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# PRIMARY GASTRIC LYMPHOMA: DISTRIBUTION AND CLINICAL RELEVANCE OF DIFFERENT EPIDEMIOLOGICAL FACTORS

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**ABSTRACT**

*Background.* **Over the last 10 years the incidence of primary gastric lymphomas (PGL), and in particular those of MALT origin, has significantly increased. Recent works correlated this epidemiological observation to Helicobacter pylori (HP) infection. On the other hand, new evidence demonstrating that occupational exposure to pesticides and solvents has played an important role in the pathogenesis of non-Hodgkin lymphomas (NHL) has emerged from studies involving large series of patients.**

*Methods.* **Thirty PGL patients, observed between 1986-1992, were subdivided according to HP infection, history of previous gastric disturbances (G) and exposure to pesticides and solvents (T).**

*Results.* **On the basis of these parameters we divided the patients into three groups: $T^+HP^+$ (8), $T^+HP^-$ (7), $T^-HP^+$ (9). $T^+$ patients had a positive history of gastric problems or a positive histological biopsy in 13.3% of cases, versus 66.7% in $T^-$ patients. The incidence of HP infection in the $T^+$ group was 53%, which proved to be comparable to the statistics for northeastern Italy, while in the $T^-$ group the incidence of infection was 100%.**

*Conclusions.* **On the whole these data suggest that HP infection could be considered a pathogenetic factor in 34% of patients, while occupational exposure to pesticides and solvents could have played a more important role in 66% of these cases.**

*Key words: Helicobacter pylori, primary gastric lymphoma, MALT, pesticides, solvents*



The incidence of primary gastric lymphomas (PGL) has significantly increased over the last 10 years.[1-4] Many etiologic factors were identified with this observation[5] and, in particular, a close association has been found between Helicobacter pylori (HP) infection and primary gastric lymphomas of MALT (*mucosal associated lymphoid tissue*) origin.[6] Helicobacter infection, with associated chronic gastritis or gastric ulcers, plays an important role in the pathogenesis of PGLs by promoting the colonization of gastric mucosa by reactive lymphocytes which subsequently undergo neoplastic transformation. This etiopathologic mechanism justifies the proposal of an antibiotic plus tripotassium dicitrobismutate therapy in low-grade PGL subtypes, in order to try to eliminate an important promoting agent.[7]

Independent epidemiological analysis on a large series of patients produced new emphasis and indications and suggested an association between non-Hodgkin lymphomas (NHL) and exposure to toxic agents, in particular pesticides (carbamates and organophophates) and organic solvents.[8,9]

A recent study performed at our Institute[10] demonstrated that acute myeloid leukemias (AML) developing after prolonged exposure to

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pesticides and organic solvents represented a distinct cytogenetic and clinicopathological group of leukemias. The clinical and biological characteristics of these exposed patients are similar to the features of AML arising in subjects who underwent chemotherapy for another tumor,[11] thus suggesting that similar transformation pathways may underlie leukemogenesis induced by cytotoxic drugs and by environmental exposure to some pesticides or organic solvents.

The aim of this study was to review all PGL cases treated at the Institute of Hematology of Ferrara between 1986-1992 in order to search for possible etiopathologic correlations.

## *Patients and methods*

### *Patients and PGL diagnosis*

Thirty patients referred to our Institute from 1986-1992 were evaluated. All cases diagnosed as PGL were reviewed by an expert pathologist (P.C.) on the basis of current histological criteria.[12,13] Primary gastric origin was proposed according to Hayes' criteria: massive gastric involvement, no peripheral or mediastinic lymph node involvement, normal WBC count.[14]

### *Exposure to toxic agents*

Enquiries were made, according to the normal practice for acute myeloid leukemias,[10] of all patients to see if there had been any possible professional and/or leisure time exposure to toxic agents (agricultural chemicals, solvents). Exposed subjects were subsequently questioned about the type and the duration of exposure, and whether they made use of standard protective equipment (masks, gloves, pressurized cabins) in their activities. An index of exposure was calculated by multiplying exposure hours × exposure days × years;[15] patients were considered *exposed* ($T^+$) when daily exposure occurred for a period of at least four years.

