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Onset and Progression of Precancerous Lesions on Gastric Mucosa of Patients Treated for Gastric Lymphoma

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ABSTRACT

Background & Aims: Patients with primary gastric lymphoma are at an increased risk of developing gastric cancer. Data on gastric precancerous lesions development in these patients are scanty. We assessed gastric precancerous lesions in a cohort of patients with primary lymphoma.
Methods: Data of patients with primary gastric lymphoma [mucosa-associated lymphoid tissue (MALT)-lymphoma or diffuse large B-cell lymphoma (DLBCL)] were analysed. Multiple (>10) biopsies were performed on gastric mucosa at each endoscopic control, beyond macroscopic lesions. Presence and distribution of intestinal metaplasia (IM) at baseline, the onset at follow-up, and progression through the stomach or transformation in the incomplete IM type were assessed. The onset of neoplastic lesions was recorded.
Results: Data of 50 patients (mean age of 63.6 ± 10.7 years; M/F: 25/25), including 40 with MALT-lymphoma and 10 with DLBCL, with median follow-up of 30.5 months (range: 9-108) and a median of 6 endoscopic controls (range: 3-14) were evaluated. At entry, IM was present in 12 (24%), and it developed in other 22 (57.9%) patients at a median follow-up of 6 (range: 3-40) months. Overall, progression of IM was observed in 7 (21.2%) cases, including extension in the stomach (n=5) or transformation into the incomplete type (n=2). Low-grade dysplasia was detected in 4, and indefinite dysplasia in other 7 patients. In one patient, low-grade dysplasia had progressed to high-grade and gastric adenocarcinoma of the fundus.
Conclusions: Our data found a frequent onset and rapid progression of precancerous lesions on gastric mucosa of lymphoma patients. This observation could explain the increased incidence of metachronous gastric cancer in these patients.

Key words: intestinal metaplasia – precancerous lesions – gastric lymphoma – gastric cancer.

Abbreviations: DLBCL: diffuse large B-cell lymphoma; IM: intestinal metaplasia; MALT: mucosa-associated lymphoid tissue.

INTRODUCTION

There is some evidence suggesting that patients with primary gastric lymphoma are at an increased risk of developing adenocarcinoma of the stomach [1-4]. Indeed, a 6-16-fold increased incidence of gastric cancer in mucosa-associated lymphoid tissue (MALT)-lymphoma patients has been calculated in epidemiological studies [5, 6]. It is well-recognized that atrophy and intestinal metaplasia (IM) on gastric mucosa are precancerous lesions for cancer development [7], and that dysplasia (low- or high-grade) is a non-invasive neoplasia [8]. Data on development of gastric precancerous lesions in patients with lymphoma of the stomach are still scanty. Rapid onset and progression of these lesions was observed in a cohort of MALT-lymphoma patients following different treatments [9]. A recent, larger study pointed out that both IM and dysplasia tend to increase overtime in patients with either MALT-lymphoma or diffuse large B cell lymphoma (DLBCL) [10].

We therefore aimed to evaluate the development and progression of precancerous lesions at long-term follow-up in a cohort of patients treated for gastric lymphoma.

METHODS

This was a retrospective analysis of prospectively collected data relative to a cohort of patients with gastric lymphoma.

