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ORIGINAL ARTICLE

# Antibiotic treatment as sole management of *Helicobacter pylori*-negative gastric MALT lymphoma: a single center experience with prolonged follow-up

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**Abstract** Relatively little is known about the long-term outcome of patients with *Helicobacter pylori* (HP)-negative gastric lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) with antibiotic therapy as sole management. We have analyzed all patients with HP-negative gastric MALT lymphoma undergoing antibiotic therapy as sole management of their disease. HP negativity was defined as negative histology, breath test and serology, and response to treatment, survival and long-term outcome was assessed together with clinico-pathological characteristics including *t*(11; 18) (q21; q21) translocation. Out of 97 patients with gastric MALT lymphoma, 24 were HP-negative, and 13 (5 females and 8 males) underwent only antibiotic management for initial therapy. Eight had stage I and five were found to have stage II disease, with three patients suffering from an underlying autoimmune disease. Antibiotic therapy consisted of standard HP eradication regimens consisting of clarithromycin in all patients, along with metronidazole in seven and amoxicillin in six plus a proton-pump inhibitor. After a median follow-up of 95 months (42–, 181+), 12/13 patients are alive. Six patients with stage I disease achieved an objective response (five complete (CR) and one partial remission, 46 %), four had stable disease (lasting 11–27 months), and three progressed. All patients with stable disease received chemotherapy, but only one patient due to clear cut progression. One patient relapsed 23 months after initial CR, and achieved a second CR with antibiotics now lasting 87 months. These results indicate that a relevant percentage of patients with HP-negative gastric MALT lymphoma may benefit from antibiotic therapy and do not require additional oncological therapies. Our data suggest that the remissions seen in these patients might be durable as evidenced by prolonged follow-up in our series.

**Keywords** MALT lymphoma · *Helicobacter pylori* · Antibiotics

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## Introduction

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is predominately found in the stomach, where it has been reported to be associated with *Helicobacter pylori* (HP) infection in up to 90 % of cases [1–3].

In view of this close association, antibiotic eradication has been used for first-line therapy of localized gastric MALT lymphomas and is currently being recommended in the most recent guidelines as the initial treatment of choice [2, 3]. It has been shown that up to 80 % of patients will achieve remission of the lymphoma following successful eradication of HP [2, 4].

A minority of patients, however, will be diagnosed with gastric MALT lymphoma without evidence of HP infection. While the percentage of such patients is thought to be in the range of 5–10 % [2], management of this cohort is currently not straightforward. For these patients, either radiotherapy or chemotherapy with or without immunotherapy has been advocated, depending on the stage of the disease, but recently, anecdotal reports and small series [5–16] have suggested that HP-negative patients may also benefit from sole antibiotic therapy. Based on these findings, the recommendation that antibiotics might be given as first-line therapy has cautiously been included in the guidelines [2, 3]. Various questions, however, remain, as response rates ranging from 0–60 % have been reported using various eradication regimens, and a recent review with pooled analysis of 110 published patients documented a complete response in 17 patients (15 %) [17].

The question of whether these studies are really comparable nevertheless remains open, and the long-term impact of antibiotic therapy cannot be extracted from most studies, as the follow-up time was relatively short. In view of this, we have re-assessed all patients treated with antibiotics judged HP-negative at our institution to assess the course and long-term outcome of HP-negative gastric MALT lymphoma patients.

## Patients and methods

We have performed a retrospective analysis of all patients with gastric MALT lymphoma in order to identify patients rated as HP-negative. The retrospective analysis had been approved by the Ethical Board of the University of Vienna. For definition of HP negativity, all patients had to have a negative histology as well as a negative breath test and negative serological testing for HP-IgG within 3 months of initial diagnosis and before initiation of any type of treatment including antibiotics. In addition, patients' charts were evaluated for initial therapy, antibiotic regimen used in cases treated with first-line antibiotics, response to treatment, time to and duration of response, application of further therapies, and survival. Histological response was centrally assessed according to the GELA-criteria as defined and recently validated by Copie-Bergman and coworkers [18]. According to the routine follow-up done at our institution for gastric MALT lymphomas, patients underwent re-gastroscopy every 3 months after antibiotic therapy and also a CT scan of thorax and abdomen to rule out extragastric progression for at least 2 years or until complete regression of the lymphoma.

