PAPER

Helicobacter and gastric MALT lymphoma

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Helicobacter pylori infection is a pre-MALT lymphoma condition. *H pylori* eradication leads to complete remission in 80% of low grade stage E1 lymphomas, with a yearly recurrence rate of approximately 5%. The possibility for complete remission in high grade lymphomas needs to be investigated in prospective studies. In addition, the significance of persistent B cell monoclonality (stable disease? danger of relapse? regression of monoclonality?) needs to be investigated in follow up studies.

Presumably no other area of gastroenterology has seen such great advances over the past 20 years as that of malignant lymphomas of the stomach. These advances may be summarised as follows:

- Lymphomas are today being detected much more frequently at an early stage
- In addition to high grade lymphomas, low grade lymphomas are increasingly being diagnosed
- A new, improved histological classification of these lymphomas has been developed
- Considerable advances have been made in our understanding of the pathogenesis of lymphoma.

The biggest breakthrough was achieved by research into the relation between *Helicobacter pylori* infection of the stomach and gastric lymphoma, which has shown that:

- Mucosa associated lymphoid tissue (MALT) of the stomach is always a sequela of *H pylori* infection
- Acquired MALT is the precondition for the potential development of a MALT lymphoma
- In more than 90% of cases, MALT lymphoma is associated with *H pylori* infection
- Prior *H pylori* infection is therefore a pre-MALT lymphoma condition
- In animal experiments MALT lymphomas can be induced by *H pylori* infection
- *H pylori* eradication alone can lead to complete remission of the MALT lymphoma.

However, numerous questions have still to be answered:

- What additional factors are needed to transform a reactive lymphocytic proliferation into a MALT lymphoma?
- Why do some low grade lymphomas regress after *H pylori* eradication, while other do not?

- What *H pylori* or T lymphocyte products influence the proliferation of lymphoma cells, and via what receptors on the tumour cells?
- Is complete remission after *H pylori* eradication lasting, and how high is the local recurrence rate?
- Are there antigen responsive tumours other than the MALT lymphomas of the stomach?

THE SITUATION PRIOR TO THE AGE OF *H PYLORI*

Until the beginning of the 1980s, gastric lymphoma was categorised in accordance with the endoscopic classification suggested by Palmer in 1950.¹ At that time the lymphomas the pathologists were able to examine were, for the most part, large advanced tumours, with infiltration of all layers of the gastric wall, infiltration of neighbouring tissue, and involvement of the regional lymph nodes.

The lymphomas found in biopsy material were frequently wrongly diagnosed as carcinomas, and for further diagnostic work up gastric resection was often recommended. The histological classification was, simply and undifferentiatedly, “lymphosarcoma”.

Three milestones in 1983 and 1984 heralded the end of this unsatisfactory state, and the beginning of a positive development. Isaacson and Wright developed the MALT concept of gastric lymphoma,² Warren and Marshall described *H pylori*,³ and from Japan came—in analogy to early carcinomas—the first reports on early gastric lymphomas with limitation of the infiltration to the mucosa and submucosa.⁴ In the following years the percentage of early lymphomas among gastric lymphomas increased rapidly. The figure for material from Vienna covering the period 1974–78 was 21.7%,⁵ in Tokyo between 1977 and 1986, 40.9%,⁶ and in our own material between 1983 and 1989, 49.6%.

At the time of their diagnosis, early lymphomas of the stomach already have a relatively large diameter, not different from that of advanced lymphomas.⁷ They can be recognised macroscopically by a number of coincident findings—thickened folds, erosions, and ulceration.^{2,8} As in early gastric carcinomas, these lesions undergo a malignant cycle,⁹ healing and reappearing again, with the result that a variegated picture including thickened folds, erosions, ulcers, scars, and regenerative mucosa is seen.