In detail, the clinical and histological data of each patient diagnosed with gastric lymphoma in the last 10 years, from January 2009 to December 2018, were collected in a specific database. When some information was lacking, the medical chart was retrieved to complete data collection for this study. Diagnosis of either low-grade, B cell MALT-lymphoma or DLBCL were performed on gastric biopsies according to the international criteria, and standard disease staging was accomplished [11, 12]. The updated endoscopic classification of gastric lymphoma was used for macroscopic classification [13]. At endoscopy, biopsies were taken on macroscopic lesions, as well as multiple specimens (>10) were obtained from antrum, incisura angularis, gastric body and fundus to search for *Helicobacter pylori* (*H. pylori*) infection and for gastritis assessment, as routine practice one from IBS-A group (2.94%; 1 of 34 IBS-A patients). The main presenting symptoms prompting upper endoscopy were classified as alarm symptoms (haematemesis, melaena, vomiting, weight loss, anaemia, thrombocytopenia) or not alarm symptoms (dyspepsia or gastroesophageal reflux) [14]. Patients were managed as in routine clinical practice. *H. pylori* eradication was performed in all infected patients with standard therapy regimens, and it was also attempted in some patients without infection. Standard immuno-chemotherapies (rituximab, R-CHOP, radiotherapy, etc) were administered to *H. pylori* negative patients and to MALT-lymphoma patients who had failed to achieve disease remission 1-year following a successful eradication or with disease progression. Moreover, immuno-chemotherapy was started immediately in MALT-lymphoma patients with disease diagnosed at stage >II1 and in all DLBCL patients, together with *H. pylori* eradication when bacteria was present.

A scheduled clinical, endoscopic and histological follow-up was performed according to the guidelines [12]. Lymphoma remission was considered achieved when the disease was absent on gastric mucosa at two consecutive histological controls. Only data of patients with at least 3 consecutive endoscopic controls were included in this study. For this study, we evaluated the onset and progression of IM on gastric mucosa as precancerous lesion, whilst data on atrophy were not taken into account. Progression was defined as IM extension from one to more gastric sites or appearance of incomplete (colonic) IM type from the complete (small bowel) IM type. Development of non-invasive neoplasia, including low- and high-grade dysplasia, as well as "indefinite dysplasia" was recorded [8]. Gastric cancer was confirmed by histology.

Statistical analysis

The frequency and percentage of each observation were calculated, and the data are reported as mean ± SD. Univariate analysis was performed by using the Fisher's exact test and Student's T test for unpaired data, as appropriate. A logistic multivariate analysis was performed to identify potential predictors for the onset of precancerous lesions on gastric mucosa. SPSS software ver. 16.0 was used for all computations.

RESULTS

A total of 54 patients with gastric lymphoma were diagnosed, but data of three patients were incomplete and one further patient underwent early gastric surgery in another hospital (all with MALT-lymphoma), so that they were excluded. Therefore, data of 50 patients (mean age of 63.6 ± 10.7 years; M/F: 25/25) were analyzed, including 40 with MALT-lymphoma and 10 with DLBCL, with median follow-up of 30.5 months (range: 9-108) and a median of 6 endoscopic controls (range: 3-14). The main clinical, endoscopic and histological data detected at entry were provided in Table I.

In the MALT-lymphoma group, antibiotic therapy as a first-line treatment was administered to 30 out of 31 patients with *H. pylori* infection and, the eradication (with one or more

Table I. Demographic and clinical characteristics of the enrolled patients.

Parameter	MALT-lymphoma (N = 40)	DLBCL (N = 10)	Overall (N = 50)
Male/female	21/19	4/6	25/25
Age (Mean±SD); years	63.2 ± 11.5	65.9 ± 7.2	63.6 ± 10.7
Smoking habit (yes or past/no)	19/21	6/4	25/25
H. pylori infection (%)	31 (77.5)	3 (30)	34 (68)
Alarm symptoms (yes/no)	11/29	6/4	17/33
Lymphoma site			
- Antrum/angulus	16	7	23
- Gastric body/fundus	19	3	22
- Diffuse	5	-	5
Endoscopic feature			
- Ulcerative	10	7	17
– Nodular	10	2	12
– Mixed	4	1	5
- Normal/hyperaemic	12	-	12
- Petechial haemorrhage	4	-	4
Lymphoma stage			
- I	27	5	22
– II	1	–	1
– III	-	2	2
- IV	2	3	5

DLBCL: diffuse large B-cell lymphoma; MALT: mucosa-associated lymphoid tissue.

attempts) was eventually achieved in all cases. Following a successful bacterial eradication, lymphoma regression was achieved in 22 (73.3%) cases. The remaining patient received a successful eradication therapy and chemotherapy as initial treatment due to stage IV disease, and lymphoma remission was achieved. The 8 patients with lymphoma persistence were treated with immune-chemotherapy and 5 achieved remission, whilst 3 were still in follow-up with active disease. *H. pylori* therapy was attempted also in 7 out of 9 MALT-lymphoma patients without evident infection, and disease remission occurred in 2 (28.6%) cases. In the remaining 2 patients, lymphoma regressed with chemotherapy.

