Blood groups Lewis^b and ABH expression in gastric mucosa: lack of inter-relation with *Helicobacter pylori* colonisation and occurrence of gastric MALT lymphoma

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Abstract

Background—Blood group Lewis^b antigens mediate *Helicobacter pylori* attachment to gastric mucosa with attachment being particularly strong in subjects with ABH blood group O.

Aims—To determine whether *H. pylori* colonisation or the occurrence of gastric mucosa associated lymphoid tissue (MALT) lymphomas might be related to gastric Lewis^b expression or occurrence of particular ABH blood groups on gastric mucosa.

Patients—Gastric resection specimens from 89 cases with gastric MALT lymphoma and gastric mucosal biopsy specimens from 95 patients undergoing upper endoscopy due to upper gastrointestinal complaints, including five cases with gastric MALT lymphoma, were studied.

Methods—*H. pylori* was visualised with the Warthin-Starry stain. Immunostaining (Lewis^b, Lewis^a, A, B) was performed by applying a three step immunoperoxidase technique and indirect immunofluorescence staining on formalin fixed and paraffin wax embedded tissue. In 40 patients red blood cell Lewis phenotype and ABH blood groups were additionally determined by haemagglutination assay.

Results—Gastric surface epithelial cells showed an immunoreactivity to blood groups A, B, and AB in 80 (43.5%), 22 (12%), and 11 (6%) cases respectively and no immunoreactivity to any of these blood group substances (blood group O) in 71 (38.5%) patients. Lewis^b expression of all gastric surface epithelial cells (secretor status) was found in 130 (70.7%) cases. Lewis^a expression of all gastric surface epithelial cells (non-secretor status) was found in 36 (19.6%) cases, secretor status remained unclassified in 18 (9.8%) patients. Colonisation with *H. pylori* was found in 134 (72.8%) cases. The occurrence of *H. pylori* was neither significantly associated with secretor status nor with certain ABH blood groups. The infiltration of gastric mucosa with MALT lymphoma was highly significantly associated with *H. pylori* colonisation ($p < 0.0003$) but neither with secretor status nor with certain ABH blood groups. There was no inter-relation between secretor status or ABH blood groups and type, stage, grade of, and survival after MALT lymphoma.

Conclusion—This study failed to show an inter-relation between secretor status or particular ABH blood groups and either *H. pylori* infection or the occurrence of gastric MALT lymphomas.

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Keywords: Lewis^b; ABH; *Helicobacter pylori*; MALT lymphoma

Helicobacter pylori has been recognised to be one of the most important gastric pathogens.¹ Infestation with this Gram negative spiral bacterium is known to be linked to the development of chronic active gastritis, duodenal ulcer, gastric ulcer, hypertrophic gastropathy, gastric adenocarcinoma and, recently, gastric mucosa associated lymphoid tissue (MALT) lymphoma.¹ Epidemiological studies showed that with age more than 50% of the population of the western world is colonised by *H. pylori*, but only a small part of these develop complications such as MALT lymphoma.

Attachment is one of the factors which is considered a prerequisite for microbial colonisation of epithelial surfaces. It is mediated by molecules on the bacterial surface, termed adhesins, which recognise proteins or glycoconjugates on the surface of eukaryotic cells. Bacteria unable to adhere to epithelium tend to be rapidly removed by shedding of surface cells and mucous layer. Boren *et al.*² showed that Lewis^b (Le^b) blood group antigens mediate *H. pylori* attachment to human gastric mucosa. Furthermore, they found that people with ABH blood group O had more *H. pylori* receptors and that gastric tissue lacking Le^b did not bind bacteria. These results imply that Le^b expression on gastric mucosa has a considerable influence on the sensitivity of the host to colonisation with *H. pylori* and possibly even on the development of *H. pylori* associated complications.

The aim of the present study was to determine whether *H. pylori* colonisation was associated with Le^b or blood group ABH expression on gastric mucosa and to show whether the occurrence of gastric MALT lymphoma is related to secretor status or a particular ABH blood group.

Patients and methods

PATIENTS

Le^b and blood group A and B reactivity of gastric tissue was studied in 184 patients

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(table 1). Gastric mucosal biopsy specimens obtained through upper endoscopy were available from 95 cases (including five cases with MALT lymphoma) and gastric resection specimens from 89 cases with MALT lymphomas.

Tissue fixed in 8% phosphate buffered formalin, pH 7.4, was processed for routine light microscopy. All cases were stained with haematoxylin and eosin. *H. pylori* was visualised with the Warthin-Starry stain. MALT lymphomas were additionally stained with Giemsa, Gomori's reticulin, and periodic acid Schiff stains.

