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BCL10 aberations and NF-kappa B activation involving p65 are absent or rare in primary gastric MALT lymphoma

BCL10 aberacije i aktivacija p65 gena NF-kappa B puta su odsutne ili retke u primarnom MALT limfomu želuca

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Abstract

Bacground/Aim. Mucosa-associated lymphoid tissue (MALT) lymphoma accounts for 5–17% non-Hodgkin lymphomas (NHL). The molecular pathogenesis of MALT lymphomas is not well-established. The aim of this study was to evaluate immunohistochemically determined nuclear coexpression of BCL10 and NF-kappaB (NF-κB) in tumor cells of gastric MALT lymphoma and its impact on the patogenesis and outcome of the disease. **Methods.** Medical records of 35 patients with newly diagnosed gastric MALT lymphoma were analyzed and biopsy specimens were immunostained for BCL10 and NF-kB expression (p65 subunit). **Results.** The median age of 35 patients diagnosed with gastric MALT lymphoma was 63.5 years (male/female = 21/14). Symptoms were present in 23/35 (65.7%) patients with the weight loss as the most common symptom. Gastric MALT lymphomas were usually localized in the stomach corpus and corpus and antrum (45.7% and 31.2%, respectively). *H. pylori* infection was confirmed in 20 out of 30 (66.7%) patients. Treatment options were as follows: immunochemotherapy in 10 (28.5%) patients, surgery in 9 (25.8%) patients, combined surgery and chemotherapy in 14 (40%) patients and supportive measures in 2 (5.7%) patients. Complete remission was achieved in 13 (37.1%) patients and partial remission in two (5.7%) patients. Sixteen (45.7%) patients had disease progression ($p < 0.001$). Cytoplasmatic expression of BCL10 in tumor cells was detected in 19 (54.3%) specimens. Nuclear expression was detected in no specimen. Cytoplasmic expression of NF- κB was present in 22 (65.7%) specimens, but nuclear expression was not detected in any specimens. **Conclusion.** Nuclear expressions (activation) of NF-κB p65 subunit and BCL10 were not detected in specimens of gastric MALT lymphoma. The correlation of nuclear coexpression of BCL10 and NF-κB in gastric MALT lymphoma was not established. These results indicate that other mechanisms and signal pathways are active in lymphogenesis of gastric MALT lymphoma, as that apoptotic inhibition is not the main, nor the only mechanism in tumorogenesis.

Key words:
lymphoma, b-cell, marginal zone; stomach neoplasms; immunohistochemistry; gene expression; signal transduction.

Apstrakt

Uvod/Cilj. Limfomi limfnog tkiva pridruženog mukozi (MALT) čine 5–17% svih non-Hodgkin limfoma (NHL). Molekularna patogeneza MALT limfoma nije razjašnjena. Cilj ove studije bio je da se imunohistohemijski utvrdi prisustvo nuklearne koekspresije BCL10 i NF-kappaB (NF-κB) u tumorskim ćelijama želudačnog MALT limfoma kao i njihov uticaj na patogenezu i ishod bolesti. **Metode.** Analizirani su klinički podaci iz istorija bolesti 35 bolesnika sa novodijagnostikovanim želudačnim MALT limfomom i uzorci tkiva biopsije želuca bojeni su imunohistohemijskom metodom na ekspresiju BCL10 i NF-κB. **Rezultati.** Prosečna starost kod 35 bolesnika sa dijagnozom želudačnog MALT limfoma iznosila je 63,5 godina (muškarci/žene = 21/14). Simptomi su bili prisutni kod 23/35 (65,7%) bolesnika sa gubitkom težine kao najčešćim simptomom. Želudačni MALT limfom bio je najčešće lokalizovan u korpusu i korpusu i antrumu (45,7% i 31,2%). Infekcija *H. pylori* bila je potvrđena kod 20 od 30 (66,7%) bolesnika. Bolesnici su lečeni imunohemioterapijom (10 bolesnika, 28,5%), hirurški (9 bolesnika, 25,8%), kombinacijom hirurgije i hemioterapije (14 bolesnika, 40%) i suportivno (2 bolesnika, 5,7%). Kompletna remisija bila je postignuta kod 13 (37,1%) bolesnika, a parcijalna remisija kod dva (5,7%) bolesnika. Kod 16 (45,7%) bolesnika došlo je do progresije bolesti ($p < 0,001$).

