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Decreasing incidence of gastric MALT lymphomas in the era of anti-*Helicobacter pylori* interventions: results from a population-based study on extranodal marginal zone lymphomas

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Background: Few studies have been carried out to date that have addressed the epidemiology of extranodal marginal zone lymphomas (EN-MZLs).

Patients and methods: We carried out a population-based study to investigate incidence rates (IRs) and time trends of EN-MZL diagnosed in the province of Modena (Italy) from 1997 to 2007.

Results: One hundred and sixty-five cases were identified from the Modena Cancer Registry that corresponded to an age-standardized IR of 2.3 cases per 100 000. A bimodal distribution of age was shown with the group of young patients mostly represented by males with cutaneous lymphoma. No time trends were observed for the IR; the incidence of gastric mucosa-associated lymphoid tissue (g-MALT) lymphomas ($N = 51$) markedly declined during the study period, dropping from 1.4 in 1997 to 0.2 in 2002 and then remaining stable until 2007; the calculated annual percent change for g-MALT was −17.0% (95% confidence interval −26.6% to −6.2%). We also observed a significant decrease in the rate of g-MALT associated with *Helicobacter pylori* (HP) infection from 61% to 17% of patients diagnosed before and after 2002 ($P = 0.007$; P for trend = 0.016).

Conclusion: This population-based study provides new insights into recent changes in the epidemiology of EN-MZL, mainly represented by the sharp reduced incidence of HP-positive g-MALT lymphomas.

Key words: extranodal lymphoma, gastric MALT, *Helicobacter pylori*, incidence change, non-Hodgkin's lymphoma, population-based study

introduction

Lymphoma of the mucosa-associated lymphoid tissue (MALT) is an extranodal lymphoma and accounts for 7%–8% of non-Hodgkin's lymphoma (NHL) cases. MALT lymphoma is characterized by infiltration of the marginal zone of reactive B-cell follicles by morphologically heterogeneous small B cells [1, 2]. Chronic inflammation frequently precedes or accompanies MALT lymphoma and may be the result of infection, autoimmunity, or other unknown stimuli [2]. MALT lymphomas can affect almost every organ and site of the body, although ∼50% of cases involve the gastrointestinal tract, with one-third of these affecting the stomach. Several infectious agents have been identified as etiologic agents of different types of extranodal MALT lymphomas. Typical of gastric mucosa-associated lymphoid tissue (g-MALT) also is an association with *Helicobacter pylori* (HP) infection that drives lymphoid colonization of the gastric mucosa and chronic stimulation of these attracted cells leading to the accumulation of genetic changes [3]. Thus far, several retrospective series of MALT lymphomas have been published [4–6]; however, few reports have addressed this topic using a population-based approach. In our current study, we report the results of a population-based analysis we conducted on extranodal MALT lymphomas that had been reported to the Modena Cancer Registry (MCR), in northern Italy, between 1997 and 2007.

materials and methods

MCR routinely collects detailed information regarding the clinical characteristics, treatment approaches, and outcomes of all cases of malignant lymphomas diagnosed in the province of Modena, northern Italy [7]. We have thus far analyzed data on cases diagnosed from 1997 to 2007. To provide accurate and clinically useful results, we decided to reclassify all

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cases according to the third revision of the International Classification of Diseases for Oncology (ICD-O-3) [8, 9]. The coverage achieved by the MCR, which refers to a population of ~634 000 people, can be regarded as excellent due to the low rate of death certificate only reports (0.1%) [10]. To identify MALT cases from the MCR archives, the ICD-O-3 9699-3 code was used, which corresponds to nonsplenic marginal zone lymphomas (NS-MZLs). The selection criteria associated with this code does not exclude cases of nodal marginal zone lymphoma (MZL), which differ from MALT lymphomas, but the inclusion of such nodal cases should not affect our results substantially as they are very rare lymphomas. For each case with a confirmed NS-MZL, a complete dataset was obtained using MCR archives and an active chart review. g-MALT cases among extranodal cases were defined as those with gastric localization, with only one involved mucosal site. The HP status was assessed by Giemsa staining of gastric biopsies. Cases were considered HP positive (HP+) if they had positive staining for HP on a diagnostic biopsy or on at least one gastric biopsy carried out within 6 months of diagnosis.