Biopsy specimens of 90 consecutively submitted non-lymphomatous cases were obtained from patients subjected to upper endoscopy due to upper gastrointestinal complaints in the gastroenterological outpatient clinic of Internal Medicine IV, Vienna University Hospital, between January and April 1995. A mean of 2.3 biopsy specimens was submitted for routine histology. Cases with gastric carcinoma and AIDS were excluded from this study.

The 94 cases of primary B cell lymphomas of the stomach, which were retrieved from our files, were classified according to the REAL classification³ and the classification of Isaacson *et al.*⁴ which, in general, are based on the updated Kiel classification.⁵ Use of the Working Formulation⁶ turned out to be inappropriate. In all cases, the T and B cell nature of the infiltrations was tested with a panel of antibodies applicable on paraffin wax sections as described previously.⁶ Primary gastrointestinal tract lymphoma was defined according to the criteria of Dawson *et al.*⁷ as predominant confinement to the alimentary tract excluding generalisation within three months after diagnosis. For staging, an adaption of the Ann Arbor system for extranodal lymphomas⁸ and its modification by Musshoff⁹ were used. Survival times of cases with MALT lymphomas were determined in a previously performed study.⁶ Details on the evaluation of data have been published.⁶

IMMUNOHISTOCHEMISTRY

Immunostaining was performed by applying a sensitive three step immunoperoxidase technique¹⁰ and indirect immunofluorescence staining on formalin fixed and paraffin wax embedded tissue sections. From 10 cases frozen sections were available as well and were used both untreated and treated with 100% ethanol for 30 minutes.

For visualisation of Le^b and Le^a, sections were incubated at 37°C for five minutes in 0.05% protease, type XXIV (Sigma, St Louis, MO, USA) in phosphate buffered saline (PBS)

before the application of the primary monoclonal antibody. Controls included omitting the primary antibody and the use of irrelevant isotype matched primary antibodies. All immunostained slides were graded systematically and blindly.

MONOCLONAL ANTIBODIES

For immunohistochemistry murine monoclonal antibodies with Le^b antigen specificity were obtained from Signet Laboratories (Dedham, MA, USA), DiaMed (Cressier Sur Marat, SUI), Ortho Diagnostic Systems (Raritan, NJ, USA), and Biotest Diagnostics (Dreieich, FRG). A monoclonal antibody with Le^a antigen specificity was obtained from Signet Laboratories (Dedham, MA, USA).

For the immunohistochemical evaluation of blood groups A and B monoclonal antibodies were obtained from Zymed (Zymed Laboratories Inc, SF, CA, USA).

For haemagglutination assays monoclonal antibodies with Le^b and Le^a specificity were obtained from DiaMed (Cressier Sur Marat, SUI), Ortho Diagnostic Systems (Raritan, NJ, USA), and Biotest (Dreieich, FRG). Antibodies with A, B, or AB specificity were obtained from the same sources.

HAEMAGGLUTINATION ASSAY

Lewis phenotype and ABO blood groups were determined in 40 consecutive cases who underwent upper endoscopy by a standard haemagglutination assay performed with a 3% suspension of peripheral blood. This group included 10 cases from whom fresh frozen gastric mucosal biopsy samples were also available. Before blood donation, subjects gave written informed consent to participate in this study.

BLOCKING STUDIES

To prove further the specificity of Le^b and Le^a labelling, blocking assays were performed with a panel of highly purified oligosaccharides (lacto-N-difucohexaose I (Le^b), lacto-N-fucopentaose I (H substance), lacto-N-fucopentaose II (Le^a), Oxford Glyco Systems, Abingdon, UK). Two protocols were applied: (1) the primary antibodies were absorbed with oligosaccharides for two hours at room temperature before applying them in immunohistochemistry; (2) prebound primary monoclonal antibodies were dissociated from their binding sites by incubating sections with oligosaccharides for two hours at room temperature. Each experiment was performed in four cases each with diffuse and focal Le^b and Le^a staining. Concentrations of 0.05 up to 2 mg/ml oligosaccharides were used for blocking. In a second set of experiments dissociation of prebound Le^b antibodies was assayed in four cases with focal Le^b staining at a concentration of 1 mg/ml with an additional panel of oligosaccharides (3-fucosyllactose, lacto-N-neotetraose, lacto-N-fucopentaose II,

TABLE 1 Study population

	Age (SD)	Male n (%)	Female n (%)
Overall	52.7 (20.8)	88 (47.8)	96 (52.2)
Gastric tissue, non-lymphomatous	47.6 (17.9)	44 (48.9)	46 (51.1)
MALT lymphoma	62.8 (13)	44 (46.8)	50 (53.2)

lacto-N-fucopentaose III, 3'sialyl-N-acetyl lactosamine, 6'sialyl-N-acetyl lactosamine, 3'-sialyl-3-fucosyl lactose, Lewis^x, 3'-sialyl Lewis^x, 3'-sialyl Le^a (Glycoset III, Oxford Glyco Systems, Abingdon, UK)) for two hours at room temperature.

