ETIOPATHOGENICAL, CLINICO-BIOLOGICAL AND EVOLUTIVE CONSIDERATIONS IN PRIMARY GASTRIC NON-HODGKIN’S MALIGNANT LYMPHOMAS

ABSTRACT

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GENERAL PART

Non-Hodgkin’s malignant lymphomas represent malignant proliferations of the immune system cells which start and affect predominantly the lymphoid organs, but may have as onset or may involve during their evolution any organ or tissue where these cells are.

Gastric lymphoma is considered to be primary when the initial symptoms of the disease are located in the stomach or when the tumour mass is located in the stomach.

The gastrointestinal tract is a common location for non-Hodgkin’s lymphomas with extranodal onset (30-40% of extranodal forms). Compared to all non-Hodgkin’s lymphomas, and regardless of their location, primary gastric lymphoma represents 4-20% of all cases of non-Hodgkin’s malignant lymphomas [1], and MALT lymphoma represents 5-8% [2].

Characteristics of mucosa-associated lymphoid tissue

The notion of primary digestive lymphoma occurred along with the description of the mucosa-associated lymphoid tissue (MALT), composed mostly of B lymphocytes. It was noticed a series of characteristics of B lymphocytes as compared to their histological counterparts with nodal onset.

The repetitive and prolonged antigenic stimulation of these lymphocytes leads to the development of an immune response, which, due to a genetic predisposition and also to the action of other local or general factors, causes the emergence of a malignant lymphoproliferation.

The particular structure and organization of the lymphoid tissue in the gastrointestinal tract favour the selective penetration of antigens and the development of an immune response [3]. The disruption of immune balance has a major role in the emergence of an organized lymphoid tissue in the
stomach, which will be the onset location of the malignant lymphoproliferation.

**Incidence. Epidemiology**

The highest incidence is found in patients over the age of 50 years, the average age being between 60-65 years, the disease being 2-3 times more frequent in males than females. Younger patients often associate HIV infection, or they are patients already diagnosed with AIDS.

**Primary gastric MALT-type lymphoma pathogenesis**

The arguments in favour of the association between Helicobacter pylori infection and MALT-type gastric lymphomas are:

1. in 92% of the cases of MALT gastric lymphomas it was demonstrated the presence of Helicobacter pylori infection on the anatomopathological samples that were analysed [4].
2. the serological test is positive for Helicobacter pylori in 85% of patients with gastric lymphoma [5].
3. the titer of anti-Helicobacter pylori antibodies determined by months or years before the appearance of malignant lymphoproliferation revealed their presence in 90.9% of cases [6].
4. in vitro studies – Helicobacter pylori stimulates the intra-tumoural T cells, which in turn promote tumour cell proliferation. Therefore, B tumour cells are not stimulated directly by Helicobacter pylori [7].
5. the regression of the gastric MALT lymphoma of low malignancy after the antibiotic therapy of eradication of Helicobacter pylori.

In a recently published study (2011), it is demonstrated the presence, in the gastric mucosal cells, of some elevated levels of cytokines, particularly of a cytokine called APRIL, which belongs to the family of the tumour necrosis factors and which has already a demonstrated role in B cells
maturation and survival. APRIL seems to be produced in excessive amounts by macrophages present in the lymphomatous gastric infiltrate and located close to the neoplastic cells. They produce APRIL both at the direct stimulation of Helicobacter pylori and also while being stimulated by T lymphocytes which are activated in turn by Helicobacter pylori [8]. It is the first study publishing the APRIL involvement in MALT lymphoma etiopathogenesis.

Cytogenetic abnormalities encountered in MALT lymphoma:
- \( t(11;18)(q21;q21) \) is the most common chromosomal abnormality found in MALT lymphoma (13-35% of cases) [9], not being encountered in the marginal zone lymphoma with nodal or splenic onset;
- \( t(14;18)(q32;q21) \) (5-20% of cases) appears extremely rare in the primary gastric lymphoma, being found most commonly in the location at the level of the salivary glands or of the MALT lymphoma ocular annexes [10]. \( t(14;18)(q32;q21) \) MALT lymphomas often associate additional chromosomal aberrations such as trisomy 3 and or 12 and 8 [11];
- \( t(1;14)(p22;q32) \) causes disruption of BCL-10 expression in neoplastic B cell nucleus, causing the activation of NFkB [12].