In the DLBCL group, lymphoma persisted in the 3 patients despite a successful *H. pylori* eradication, and they achieved remission following oncologic therapy. Five out of 7 *H. pylori* negative patients achieved remission with oncologic therapy, and 2 are still in follow-up with persistent disease.

At baseline, complete IM was present in 12 (24%) patients (11 MALT-lymphoma and 1 DLBCL), whilst no case of dysplasia was detected. At follow-up, IM onset occurred in 22 (57.9%) out of 38 patients (without this lesion at initial diagnosis) following a median of 6 (range: 3-40) months. Then, at the end of the follow-up, IM was eventually detected in 34 (68%) of included patients. Progression of IM was observed in 7 (21.2%) of these patients, including extension in the stomach (n=5) or transformation into the incomplete type (n=2). Moreover, low-grade dysplasia was detected in 4, and indefinite dysplasia in other 7 patients (Fig. 1). In one patient, low-grade dysplasia progressed to high-grade and gastric adenocarcinoma of the fundus. He was an 81-year old patient, with several comorbities (heart, kidney, liver, and clotting impairment), with diffuse, complete type IM at baseline. He refused chemotherapy or surgery and he died 6 months following cancer diagnosis. In the other 3 patients, low-grade dysplasia regressed in 2 cases following endoscopic ablation (1 case) or without treatment (1 case), and it was down staged to indefinite dysplasia in the remaining patient, still in follow-up.

The results of univariate analysis were provided in Table II. As showed, smoking habit and lymphoma localization in proximal stomach (corpus and/or fundus) were significantly associated with precancerous lesions, either present at baseline or developed at follow-up. The multivariate analysis failed to identify independent factors (age, sex, smoking habit, lymphoma type, lymphoma site, antibiotic or oncologic therapy, and follow-up duration) predictive for precancerous lesions onset in those patients without its presence at baseline.

Table II. Factors associated with presence of intestinal metaplasia (IM) on gastric mucosa.

Parameter	IM present (N = 34)	IM absent (N = 16)	P value
Male/female	17/17	8/8	0.2
Age (Mean±SD); years	65.1 ± 10.6	60.1 ± 10.7	0.5
Smoking habit (yes/not)	21/13	4/12	<0.001
H. pylori infection (yes/not)	22/12	12/4	0.2
Lymphoma site (proximal/distal)	18/11	4/11	0.03
Lymphoma type (MALT/DLBCL)	28/6	12/4	0.2

DLBCL: diffuse large B-cell lymphoma; IM: intestinal metaplasia; MALT: mucosa-associated lymphoid tissue

