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Helicobacter pylori detected in pharyngeal and laryngeal pathologies in patients with proven gastric colonization

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Helicobacter pylori detected in pharyngeal and laryngeal pathologies in patients with proven gastric colonization

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ABSTRACT: *Background.* Helicobacter pylori is known to cause gastric cancer. Presence and carcinogenicity in the upper aerodigestive system is doubtful. This study examined the prevalence of Helicobacter pylori and related factors in biopsies from the upper aerodigestive tract (UADT) in patients with gastric colonization by Helicobacter pylori.

Methods. In a case series study, 26 patients with histopathologically confirmed gastric colonization were identified. A polymerase chain reaction (PCR) was performed on matched formalin-fixed and paraffin-embedded tissues of the stomach and the oral cavity, pharynx, or larynx.

Results. Helicobacter pylori was found in 38% of the samples from the oral cavity, pharynx, and larynx. An association with malignancies in these regions or possible risk factors, such as age, smoking, or alcohol, was not found.

Conclusion. The upper aerodigestive system seems to be an additional reservoir in a significant percentage of patients presenting with Helicobacter pylori gastritis. © 2013 Wiley Periodicals, Inc. *Head Neck* **00:** 000–000, 2013

KEY WORDS: Helicobacter pylori, oral cavity, larynx, pharynx, polymerase chain reaction

INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most common bacterial infections worldwide.[1] It was first described in 1984 by Marshall and Warren.[2] These researchers contributed to a change in the concept of the influence of bacteria on carcinogenesis. They were awarded with the Nobel Prize in Medicine and Physiology "for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease" in 2005.[3] *H. pylori* is the first bacterium to be classified as a definite carcinogen for gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach and duodenum by the World Health Organization.[4]

Transmission of *H. pylori*, its major virulence factors, and its interaction with the host are not fully understood.[5,6] Colonization of *H. pylori* in the upper aerodigestive tract (UADT), namely the oral cavity, pharynx, and larynx, has been debated in recent publications. Dowsett and Kowolik[7] mentioned that there is little doubt that *H. pylori* can be found in the oral cavity. A study by Elsheikh and Mahfouz[8] described a possible effect of *H. pylori* in recurrent aphthous ulcerations in MALT of the pharynx. A study by Shi et al[9] showed a colonization of *H. pylori* in the larynx and assumed a correlation between its presence in the larynx and laryngeal squamous cell carcinoma in male patients. Although the presence of *H. pylori* in the UADT is more and more accepted, the question of whether *H. pylori* could pose a risk for malignant tumors remains open. One hypothesis is that the role of *H. pylori* in carcinogenesis may be comparable to the role of Epstein–Barr virus and the human papillomavirus, which are associated with head and neck cancers.[10,11] In contrast to the proven carcinogenicity of Epstein–Barr virus and human papillomavirus in the UADT, the role of *H. pylori* is unknown and has been debated increasingly in the last several years. Given the high gastric prevalence of *H. pylori* worldwide, even only a small percentage of patients with simultaneous gastric and UADT infections could be clinically and therapeutically relevant. The presence of *H. pylori* in UADT tumors or nearby mucous membranes could be an argument for a possible role of *H. pylori* in the generation of malignant tumors of the UADT. To examine these relations further, we tested, retrospectively, the colonization of *H. pylori* in biopsies of the UADT from patients with proven

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colonization of the stomach. We used a polymerase chain reaction (PCR) on the DNA of *H. pylori* with high specificity and sensitivity.[1,8,12] The gastric samples served as positive controls.

MATERIALS AND METHODS

All samples were collected at the University Hospital Zurich in the period of 1990 to 2009 and stored in the archives of the Institute of Surgical Pathology. We searched for patients with a positive *H. pylori* biopsy of the stomach with an antecedent UADT biopsy. Both the UADT and gastric biopsies were examined. We included only patients who had their UADT biopsy before the diagnosis of *H. pylori* was made in the stomach because its diagnosis would usually have led to eradication therapy and negative results.

The diagnosis of *H. pylori* in the gastric sample was made by pathologists using the histochemical stain Giemsa-C on formalin-fixed and paraffin-embedded tissue sections. The data about consumption of alcohol and nicotine were taken retrospectively from the patient's medical files. Patients who had chemotherapy or radiotherapy before their UADT biopsy were excluded from the sample because such a therapy leads to an alteration of the surface epithelia and the microbiology of the UADT.[13,14]

Five specimen cylinders for each patient were cut from the paraffin bloc on a microtome from both the gastric biopsy and the UADT biopsy. The cylinders had a dimension of 600-μm in diameter and 3-mm in length.