Statistical analyses were carried out with Stata 8.2/SE software. All comparisons were performed with Fisher's exact test or chi-square test. Multivariate analysis was carried out by means of logistic regression. The multimodality of age distribution was assessed through a nonparametric kernel density estimation technique proposed by Silverman [11]. All tests were two-sided with a level of significance of 5%. Standardized incidence rates (IRs) were calculated according to the world standard population [12]. Incidence for trends over a fixed period of time was evaluated by the annual percent change (APC) and joinpoint analysis was used to detect trend changes [13]. All follow-up data from the MCR were updated on 30 June 2008.

results

Overall, 165 patients with NS-MZL were identified among the 2532 NHL cases diagnosed in the province of Modena from 1997 to 2007, representing 7.3% of all NHL and 8.5% of B cell NHL patients in this province. g-MALT lymphomas were by far the most frequent subtype of MALT lymphomas accounting for 51 cases (30.9%) and representing 77% of the g-MALT patients. Overall, 57 cases had stage IV disease (36%); stage IV was defined in 11 patients with g-MALT (22%). Clinical characteristics of NS-MZL included in the current study are shown in Table 1. In 26 cases (15%), a second cancer was also diagnosed involving the same organ in 3 cases (two stomach and one colon). The most frequent second tumors were lung, gastric, and colon with five cases each. For patient with g-MALT lymphomas, a second cancer was diagnosed in 12 cases (24%); gastric adenocarcinoma was diagnosed in 2 cases.

The overall world standardized IR of NS-MZL is calculated to be 2.3 cases per 100 000 (1.3 and 1.0 for males and females, respectively). The age at diagnosis of NS-MZL in our population showed a bimodal distribution with a first peak at ~30 years and a second at ~70 years (Figure 1). Using a cut-off of 45 years, and carrying out multivariate logistic analysis, we found that young patients were typically males with skin involvement and localized disease (Table 2).

During the study period, we did not observe significant temporal trends for NS-MZL as a whole with an APC of −3.8% [95% confidence interval (CI) −8.0% to 0.5%]. However, we did observe a relevant decline in the incidence of g-MALT from 1.4 in 1997 to 0.2 in 2002, which then remained stable without relevant changes until 2007 (0.1). The observed incidence change corresponded to an APC of −17% (95% CI −25.2% to −6.8%). No significant changes were observed for other subtypes of NS-MZL (Figure 2A). To better characterize this phenomenon, we looked at rates of HP infection among our cohort of g-MALT lymphomas. Staining for HP on gastric biopsies was carried out in 37 cases (73%); all 14 cases with no staining for HP were diagnosed during the first years of the study period. Overall, 17 cases were classified as HP+ out of 37 tested patients (46%). The yearly cumulative count of HP+ cases is shown in Figure 2B. Rate of HP+ g-MALT lymphomas declined during the study period with a statistically significant trend ($P = 0.016$). Interestingly, the decline was only observed before 2002, whereas the cumulative count of HP+ reached a plateau from 2002 to 2007. We then compared cases diagnosed between 1997 and 2001 versus those diagnosed between 2002 and 2007

Table 1. Incidence rates (A) and clinical characteristics (B) of 165 patients with nonsplenic marginal zone lymphoma (ICD-O-3 9699-3) diagnosed from 1997 to 2007