Clinical characteristics including stage at diagnosis; risk factors as defined in the International Prognostic Index (IPI) including age, Hb, and lactate dehydrogenase (LDH)-level; performance status; presence or absence of an underlying autoimmune disease; paraneoplastic monoclonal immunoglobulin production; hepatitis A, B, or C; and potential symptoms were assessed from our records. Histology at diagnosis was centrally assessed according to the criteria for extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) outlined in the 2008 WHO classification [1], the MALT lymphoma-specific translocation *t*(11; 18)(q21; q21), and the presence or absence of plasmacytic differentiation were also recorded.

## Results

From our records, we could identify a total of 97 patients with gastric MALT lymphoma diagnosed and treated at our institution with the respective information available.

Out of these 97 patients, 47 were male and 50 were female with the median age being 64 years. In terms of treatment, 27 % received chemo/immunotherapy, 66 % antibiotics, while only a minority had surgery (2 %), radiation (1 %) or wait and see (3 %) for initial management. A total of 44 % had complete remission (CR), 18 % partial remission (PR), 33 % stable disease, while only 4 % progressed during initial therapy. Out of the whole collective, 15 % have died, while the remaining 85 % of patients are alive after a median follow-up time of 53 months.

A collective of 24 were judged to be HP-negative according to histology, breath test, and serology. Nine had been diagnosed between 1999 and 2004 (9/49, 18 %), while 15 of 48 (31.2 %) were diagnosed between 2004 and 2014, suggesting an increase in the rate of HP-negative gastric MALT lymphomas. In our series, HP status was not significantly associated with progression/relapse following first-line therapy ($p=0.066$).

Out of these 24 patients, 13 were given antibiotic therapy only and thus comprised the population for this analysis (for patient characteristics, see Table 1), including 6 patients who had been part of a prior publication [7]. All patients were reassessed for response and survival, and histology was also reevaluated. Eight patients were male and five female, with eight patients judged to have stage I and five with stage II disease. All patients were in excellent general condition (PS=0), and none were anemic or had an elevated LDH-level upon diagnosis. Three patients (23 %) presented with an underlying autoimmune condition, chronic autoimmune thyroiditis in one and Sjögren's syndrome in two cases and 4/13 (31 %) had monoclonal immunoglobulin production

**Table 1** Characteristics of patients undergoing HP-eradication

| sex/age | Stage | Response | Duration of response | Progression/Relapse | further therapies | Survival |
|---|---|---|---|---|---|---|
| m/61 | I | CR | 23 mos | yes | HP-eradication (2nd CR) | +95 mos |
| m/70 | I | CR | 19 mos | yes | bortezomib (CR) | 76 mos (died unrelated) |
| f/35 | II | SD | 17 mos | no | Ritixumab + 2CdA (CR) | +69 mos |
| m/55 | I | SD | 15 mos | no | Rituximab + 2CdA (CR) | +55 mos |
| f/69 | I | PR | 26 mos | no | Fludarabine (CR) | +107 mos |
| m/55 | II | PD | — | – | Rituximab + CHOP (CR) | +87 mos |
| m/46 | I | SD | 27 mos | no | Thalidomide, fludarabine, 90Y-ibritumomab-tiuxetan (CR) | +114 mos |
| m/61 | I | SD | 25 mos | no | Rituximab + lenalidomid (CR) | +30 mos |
| m/48 | II | PD | — | – | Rituximab + 2CdA (CR) | +47 mos |
| f/50 | II | PD | — | – | Rituximab + Lenalidomid, Rituximab + Bendamustin (CR) | +25 mos |
| m/69 | I | CR | +14 mos | no | —— | +20 mos |
| m/50 | I | CR | +175 mos | no | ——— | +178 mos |
| f/69 | I | CR | +9 mos | no | ——— | +11 mos |

detected in the peripheral blood. The immunoglobulins corresponded to the lymphoma phenotype in all four patients (IgM/lambda in three and IgG/lambda in one). No evidence of infection with hepatitis A, B, or C was found in our patients. The rate of *t*(11; 18) (q21, q21) was low with 3/13 (23 %) testing positive.