Primary gastric diffuse large B-cell lymphoma (PG – DLBCL) pathogenesis

Large B-cell lymphoma is the most common histological type of primary gastric lymphoma. It is an aggressive lymphoma that can occur "de novo" or by transformation of MALT lymphoma. Differentiating between the two types, "de novo" and resulted from a MALT lymphoma, is clinically and
histologically difficult and can be done only immunohistochemically and by molecular biology techniques.

**Positive diagnosis** is established by corroborating clinical data with results of paraclinical testing. Accurate diagnosis is established by histopathological and immunohistochemical examination, supplemented by cytogenetic and molecular biology tests. A complete diagnosis requires a histopathological inclusion in one of the types mentioned above and a correct staging, both of them having an impact on the therapeutic decision.

**Staging** – The Extranodal Lymphoma Study Group (IELSG) has established a new staging system of primary gastrointestinal lymphomas, particularly applicable in gastric lymphomas. In this staging, stage III is not defined, and stage IV corresponds to the disseminated disease. It is actually a modification of the system proposed by Radaszkiewicz in 1992. Later, in 2003 a new staging system, more detailed, called Paris system, was proposed to describe more efficiently the tumour infiltration depth, the lymph nodes extension and damage, and also the local extension with invasion of neighbouring tissues [13]. It is a system similar to the TNM classification of solid malignant tumours, but quite difficult to use currently in medical practice.

**Prognosis**

Such as in the case of lymphomas with nodal onset, IPI is important and it is applied particularly in primary gastric lymphomas with a high degree of malignancy. Low-risk category of patients has good prognosis and survival of these patients reaches 80% at 5 years after the end of therapy. Most of the specialised literature data show a 5-year survival correlated with the stage of disease: 90-95% for stage I, 75% for stage II, 30-40% for stage IV. The latest
prognosis data provided by IELSG at Lugano in 2011, indicate as factors with prognosis implications: the presence of lymph node damage, the presence of B symptoms, low serum albumin level, values of IPI> 3 [14].

**Treatment**

In the management of primary gastric lymphoma of low malignancy there should be taken into account the following:

- presence of t(11;18) and also that of t(1;14)(p22; q32) in patients with MALT lymphoma causes lack of response to the eradication therapy;
- treatment with antibiotics is the first-line option in primary gastric MALT lymphoma followed by a thorough haematological and endoscopic monitoring;
- endoscopic examination is recommended as the initial diagnosis of low malignancy established on the pieces of gastric biopsy does not exclude the coexistence of an aggressive large cell component requiring chemotherapy;
- radiotherapy or Rituximab monotherapy are therapeutic options for patients unresponsive to eradication therapy or they are Helicobacter pylori negative.

Therapeutic strategy in primary gastric diffuse large B-cell lymphoma has changed: surgical resection was abandoned, its place being taken by conservative therapy. Regardless of location, the diffuse large B-cell lymphoma is treated with aggressive polichemical therapy, the standard of treatment consisting in the combination of Rituximab with a polichemical therapy containing anthracycline.
SPECIAL PART

Objectives:

- evaluate the patients using a diagnosis algorithm including clinical, biological and imaging parameters, and also the histopathological and immunohistochemical examination of gastric biopsy fragments;
- highlight the prognosis and predictive factors of response to therapy;
- identify a prognosis profile at diagnosis;
- assess the effectiveness of therapeutic means;
- highlight the characteristics of the group in terms of histopathology and immunohistochemistry, the investigations used to make a diagnosis and also regarding therapy.

Material and method:

Our study is based on a group of 65 patients diagnosed with primary gastric lymphoma, hospitalized at “Fundeni” Haematology Clinic of Bucharest and at the Haematology Clinic of Craiova, in the period 2005-2010.

In the study, patients were clinically and paraclinically examined at the time of hospitalization, and after the specific therapy, evaluation was performed every 6 months during the first 2 years of complete remission and annually thereafter up to five years. Diagnosis was based on available imaging examinations (upper gastrointestinal endoscopy, endoscopic ultrasound) and it was confirmed by histopathological and immunohistochemical examination of gastric biopsy fragments or of pieces of surgical resection. Subsequent to the surgical intervention, patients were under treatment and hospitalization according to the therapeutic protocols in force at the moment.
Inclusion criteria:

- primary tumour location in the stomach with or without intra-abdominal structures involved;
- histopathological examination of gastric lesions which indicated the diagnosis of non-Hodgkin’s malignant lymphoma;
- positive diagnosis established on the histopathological examination of the gastric tumour, even in the context of the existence of supradiaphragmatic adenopathies or of the damage of the haematogenous bone marrow at the biopsy bone puncture.

