The Possible Role of *Helicobacter pylori* in the Development of Sjogren's Syndrome and Chronic Sialadenitis

Alireza Monsef Esfahani 1; Soussan Irani 2,*, Shahram Sabeti 3; Farahnaz Bidari Zerehpoush 3

1Department of Pathology, Hamadan University of Medical Sciences, Hamadan, IR Iran
2Department of Oral Pathology, Hamadan University of Medical Sciences, Hamadan, IR Iran
3Department of Pathology, Loghman Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
*Corresponding author: Soussan Irani, Department of Oral Pathology, Hamadan University of Medical Sciences, P. O. Box: 65178-38741, Hamadan, IR Iran. Tel: +98-8118354250, Fax: +98-8118354220, E-mail: Address:soussanirani@gmail.com

**Received:** September 1, 2014; **Revised:** October 26, 2014; **Accepted:** November 2, 2014

**Background:** Sjogren’s syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration of exocrine glands, which can be triggered by environmental factors such as viral infection. Chronic obstructive sialadenitis is the most common type of chronic sialadenitis and many different bacterial infections develop as a result of ductal obstruction.

**Objectives:** This study was conducted to assess the association of these lesions with the presence of *Helicobacter pylori*.

**Patients and Methods:** A total of 56 biopsies diagnosed as Sjogren’s syndrome (SS) and chronic sialadenitis (CS) due to sialolithiasis in submandibular glands, sublingual and minor salivary glands were selected (56 samples as examined group and 20 samples as control group). All the paraffin blocks were cut for hematoxylin and eosin (H and E) staining to confirm the diagnoses and then the samples were prepared for immunohistochemistry (IHC) staining to detect *H. pylori*. Chi-squared test was used for statistical analysis.

**Results:** Chi-squared test showed a significant difference between *H. pylori* positivity in the groups examined (P = 0.046) and between SS group and normal tissue samples (P = 0.01). There was no significant difference between gender and *H. pylori* positivity in examined groups examined (P = 0.574, P = 0.543, respectively). In addition, there was no significant difference between gender and *H. pylori* positivity in SS group (P = 0.119, P = 0.331, respectively) also in CS group (P = 0.981, P = 0.571).

**Conclusions:** Bacterial infection has been suggested in the pathogenesis of both SS and CS. In addition, *H. pylori* is a resident of the oral cavity, thus may be involved in the development and progression of these lesions. Hence, search for *H. pylori* antibody in blood of patients with SS is suggested.

**Keywords:** Sjogren’s Syndrome; Chronic Sialadenitis; *Helicobacter pylori*; Oral Cavity

1. **Background**

Sjogren’s syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands. It affects salivary glands and associated with autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis (1). SS is one of non-infectious causes of salivary gland tissue inflammation (2). Patients with SS suffer from progressive dryness of eyes and mouth due to insufficient salivary and lacrimal secretions (3). In histological examination, characteristic features of salivary glands can be seen including destruction of the acinar structure, total replacement of the salivary acinar structure by lymphocytic infiltrate, and also various changes in ductal structure such as epimyoepithelial islands which can be seen mostly in parotid gland tissue (2-4). According to previous studies, sensitivity and specificity of the parotid biopsy is comparable with that of labial biopsy in diagnoses of SS (4). In addition, patients with SS have an increased risk of developing gastric lesions, such as gastric atrophy (5). Previous studies showed chronic gastric inflammation in 80% of patients with SS (6). In histopathological examinations, epithelial and glandular alterations are similar to those of gastritis with *H. pylori* infection (7). Chronic obstructive sialadenitis is the most common type of CS (8). Periductal lymphocytic infiltration, acinar atrophy and periductal fibrosis are the histological features of chronic obstructive sialadenitis. Sialolithiasis is the most common cause of chronic obstructive sialadenitis and many different bacterial infections develop as a result of ductal obstruction (2). *H. pylori* is a resident of human gastric mucosa. The association of *H. pylori* with pathogenesis of peptic ulcers, gastric adenocarcinoma and low-grade B-cell mucosa-associated lymphoid tissue lymphoma has been proved (9). Many studies indicated that *H. pylori* can be isolated from the oral cavity, the dorsum of the tongue, salivary secretions and dental plaque (supragingival plaque and subgingival plaque) in patients with or without periodontitis (10, 11). *H. pylori* exists in the oral cavity even...
after systemic eradication therapy, suggesting that patients with positive results for gastric *H. pylori* have *H. pylori* in the oral cavity as well. Particularly in cases with gingivitis or periodontitis, the oral cavity can be considered as a reservoir capable of increasing the risk of gastric re-infection (12). The presence of *H. pylori* in some other oral lesions has been reported. For example, in patients with burning, halitosis and lingual dorsum hyperplasia, 87% of patients had positive results for *H. pylori* (13). In addition, in atrophic glossitis, benign migratory glossitis and burning mouth syndrome, *H. pylori* was detected in 16% of patients (14). In one study, *H. pylori* was detected in patients with aphthous stomatitis in 52% of cases (15). In another study, 38.9% of patients with recurrent aphthous stomatitis showed *H. pylori* positivity (16). Previous studies showed that SS was triggered by environmental factors such as a viral infection (17). Infection has also been considered as an etiological factor in developing SS and CS due to sialolithiasis (2).

