%)**	**15 – 100**

Table 7.
Direct efficacy of various types of therapy depending on the morphological subvariant of gastric MALT lymphomas.

In an earlier historical period (since 1973), 12 patients underwent surgical treatment of small-cell gastric MALT lymphomas: 11 patients underwent radical surgical treatment. The median duration of complete remissions in radically operated patients was 73 months (21 - 168 months), however, with a significant negative impact on the quality of life of patients.

The indication for chemotherapy (LVPP, COP, CHOP regimens) was the absence of *H. pylori* infection, while in all patients stabilization of the tumor process was only achieved. The efficacy of treatment in the group of intermediate subvariant of gastric MALT lymphoma was evaluated in 22 patients. The majority - 14 (63.7%) - received anthracycline-containing chemotherapy in combination with anti-*Helicobacter pylori* therapy. *H. pylori* eradication occurred in all patients within 1 to 8 months (median - 3 months), and complete remissions were achieved in 10 of them (71.4%). The median duration of CR was 37.5 months (1 - 53 months). Our experience of using induction standard chemotherapy in combination with anti-*Hp*-therapy for *H. pylori*, a positive MALT lymphoma of the intermediate subvariant, demonstrates a high frequency of achieving remissions and a stable long-term effect.

Radical surgical treatment was performed for 7 patients (31.8%): 2 - gastrectomy, 5 - distal subtotal gastrectomy were performed. The median duration of CR was 50 months (2–96 months).

The efficacy of treatment of the mixed subvariant MALT gastric lymphoma was assessed in all 15 patients, most of whom underwent surgical treatment at one of phase of disease (12/15) and only three received systemic chemotherapy alone. The immediate results of treatment of mixed gastric MALT lymphoma were better in 7 initially radically operated patients with subsequent adjuvant chemotherapy - the duration of CR was 57 months (mediana).

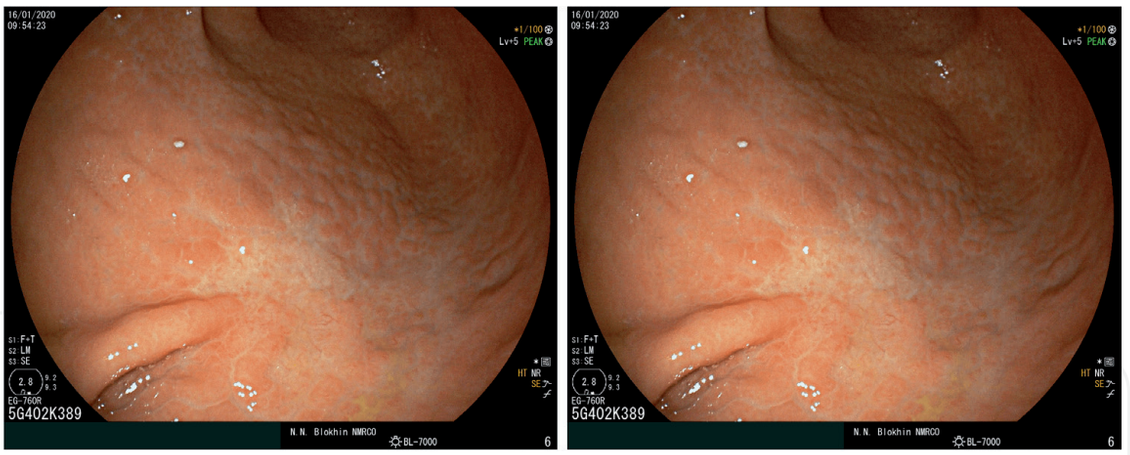

Figure 3.
a) Endoscopic findings in subject with Hp + *MALT-lymphoma prior anti-*Hp*-therapy. b) -after anti-*Hp*-therapy (from the archive of Malikhova O.A.).*

The results of standard anthracycline-containing chemotherapy turned out to be less impressive: out of 3 patients, complete remission at stage I of the process was achieved and persists for 39 months in 1 patient.