Preparation of genomic DNA for polymerase chain reaction

For DNA extraction, the 5 specimen cylinders were manually homogenized in 100 μl of Tris-EDTA-Tween lysis buffer (50 m*M* Tris in pH 8.5, 1 m*M* EDTA, and 0.5% Tween 20, which was sterile filtered). The mixture was heated to 95°C and mixed vigorously for 10 minutes. While cooling down to 4°C, it was centrifuged for 30 minutes at 16,100 G. The solid paraffin "lid" was then immediately removed and 2.5 μl of Proteinkinase K (Qiagen, Hilden, Germany) was added and the mixture was incubated for 12 hours at 55°C.

The DNA concentration was measured using NanoDrop 1000 (Thermo Scientific, Wohlen, Switzerland) before the Proteinkinase K was inactivated at 95°C for 10 minutes. The critical concentration of DNA was defined as 1 ng/μl; samples with a lower concentration were excluded. An aliquot was used for the PCR. Samples were frozen at -20°C. A total volume of 50 μl PCR master mix was prepared using 40 ng of DNA and the AmpliTaq Gold DNA polymerase reagents (Applied Biosystems, Rotkreuz, Switzerland).

Polymerase chain reaction

PCR was performed on an Eppendorf Mastercycler (Vaudaux-Eppendorf, Schönenbuch, Switzerland) with the primer pair CRF-4/CRR-1 (forward primer 5′-AGTGGAG GTGAAAATTCC-3′, corresponding to *H. pylori* 23S rRNA position 2105-2123 and reverse primer 5′-TAAGA GCAAAGCCCTTAC-3′, corresponding to position 2239-2172). All used primers were previously published.[15] The expected product length was 135 bp. The PCR was performed with 35 cycles consisting of denaturation at 94°C for 30 seconds, annealing at 55°C for 30 seconds, and extension at 72°C for 30 seconds, followed by a final extension of 7 minutes.

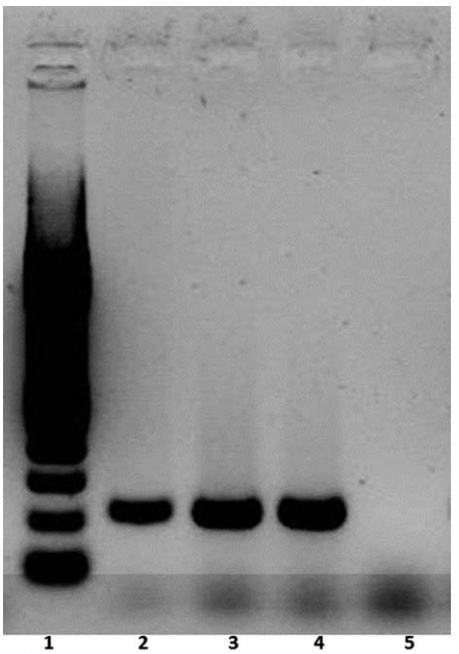

FIGURE 1. 1: Ladder 100 base pair. 2: Patient #1 gastric sample (positive). 3: Patient #1 oral sample (positive). 4: Patient #2 gastric sample (positive). 5: Patient #2 pharyngeal sample (negative).

Electrophoresis

Formation of the PCR product was checked on 1.5% agarose gel electrophoresis at 100 Volt, Gel Red (Biotium, Hayward, CA) was added to the gels (dilution 1:10,000) and used as DNA intercalating fluorescent dye. The Gel Red–stained DNA in the gels was visualized in an ultraviolet transilluminator box (BioRad, Pearl River, NY),[8] as shown in Figure 1.

A previous study by Soltermann et al,[16] provided a positive control for the PCR. For each patient, the histopathologically proven infection of *H. pylori* in the stomach was used as an internal individual positive control. As a negative control, a sample without DNA was used.

Statistical analysis

The results of the study and control groups were statistically analyzed by the Fisher's exact test and Mann–Whitney *U* test; statistical significance was indicated by a level of $p < .05$ using SPSS/PASW 19.0.0 software (IBM, Armonk, NY).

RESULTS

The database of the Institute of Surgical Pathology contained more than 600,000 patients in the time period of

TABLE 1. Characteristics of 26 patients with a proven gastric colonization of Helicobacter pylori.