### *HP infection*

The presence of H. pylori was investigated by means of Giemsa staining and an immunoperoxidase technique that included the utilization of the monoclonal antibody CB26.[16]

### *Gastritis or gastric ulcer history*

Patients were also reviewed for histologic gastric biopsies made prior the diagnosis of NHL and for clinical precedents of gastric disturbances. A previous 5-year history of gastric disturbances was applied in order to discriminate between positive ($G^+$) and negative ($G^-$) gastritis patients. Subjects with autoimmune diseases were not considered for this study.

### *Therapy*

Twenty-five patients underwent gastrectomy and 28 received a chemotherapy regimen consisting of the following drugs: in 14 cases cyclophosphamide, vincristine, prednisone (COP), in 10 cases COP+epirubicin, in 4 cases COP+mitoxantrone; 2 patients underwent surgery without chemotherapy.

### *Statistical analysis*

The Kaplan-Meier technique[17] was employed to calculate overall survival rate (OS) while the log-rank test[18] was used to compare the prognostic impact on survival of different variables. The Fischer exact test, t-test and analysis of variance were used throughout. Data were analyzed in October, 1993 using the SPSS statistical package.

## *Results*

### *Patients and PGL diagnosis*

Thirty PGLs were observed during the period between 1986 and 1992. Overall, they represented 12.4% of all NHL cases diagnosed and treated in those years at our Institute. According to the Hayes criteria twenty-seven PGLs were evaluable; three cases were not included because of extensive diffusion of the disease. The principal clinical features of these patients are summarized in Table 1.

### *Exposure to toxic agents*

Fifteen patients (11 farmers, 2 beauticians, 1 shoe factory worker and 1 factory painter) were considered to be in the exposed category. All farmers were exposed to pesticides, including carbamates and organophosphates, while the

Table 1. Main clinical laboratory parameters at presentation in 27 patients with PGL.

| | |
|---|---|
| Age (yr)* | 61.1 (11.04) |
| Sex M/F° | 12/15 |
| Hb g/dL* | 11.7 (1.3) |
| WBC $10^9$/L* | 7.8 (2.3) |
| Plt $10^9$/L* | 332 (112) |
| Histology H/L | 7/20 |
| CR° | 20 (74%) |

*Legends: M: male; F: female; H: high grade; L: low grade; CR: complete remission. *median (SD: standard deviation); °n.pts.*

other four were exposed to organic solvents. Direct exposure to pesticides for 8 hours a day was a habitual occurrence for these patients that lasted for at least ten days a month, six months a year, for 20 years or more, whereas daily exposure to organic solvents continued for at least 15 years. The average exposure index for patients in contact with pesticides and organic solvents was 15,000 and 25,000 hours, respectively. None of them had a positive history of exposure related to hobbies or other non-professional activities. The nine cases with a negative history of exposure to myelotoxic agents were placed in the unexposed category (5 homemakers, 3 white collar workers, 1 teacher). In three $HP^+$ cases (2 $G^+$, 1 $G^-$), the occupational activity could not be investigated.

*Hp infection*

Twenty-seven patients were evaluated for HP infection: 20 (74%) were found to be positive and 7 negative.

*Gastritis or gastric ulcer history*

Ten patients had a positive history and/or histological confirmation of gastric disturbances, while 17 presented no such history or histological evidence of gastritis or ulcers.

*History of gastritis, toxic exposure and Hp infection*

Patients were subsequently subdivided according to H. pylori infection ($HP^+$, $HP^-$), exposure to toxic agents ($T^+$, $T^-$) and history of gastritis ($G^+$, $G^-$). This distribution is shown in Table 2.

*Statistical analysis*

The OS was 70% at five years. Neither grade of malignancy, sex, exposure, HP infection nor history of gastritis was found to be correlated with prognosis. A significant difference emerged in the distribution of $G^+$ patients between $HP^+$ (10/20 patients) and $HP^-$ (0/7) (p=0.022), and between $T^+$ (2/15) and $T^-$ (6/9) (p=0.013). No differences were observed within the analyzed groups as far as sex distribution, age at diagnosis, grade of malignancy (H = high, L = low) or principal clinical hematological parameters were concerned.