The fact that early lymphomas already have a relatively large diameter—on average approximately 8 cm—when diagnosed, could have

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Abbreviations: MALT, mucosa associated lymphatic tissue; PCR, polymerase chain reaction

Figure 1 Partial destruction of a gastric gland by infiltrates of a low grade MALT lymphoma (immunohistochemistry with CD 20 antibody).

Figure 2 Multiple lymphoepithelia lesions in a low grade MALT lymphoma (immunohistochemistry with a pancytokeratin antibody).

prompted us to suspect that there must be a growth stimulating factor on the surface of the mucosa.

Recognition of the early lymphoma was a step forward, as shown by the following data: the depth of infiltration correlates with the involvement of the regional lymph nodes and with the degree of malignancy of the tumour¹⁰; the deeper the infiltration, the greater the number with lymph node involvement, and the more cases with high grade malignancy. The fact that depth of infiltration is the major prognostic factor in cases with gastric lymphoma is therefore logical.¹¹

Advances in the early endoscopic–biptic diagnosis is also reflected in the change in the relative proportions of low grade and high grade lymphomas. While, formerly, a preponderance of the lymphomas diagnosed were high grade,¹² in the 1990s a higher percentage of low grade lymphomas were detected—the percentage of low grade lymphomas in our material from 351 patients in the period 1993–98 was 77.2%.

At the end of the 1980s the first good histological classification was proposed by Isaacson and colleagues.¹³ Because the site of the tumour origin is the perifollicular marginal cell, in the revised European–American classification of lymphoid neoplasms¹⁴ and the new WHO classification of tumours of the digestive system,¹⁵ the lymphoma is also termed a marginal B cell lymphoma. Primary T cell lymphomas of the stomach are very rare. Among our 220 surgical specimens with gastric lymphomas, only two were T cell lymphomas.¹⁰

The decisive advance in biopsy based diagnosis of low grade malignant gastric lymphomas was the establishment of the following histological criteria by Isaacson and colleagues^{16–17}:

- (1) Replacement of gastric glands by uniform infiltrates comprising centrocytoid cells (see fig 3)
- (2) Clear evidence of lymphoid destruction of gastric glands of foveolae (figs 1 and 2).

The diagnosis of gastric low grade MALT lymphoma should be made only when invasive and destructive tumour growth is proven. That is, when foveolae and/or glands are partially or almost completely destroyed by the lymphoid cells.

For an accurate histological diagnosis of a gastric MALT lymphoma, the first diagnostic work up often needs to be followed by a problem oriented endoscopic–biptic investigation with the additional aim of detecting possible focal transformation to high grade lymphoma. For such an investigation, at least 15 biopsy specimens should be obtained from any endoscopically suspicious lesion.¹⁸

DISCOVERY OF THE RELATION BETWEEN *H PYLORI*, MALT, AND MALT LYMPHOMAS

The paths of *H pylori* and gastric MALT lymphoma research crossed for the first time in 1988 with the recognition that the

Figure 3 Complete remission of a low grade MALT lymphoma after *H pylori* eradication with the typical picture of an empty lamina propria.

cause of acquired gastric MALT is chronic infection with *H pylori*.^{19–20} The first piece of the puzzle that helped clarify this relation was an epidemiological study which showed the dependence of the incidence of MALT lymphoma on the *H pylori* infection rate.²¹ The second was the fact that the early lymphomas—like acquired MALT—are located mainly in the gastric antrum.⁷

Analysis of surgical specimens of gastric MALT lymphoma showed *H pylori* gastritis in 92.0–98.3%.^{10–22} Furthermore the case–control study performed by Parsonnet and colleagues²³ showed a statistically significantly higher *H pylori* infection rate among MALT lymphoma patients long before development of the lymphoma. This is proof of the fact that *H pylori* gastritis is a pre-MALT lymphoma condition. Finally, animal experiments showed that lifelong infection of mice with *H felis* led to the development of gastric MALT lymphomas in 26% of cases.^{24–25} In a further study, the group of Adrian Lee transplanted gastric lymphoma cells subcutaneously or intraperitoneally in young mice. Only those animals infected with *H pylori* developed lymphomas; control animals with no *H pylori* infection did not. However, the lymphomas were not located at the sites of the subcutaneous or intraperitoneal transplantation, but in the stomach of the animals.²⁶ Over a long follow up period, some of these lymphomas underwent transformation from low grade to high grade lymphomas.²⁷