Sex	Age, y	UADT diagnosis	UADT site	Latency, mo	Nicotine	Alcohol	*H. pylori* in UADT
Male	58.3	Benign disease	Oral cavity	0	No	No	Positive
Male	38.5	Malignancy	Pharynx	2	No	No	Negative
Male	37.4	Benign disease	Larynx	0	Yes	No	Positive
Female	36.3	Benign disease	Pharynx	56	No	No	Positive
Female	46.7	Malignancy	Larynx	37	Yes	Yes	Positive
Female	22.6	Benign disease	Pharynx	57	Yes	No	Negative
Male	42	Benign disease	Larynx	30	Yes	Yes	Negative
Female	39.2	Malignancy	Larynx	3	No	No	Positive
Male	30.1	Benign disease	Pharynx	15	Yes	Yes	Negative
Male	53.2	Malignancy	Oral cavity	4	Yes	Yes	Positive
Male	71.9	Malignancy	Pharynx	2	Yes	Yes	Negative
Male	67.6	Malignancy	Pharynx	2	Yes	Yes	Negative
Female	68.6	Malignancy	Pharynx	14	Yes	No	Positive
Female	65.7	Malignancy	Oral cavity	17	Yes	No	Negative
Female	61.7	Malignancy	Pharynx	2	Yes	Yes	Negative
Male	53.7	Malignancy	Oral cavity	48	Yes	Yes	Negative
Male	46.3	Benign disease	Larynx	93	No	No	Negative
Male	53.3	Malignancy	Larynx	11	No	Yes	Negative
Male	52.9	Malignancy	Pharynx	3	Yes	Yes	Negative
Male	53.9	Malignancy	Pharynx	0	Yes	No	Positive
Male	51.1	Malignancy	Larynx	10	Yes	Yes	Negative
Female	45.2	Benign disease	Larynx	45	No	No	Negative
Male	76.1	Malignancy	Pharynx	15	No	No	Negative
Female	60.8	Malignancy	Oral cavity	60	Yes	Yes	Negative
Male	49.6	Malignancy	Pharynx	41	Yes	No	Positive
Male	60.1	Malignancy	Pharynx	35	Yes	Yes	Positive

Abbreviations: UADT, upper aerodigestive tract; H. pylori, Helicobacter pylori.

1990 to 2009, and 2830 *H. pylori*–positive biopsies of the stomach were found. Thirty-six patients had an antecedent UADT biopsy. Ten patients were excluded because of a DNA concentration of <1 ng/µl. The samples of the remaining 26 patients were included into the study. They met the key requirement of providing 2 surface epithelia; one from the stomach with an *H. pylori*-positive PCR, and the other from an UADT site with unknown *H. pylori* status. Characteristics of the 26 cases are listed in Table 1.

No relationship between the patient's age or sex and the presence of *H. pylori* in the UADT was detected. The mean age of *H. pylori*–positive patients was 50 years (range, 36–69 years) and the *H. pylori*–negative patients were 52 years (range, 23–76 years; $p = .64$). Eleven of 16 patients (69%) with UADT *H. pylori*–negative were men, compared to 6 of 10 patients (60%) who were *H. pylori*–positive.

Thirteen (50%) biopsies were from the pharynx, 8 (31%) from the larynx, and 5 (19%) from the oral cavity. *H. pylori*–positive biopsies were detected with similar frequency at all 3 sites. *H. pylori*–positive results were found in 5 of 13 (38%) biopsies of the pharynx, in 3 of 8 (38%) of the larynx, and in 2 of 5 (40%) of the oral cavity. As indicated in Figure 2, the histopathologic diagnosis was malignancy in 7 of 10 (70%) *H. pylori*–positive biopsies of the UADT, the other 3 were benign diseases. The proportion of malignancies was similar in the *H. pylori*–negative biopsies, in which the diagnosis was a benign disease in 5 of 16 (31%) cases and malignancies in 69%.

In the *H. pylori*–positive group, the mean time between the gastric and the UADT biopsy was 18.8 months (range, 0–55 months) and in the *H. pylori*–negative group, 25.4 months (range, 2–93 months). The difference between these 2 periods was not significant ($p = .35$).