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Citoplazmatska ekspresija BCL10 bila je nađena kod 19 (54,3%) tumorskih ćelija. Nuklearna ekspresija nije uočena ni u jednom uzorku. Citoplazmatska ekspresija NF-κB bila je prisutna u 22 (65,7%) uzorka, ali nuklearna ekspresija nije potvrđena ni u jednom uzorku. **Zaključak.** Nuklearna ekspresija (aktivacija) p65 subjedinice NF-κB puta i BCL10 nije otkrivena u uzorcima želudačnog MALT limfoma. Korelacija nuklearne koekspresije BCL10 i NF-κB u tumorskim ćelijama želudačnog MALT limfoma nije utvrđena. Ovi rezultati ukazuju da su neki drugi mehanizmi i signalni putevi aktivni u limfogenezi želudačnog MALT limfoma i da inhibicija apoptoze nije glavni i jedini mehanizam tumorogeneze.

Ključne reči:
limfom, malt; želudac, neoplazme; imunohistohemija; geni, ekspresija; signali, transdukcija.

Introduction

Mucosa-assciated lymphoid tissue (MALT) lymphomas are defined as extranodal B-cell lymphomas of marginal zone that originate from lymphatic tissue associated with mucosal and glandular epithelium [1]. MALT lymphomas account for 5–17% of non-Hodgkin lymphomas (NHL) [2]. They can occur in any organ, most commonly in the stomach, lungs, salivary glands and thyroid gland. MALT lymphoma of the stomach account for about 40% of all primary gastric NHL [3]. They predominantly occur between 50 and 60 years of age and there is no gender preponderance [4]. Morphologically, they are present as multifocal gastric lesions usually accompanied with gastrointestinal symptoms. At presentation, the disease is localized and usually have indolent course with histological transformation to large-cell lymphoma in 10% of cases later on [2]. The 5-year survival is between 95% and 85% [5]. Association with *H. pylori* infection in 90% of gastric MALT lymphomas was proven [6, 7]. It is assumed that malignant transformation of B lymphocytes is caused by chronic antigenic stimulation with *Helicobacter* infection. As a result of direct and indirect (T-cells specific for *H. pylori*) antigen stimulation B cells proliferate and can, at times, undergo a neoplastic transformation following the acquisition of genetic abnormalities [3]. In more than half of patients with MALT lymphomas structural cytogenetic abnormalities with translocation t (11; 18), t (1; 14), t (14; 18) are described, while the most common numeric cytogenetic abnormality is trisomy 3. These translocations result in the generation of the novel fusion proteins, aberrant nuclear BCL10 expression and activation of the nuclear factor kappaB (NF-κB) pathaway. NF-κB induction appears to drive antigen independent growth of lymphoma cells.

BCL10 activates NF-κB transcription factor and inhibits apoptosis. Binding beetween BCL10 and MALT1 is crucial for the oligomerisation and self-activation of MALT1, which leads to NF-κB activation [3]. Physiologicaly, BCL10 is found to be abundant in the cytoplasm of B lymphocytes in germinative center and moderately expressed in the cytoplasm of B lymphocytes of the marginal zone of follicules. An ectopic, nuclear localization of BCL10 was observed in some cells of gastric MALT lymphoma. The degree of BCL10 expression correlates to the type of cytogenetic abnormality. In gastric MALT lymphoma with t (11; 18) nuclear BCL10 expression is usually moderate; in t (1; 14) nuclear expression of BCL10 is prominent; while t (14; 18) is characterized with cytoplasmatic expression of BCL10 [8].