2. Objectives

This study was conducted to assess the association of these lesions with the presence of *H. pylori*.

3. Patients and Methods

A total of 56 biopsies diagnosed as Sjögren’s syndrome (SS) and chronic sialadenitis (CS) due to sialolithiasis in submandibular, sublingual and minor salivary glands and 20 tissue samples taken from the labial mucosa of the lower lip and floor of mouth (as submandibular and sublingual salivary glands excretory ducts drain to the floor of mouth) with pathology report as “without significant pathological changes” were selected as the control group from the archive of Pathology Department of Loghman Hospital, Tehran, Iran. All the paraffin blocks were cut for H&E staining to confirm the diagnoses and then the samples were prepared for IHC staining.

In brief, formalin-fixed, paraffin-embedded tissues were all cut into 4 μm. The slides were then deparaaffinized, rehydrated and pre-treated with trypsin for 40 minutes at 37°C according to manufacturer’s instructions (Novocastra, UK). The endogenous peroxidase activity was blocked, followed by incubation with lyophilized rabbit polyclonal antibody (Novocastra, UK) at a dilution of 1:20 for one hour. DAB was used to visualize the complex. Finally, the sections were counterstained with haematoxylin and mounted. *H. pylori* positive and negative human gastric samples served as positive and negative controls, respectively. Statistical analysis was performed using SPSS version 21.0.1, Chi-squared test and independent-samples T test were used. Significance was set at P < 0.05.

4. Results

In this study, there were 34 (44.7%) male and 42 (55.3%) female. In general, the ages of patients and control group ranged from 19 to 70 years, with a mean age of 38.83 years.

Demographic characteristics of samples and *H. pylori* detection status is summarized in Table 1. Chi-squared test showed a significant difference between *H. pylori* positivity in the groups (P = 0.046) and between SS group and normal tissue samples (P = 0.013). There was no significant difference between gender and *H. pylori* positivity in examined groups (P = 0.574, P = 0.543, respectively). In addition, there was no significant difference between gender and *H. pylori* positivity in SS group (P = 0.119, P = 0.331, respectively) and in CS group (P = 0.981, P = 0.571). Independent-Samples T test showed a significant difference between SS and CS groups and age (P = 0.002).

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>No. of Patients</th>
<th>Mean Age Range, y</th>
<th>H. pylori Detection Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjogren's syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>45.40</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>27-70</td>
<td></td>
</tr>
<tr>
<td>Chronic sialadenitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>33.19</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>19-46</td>
<td></td>
</tr>
<tr>
<td>Normal tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>39.35</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>20-70</td>
<td></td>
</tr>
</tbody>
</table>

a Data are presented as No. (%).

5. Discussion

Exposure of bacteria to host tissues results in some pathologic outcomes. Several immune effectors function to minimize microbial interactions with host tissues (bacterial-epithelial contact). There is growing evidence from animal models indicating that certain bacteria can trigger immunopathology (18). The association between infection and autoimmune diseases has been found previously (19).