A history of smoking or alcohol consumption was not related to the presence of *H. pylori* in UADT. Eleven of 16 of the *H. pylori*–negative patients (69%) consumed nicotine and 7 of 10 (70%) of the *H. pylori*–positive

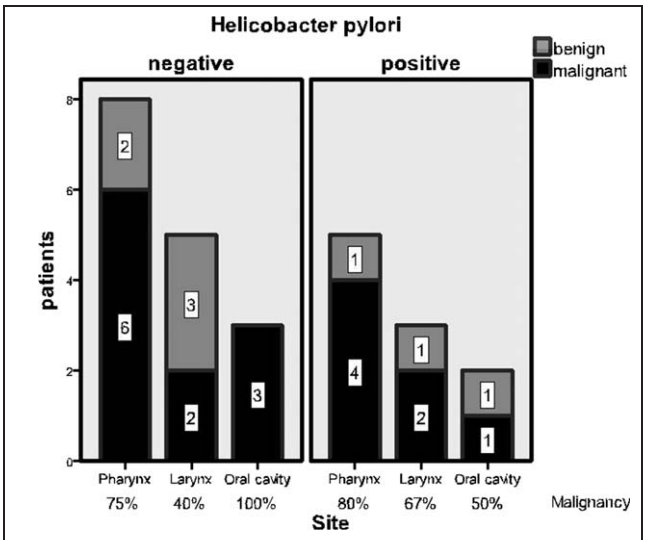

FIGURE 2. The histopathologic diagnosis was malignancy in 7 of 10 (70%) Helicobacter pylori (*H. pylori*)-positive biopsies of the upper aerodigestive tract (UADT), the other 3 were benign diseases.

group. Among the *H. pylori*–positive patients, 3 of 10 consumed alcohol and 10 of 16 of the *H. pylori*–negative group.

Younger patients showed biopsies with benign diseases significantly more often than did older patients, who showed more malignancies ($p = .03$). However, the presence or absence of *H. pylori* was not related to age, nor to UADT diagnosis, UADT site, the period between biopsies, smoking, or alcohol.

DISCUSSION

The first question of this study was whether or not *H. pylori* regularly colonizes the mucosa of the UADT. Using PCR, we found a prevalence of 38% (10 of 26) *H. pylori*–positive biopsies in the corresponding UADT samples of patients with confirmed gastric colonization. No association was noted between the presence of *H. pylori* and specific pathologies in the UADT or other factors. *H. pylori* was found in roughly one third of the samples, irrespective of the site of the lesion, whether the UADT pathology was cancer or not, and of the age, sex, or risk factors of the patients.

These results were obtained retrospectively in a small and highly selected sample of 26 patients from a general histopathological data base, which does not allow inference to the actual prevalence of *H. pylori* in the UADT of the general population. Prevalence of *H. pylori* in the UADT depends on the methods used for measurement and probably also on the gastric prevalence of *H. pylori* in the general population. Western countries with high hygienic standards tend to have lower general prevalence than developing regions. Also using PCR, Ozyurt et al[17] studied patients in Turkey and found *H. pylori* in 59% of the laryngeal mucosa samples of patients with laryngeal disorders and 59% of the nasal mucosa samples of patients with nasal polyps. This study compared these findings to the prevalence in normal nasal mucosa, which was 70% and not significantly different from the patients' prevalence. However, another Turkish study using PCR by Kaptan et al[12] examined patients with chronic pharyngitis. It found *H. pylori* in 34% in the pharynx of patients with concomitant gastric *H. pylori* and in 20% in the pharynx of patients without gastric colonization. A study from China by Shi et al,[9] again using PCR, showed *H. pylori* in 76% in the larynx of Chinese male patients with a laryngeal squamous cell carcinoma and 32% in the cancer-free group. Elsheikh and Mahfouz[8] from Egypt, also using PCR, showed *H. pylori* in 33% in aphthous ulcerations in MALT of the pharynx.

Other methods similar to those based on measuring immunoglobulin G antibodies to *H. pylori* in the serum have reported conflicting results with generally higher prevalence, again possibly depending on the general gastric prevalence of *H. pylori*. An Iranian study by Rezaii et al,[18] found antibodies against *H. pylori* in 94% of patients with laryngeal cancer and 93% of patients with hypopharyngeal cancer versus 52% in a control group ($p < .01$). In contrast, Grandis et al,[19] in the United States, found no association of *H. pylori* and head and neck cancer with 57% seropositivity in patients with a squamous cell carcinoma of the head and neck versus 62% in a control group using a similar method. These results were supported by another study in the United States and with comparable methods by Nurgalieva et al,[20] which found a positive serological test in 33% of patients with a squamous cell carcinoma of the laryngopharynx versus 27% in the control group.