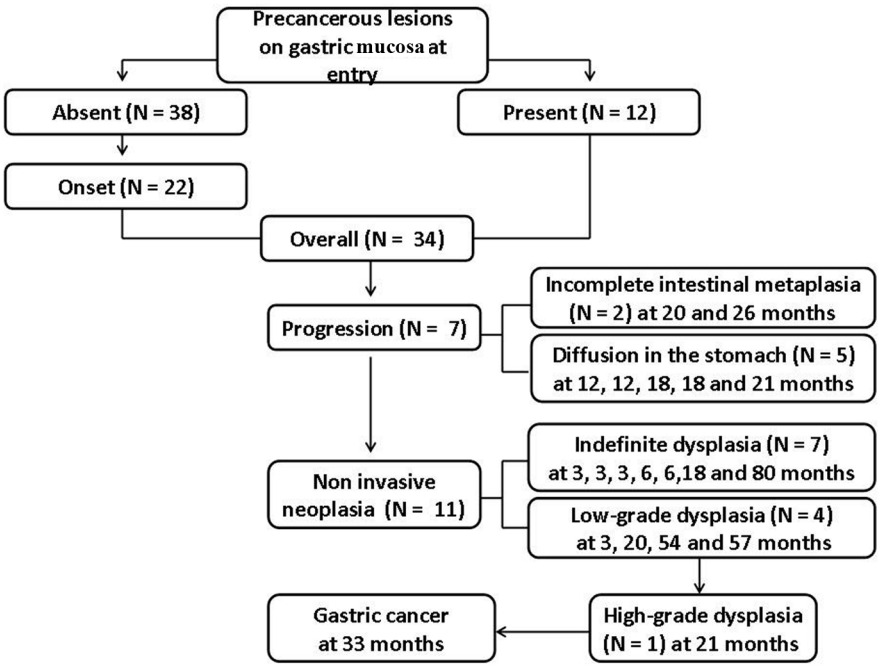

Fig. 1. Precancerous and neoplastic lesions developed on gastric mucosa at follow-up.

DISCUSSION

It has been estimated that there are more than 13,000 new cases per year of gastric MALT-lymphoma diagnosed worldwide [15]. Lymphoma of the stomach is mainly triggered by *H. pylori* infection [16], and bacterial eradication achieves disease regression in near 80% of MALT-lymphoma cases treated in early (I-II1) stage [17], as well as in some DLBCL patients [18]. Moreover, eradication therapy may lead to lymphoma regression in up to 15% of cases, even in *H. pylori* negative patients [19]. Unfortunately, there is evidence that patients with gastric lymphoma are at an increased risk of developing metachronous cancer of the stomach [1-4]. Such increased risk was putatively attributed to the persistence of lymphoma or chemotherapy [20, 21]. However, a role for precancerous lesions on the gastric mucosa of lymphoma patients would appear more likely. Indeed, while not appearing predisposing to gastric lymphoma [22], precancerous lesions are widely recognized as precursors of gastric cancer [7]. Only few data are currently available on such a topic in lymphoma patients [8, 9]. Our data showed that IM shortly (median 6 months) de novo developed in more than half of the patients, whilst it was present at lymphoma diagnosis in the other 25% of cases, so that as many as 68% of included patients finally harboured IM. This prevalence is consistent with the 75% prevalence observed in another study [23]. Moreover, we observed that complete IM speedily progressed to incomplete IM or diffused into the gastric mucosa in as many as 33% of cases. This is a relevant finding when considering that both IM extension (i.e. metaplastic pangastritis) and incomplete IM type are independent factors increasing the gastric cancer risk [24, 25]. We also observed that indefinite dysplasia and low grade dysplasia developed in 30% of patients with IM, and in one case progressed to high grade dysplasia and gastric cancer. Our data are consistent with the results of another study where rapid onset and progression of precancerous lesions were observed in a cohort of 45 MALT-lymphoma patients, where a 50%-60% prevalence of precancerous lesions was detected within a median period of 18 months (range 2–83) [8]. Moreover, we confirmed that both IM and dysplasia increased overtime in patients with either MALT-lymphoma or DLBCL, as reported in another study [9]. Finally, our data found that the presence or development of precancerous lesions in lymphoma patients was more frequent in smokers and in those with neoplastic lesions localized in the proximal stomach.

Overall, these observations document a frequent onset and progression of precancerous lesions on the gastric mucosa of lymphoma patients, and this phenomenon might be involved in the increased risk for metachronous gastric cancer. Although the reason remains unclear, a hypothesis has been recently pointed out to explain the quick IM development following lymphoma remission. Gastric lymphoma is characterized by the presence of lymphoepithelial lesions – namely a pathognomonic damage of gastric glands that are infiltrated and destructed by tumoral B lymphocytes. It has been suggested that, following this complete injury, the original gastric glands are replaced by rising metaplastic glands [26]. Further histological studies are required to test this hypothesis.