In contrast, in another strain of mice, lifelong infection with *H felis* led to a severe form of gastritis with atrophy, but no lymphomas. Experimental gastric lymphoma induction in BALB/C mice is also possible using *H heilmannii*, but the rates differ—from 14% to 89%, depending on the host of the infection.²⁸

These animal experiments suggest that the factors necessary to induce development of a gastric lymphoma in acquired MALT are probably to be sought among different bacterial and host factors.

In this context it is of interest to note that patients with *H. heilmannii* gastritis apparently develop a MALT lymphoma more frequently than those with *H. pylori* gastritis: in our material from 1988 to 1998, eight MALT lymphomas among 543 patients with *H. heilmannii* gastritis (1.47%) compared with 1745 MALT lymphomas among 263 680 patients with *H. pylori* gastritis (0.66%). As with the BALB/C mice in the animal experiments performed by the group headed by Adrian Lee, *H. heilmannii* gastritis was lower grade and less active than *H. pylori* gastritis.²⁹ In support of this association with a milder form of gastritis is the fact that a matched control study of all material showed that, in patients with gastric MALT lymphoma, gastritis is of lower grade in comparison with other *H. pylori* induced diseases, and there is no difference between the gastric score in the antrum and corpus.³⁰

With regard to *H. heilmannii* infection of the gastric mucosa, further studies have since shown that several types of *H. heilmannii* exist, which can be transmitted by various domestic animals (dogs, cats, pigs) and may also present as a mixed infection of the gastric mucosa.³¹

It is thus possible that special antigens, arising directly from those strains of *Helicobacter* that are weakly pathogenic, or indirectly via T lymphocytes, result in a positive selection of tumour cells via the antigen receptor. This is supported by a study showing that MALT type lymphoma B cells are hypermutated postgerminal centre lymphocytes that have undergone antigen selection.³² Furthermore, it has been reported that changes to the p53 suppressor gene are involved in the development and transformation of MALT lymphomas; partial inactivation leads to the development of low grade MALT lymphomas, and complete inactivation to high grade MALT lymphomas.³³

Molecular-genetic studies of MALT lymphoma of the stomach presently available do not yet reveal the whole picture, and further work is needed. The stepwise acquisition of genetic abnormalities can be divided into early and later molecular events. Early molecular events in the evolution of gastric MALT lymphoma include trisomy 3 (33% of gastric MALT lymphomas), but this event does not seem to play a major role in progression.³⁴ The t(11;18)(q21;q21) chromosome translocation is also an early, frequent, and specific aberration in low grade MALT lymphomas.³⁵⁻³⁷ This translocation seems to be absent in high grade gastric lymphomas, which suggests that low grade MALT lymphomas that are positive for the t(11;18)(q21;q21) translocation may represent a subgroup for progression to advanced lymphoma. Another molecular event in the early phase of lymphomagenesis is Bcl-2 protein overexpression. Therefore, inhibition of apoptosis seems to be involved in lymphomagenesis.³⁸ Expression of p53 protein is inversely correlated to Bcl-2 expression, and it is more common in high grade gastric lymphomas. Therefore, mutations of the p 53 gene may be related to histological transformation of low to high grade lymphoma.³⁸⁻⁴⁰

H PYLORI ERADICATION AND MALT LYMPHOMA

The discovery of complete remission of the low grade MALT lymphoma was initiated by attempts to improve the endoscopic-biopic differential diagnosis between reactive lymphatic infiltrates and low grade MALT lymphoma infiltrates. We advanced the hypothesis that reactive lymphatic infiltrates should disappear, but lymphoma infiltrates persist, in response to *H. pylori* eradication.⁴¹

To our great surprise our first analysis of 32 patients studied in 1992 showed that the MALT lymphomas could also disappear: in six out of 10 patients with low grade MALT lymphomas follow up revealed regression of lymphoma. Two of

these six patients were submitted to gastric resection; in both cases we found an empty lamina propria with small remnants of aggregates of T lymphocytes, indicating regression of the tumour—a picture once seen only after successful chemotherapy or radiotherapy of gastric MALT lymphomas (see fig 3).