(A) incidence rates	M	F
Percentage of all neoplasms	0.36	0.34
Crude rate (×100 000)	2.3	2.2
Word age-standardized rate (×100 000)	1.3	1.0
(B) Clinical characteristics of patients	**Missing, *N***	***N* (%)**
Parameter		
Gender	—	
Male		85 (52)
Median age in years (range)	—	68 (16–97)
PS	—	
>1		55 (33)
AA stage	5	
I		81 (51)
II		18 (11)
III		4 (2)
IV		57 (36)
BM	1	
Involved		42 (26)
B symptoms	4	
Present		24 (15)
LDH	54	
>UNL		10 (9)
Sites of disease	2	
Extranodal		
GI (all cases)		60 (36.3)
Gastric		51 (30.9)
Nongastric		9 (5.4)
Skin		31 (18.7)
Salivary/lachrymal		10 (6.1)
Lung		6 (3.6)
Pharynx/larynx		2 (1.2)
Liver		2 (1.2)
Other EN sites		5 (3)
Multiple EN sites		10 (6.1)
Non-extranodal		39 (23.6)

PS, performance status; AA, Ann Arbor; BM, bone marrow; LDH, lactic dehydrogenase; GI, gastrointestinal; EN, extranodal; UNL, upper normal limit.

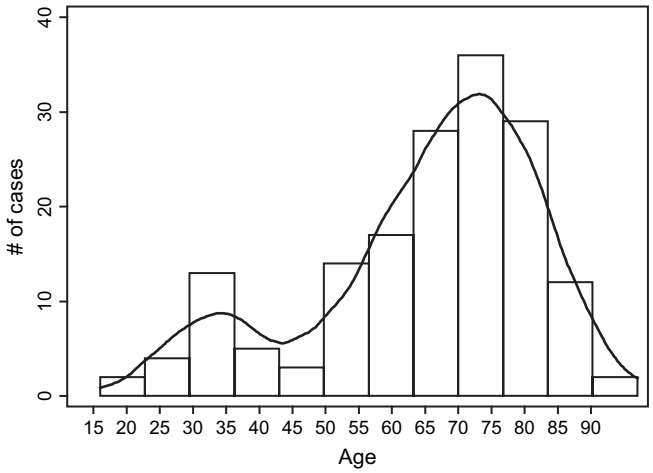

Figure 1. Distribution of the age of the patients at diagnosis of nonsplenic marginal zone lymphoma. Histogram, frequency of patients per age group; solid line, smoothed function describing the patients' distribution according to age.

Table 2. Clinical characteristics of patients with nonsplenic marginal zone lymphoma according to age group

Parameter	Age <45 (N = 26) (%)	Age ≥45 (N = 139) (%)	Univariate	Logistic regression	
			P value	OR	P value
Male gender	73	48	0.019	0.32	0.040
AA stage (III–IV)	19	42	0.045		
BM +	8	29	0.026		
Skin involvement	60	12	<0.001	0.07	<0.001
Mediastinal LN	16	4	0.032	0.11	0.006

AA, Ann Arbor; BM, bone marrow; LN, lymphnode.

and found that the rate of HP+ cases decreased from 67% to 19% (P = 0.007).