NF-κB is a dimeric transcription factor that belongs to the family of Rel (reticuloendotheliosis) proteins, composed of five proteins (p50, p52, p65, c-Rel, RelB). NF-κB is predominantly located in the cytoplasm of the cells as inactive cytoplasmic complex with the inhibitor κB (IκB) [9]. After phosphorylation of IκB, NF-κB is released from the complex NF-κB/IκB and goes into the nucleus, where it controls the transcription of various genes that play a key role in the regulation of many cellular processes such as inflammation, proliferation, immunity, angiogenesis and apoptosis [10]. NF-κB signaling pathway is activated after stimulation of cell proinflammatory cytokines, mitogens, growth factors, antigens, oxidative stress triggers and intercellular contact and plays an important role in the development of various tumors. Activity of NF-κB pathway in tumor cells is assesed on the basis of the nuclear localization of its subunits (commonly p50, p52 and p65).

The aim of this study was to determine nuclear coexpression of BCL10 and NF-κB in tumor cells of gastric MALT lymphoma and its impact on the patogenesis and outcome of the disease.

Methods

We analyzed medical records of 35 patients with newly diagnosed gastric MALT lymphoma between January 2001 and July 2007. The study was conducted in retrospective-prospective manner. The patients were followed until March 2010. The study included 35 patients: 21 male and 14 female. The median age was 63.5 years (range 35–77 years). There were 17 (48.6%) patients younger than 65 years and 18 (51.4%) patients older than 65 years. Clinical characteristics of patients were sumarized in Table 1. Histopathologic diagnosis was made according to the Revised European American Lymphoma/World Health Organization (REAL/WHO) classification. The presence of *H. pylori* in gastric mucosa was determined by standard Geimsa staining of biopsy sample.

The immunoexpression of BCL10 and NF-κB was determined in biopsy tissue samples of gastric MALT lymphomas by standard avidin-biotin-streptavidin immunohistochemical method. The expression of NF-κB in tumor cells of gastric MALT lymphoma was determined by using monoclonal antibody p65 NF-κB (Thermo Vision Corporation; dilution 1 : 50). The expression of BCL10 was determined by using monoclonal antibody BCL10 (DAKO; dilution 1 : 25). Paraffin embedded normal lymphoid tissue was used as a positive control.

Table 1

Clinical features of patients with gastric MALT lymphoma (χ^2-test)

Patients caracteristics	n	%	*p*
Age (years)			
< 65	17	48.6	0.866
> 65	18	51.4	
Gender			
male	21	60	0.237
female	14	40	
B symptoms			
yes	12	33.3	0.063
no	23	65.7	
Karnofsky index			
> 60%	30	85.7	0.0001
< 60%	5	14.3	
Disease symptoms			
epigastric pain	25	71.4	
epigastric pain + melena	8	22.9	0.001
peritoneal effusion	1	2.9	
without symtoms	1	2.9	
Disease dissemination			
yes	21	60	0.237
no	14	40	
Macroscopic tumor pattern			
ulceration	24	68.6	0.0001
polypus	3	8.6	
diffuse-infiltrative pattern	8	22.9	
H. pylori infection			
positive	20	57.4	0.007
negative	10	28.1	
not done	5	14.3	

MALT – Mucosa-associated lymphoid tissue.

BCL10 immunoreactivity was interpreted as positive or negative, as well as cytoplasmic, cytoplasmic and nuclear, or nuclear. Staining intensity was graded as weak, moderate or strong. Approximate cutoff of ≥ 20% was used to classify tumors as having weak and strong expression. NF-κB p65 immunoreactivity was categorized as cytoplasmic (inactive) or nuclear staining (active). Positive staining patterns were claimed if protein expression was detected in more than 10% of the cells.

A treatment response was evaluated a month after the therapy completition. Data were summarized by frequency and percentage for categorical variables. For continuous variables, the medians and ranges were computed. Statistical tests were 2-sided at the 5% level of significance. Univariate analysis using the nonparametric Wilcoxon rank-sum test or the Kruskall-Wallis rank-sum test when appropriate were performed to investigate the association between continuous variables and categorical variables. Statistical analyses were performed by using statistical package SPSS (version 11.5 for Windows).