STATISTICS

For statistical evaluation the χ^2 test was used. For analyses stratified by lymphoma status the Mantel-Haenszel test was used. In cases with MALT lymphoma product limit survival estimates for censored survival times were calculated, and a comparison of survival curves according to the log rank test was performed.¹¹ Survival times were calculated from all deaths.

Results

IMMUNOSTAINING OF GASTRIC TISSUE

Secretor status was found in 130 (70.7%) cases and was disclosed by labelling of all gastric

surface epithelial cells by the Le^b monoclonal antibodies (fig 1). Patients showing decoration of all gastric surface epithelial cells by the Le^a monoclonal antibody (fig 2) were classified as non-secretors (36 (19.6%) cases). In this group focal Le^b staining was also found in all but one case. Finally, patients showing focal Le^b labelling and no or only focal Le^a staining remained unclassified with respect to secretor status (18 cases (9.8%)).

Immunoreactivity to blood groups A, B, and A and B was found in 80 (43.5%), 22 (12%), and 11 (6%) cases, respectively. No staining with any of these two antibodies was seen in 71 (38.5%) patients. Blood group A or B immunoreactivity was detected on surface epithelial cells and on endothelial cells with the exception of three cases in which blood group B antigen was only found on endothelial cells but not on gastric surface cells. In one of these cases Lewis phenotype was determined by an haemagglutination assay and disclosed a Le (a+b-) phenotype.

Tumour cells of MALT lymphomas were negative for blood groups A, B, Le^a and Le^b. Gastric epithelial cells in close proximity and distant to areas of lymphomatous infiltration showed a similar staining pattern for Le^b, Le^a, and ABH blood groups.

RED BLOOD CELL PHENOTYPE AND LE^b IMMUNOREACTIVITY

Subjects with Le (a-b+) RBC phenotype (secretors) showed Le^b staining of all gastric surface epithelial cells in all 21 cases. In Le (a+b-) subjects, considered as non-secretors, Le^a staining of all gastric epithelial cells was found in all nine cases. In the Le (a-b-) cases Le^b or Le^a staining of all gastric epithelial cells was found in four and two of 10 cases, respectively. In the remainder either focal or no staining of Le^b or Le^a was found.

Alcohol fixation of frozen sections or examination of untreated frozen sections did not alter the result obtained in paraffin wax embedded material as shown in 10 cases.

ABH blood groups determined by immunohistochemistry were identical to those determined by haemagglutination.

BLOCKING STUDIES

Reactivity of the Le^b and Le^a monoclonal antibodies was blocked with lacto-N-difucohexaose (Le^b) or lacto-N-fucopentaose II (Le^a), respectively. Absorption of the primary antibodies with 1 mg/ml of the respective oligosaccharides completely inhibited staining in all cases. Additionally, incubation of the slides with 1 mg/ml lacto-N-difucohexaose (Le^b) or lacto-N-fucopentaose II (Le^a) resulted in dissociation of prebound Le^b and Le^a antibodies.

Focal Le^b immunoreactivity found in non-secretors could be blocked neither by 2 mg/ml lacto-N-fucopentaose II (Le^a) nor by 2 mg/ml lacto-N-fucopentaose I (H substance) nor by the panel of oligosaccharides described in

Figure 1: Labelling of gastric surface epithelial cells by the Le^b monoclonal antibody (brown staining). Gastric glands remain unstained. Immunoperoxidase, original magnification $\times 200$.

Figure 2: Labelling of gastric surface epithelial cells by the Le^a monoclonal antibody (brown staining). Immunoperoxidase, original magnification $\times 200$.

Methods (GlycoSet III, Oxford Glyco Systems, Abingdon, UK).

COLONISATION WITH *H. PYLORI*

Colonisation with *H. pylori* was found in 134 (72.8%) patients, including 55 (61.1%) of MALT lymphoma negative and 79 (84%) of MALT lymphoma positive cases. In two cases *H. pylori* status remained unclear. The occurrence of MALT lymphomas was highly significantly associated with *H. pylori* colonisation ($p < 0.0003$).