In 1993 Wotherspoon and colleagues⁴² reported regression of low grade gastric MALT lymphomas in five out of six patients. The same group investigated the proliferation behaviour of tumour cells from low grade and high grade MALT lymphomas in cell cultures with and without *H. pylori*, and with and without T lymphocytes. It was found that the cells of the low grade MALT lymphomas proliferate only when the culture medium contains both *H. pylori* and T lymphocytes, but not when either *H. pylori* or T lymphocytes are absent. In contrast, proliferation of high grade lymphoma cells was not influenced by the absence of *H. pylori* or T lymphocytes.⁴³

German MALT lymphoma study

Encouraged by these initial results we began to study the treatment of low grade gastric MALT lymphomas consisting solely of eradication of *H. pylori*. We have already published a number of reports on initial results, and also the results of follow up examinations.⁴⁴⁻⁴⁶ We concluded this study after we had entered 120 patients, who still remain under surveillance.

We admitted only patients with a histologically unequivocal diagnosis of MALT lymphoma. We also complied with the recommendation of Isaacson and Norton that MALT lymphoma should be diagnosed only when the endoscopic findings are compatible with MALT lymphoma.⁴⁷ Endoscopy and biopsy follow up examinations were performed after *H. pylori* eradication, initially at intervals of two months and then, after achieving complete remission, at intervals of six months. In patients with partial remission and in those showing no change to tumours, surgical treatment, radiotherapy, or chemotherapy was recommended.

Results obtained after a median follow up period of 48 months were: 81% complete remission, 9% partial remission, and 10% non-responders.

Of the 12 non-responders, two have died of their lymphoma, and nine have been operated on. The work up of the surgical specimens revealed one T cell lymphoma, five secondary high grade lymphomas, and three low grade lymphomas. Two patients received chemotherapy.

Of the 11 patients with partial remission after *H. pylori* eradication, one has since died of a stroke, six have been operated on, two received chemotherapy, and the remaining two have stable disease with no progression, and are still under surveillance only.

On the basis of the endoscopic appearance it is not possible to predict whether *H. pylori* eradication will result in remission of the lymphoma. Nor does the diameter of the tumour provide any clues as to its remission behaviour. The patient with the largest MALT lymphoma having a diameter of 10 cm, has now been in complete remission for seven years since *H. pylori* eradication.

This is in contrast to the depth of infiltration: only in the case of early lymphomas with infiltration of the mucosa and submucosa can complete remission be expected in a high percentage of patients. That is why endoscopic ultrasonography is of great importance in pretreatment staging. We have never seen complete remission of lymphomas infiltrating the muscularis propria and serosa.⁴⁸ However, a single study has also reported complete remission of deeply infiltrating lymphomas.⁴⁹

A good marker for the prognosis of lymphoma remission following *H. pylori* eradication appears to be the determination of t(11;18). While all patients lacking any evidence of this translocation after *H. pylori* eradication showed complete remission, 75% of those in whom t(11;18) was detected had no remission.^{50 51}

Table 1 Results of treatment of gastric MALT lymphoma with *H pylori* eradication