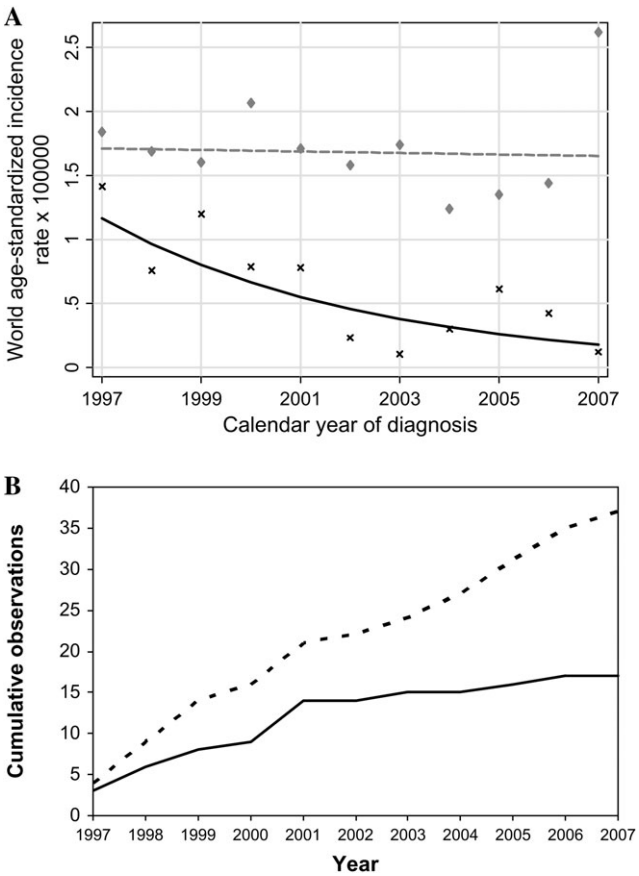

Figure 2. (A) Trend for the world age-standardized incidence rate of nonsplenic marginal zone lymphoma (NS-MZL) in the calendar period 1997–2007 for gastric mucosa-associated lymphoid tissue (g-MALT) and for other cases of NS-MZL. Black line, trend for g-MALT; black cross, yearly incidence of g-MALT; gray line, trend for NS-MZL cases other than g-MALT; gray diamond, yearly incidence of NS-MZL other than cases of g-MALT. (B) Cumulative numbers of gastric biopsies and of HP-positive (HP+) gastric biopsies carried out between 1997 and 2007 in patients with g-MALT lymphoma. Dashed line, cumulative number of gastric biopsies; solid line, cumulative number of HP+ gastric biopsies; HP, *Helicobacter pylori*.

discussion

In our present study, we analyzed all cases of MZL diagnosed over a decade in the province of Modena, in northern Italy. The population-based approach we used to identify cases allowed us to make some interesting observations regarding the epidemiology of this rare subtype of lymphoma.

We first observed a higher standardized IR than that recently published [14], confirming a previous observation of a high incidence of MALT lymphomas in northern Italy [15]. Second, looking at the age-standardized IRs, we observed a bimodal distribution of patients with two peak ages, the first at ∼30 years and the second at ∼70 years. By logistic regression analysis, we showed that the younger group of patients was mainly represented by males with cutaneous involvement. This observation needs further confirmation in larger studies; considering the striking role of infections in the pathogenesis of MZL, it may indicate to investigate specific behaviors that may favor lymphoid colonization of the skin among young individuals.

More interestingly, we showed that during the study period, there was a marked decrease in the incidence of g-MALT lymphomas, dropping from 1.4 cases per 100 000 in 1997 to 0.1 in 2007, corresponding to an APC of −17%. This observation confirms recently published data from The Netherlands [14] on a similar period of observation. Different from this Dutch study, however, we also provide data on HP infection among g-MALT lymphomas showing a statistically significant trend toward reduced rates of HP+ cases that became rare after 2001. Both studies show the same reduction of the incidence of g-MALT lymphomas in two different European regions and confirm the 'empirical' observation, shared by most onco-hematologists, of a decreased number of new cases of g-MALT lymphomas.

These results raise important questions regarding possible explanations for these changes. The first question that needs to be addressed is whether the observed decrease in the incidence of g-MALT lymphomas represents a real phenomenon or is

more likely the consequence of confounding factors. The most important confounding factor is represented by a modification to the diagnostic approach to g-MALT lymphomas. Though a 'diagnostic bias' must be acknowledged, we believe that it can only partly explain the magnitude of the observed phenomenon as the diagnostic criteria for MALT lymphomas have not been modified since they were first defined in 1994 [16] and the incidence decline is observed in only one subtype of these cancers. Other possible confounding factors include the possibility that the observed decline is the tail of a 'screening effect' caused by the wide use of endoscopic procedures starting from the late 1980s, that not all cases are identified by the registry, and that the reduced number of cases may reflect a modification in the interest in the diagnosis of such an indolent lymphoma. Based on our present data, we believe that a screening effect and a registration bias are not likely to justify the decrease as they do not explain the change in the rate of HP+ cases and as the majority of cases referred to the MCR are identified from the pathology department with only very few cases registered from the archive of hospital admissions or from death certificates. Finally, as far as the changing interest in the diagnosis of g-MALT is concerned, this is not a measurable phenomenon but is likely to have played only a minimal role, if any.