Patients immunohistochemically classified as secretors showed *H. pylori* colonisation in 78.3% (101 cases), non-secretors in 72.2% (26 cases) (NS, $p < 0.4$; 95% confidence interval (95% CI) 0.5–3.2). In cases undefined with respect to secretor status *H. pylori* was found in 38.9% (seven cases) ($p < 0.001$ v secretors, 95% CI 0.07–0.8). The respective figures in the gastric MALT lymphoma group were 87.1% (61 cases), 86.7% (13 cases), and 62.5% (five cases) (NS, $p < 0.96$; 95% CI 0.2–5.4) and in controls 67.8% (40 cases), 61.9% (13 cases) (NS, $p < 0.6$; 95% CI 0.5–3.7), and 20% (two cases) ($p < 0.02$ v non-secretors, 95% CI 0.02–0.9).

H. pylori was visualised in 59 (73.8%) cases with blood group A, in 17 (77.3%) with blood group B, in seven (63.6%) with blood group AB, and in 51 (71.8%) with blood group O (NS).

ASSOCIATION OF LE^b IMMUNOREACTIVITY WITH GASTRIC MALT LYMPHOMAS

Secretor status was found in 71 (75.5%) cases with MALT lymphoma and in 59 (65.6%) MALT lymphoma negative cases (NS, $p < 0.17$;

95% CI 0.79–3.56). Eight (8.5%) cases with MALT lymphoma and 10 (11.1%) MALT lymphoma negative cases remained undefined with respect to secretor status.

Fifty five (58.5%) MALT lymphomas were of low grade malignancy and 39 (41.5%) of high grade malignancy. Evidence of low grade components was found in five cases with high grade malignancy. Secretor status was found in 43 (78.2%) cases with low grade MALT lymphoma and 28 (71.8%) with high grade MALT lymphoma (NS).

In 89 cases the stage of the MALT lymphoma was evaluated (table 2). Secretor status was not significantly correlated with any stage (table 2). There was also no significant correlation between histological type and Le^b staining pattern (table 3).

In 80 cases with MALT lymphoma survival times were available. The mean survival time was 33.8 months. The mean survival in secretors was 33.7 months, that of non-secretors 42 months, and that of cases remaining undefined with respect to secretor status 17.7 months (NS).

ASSOCIATION OF ABO IMMUNOREACTIVITY WITH GASTRIC MALT LYMPHOMAS

Blood groups A, B, O, and AB were found in 39 (41.5%), 13 (13.8%), 36 (38.3%), and six (6.4%) patients in the lymphoma group. The respective values in the control groups were 41 (45.5%), nine (10%), 35 (38.9%), and five (5.6%) (NS).

Blood group A immunoreactivity was found in 22 (40%), B in seven (12.7%), AB in three (5.5%), and no reactivity (blood group O) in 23 (41.8%) cases with low grade MALT lymphoma. The respective figures in patients with high grade MALT lymphoma were 17 (43.6%), six (15.4%), three (7.7%), and 13 (33.3%) (NS).

There was no intercorrelation between ABH blood groups and type (table 3) or stage (table 2) of gastric MALT lymphomas. Due to few cases with high grade lymphomas and with stage EII2 a statistical analysis was not performed in these groups.

The mean survival in subjects with blood groups A, B, O, or AB was 38.3, 36.3, 29.7, and 23.8 months respectively. This difference was not significant ($p = 0.18$, log rank test).

Discussion

Our study does not support the hypothesis of Boren *et al* that secretor status and ABH blood group O influence *H. pylori* prevalence.² In our hands, *H. pylori* colonisation was neither dependent on secretor status nor on the occurrence of certain ABH blood groups. We therefore confirm serological studies, which also failed to find an inter-relation between *H. pylori* and secretor status¹² and which also disclosed that the relative risk of infection with *H. pylori* is similar in secretors and non-secretors and not dependent on particular ABH blood groups.^{13, 14} Our findings concerning blood group O and secretor status are

TABLE 2 Inter-relation of secretor status and ABH immunoreactivity with stage (modified Ann Arbor classification) of primary gastric MALT lymphomas

Stage	n (%)	Secretors	A	B	AB	O
EI1	25 (26.6)	16	12	3	1	9
EI2	30 (31.9)	25	11	6	1	12
EII1	25 (26.6)	21	11	2	0	12
EII2	9 (9.6)	6	4	2	2	1

Results are expressed as number of cases (stage was available in 89 cases).