There were excluded from the study the patients diagnosed by lymph node biopsy with histopathological and immunohistochemical examination, and who have also presented gastric lesions in evolution.

Results and discussions:

The study group is composed of 65 patients diagnosed with primary gastric lymphoma, in the period 2005-2010, at „Stefan Berceanu” Haematology Clinic of “Fundeni” Clinical Institute of Bucharest and at the Haematology Clinic of „Filantropia” Municipal Hospital of Craiova.

The associated risk factors encountered were: chronic gastritis, multifocal gastritis and gastric ulcer, two of the patients presenting associated autoimmune diseases, cited in the specialised literature as risk factors in the emergence of the primary gastric lymphoma (autoimmune thyroiditis).

In terms of clinical symptoms, there is a high incidence of non-specific symptoms (epigastric pain, nausea, vomiting) that can imitate any digestive disorder, 80% of patients presenting intermittent epigastric pain of variable intensity. At onset, the only complication encountered was upper gastrointestinal bleeding (9 patients, representing 13.85% of all patients, a percentage lower than the specialised literature data, where upper
gastrointestinal bleeding is cited as complication at diagnosis in a proportion of about 20% of cases) [15]. Among patients with gastrointestinal bleeding at diagnosis, there were 3 with MALT lymphoma and 6 with diffuse large B-cell lymphoma. None of them presented perforation and acute abdomen.

Patients were divided into two groups, all cases being assigned histopathologically according to the WHO classification of malignant lymphoproliferations on the basis of the histopathological and immunohistochemical examination:

- marginal zone MALT-type lymphoma;
- primary gastric diffuse large B-cell lymphoma (PG – DLBCL).

Most of the patients (49 patients, representing 75.38%) were diagnosed with diffuse large B-cell lymphoma, marginal zone MALT-type lymphoma being diagnosed in the remaining patients (16 patients, representing 24.62%). Although in the specialized literature there are cited from 2 to 5% other histological types (follicular lymphoma, mantle-zone lymphoma, peripheral T-cell lymphoma) [16], none of the patients in the studied group presented these rare forms of primary gastric lymphoproliferation.
CONCLUSIONS

1. The histological distribution (according to WHO classification) of non-Hodgkin’s malignant primary gastric lymphomas shows a predominance of diffuse large B-cell lymphomas (75.38%), primary MALT-type lymphomas representing 24.62%. We did not encounter other histological types in the studied group.

2. There can be noticed a slight prevalence in females (55.38%) than males (44.62%), both for MALT lymphoma (62.50%) and for diffuse large B-cell lymphoma (53.06%). The average age of the group is 52.54 years, 53.62 years for patients with MALT lymphoma and 52.20 years for patients with primary gastric diffuse large B-cell lymphoma.

3. The most common clinical symptoms were non-specific, most of the patients presenting associated symptoms (epigastric pain, early satiety, nausea, vomiting). B symptoms were present in 26.15% of patients and their presence did not influence significantly patient status at final evaluation (Fisher test 0.259). Upper gastrointestinal bleeding was present in 9 cases, 3 with MALT lymphoma and 6 with diffuse large B-cell lymphoma, not being noticed a higher incidence of upper gastrointestinal bleeding in the group with aggressive lymphoma in terms of histology.

4. From pathological personal history we have noted the presence of chronic gastritis (11 patients), multifocal gastritis (4 patients) and gastric ulcer (3 patients). In other two patients there were present autoimmune diseases (autoimmune thyroiditis).

5. The most commonly encountered macroscopic appearance was the mixed one (ulcerative-vegetative tumour), being the most commonly located in the gastric body.
6. Diagnosis algorithm requires histopathological examination completed by immunohistochemical examination of the gastric biopsy fragments obtained by upper gastrointestinal endoscopy or of the gastric resection pieces. Positive diagnosis is followed by the staging algorithm that includes objective examination, biological and imaging investigation (echo-endoscopy, computed tomography) and biopsy bone puncture.

7. In the group of patients affected by primary gastric diffuse large B-cell lymphoma we found a statistically significant relationship between the IPI value at diagnosis and the achievement of a complete remission at the end of the therapeutic protocol (Fisher test 0.020).