3.3.2 Relapses

With *H. pylori* - positive MALT gastric lymphomas of a small cell structure, out of 14 patients treated with antibiotics, relapse occurred only in 1 patient (7.1%) - 7 months after the CR. In this group, among radically operated patients, relapses were detected in 3 cases (27.3%).

In the group of patients with an intermediate variant, who received fundamentally different therapy (surgical treatment and systemic PCT (palliative chemotherapy)), the course of the disease was comparable in terms of the frequency of relapse: 30.0% and 37.5%, respectively. The difference is noted only in the timing of the detection of relapse: with conservative treatment, all relapses occurred in the first 2 years, and after surgical treatment later - in terms of 2 to 5 years (after 2, 3 and 5 years).

Attention should be paid to the predominant development of local recurrence in the stomach, regardless of the type of treatment and the type of NHL.

With the mixed sub-variant MALT, no relapses were detected.

3.3.3 Long-term results

Survival rates were calculated for 5-year and 10-year periods, which is explained by the long period of observation of patients. The overall 5-year survival rate (OS) was 96.8% in the case of MALT lymphoma of the small-cell subvariant. The indicators of 5-year OS are significantly lower with the intermediate subvariant - 71.4% ($p = 0.008$). These differences become even more pronounced to 10 years follow-up (**Table 8**). A small number of cases of mixed-type MALT lymphoma does not allow us to speak of significant differences.

The analysis of the influence of other characteristics on survival allowed us to establish that gender and age are not prognostically significant. Information about the further life of patients, depending on the methods of therapy used, is strategically important: a sparing conservative approach - anti-*H. pylori* antibiotic therapy - and an aggressive surgical method provide a high 5-year OS in the small

Morphological subvariant	N	OS -Survival rate (%)			
		1 year	3 years	5 years	10 years
Overall survival					
Small cell	31	96.8 ± 3.2	96.8 ± 3.2 p = 0,00	96.8 ± 3.2	89.1 ± 0.6
Intermediate	22	85.7 ± 7.6	71.4 ± 9.9	71.4 ± 9.9	52.9 ± 13.6
Mixed	15	92.9 ± 6.9	85.7 ± 9.4	85.7 ± 9.4	85.7 ± 9.4
Disease-free survival (DFS) (%)					
Small cell	25	92 ± 5.4	88 ± 6.5	88 ± 6.5	78.7 ± 8.5
Intermediate	16	80.2 ± 10.3	66.7 ± 12.2	59.3 ± 12.9	50.8 ± 13.5
Mixed	15	100	100	100	100
Event-free survival (EFS) (%)					
Small cell	31	86.6 ± 6.2	79.7 ± 7.4	77.8 ± 8.2	68.7 ± 8.7
Intermediate	22	66.7 ± 10.3	52.4 ± 10.9	47.6 ± 10.9	28.2 ± 13.6
Mixed	15	86.7 ± 8.8	86.7 ± 8.8	80 ± 10.3	80 ± 10.3

Table 8.
Long-term results of MALT lymphoma therapy depending on the morphological subvariant.

cell subvariant of gastric MALT lymphoma, but with a significant deterioration in the quality of life in using a surgical approach.

Comparison of the conservative (chemotherapy + anti-Helicobacter antibiotic therapy) approach with the surgical approach in the intermediate variant demonstrates that OS indicators are comparable only in the first year of observation and amount to 83.8% and 80%, respectively; on the 3rd and 5th year of observation, the difference in these OS indicators increases by 25%: 81.8% and 55.8%, respectively. Disease-free survival is 15% higher with conservative therapy by the end of the first year (83.3% versus 67.5% with surgical treatment). This means that surgery for an intermediate variant of MALT lymphoma does not provide long-term control of the disease.

The analysis of survival rates in mixed gastric MALT lymphoma was not performed due to insufficient number of observations. Thus, the analysis of long-term results confirmed the clinical, morphological and prognostic heterogeneity of this tumor, a favorable prognosis of primary MALT gastric lymphoma in general, and significant differences in survival in different morphological subvariants.

4. Discussion

Currently, according to practical recommendations, as a second-line treatment for patients in whom antibiotic therapy did not lead to remission, rituximab is prescribed as a monotherapy: 4 weekly administrations at a standard dose of 375 mg/m2 [9, 10].