Results

The most common symptom at presentation was epigastric pain registered in 25 (71.4%) patients ($p < 0.001$) (Table 1). Epigastric pain associated with gastrointestinal bleeding was registered in additional 8 (22.9%) patients. B symptoms were present in 23 (65.7%) patients with weight loss as the most common ($p < 0.063$). MALT lymphoma was usually localized in the gastric corpus (16 or 45.7% patients). The corpus and antrum were often simultaneously affected (11 or 31.2% patients; $p < 0.001$). Tumor lesions usually appeared as macroscopic ulcerations (24 or 68% patients), diffuse infiltrative growth was seen in 8 (22.9%) patients whilst polypoid growth pattern was seen in only 3 (8.6%; $p < 0.0001$) patients. Giemsa staining confirmed *H. pylori* infection in 20 out of 30 tested patients (histochemical analysis was not done in 5 specimens due to technical reasons) (Table 1). The most of the patients (14 or 40%) were in clinical stage IV according to the Lugano staging system while 8 (22.9%) were in clinical stage I and 13 (37.1%) in clinical stage II at the time of presentation. The most of the patients (21 or 60%) had disseminated disease at presentation. Disseminated disease was defined as the presence of multifocal lesions or as nonmucosal organs infiltration (distant lymph node, bone marrow, spleen, liver, pleura) together with the presence of the disease in one MALT tissue. The patients were treated as follows: immunochemotherapy in 10 (28.5%) patients, surgery in 9 (25.8%) patients, combined surgery and chemotherapy in 14 (40%) patients. *H. pylory* eradication in combination with chemotherapy was performed in 2 (5.7%) patients and supportive measures in 2 (5.7%) patients. Complete remission was achieved in 13 (37.1%) of the patients and partial remission in two (5.7%) patients. Sexteen patients had disease progression (45.7%; $p < 0.001$). There was no reliable data on treatment outcome in 4 patients (uncomplete medical records). The most of the patients (8 out of 13) achieved a complete remission when treated with a combined modality (surgery and chemotherapy). There was no significant difference in treatment modality among patients with progressive disease ($p > 0.05$).

The results of immunoexpression in tumor specimens of gastric MALT lymphoma are showed in Table 2.

BCL10 cytoplasmic expression was detected in 19 (54.3%) biopsy specimens: 15 had moderate, three low and one prominent cytoplasmic positivity (Table 2). In 16 (45.7%) specimens, BCL10 expression was not found in the nucleus, nor in the cytoplasm. BCL10 nuclear expression was found in no specimen.

Table 2

Immunoexpression in tumor specimens of gastric MALT lymphoma

Cytoplastatic staining	BCL10 (%)	NF-κB (%)
Positive	54.3	65.7
Negative	45.7	34.3

MALT – Mucosa-associated lymphoid tissue.

NF-κB cytoplasmatic expression was found in 22 (65.7%) patients (Tables 1 and 2). In four (11%) patients cytoplasmic and nuclear expressions of NF-κB were positive, but nuclear expression was present in less than 10% of cells, which is not considered significant in terms of activity of this transcription factor. In other words, cytoplasmic activity means the presence, but not the activity of NF-κB transcriptional factor.

Since nuclear expression of BCL10 or NF-κB was not found it could be concluded that some other mechanisms and signal pathways are active in lymphogenesis of gastric MALT lymphoma. So, the found cytoplasmic expression was not correlated to clinical patients features.

Discussion

The patients in this study diagnosed with gastric MALT lymphoma were mostly older than 50 years, with good performance score as alredy reported [5]. In contrast to recent tendencies (in developed health systems) to diagnose the disease at an early stage, gastric lymphoma in our patients was usually diagnosed at an advanced stage. Also, according to literature data, gastric MALT lymphoma is most frequently localized in the gastric antrum and presented as multiple ulcerations, but in our patients lymphoma was localized in the corpus and presented mostly as ulcerative lesions. Therapeutic approach in patients with gastric MALT lymphoma is controversial and not standardized. Our patients were first seen by the surgeon, since the main symptom at presentation was abdominal pain. Therefore the most common therapeutic approach was surgery and the reason while eradication therapy for *H. pylory* was not common.