All patients were given HP eradication consisting of clarithromycin 2× 500 mg plus a PPI (pantoprazole 2× 40 mg) for 7 days in seven patients while five were given eradication for 14 days. This regimen was combined with metronidazole 2× 500 mg daily in seven patients and with amoxicillin 2× 1 g daily in six patients. The PPI was given continuously for the first year after diagnosis in all patients with gastric MALT lymphoma, then depending on symptoms at the physician's discretion.

After a median follow-up of 95 months from initial diagnosis (range; 42–181), 12 patients are alive, while 1 patient has died unrelated to lymphoma. In terms of response, five patients achieved CR and one patient responding residual disease (rRD)/PR, resulting in an overall response rate of 46 % in our series. All six responding patients had stage I at the time of antibiotic treatment. One patient relapsed after being in remission for 23 months, and again, no evidence of HP infection could be documented. He was retreated with clarithromycin, amoxicillin, and pantoprazole and again achieved a CR, now ongoing for 95 months. The time to achieve CR was 3 months in one, 6 months in two and 9 months in one patient while one patient showed PR after 23 months which converted to CR at 36 months. The time to achieve PR was 11 months in the remaining responder. Four patients in CR are still without evidence of disease after a follow-up of 9, 95, and 178 months, while one patient relapsed after 19 months in CR and received alternative therapy. The patient in PR progressed after 26 months and was given fludarabine-based chemotherapy resulting in CR. Three patients (23 %) showed evidence of progression and were given alternative therapies within 4 months of antibiotic therapy. Four patients (38 %) were rated as no change/stable disease, and were given chemotherapy at an interval of 11–27 months after therapy. However, only one of these patients was treated due to progression from stable disease (SD) after 11 months, while the remaining patients showed no evidence of progression before administration of chemotherapy.

There was no difference in the estimated median time to progression between HP-negative and HP-positive patients in our series, with HP positives having an estimated time to progression of 28 months (confidence interval (CI) 95 %= 15–40) versus HP negatives at 20 months (CI 95 %=5–30, $p$=0.284). Within the cohort of HP-negative patients, there was no significant difference in the estimated time to progression between patients treated with antibiotics versus other forms of therapy ($p$=0.107), and there was no significant difference in the frequency of progressive disease ($p$=0.382) between these groups. In total, 2 out of 92 patients developed gastric adenocarcinoma, both cases occurred in HP-positive patients.

Out of the three patients with autoimmune disease, one had CR, while the other two patients had stable disease. One patient with *t*(11; 18) (q21; q21) had a PR, while two had SD (for 11 and 27 months).

## Discussion

In our analysis, we could identify 24/97 patients with HP-negative gastric MALT lymphoma managed at our institution,

corresponding to a rate of 24.7 %. While this is much higher than the percentage published in various papers, where it was estimated to be 5–10 % [2, 17], a recent paper from Korea has shown a comparable percentage at 13/66 patients (19.7 %) being HP-negative [16]. In some pathology centers, an increasing trend toward HP-negative MALT lymphomas has been noted during the past 10 years, being in the range of up to 50 % in some countries (A. Wotherspoon, unpublished data). This is also suggested by our cohort of patients diagnosed after 2004, who had a much higher rate at 32 % compared to 18 % before 2004. While there is decreased childhood infection with HP resulting from better socio-economic conditions, one might speculate that this trend might also partly be due to the liberal use of antibiotics in the general population with HP infection or in individuals with symptoms suggestive of HP infection, and thus might be further increasing in the future. One cannot, however, rule out a selection bias in a referral center such as ours due to the clearly defined treatment algorithm in HP-positive as opposed to HP-negative gastric MALT lymphomas [2, 3] with the former more likely being treated outside of specialized centers.