A possible limitation of our study is that we did not assess atrophy among precancerous lesions. However, we decided to assess only IM because the consistency of diagnosis for IM (k of agreement = 0.9) is distinctly higher than that of atrophic gastritis (k = 0.6) [27]. Moreover, IM by definition includes atrophy, but not the reverse [28]. In addition, the carcinogenetic potential of IM is twice as compared with atrophy, representing the successive stage in the tumoral cascade of gastric cancer [29, 30]. Therefore, our choice should be considered as a cautious and more appropriate approach for a retrospective analysis.

CONCLUSION

Our data found a frequent onset and progression of precancerous lesions on the gastric mucosa of lymphoma patients. This observation could explain, at least in part, the increased incidence of metachronous gastric cancer in these patients. An appropriate follow-up is advised for these lesions, according to current guidelines [31].

Conflicts of interest: No conflicts to declare.

Authors' contributions: A.Z. conceived and designed the study; A.Z, A.R, and S.L. data acquisition; L.R. statistical analysis; T.C.T interpreted the results; A.Z. analysed the data and drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work

REFERENCES

1. Morgner A, Miehlke S, Stolte M, et al. Development of early gastric cancer 4 and 5 years after complete remission of Helicobacter pylori associated gastric low grade marginal zone B cell lymphoma of MALT type. World J Gastroenterol 2001;7:248-253. doi:10.3748/wjg.v7.i2.248
2. Wundisch T, Thiede C, Morgner A, et al. Long-term follow-up of gastric MALT lymphoma after Helicobacter pylori eradication. J Clin Oncol 2005;23:8018-8024. doi:10.1200/JCO.2005.02.3903
3. Sakr R, Massoud M, Aftimos G, Chahine G. Gastric adenocarcinoma secondary to primary gastric diffuse large B-cell lymphoma. J Gastric Cancer 2017;17:180-185. doi:10.5230/jgc.2017.17.e11
4. Inaba K, Kushima R, Murakami N, et al. Increased risk of gastric adenocarcinoma after treatment of primary gastric diffuse large B-cell lymphoma. BMC Cancer 2013;13:499. doi:10.1186/1471-2407-13-499
5. Capelle LG, de Vries AC, Looman CW, et al. Gastric MALT lymphoma: epidemiology and high adenocarcinoma risk in a nation-wide study. Eur J Cancer 2008;44:2470-2476. doi:10.1016/j.ejca.2008.07.005
6. Amiot A, Jooste V, Gagniere C, et al. Second primary malignancies in patients treated for gastric mucosa-associated lymphoid tissue lymphoma. Leuk Lymphoma 2017;58:1-11. doi:10.1080/10428194.2017.1283033
7. Rugge M, Genta RM, Graham DY, et al. Chronicles of a cancer foretold: 35 years of gastric cancer risk assessment. Gut 2016;65:721-725. doi:10.1136/gutjnl-2015-310846
8. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000;47:251-255. doi:10.1136/gut.47.2.251