Once possible confounding factors have been examined, the other hypothesis that must be considered is that the reduced incidence of g-MALT is associated with changes in the rates of HP infection among the healthy population. Our data cannot provide a definitive answer to this question as we only found that cases of g-MALT lymphomas diagnosed in recent years are fewer and different from those diagnosed in the past and that this is most exclusively due to the disappearance of HP+ lymphomas. The hypothesis that incidence change of g-MALT is a consequence of the reduced prevalence of HP infection, however, can be corroborated by some considerations. From a biologic point of view, the possibility that modifications in the rates of HP infections may result in the modification of the epidemiology of g-MALT is supported by the well-documented etiologic role of HP in the oncogenesis of g-MALT lymphomas. HP is a common bacterium and ~50% of the world population has been estimated to be infected, with prevalence varying by geographic area, age, race, and socioeconomic status [17, 18]. Comparisons of prevalence rates by age indicates that acquisition of HP is decreasing in recent cohorts and in younger individuals; this finding is most apparent in developed countries and may be linked to improvements in hygiene practices [19–22]. In addition to reduced rates of HP infection that mostly occur in during childhood, tests to detect HP infection are widely prescribed in Western countries and subjects with HP infections are usually addressed to anti-HP eradicating therapies. A changed policy in the approach of patients with dyspepsia/pyrosis and positive breath test switching from gastroscopy + biopsy first to early generalized anti-helicobacter treatment without gastroscopy is likely to be also a reason.

Thus, it is likely that the reduced incidence of HP+ g-MALT lymphomas can be caused by reduced rates of HP infections or by a greater control of HP among infected people. However, the limited number of patients studied in our series and the lack of data on the prevalence of HP infection in the same population does not allow us to fully demonstrate that the incidence changes observed for g-MALT lymphomas are due to reduced rates of HP infections. Studies of larger populations are thus warranted that will link the resulting data on the prevalence of HP infections and on the incidence of g-MALT lymphomas. Moreover, similar studies from other regions are also useful to define if the observed incidence change is a local phenomenon or if it reflects a more generalized trend.

Finally, the same hypothesis that the reduced prevalence of HP infection has caused a reduced incidence of g-MALT lymphomas should be tested also for other HP-related conditions and cancers such as gastric adenocarcinoma. As demonstrated by recently published randomized trials, anti-HP intervention is an effective prophylaxis for gastric adenocarcinoma in patients with peptic ulcer [23] and of metachronous gastric carcinoma after endoscopic resection for early gastric cancer [24]. Based on data from the MCR also for gastric cancer, a trend toward reduced IR can be hypothesized for the same period (APC −3.51%, 95% CI −5.6% to −1.4%) [25]. Gastric cancer and lymphomas, however, show relevant differences that should be considered when a comparison is made. First, the etiology of gastric cancer is more heterogeneous than that of g-MALT lymphoma and change in the rate of HP infection may have minimal impact. Then, due to its often indolent course, a diagnosis of MALT lymphoma may remain missed for several years, while a gastric carcinoma is likely to become rapidly symptomatic with more timely diagnoses. Based on these considerations, gastric cancer and lymphoma are different tumor models and if an effect of anti-HP interventions exists also for gastric cancer, this should be addressed by different and well-designed population-based studies.

In conclusion, we have used a population-based approach to study extranodal MZLs, which has given us novel insights into the incidence patterns of this rare type of disease. The most important finding was a drop in the incidence of gastric MZL that was strongly associated with the reduction of HP+ g-MALT cases. Although the observation was based on a small series, our analysis strongly indicates that a larger study population should be examined to further evaluate the hypothesis that a higher control of HP infections may have modified the epidemiology of g-MALT lymphomas.

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disclosure

The authors confirm that they do not have any conflict of interest to declare.

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