In addition to already published series, our data again underscore the fact that patients without evidence of HP infection may benefit from antibiotic therapy following diagnosis of gastric MALT lymphoma. In our analysis, 5/13 patients had CR and one PR, indicating an overall response rate of 46 %. Notably, our series is among those with the longest follow-up at a median of 95 months (range; 42–181), while a pooled analysis has found only seven HP-negative patients followed between 25–48 months [17]. While these data show that responses to antibiotics might indeed be durable in HP-negative patients, this response rate is higher than the 15 % stated in a recent review [17]. Responders in our series were all patients with (early) stage I disease, while none of the patients with stage II responded to antibiotic therapy. As most series have reported that HP-negative gastric MALT lymphomas are more often diagnosed in higher stages than HP-positive cases [16, 17, 19, 20], this might partly explain the different response rates between studies due to inclusion of different stages.

In fact, it appears slightly puzzling that antibiotic treatment designed to eradicate HP has an effect on apparently HP-negative gastric MALT lymphoma at all, and various explanations have been suggested. These include the potential bias of HP testing, i.e., the possibility of false negative histological results or breath tests [2, 17], which nevertheless should be minimized to a certain extent by using serology as the ultimate tool to assess the absence of contact with HP at least within the recent time. In addition, it has been postulated that bacteria other than HP might have been causative in the pathogenesis of these lymphomas, such as *Helicobacter heilmannii* [21] or as yet undetected agents. In addition, it has already been hypothesized that direct immunomodulatory or even antineoplastic effects of antibiotics, especially clarithromycin, may have contributed to the effect [7]. More recently, this has been substantiated by promising anti-lymphoma activity of clarithromycin in patients with MALT lymphoma refractory to prior therapies including other antibiotics [22, 23]. In fact, the dose of 2× 500 mg per day applied in our patients is higher than used in other series and offers an additional potential explanation for the responses seen in our cohort.

Our results suggest that the activity of antibiotic therapy might have been underestimated due to premature initiation of oncological therapy in the absence of CR after a short follow-up. In fact, the time to best response was 3–9 months in the majority of responders; but in two patients, it took 11 and 23 months, respectively, to achieve rRD/PR, with the latter converting to CR after 36 months without any further therapy. In view of this, it appears reasonable to withhold further therapy in the absence of progression. This is further underscored by the fact that patients with SD following antibiotic therapy also have the potential for long-term stabilization. While one cannot rule out that this long stable course might reflect an intrinsic clinical property of the disease rather than necessarily an effect of therapy, it is still remarkable that only one patient who was given further therapy required this due to progressive disease diagnosed 9 months after antibiotic therapy, while the remaining patients were treated rather due to absent regression after 11–27 months. These findings are also in keeping with a recent report from Korea published by Choi et al. [16], who reported a response rate of 40 % and duration of CR between 26.4–35 months and one patient with PR for 16.2 months, without evidence of relapse/progression in these cases. Importantly, none of the non-responding patients suffered complications during the time of antibiotic treatment and initiation of further treatment, underscoring the safety of our approach.

The responses and stabilizations seen de facto mostly in patients with stage I disease again suggest that this might be a potential prognostic parameter for response to antibiotics, while no other predictive factors can be extrapolated from our data. The rate of *t*(11; 18) (q21; q21) was relatively low in our patients, while it had been reported to be in the range of 50 % [16, 24] in different series from Europe and Asia. While the small sample size suggests that these data have to be interpreted with caution, they do not suggest an impact of *t*(11; 18) (q21; q21) or the presence of autoimmunity on response to antibiotics.

Taken together, our data are in line with a growing body of evidence that antibiotic therapy may also be successfully used with long-term efficacy in a subset of patients with HP-negative gastric MALT lymphoma. In order to further identify the optimal candidates for sole antibiotic therapy a prospective multicenter study is clearly warranted.

**Conflict of interest** The authors disclose no potential conflict of interest for this manuscript. All authors have analyzed the data, helped in drafting and writing the manuscript and have approved of the final version of the paper.

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