First author	Reference	Year	Number of patients	Complete remission (%)
Stolte	Not published	1992	10	60
Wotherspoon	42	1993	6	83
Bayerdörffer	44	1995	33	69
Savio	56	1995	12	92
Roggero	57	1995	26	60
Fischbach	58	1996	15	93
Montalban	59	1997	9	89
Pinotti*	60	1997	49	67
Neubauer†	45	1997	50	80
Nobre-Leitao	61	1998	17	100
Steinbach	49	1999	28	50
Kato	62	1999	19	84
Nakamura	63	1999	37	35
Suzuki	64	1999	16	88
Oda	65	1999	30	50
Yamashita	66	1999	25	64
Suekane	67	1999	22	68
Thiede†	68	2000	84	81
Dragosics	Pers. comm.	2000	19	84
Fischbach	Pers. comm.	2000	83	62
Fischbach	69	2000	36	89
Ruskoné-Formestaux	70	2001	34	56
Own results†		2001	120	81

*Follow up study by Roggero *et al*⁵⁷; †follow up studies by Bayerdörffer *et al*.⁴⁴

Histological diagnosis of complete remission in biopsy material remains a big problem. The histological examination of 15 surgical specimens of non-responders and of patients with partial remission showed the uncertainty of a biopsy based diagnosis of regression: in cases with regression of the lymphoma in the plane of the mucosa, we found residual lymphoma in the deeper layers of the gastric wall. Even when areas of lymphomas are found in the mucosa in the surgical specimen, the histological diagnosis of lymphoma may nevertheless remain uncertain; in all 15 surgical specimens we failed to detect the most important criterion for the diagnosis of MALT lymphoma—lymphoepithelial lesions—following *H pylori* eradication.

The polymerase chain reaction (PCR) performed on the VDJ rearrangement of the immunoglobulin heavy chain is unable to help us out of this dilemma. At the primary lymphoma diagnosis prior to treatment, PCR was positive in only 71% of cases. On the other hand, PCR remained positive in 45% of the patients with endoscopic, endosonographic, and histological complete remission.⁵²

Similar results have been reported by other authors.^{53–54} In order to find the source of the monoclonal B cells we carried out PCR studies following microdissection of superficial areas and basal lymphatic aggregates in the mucosa. It was found that the source of the monoclonal B cells is located mainly in the basal lymphatic aggregates.⁵² Future examination of these patients will have to show whether these monoclonal cells can lead to a recurrence, and whether this can occur only after *H pylori* reinfection, or also in *H pylori* negative patients.

Of our 97 patients with complete remission of the lymphoma, four have since died. The causes of death were myocardial infarction, stroke, and arterial embolism. So far we have diagnosed nine recurrences, including one high grade lymphoma in the nose, and eight low grade recurrent lesions, one following reinfection with *H pylori*, in which *H pylori* eradication therapy again resulted in complete remission of the lymphoma. One patient underwent surgery and one received radiotherapy. In the other five patients, endoscopic appearance remained normal; subsequent histological examinations failed to reveal any lymphoma.

Results of further follow up examinations will have to determine whether the histological finding at a tiny lymphoma focus and/or positive PCR following complete

remission of lymphoma has any significance at all, whether any of these cases can be classified as “stable disease” in a “dormant phase”⁵⁵ or whether these cells may still give rise to a recurrence.

In three patients with complete remission of the lymphoma we diagnosed early gastric cancer 4–6 years after *H pylori* eradication. All three cancers were limited to the mucosa, had a diameter of 4–5 mm, and were treated successfully by endoscopic mucosa resection.

Results from other studies

On reviewing the literature and summarising the results of treatment of gastric MALT lymphoma in different stages with *H pylori* eradication^{42–44, 45–49, 56–70} we found complete remission rates of between 35% and 100% (see table 1).