Table 2. Patient distribution according to Helicobacter pylori infection ($HP^{+/-}$), exposure to toxic substances ($T^{+/-}$), history of gastric disturbances ($G^{+/-}$), histology (L/H).

| | $HP^+$ | $HP^-$ | total |
|---|---|---|---|
| G+ | 10 | 0 | 10 |
| G– | 10 | 7 | 17 |
| total | 20 | 7 | 27 |

p= 0.022

| | $T^+$ | $T^-$ | total |
|---|---|---|---|
| HP+ | 8 | 9 | 17 |
| HP– | 7 | 0 | 7 |
| total | 15 | 9 | 24 |

p= 0.019

| | T+ | T- | total |
|---|---|---|---|
| G+ | 2 | 6 | 8 |
| G– | 13 | 3 | 16 |
| total | 15 | 9 | 24 |

p= 0.013

| | L | H | total |
|---|---|---|---|
| T+ | 10 | 5 | 15 |
| T– | 7 | 2 | 9 |
| total | 17 | 7 | 24 |

p= 0.7

### *Discussion*

The present series of patients is comparable to those described in literature[1-4] with regard to the incidence of PGL among total NHLs (12.4%), overall survival (70% at 5 yrs), average patient age (62 yrs) and male/female ratio (12/15). The incidence of PGL among total NHLs treated in our Institute was found to have increased over the previous seven-year period (12.4 vs 7.4%), a fact corroborated by other studies.[13] Seven high grade PGLs are included in the present series: all of these cases clearly evolved from low grade phases, as was confirmed by the presence of residual zones of centrocytic-type cells.

The importance of occupational and environmental factors in the pathogenesis of acute leukemias and NHL has received decisive documentation in recent studies.[8,10] Twenty-four patients were evaluated regarding exposition. The possibility that unexposed subjects might have occasionally come into contact with pesticides or solvents could not be excluded, but these patients were still considered negative because they did not directly use toxic substances and since any exposure was not prolonged. These two criteria were maintained as absolute guidelines for defining a patient as *exposed* or *unexposed.*[10] One particularly interesting observation, in our opinion, was that all $HP^-$ patients were exposed and that there was a group of 8 patients who were both exposed and $HP^+$. It should also be noted that the majority of male subjects were farmers: in the agricultural field men were most frequently involved in activities related to the use of pesticides. On the other hand, two women suffered exposure as the result of a typical female occupation, i.e. beautician. This could be considered indirect proof of the way occupational exposure is related to the historical and social habits of the population in this particular region.

Recent evidence indicating a correlation between PGLs and HP infection has aroused great interest. HP infection has been proposed as one of the most probable exogenous agents involved in the pathogenesis of PGLs.[6] HP infection favors the accumulation of organized lymphoid tissue in the stomach by causing chronic gastritis or gastric ulcers, and may create the background against which PGLs could develop as a consequence of exposure to additional exogenous agents.

The incidence of HP infection in our series was slightly lower than that recorded by Wotherspoon et al:[6] 74 vs 92%. We think that this apparent discordance may reflect the existence of additional pathogenetic factors, which is why we adopted this particular rationale for defining different groups of patients on the basis of exposure and HP infection, taking into consideration previous history of gastric disturbances. The natural history of HP infection is characterized by a continuum of progressive damage, beginning with simple colonization and developing, via chronic gastritis, into gastric ulcers.[19] An analysis of cases with a history of gastric involvement further strengthens the correlation between HP infection and PGLs: there was a positive history in 6 (66.7%) patients in the $T^-$ group, as against only 2 (13.3%) in the $T^+$ group.

Reconsidering the incidence of HP infection within the previously defined subgroups, we see that among $T^+$ patients the incidence reached 53%, which is comparable with that reported for the population in Northern Italy. On the other hand, all $T^-$ cases were $HP^+$, confirming the role that HP plays in promoting PGL development in this subset of patients.

### *Conclusions*

Overall these data suggest that HP infection in our series could be considered a pathogenetic factor in 1/3 of patients, while for the other 2/3 occupational exposure to pesticides and solvents would seem to play a more important role. The incidence of HP infection in the exposed patients was the same as in normal subjects, while gastritis or gastric ulcer history was present in only 13.3% of cases. On the other hand, 66.7% of non exposed subjects presented a history of gastritis or gastric ulcers. The role played by HP and toxic agents is probably that of developing similar conditions in which different additional factors can promote the advancement of NHL.

On the basis of these data it may be suggested that eradication of HP infection with specific anti-HP antibiotic therapy, as recently proposed by Wotherspoon,[7] should prove to be effective in subjects with no history of toxic exposure; however, the need for a different therapeutic approach for patients who have been exposed must be emphasized. Chromosome studies and molecular biology may further help to distinguish these two pathogenetically different entities.

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