A, B, and AB indicate reactivity with respective antibodies. 0 Indicates a lack of reactivity with either of these antibodies.

TABLE 3 Secretor status and ABH immunoreactivity in various histological types of primary gastric MALT lymphomas

Classification	REAL	ABH reactivity					
		n (%)	Secretors	A	B	AB	O
Isaacson							
CCL and ICL	MZBCL	55 (58.5)	43	22	7	3	23
CB	DLBCL	35 (37.2)	24	16	4	3	12
IB	DLBCL	1 (1.1)	1	0	0	0	1
LB	Burkitt	1 (1.1)	1	0	1	0	0
High grade unclassified	HGU	2 (2.1)	2	1	1	0	0

Results are expressed as number of cases.

Isaacson=classification of gastric MALT lymphomas put forward by Isaacson; REAL=REAL classification; CCL=centrocyte-like; ICL=immunocytic-like; CB=centroblastic; IB=immunoblastic; LB=lymphoblastic; MZBCL=marginal zone B cell lymphoma; DLBCL=diffuse large B cell lymphoma; Burkitt=Burkitt's lymphoma; HGU=high grade unclassified.

particularly interesting as those with blood group O¹⁵⁻¹⁷ and non-secretors^{12 15 17 18} were found to show increased susceptibility to gastrointestinal diseases, such as gastric or duodenal ulcer. The occurrence of gastric and duodenal ulcer, however, is itself highly significantly associated with *H. pylori* infection.¹ The increased susceptibility to gastric and duodenal ulcer in patients with blood group O and in non-secretors cannot be explained with increased susceptibility to *H. pylori* infection. Mechanisms causing this inter-relation have therefore still to be determined.

Expression of Le^b and Le^a antigens in gastric epithelia as related to secretor or non-secretor status and Lewis status of red blood cells has not been extensively studied. In this series focal staining with Le^b monoclonal antibodies was found in almost all non-secretors. According to the literature immunohistochemical visualisation of Lewis substances on tissues of various origins resulted in varied findings. Some groups showed that gastric mucosa of non-secretors does not express Le^b,^{19 20} others found aberrant expression of Le^b on gastric,²¹⁻²³ small intestinal,²⁴ and urothelial²⁵ epithelium in non-secretors. Concerning the association of secretor status with *H. pylori* colonisation focal expression of Le^b in non-secretors could be of clinical relevance, as it might suffice to allow attachment of the bacteria to gastric mucosa. We therefore verified the correctness of our findings by a number of controls including blocking studies with oligosaccharides. Binding of the monoclonal Le^b antibodies seemed to be specific in all cases. However, owing to the difference in results obtained by various groups additional studies are needed to clarify further the association of secretor status and Le^b expression in gastric mucosa.

The hypothesis that the availability of *H. pylori* receptors might influence the development of MALT lymphomas was also tested in this study. The origin of MALT lymphomas has been closely linked to infestation with *H. pylori*. Because the stomach normally contains no lymphoid tissue, the onset of B cell lymphoma of MALT type is to be preceded by the acquisition of lymphoid tissue resembling intestinal Peyer's patches induced by *H. pylori* colonisation.^{26 27} Histological studies showed that the organism was present in gastric mucosa in almost all people with gastric lymphoma.²⁸ A nested case-control study involving two large cohorts showed that non-Hodgkin's lymphoma affecting the stomach is associated with previous *H. pylori* infection.²⁹ Finally, eradication of *H. pylori* may result in complete remission in some patients.³⁰⁻³² In our study *H. pylori* was also significantly over-represented in patients with MALT lymphomas. According to our study hypothesis attachment of these bacteria to gastric epithelium via Le^b might elicit a more vigorous immune response and thus be one factor supporting the development of MALT lymphomas. However, no inter-relation between the infiltration with gastric MALT

lymphomas, their grade, stage, and prognosis and secretor status or specific ABH blood groups expressed on gastric epithelia was detected. We therefore propose that secretor status does not contribute to the formation of MALT lymphomas. A possible explanation might be the availability of Le^b receptors in non-secretors or of other factors mediating *H. pylori* attachment¹ such as phosphatidylethanolamine and GM3 ganglioside in subjects developing MALT lymphomas. Alternatively, strong adhesion of bacteria to gastric surface epithelial cells may not be a prerequisite for the formation of MALT lymphomas.

We conclude that secretor status and specific ABH blood groups were neither inter-related with *H. pylori* status nor with occurrence of MALT lymphomas.

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