8. A statistically significant value in the same group as concerns the patient status at the final evaluation (RC, RP, death) have: sex (Fisher test 0.0271), presence of serous infiltration (Fisher test 0.0271), IPI (Fisher test 0.0047), bulky tumour reduction after two courses of polychemotherapy in patients who did not have gastric resection (Fisher test 0.028), presence of disease relapse (Fisher test 0.0018), value of beta2-microglobulin (Fisher test 0.092). The remaining parameters that were studied do not statistically influence the patient status at final evaluation (presence of B symptoms, gastric resection, inclusion of Rituximab in the treatment protocol, stage of disease, and value of serum albumin).

9. There is a statistically highly significant correlation noticed in the group with diffuse large B-cell lymphoma between the presence of disease relapse and the patient status at final evaluation (p = 0.00001). The achievement of a complete remission at the end of the therapeutic protocol (p = 0.003) and the value of beta2-microglobulin at diagnosis are also significantly statistically correlated with patient status at final evaluation (p = 0.047).
10. The estimation of parameters of importance in the achievement of a complete remission in the whole group, regardless of the histological type, showed a statistically significant relationship between IPI value (Fisher test 0.020374), stage of disease (Fisher test 0.0241) and the achievement of a complete remission at the end of the therapeutic protocol. Therefore, patients in the early stages of disease and having the IPI value of 1 or 2 obtain, in a higher percentage, a complete remission of disease compared with those in advanced stages and having the IPI value greater than or equal to 3.

11. The evaluation of the important parameters of the final status of patients throughout the group, regardless of histological type, showed a highly statistically significant relationship between the achievement of a complete remission at the end of the therapeutic protocol (Fisher test <0.00001), the presence of disease relapse (Fisher test 0.0000251) and the patient status at final evaluation. A statistically significant relationship with patient status at the final evaluation has: sex (Fisher test 0.0089), the value of beta2-microglobulin (Fisher test 0.0383), the value of serum LDH (Fisher test 0.026), the presence of serous infiltration (Fisher test 0.0321), the stage of disease (Chi-square test 0.0316), and the gastric resection (Fisher test 0.0227). There was noted no influence on patient status at final evaluation because of the presence of B symptoms, ESR value, haemoglobin value and serum albumin value.

12. The achievement of a complete remission at the end of the therapeutic protocol \( p = 0.00001 \) and the presence of disease relapse \( p = 0.00001 \) are highly significantly statistically correlated with patient status at the final evaluation in the general group, regardless of the histological type. The value of beta2-microglobulin at diagnosis is also
significantly statistically correlated with patient status at the final evaluation ($p = 0.047$).

13. Gastric resection does not correlate statistically with response to therapy and patient status at final evaluation nor in the group of aggressive lymphoma or in the whole group. This finding is concordant with recent specialised literature data, which have limited the use of gastric resection only in localized stages of MALT lymphoma (II) and in the case of complications such as perforation, upper gastrointestinal bleeding and others that may occur at onset or may be induced by cytostatic therapy.

14. Including Rituximab in conventional therapy in the case of diffuse large B-cell lymphoma does not confer additional benefit in terms of response to therapy, that being a result concordant with specialised literature data.

15. Survival up to 5 years was of 86.95% for the group of patients diagnosed in 2005-2006 who underwent evaluation after 5 years (23 patients of which 20 are found alive after 5 years 20, occurring three deaths). Survival up to 2 years for the entire group was of 93.84%, 61 of the 65 patients of the group being alive after two years. Survival for the entire group at the end of the evaluation was of 90.76%.

16. At the final evaluation of the entire group there has been found that a number of 50 patients of all the 65 patients were in complete remission (representing 76.92%), 9 patients were in partial remission (representing 13.84%) and there occurred 6 deaths.

17. There couldn’t be evaluated the prognosis factors and the effectiveness of the different therapeutic methods in MALT lymphoma because of the small number of cases.

18. The characteristics of the studied group are: predominance of aggressive forms (because of the inclusion in the studied group only of
the patients with MALT lymphoma who were hospitalized in Clinics of Haematology); there were identified only two histopathological types of disease, although in the specialised literature there are cited other histological types from 2 to 5% ; use of echo-endoscopy in a small number of patients (19 patients) and the large number of patients undergoing surgical resection (41 patients) is in disagreement with recent data published in the specialised literature advocating the preservation of the stomach and the sticking to the prescripts of surgical therapy only to solve complications (perforation, upper gastrointestinal bleeding) and sometimes to the use of subtotal gastric resection in the initial stages of MALT lymphoma.
References