In a study by G. Martineli, E. Zucca et al. 27 patients were enrolled exclusively with NHL gastric MALT lymphoma who received weekly rituximab injections [10]. In this work, the clinical activity of rituximab was confirmed in patients with gastric MALT lymphoma, refractory to antibiotic therapy or without association with *Helicobacter pylori*: the overall response (OR) was 77%, CR - 46%. With a median follow-up of 33 months, only 2 relapses were detected - after 26 and 14 months.

The IELSG-19 study as of today is the largest randomized trial comparing rituximab + chlorambucil with chlorambucil alone, in which the combination has

shown the best results (OR) - 95% vs. 85%; CR - 79% vs. 63%). Based on data from this study (NCT 00210353) [11]. C. Thieblemont et al. the International Prognostic Index of Extranodal Lymphoma - MALT-IPI was developed [12]. Three factors were identified that influence event-free survival: age ≥ 70 years, Ann Arbor stage III or IV, and increased LDH levels. 5-year EFS in the low, intermediate and high risk groups was 70%, 56% and 29%, respectively.

The addition of rituximab to bendamustine provided significant advantages in a prospective study involving 60 patients with untreated extranodal MALT lymphoma: OR was 100, CR - 98%, 7-year EFS and PFS (progression-free survival) were 88% and 93%, respectively [13].

Fludarabine-containing regimens are excluded by most of the clinical recommendations from treatment standards and NHL due to the increased risk of developing second tumors [14].

In August 2020, a new treatment option for MZL relapses was registered in the Russian Federation - the lenalidomide + rituximab (R2) regimen. The high efficacy of this combination compared to rituximab + placebo was confirmed in the AUGMENT study for phase III, involving 358 patients with recurrent/refractory follicular lymphoma (295 patients) and marginal zone lymphoma (63 patients): median PFS was 39.4 months in the R2 group compared to 14.1 months in the placebo group [15].

The efficacy and safety of ibrutinib in relapses and refractory MZL was demonstrated in a st median udy of phase II involving 63 patients, of which 32 (51%) with extranodal MALT lymphomas [16]. With a median follow-up of 19.4 months median response time was not reached, and PFS - 14.2 months (mediana).

Blockade of the phosphatidylinositol 3-kinase (PI3K) pathway seems to be a very promising direction in the treatment of relapses or refractory MZL. However, drugs from this group are currently not registered in the Russian Federation.

5. Conclusion

MALT gastric lymphoma is a variant of MZL with an indolent prognosis and long survival, but a high tendency to develop relapses over time.

Diagnosis and differential diagnosis of lymphoma is difficult and includes morphological and immunohistochemical analysis. In this study, morphoimmunological criteria for the diagnosis of MALT gastric lymphoma and differential diagnosis with processes similar in histological picture (reactive infiltrates, peripheral small-cell B-cell lymphomas of the stomach) were developed.

Most informative morphological combinations were selected to differentiate MALT-lymphoma from neoplasias with a similar morphological pattern or reactive lymphoid infiltration. Tumor cell size was considered the most important morphological criterion in tumor tissue analysis: the larger the tumor cells, the greater the changes in their cytomorphological appearance involving nuclear shape, chromatin status and increased cytological atypia.

Potential value of frozen and paraffin section immunohistochemistry was assessed in the common and differential diagnoses of MALT-lymphoma. The immunological diagnosis must be made basing on changes in immunoarchitecture if other immunological criteria are absent.

The consistent application of different treatment methods is the key to the success in treating this category of patients. Conservative anti-*Helicobacter pylori* therapy in the early stages in primary patients gives good results and is a strategy necessary to maintain adequate organ function and prevent the toxic effects of chemotherapy, which, in turn, is used in the progressive refractory course of the disease. New drugs and targeted agents open up the possibility of treating people

with severe pre-treatment (inadequate therapy in the early stages of the disease), as well as in certain categories of elderly patients with severe comorbidity.

Conflict of interest

We hereby inform you that there is no conflict of interest.

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