Focal lymphocytic infiltration around the ducts is the first histopathological feature in newly diagnosed SS cases suggesting that antigen presentation of glandular or acinar epithelium has a crucial role in SS pathogenesis (20). Epithelial cells produce locally different B-cell targeted cytokines, and B-cell activating factor (BAFF) (21). Previous investigations indicated that proinflammatory cytokines such as IL-1 and IL-6 are produced by epithelial cells and lymphocytes in SS, which strongly suggest that both epithelial cells and lymphocytes (autoimmune epithelialitis) are important to initiate SS (22). On the other hand, T-cell CD4 lymphoid hyperplasia in SS contributes to B-cell hyperactivity due to exogenous or autoantigens. In addition, B-cell activation is another finding in patients with SS. Thus, in SS, T cells in the salivary glands must be stimulated by antibodies, which enhance B cell proliferation (23). Growing evidence indicates that patients with
SS have an increased risk of lymphomas as well as gastric lesions (5). In the current study, 72% of SS samples, 54.8% of CS samples and 35% of normal tissues showed H. pylori positivity in IHC staining (Table 1). The present study also demonstrated a statistically significant difference in H. pylori positivity between SS tissues and normal tissue samples. Figure 1 shows the presence of H. pylori in both SS and CS samples.

**Figure 1. Presence of H. pylori in Both Sjogren’s Syndrome and Chronic Sialadenitis Samples**

In a study on patients with SS (primary and secondary) carried out by El Miedany et al. it was shown that prevalence of H. pylori infection and average titers of anti-H. pylori antibodies were significantly higher compared to patients with connective tissue diseases or healthy control subjects. Due to a high prevalence of H. pylori infection in the studied group, the authors considered a significant correlation between H. pylori infection and disease duration, and suggested that the longer the duration of SS, the greater the likelihood of having H. pylori infection in patients (24). Aragona et al. working on patients with different autoimmune diseases showed that 79.4% of patients with primary SS had antibodies against H. pylori and there was also a significant difference between the SS group and patients with various autoimmune diseases regarding H. pylori serum antibody (25). Banno et al. found H. pylori antibody in 75.5% of SS patients. There was also a significant difference between the level of H. pylori antibody in patients and control groups (26).

Previous investigations demonstrated that H. pylori can produce extracellular products that cause local and systemic immune responses resulting in tissue damage (27). H. pylori infection induces a humoral response which may contribute to surrounding tissues damage (28). H. pylori pathogenesis acts through two mechanisms. Firstly, H. pylori interaction with surface epithelial cells develops direct cell damage or produces pro-inflammatory mediators (29). Secondly, H. pylori reaches the underlying mucosa, hence stimulates immune response, which in turn leads to liberation of different cytokines and oxygen radicals (30). The presence of H. pylori in the lamina propria has been proven indicating H. pylori invasion to the underlying tissues, induction and development of inflammation (31). In addition, H. pylori was detected inside the blood vessels, which may explain H. pylori bacteremia and systemic immune responses (32). Ito et al. found that H. pylori is able to pass through the endothelial layer (31). Endothelial cell injury may induce vasculitis, which results in the release of inflammatory mediators and systemic immune response (33). Within H. pylori infected gastric mucosa, IL-8 is increased (34). CD4+ T cells migrate to gastric mucosa and cause epithelial damage through proliferation, apoptosis and metaplasia (35). This might be caused by a direct bacterial effect like IL-8 or as a consequence of cellular immune response (36). CD4 T cell absence in H. pylori associated gastritis leads to increased gastritis dominated by an infiltration of CD8 T cells (37). Thus, it seems that CD8 T cells contribute to H. pylori-induced pathology. H. pylori antigen-presenting cells have interactions with CD4 expressing cells, which bind to B-cells in the marginal zone leading to T-cell activation, lymphoid follicle formation, and B-cell proliferation in gastric mucosa and therefore development of gastric lymphoma (38).

Patients with SS also have over a 44-fold increased risk of development of B-cell non-Hodgkin’s lymphoma (39). There is some evidence of gastric and parotid MALT lymphoma regression after H. pylori eradication (40). It was suggested that possible mechanisms for infection could be direct infection of salivary gland tissue by H. pylori or recirculation of organism related antigens from another site of infection (41). Taken together, it is suggested that during H. pylori related MALT lymphomas, there is a close interaction among epithelial cells, T cells and B cells.