9. Lamarque D, Levy M, Chaumette MT, et al. Frequent and rapid progression of atrophy and intestinal metaplasia in gastric mucosa of patients with MALT-lymphoma. Am J Gastroenterol 2006;101:1886-1893.
10. Rentien AL, Lévy M, Copie-Bergman C, et al. Long-term course of precancerous lesions arising in patients with gastric MALT lymphoma. Dig Liver Dis 2018;50:181-188. doi:10.1016/j.dld.2017.10.014
11. Ruskoné-Fourmestraux A, Fischbach W, Aleman BM, et al. EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. Gut 2011;60:747-758. doi:10.1136/gut.2010.224949
12. Zucca E, Copie-Bergman C, Ricardi U, et al. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl 6):vi144-vi148. doi:10.1093/annonc/mdt343
13. Zullo A, Hassan C, Andriani A, et al. Primary low-grade and high-grade gastric MALT-lymphoma presentation. J Clin Gastroenterol 2010;44:340-344.
14. Caselli M, Zullo A, Maconi G, et al. "Cervia II Working Group Report 2006": guidelines on diagnosis and treatment of Helicobacter pylori infection in Italy. Dig Liver Dis 2007;39:782-789. doi:10.1016/j.dld.2007.05.016
15. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health 2016;4:e609-e616. doi: 10.1016/S2214-109X(16)30143-7
16. Zullo A, Hassan C, Ridola L, Repici A, Manta R, Andriani A. Gastric MALT lymphoma: old and new insights. Ann Gastroenterol 2014;27:27-33.
17. Zullo A, Hassan C, Cristofari F, et al. Effects of Helicobacter pylori eradication on early stage gastric mucosa-associated lymphoid tissue lymphoma. Clin Gastroenterol Hepatol 2010;8:105-110. doi:10.1016/j.cgh.2009.07.017
18. Paydas S. Helicobacter pylori eradication in gastric diffuse large B cell lymphoma. World J Gastroenterol 2015;21:3773-3776. doi:10.3748/wjg.v21.i13.3773
19. Zullo A, Hassan C, Ridola L, et al. Eradication therapy in Helicobacter pylori-negative, gastric low-grade mucosa-associated lymphoid tissue lymphoma patients: a systematic review. J Clin Gastroenterol 2013;47:824-827. doi:10.1097/MCG.0b013e318286ff72
20. Copie-Bergman C, Locher C, Levy M, et al. Metachronous gastric MALT lymphoma and early gastric cancer: is residual lymphoma a risk factor for the development of gastric carcinoma? Ann Oncol 2005;16:1232-1236. doi:10.1093/annonc/mdi242
21. Zauber NP, Berman EL. Synchronous and metachronous primary gastric lymphoma and adenocarcinoma: a clinicopathologic study of 12 patients. Cancer 1998;82:226–227. doi:10.1002/(sici)1097-0142(19980101)82:1<226::aid-cncr28>3.0.co;2-3
22. Ishikura N, Usui Y, Ito H, et al. Helicobacter pylori (HP) infection alone, but not HP-induced atrophic gastritis, increases the risk of gastric lymphoma: a case-control study in Japan. Ann Hematol 2019;98:1981-1987. doi:10.1007/s00277-019-03721-y
23. Capelle LG, den Hoed CM, de Vries AC, et al. Premalignant gastric lesions in patients with gastric mucosa-associated lymphoid tissue lymphoma and metachronous gastric adenocarcinoma: a case-control study. Eur J Gastroenterol Hepatol 2012;24:42-47. doi:10.1097/MEG.0b013e32834d85e6
24. González CA, Pardo ML, Liso JM, et al. Gastric cancer occurrence in preneoplastic lesions: a long-term follow-up in a high-risk area in Spain. Int J Cancer 2010;127:2654-2660. doi:10.1002/ijc.25273
25. Zullo A, Hassan C, Romiti A, et al. Follow-up of intestinal metaplasia in the stomach: when, how and why. World J Gastrointest Oncol 2012;4:30-36. doi:10.4251/wjgo.v4.i3.30
26. Zullo A, Licci S. Why does intestinal metaplasia develop early on gastric mucosa of mucosa-associated lymphoid tissue lymphoma patients? Ann Gastroenterol 2020;33:103. doi:10.20524/aog.2019.0440
27. Capelle LG, de Vries AC, Haringsma J, et al. The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. Gastrointest Endosc 2010;71:1150-1158. doi:10.1016/j.gie.2009.12.029
28. Rugge M, Capelle LG, Cappellesso R, Nitti D, Kuipers EJ. Precancerous lesions in the stomach: from biology to clinical patient management. Best Pract Res Clin Gastroenterol 2013;27:205-223. doi:10.1016/j.bpg.2012.12.007
29. Zullo A, Hassan C. How harmful is the presence of intestinal metaplasia in the stomach? Gastroenterology 2009;136:1461-1462. doi:10.1053/j.gastro.2008.11.064
30. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process. First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 1992;52:6735-6740.
31. Pimentel-Nunes P, Libânio D, Marcos-Pinto R, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy 2019;51:365-388. doi:10.1055/a-0859-1883