Our study found prevalence of *H. pylori* in the UADT mucosa to be at the lower end of the distribution of the above-cited studies, particularly when accounting for the use of highly sensitive PCR methods and the 100% gastric colonization, which was an inclusion criterion of our study. This inclusion and selection process led to a highly variable temporal relation between the UADT and gastric biopsies with a mean of around 2 years. The time span reached up to 93 months preventing any conclusions on the actual concomitant presence of gastric and UADT *H. pylori*. PCR on *H. pylori* DNA is most likely the best available and most appropriate means to detect *H. pylori* in the UADT.[1,8,12] It has a high specificity and sensitivity and allows the specific detection of a small amount of bacteria. No cross reaction with DNA samples obtained from 12 other bacterial species was found.[15] Even though PCR methods for *H. pylori* are not well established in UADT samples, its proven usefulness in formalin-fixed and paraffin-embedded samples of gastric tissues[8,21] may be extended to the UADT. In vivo PCR seems to be the most effective method available for the detection of *H. pylori* in the UADT compared with other methods.

Urease-based tests have a low specificity in the UADT because various urease-producing bacteria, such as Klebsiella and Proteus, are found regularly in the UADT.[7,22–24] The *H. pylori* isolation by culture has a low sensitivity[8,25]; it could not have been performed in our retrospective setting, and it has shown false results in several studies.[7,12] A study by Teoman et al,[26] found PCR from dental plaque to be positive in 18 of 67 subjects, whereas the culture was negative.

Serologic testing using immunoglobulin G does not discriminate between current and former infections,[8] and it cannot provide specificity of *H. pylori* in the UADT. Detection of *H. pylori* by histopathological staining may provide such specificity as it does in gastric mucosa. However, light microscopy methods to detect *H. pylori* in the UADT lead to contradictory results, according to a study by Aslan et al[27] examining the prevalence of *H. pylori* in the tonsils of patients with tonsillitis. These authors did not find *H. pylori* in any of the specimens studied under light microscopy, even though the urease-Test was positive. Moreover, Lukes et al[1] described low specificity because of other bacteria with a similar optical appearance leading to false-positive results in light microscopy.

There is consensus that *H. pylori* is very common in the stomach worldwide,[1] and it is well known that *H. pylori* can cause gastric cancer and MALT lymphoma.[4] Our results showed the presence of *H. pylori* in the oral cavity, pharynx, and larynx in 38% of patients with a proven gastric colonization. However, this finding does not allow conclusions about the relations between malignancies of the UADT and the presence of *H. pylori*. The high rate of malignancies of about 70% in our sample is probably related to the fact that invasive biopsies of the UADT were more readily carried out when malignant disease was suspected rather than benign lesions. Moreover, the rate was irrespective of the detection of

H. pylori. Studies using PCR and providing clear results of a role of *H. pylori* in the carcinogenesis of the UADT are rare, and the mechanisms remain unclear. The study by Shi et al[9] showed that *H. pylori* was more common in the larynx of male Chinese patients with laryngeal carcinoma (76%) than in the control group (32%). However, these authors excluded all patients with any symptoms of an unhealthy digestive system, making the prevalence of the control group doubtful compared to the general population. In a case-control study by Rezaii et al,[18] including 70 patients with laryngeal carcinoma and 28 patients with hypopharyngeal carcinoma, the prevalence of *H. pylori* in the larynx was significantly more common than in the control group of 105 matched subjects. Based on these results, *H. pylori* was found to be an independent risk for laryngopharyngeal carcinoma with an odds ratio of more than 11. However, the use of a serologic test for *H. pylori* in the UADT remains doubtful.

Our results were based on a stable PCR, but they leave open the question of an association of *H. pylori* and pathologies in the UADT. The results of this study finding evidence of *H. pylori* in the UADT in 38% of patients with a proven gastric colonization make the presence of *H. pylori* very likely in a subset of patients with both malignancies and benign diseases of the UADT. Given the well-documented role of *H. pylori* in the development of gastric cancer and the results of this study showing a higher than expected prevalence of *H. pylori* in cancer of the UADT, further research with prospective trials in patients with UADT cancer and in well-selected control subjects is warranted. Prospective studies based on larger populations should help to establish or exclude *H. pylori* as a possible factor for both malignancies and benign diseases of the UADT.

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