The molecular pathogenesis of MALT lymphomas arising in the gaster is not well-established, but it is known that malignant transformation disrupt the cell signaling pathway and allows its autonomous behavior. As shown by others, at least three of the chromosomal translocations were identified in MALT lymphomas [t (11; 18), t (14; 18), and t (1; 14)] and result in deregulation of BCL10 and downstream activation NF-κB pathway [11, 12].

We used BCL10 immunostaining to indirectly assess for MALT lymphoma-associated translocations since BCL10 immunostaining has been reported to show characteristic expression patterns that correlate with the presence of specific translocations. In MALT lymphomas carrying the t (1; 14), BCL10 is predominantly and strongly expressed in the tumor cell nuclei. In MALT lymphomas with the t (11; 18) or t (14; 18), BCL10 is moderately expressed in the nucleus or strongly expressed in the cytoplasm of tumor cells, respectively [8, 12, 13]. However, nuclear expression of BCL10 can be found in up to 50% MALT lymphomasa without specific translocation [14, 15]. Therefore, the significance of nuclear expression of BCL10 in lymphogenesis stil remains unexplained.

In 16 (45.7%) samples of gastric MALT lymphoma in this study, immunohistochemical BCL10 staining was not detected either in cytoplasm or nucleus, suggesting that it is not the central mechanism responsible for lymphogenesis. Beside ectopic nuclear localization of BCL10 an altered function of mutant forms of BCL10 protein could be also responsible for lymphogenesis. However, mutated forms of BCL10 protein are difficult to detect using immunohistochemical metod [16]. Thus, although BCL10 immunostaining can be used as an initial screen for the t (11; 18) in MALT lymphomas, the presence of BCL10 nuclear expression should not be used as a surrogate for the presence of the t (11; 18). Nuclear expression of BCL10 has prognostic significance since it is a common feature of disseminated forms of gastric MALT lymphoma [15, 17]. Disseminated forms are associated with structural cytogenetic aberrations as t (1; 14) and t (11; 18) and usually without the effect of *H. pylori* eradication therapy) [8, 18]. However, 60% in our study group presented with disseminated form of the disease, but none of the patients had nuclear expression of BCL10.

Immunohistochemical staining was also performed to evaluate the expression of p65 subunits of NF-κB. In many different tumor types, and in some gastric and ocular adnexal MALT lymphomas, the evidence of NF-κB activation has been shown in a subset of cases [19]. As the p65 subunit is involved in many activated forms of NF-κB, immunohistochemical detection of nuclear p65 staining is used as evidence of NF-κB activation [20]. In all the studied cases, the staining pattern was only cytoplasmic, and therefore negative, suggesting that NF-κB is inactive. These results further suggest that MALT lymphoma-associated translocations that are known to activate NF-κB were absent or rare in our studied cases of gastric MALT lymphomas. However, we cannot exclude the possibility that NF-κB activation still exist in these MALT lymphomas cases, involving other members of Rel proteins family (p50, p 52).

In this study, in 35 MALT lymphoma specimens, nuclear coexpression of BCL10 and NF-κB in tumor cells was not found. It is interesting to note that Talwalker et al. [20] found

BCL10 positivity in some cases of breast MALT lymphomas despite NF-κB negativity in all of them, but none of the cases had MALT1 gene rearrangements confirmed by fluoreseence in situ hybridization (FISH). This suggests that BCL10 immunostaining overestimates the frequency of MALT1 gene rearrangements [21]. Moreover, Sagaert et al. [22, 23] studied 77 patients with MALT lymphoma and found translocations involving MALT1 and BCL10 gene in only 1% of patients, concluding that other structural or numerical chromosome disorders may be responsible for tumorigenesis and lymphogenesis. Similar conclusions can be widrawn from our study *ie* that lymphogenesis pathway in our cases should be explained other than by activation of BCL10 and NF-κB.

Conclusion

Nuclear expression of NF-κB p65 subunit and BCL10 were not detected in studied specimens of gastric MALT lymphoma. These results indicate that other mechanisms and signal pathways are active in lymphogenesis of gastric MALT lymphoma, and that apoptotic inhibition is not the main, nor the only mechanism in tumorogenesis.

Conflict of interest

The authors do not have any conflicts of interest to declare.

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