Lymphomas arising in *H heilmannii* gastritis can also be cured by eradication therapy.⁷¹ Even in individual cases of high grade MALT lymphoma, *H pylori* eradication can lead to complete remission of the tumour.^{72–77} *H pylori* eradication has even resulted in regression of lymphoma located elsewhere than in the stomach. This has been reported for cases showing regression of a salivary gland lymphoma,⁷⁸ a duodenal lymphoma,⁷⁹ an IPSID lymphoma,⁸⁰ and a rectal lymphoma.⁸¹

CONCLUSION

Our study and results reported in the literature confirm that *H pylori* and *H heilmannii* gastritis is a pre-MALT lymphoma condition, and that *Helicobacter* eradication therapy can lead to complete remission in about 80% of cases of low grade lymphoma, but that some 5% recurrences per year can occur. Even in individual cases of high grade MALT lymphoma and lymphomas of the duodenum, small intestine, rectum and salivary glands *Helicobacter* eradication can lead to complete remission of the tumour.

It should, however, be noted that the diagnosis of complete remission is uncertain, and that despite endoscopically, endosonographically, and histologically diagnosed complete remission, monoclonal B cells are still detected in the gastric mucosa of 45% of these patients. Further follow up investigations will need to show the significance of this B cell monoclonality. Also in need of clarification is the question whether further regression of these monoclonal cells over the

course of time is to be expected, whether we are dealing with a non-proliferative, stable disease in a dormant phase, or there is a danger of relapse.

Until these questions have been answered, and as long as no long term results covering follow up periods of more than five years are available, *Helicobacter* eradication as sole treatment of MALT lymphomas remain experimental, and should be limited to studies in which regular endoscopic–bioptic follow up examinations can be performed.

Nevertheless, the present results already provide support for the title of the review by Peter Isaacson: “Gastric MALT lymphoma: from concept to cure”.⁸²

SUMMARY

Over the past 20 years, enormous advances have been made in the field of MALT lymphomas of the stomach. Until the beginning of the 1980s, this lymphoma was diagnosed almost only in an advanced stage and, for the most part, as a highly malignant lesion. It was only after publication of the MALT lymphoma concept by Isaacson in the year 1983 that it became possible to diagnose early stages of this lymphoma.

Our current knowledge of the relation between *H pylori* infection and MALT lymphomas was initiated by the discovery that mucosa associated lymphatic tissue (MALT) of the stomach is always a consequence of an *H pylori* infection.

On the basis of these discoveries, the hypothesis was developed that the differential diagnosis of MALT lymphoma and reactive lymphatic infiltrates in biopsy material could be improved by eradicating *H pylori*. This hypothesis stated that the reactive infiltrate should disappear after *H pylori* eradication, but the lymphoma infiltrates should persist. However, the investigations based on these considerations showed that early stage, low grade MALT lymphoma with infiltration of the mucosa and submucosa also healed after *H pylori* eradication therapy.

This prompted us, in 1994, to initiate a study on the treatment of low grade MALT lymphomas by *H pylori* eradication alone. After reaching a total of 120 patients, we terminated this study. The result was 81% complete remission, 9% partial remission, and 10% non-responders. Comparable studies performed in Europe and Japan produced similar results (complete remission rates of between 35% and 93%).

Analysis of our own cases revealed that the endoscopic findings could not be used to derive a prognosis for remission following *H pylori* eradication. Of greater importance is the depth of penetration of the lymphoma. Only for lymphomas infiltrating mucosa and submucosa, but not for those infiltrating deeper layers of the wall, were we able to achieve complete remission.

PCR for the diagnosis and follow up of remission is not reliable: at primary diagnosis it shows monoclonality in 71% of the lymphomas, but also in 45% of cases with complete remission. The source of this monoclonality is persistent basal lymphocytic aggregates. In nine of our patients with complete remission, recurrence of lymphoma was found: high grade lymphoma of the nasal mucosa in one, and local recurrence in eight. These latter were, however, diagnosed only on the basis of histological work up, endoscopic appearance being normal. The question whether these recurrences were perhaps merely a non-proliferative “dormant phase” of monoclonal B cells remains to be answered. Case reports published in recent years have shown that high grade lymphomas can also undergo complete remission following *H pylori* eradication treatment.

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