In conclusion, bacterial infection has been suggested in the pathogenesis of both SS and CS. In addition, H. pylori is a resident of the oral cavity, thus can be involved in development and progression of these lesions. It is suggested to search for the H. pylori antibody in the blood of patients with SS. Regarding the high risk of MALT in patients with SS, which had regressed after H. pylori eradication, eradication of H. pylori in these patients can be helpful for patient survival, especially in the early stages of SS.

**Funding/Support**

This study was supported by a Grant from the Hamadan University of Medical Sciences.

**References**


2. Neville BW, Damm DD, Allen CM, Bouquot JE. *Oral & Maxillofacial
Pathology. 3 ed(35A):W.B.Saunders; 2009.
3. Hayashi T. Dysfunction of lacrimal and salivary glands in Sjo
gren's syndrome: nonimmunologic injury in preinflammatory
JL, et al. Parotid gland biopsy compared with labial biopsy in
the diagnosis of patients with primary Sjogren's syndrome. Rheuma-
5. Ostuni PA, Germana B, Di Mario F, Rugge M, Pibani M, De Zambia-
6. Kilpi A, Bergroth T, Konttinen YT, Maury CP, Reitamo S, Wegelius
O. Lymphocyte infiltrations of the gastric mucosa in Sjogren's
syndrome. An immunoperoxidase study using monoclonal an-
7. Ebert EC. Gastrointestinal and hepatic manifestations of Sjogren
8. Seifert G. Aetiological and histological classification of sialadeni-
9. Kim SS, Ruiz VE, Carroll JD, Moss SF. Helicobacter pylori in the
pathogenesis of gastric cancer and gastric lymphoma. Cancer
10. Gebara EC, Panunzi C, Faria CM, Chehter I, Mayer MP, Lima LA.
Prevalence of Helicobacter pylori detected by polymerase chain
reaction in the oral cavity of periodontitis patients. Oral Micro-
11. Riggo MP, Lennan A. Identification by PCR of Helicobacter pylori in
sublingual plaque of adult periodontitis patients. J Med Mi-
Helicobacter pylori in the oral cavity is associated with gastro-
13. Adler I, Denninghoff VC, Alvarez MI, Avagaina A, Yoshida R, El-
sner B. Helicobacter pylori associated with glossitis and halito-
14. Gall-Trosell K, Mrozak-Stipetic M, Jurak I, Ragland WL, Pavelic J,
H石家ctor. Helicobacter pylori colonization of tongue mucosa-increased
incidence in atrophic glossitis and burning mouth syndrome
15. Mansour-Ghanaei F, Asmar M, Bagherzadeh AH, Ekbataninejad S.
Helicobacter pylori infection in oral lesions of patients with re-
17. Low HZ, Witte T. Aspects of innate immunity in Sjogren's syn-
18. Hooper LV, Littman DR, Macpherson AJ. Interactions be-
Role of infectious agents in systemic rheumatic diseases. Clin Exp
20. Vougalosir M, Trzoufas AG. Current Aspects of Pathogenesis in
22. Moutsopoulos HM. Sjogren's syndrome: autoimmune epitheli-
23. Youinou P, Devauchelle-Pensec V, Pers JO. Significance of B cells
24. El Miedany YM, Baddour M, Ahmed I, Fahmy H. Sjogren's syn-
drome: concomitant H pylori infection and possible correlation
Vitali C, et al. Presence of antibodies against Helicobacter pylori
and its heat-shock protein 60 in the serum of patients with Sjo-
R. Seroprevalence of Helicobacter pylori and association with
27. Perez-Perez GI, Dworkin BM, Chodos JE, Blaser MJ. Campylobacter
28. Farinha P, Gascony RD. Helicobacter pylori and MALT lympho-
29. Naumann M, Crabtree JE. Helicobacter pylori-induced epithe-
Increased oxidative DNA damage in Helicobacter pylori-infected
31. Ito T, Kobayashi D, Uchida K, Takemura T, Nagaoka S, Kobayashi I,
et al. Helicobacter pylori invades the gastric mucosa and trans-
33. Ferrer C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Mo-
tagna G, et al. Systemic sclerosis: demographic, clinical, and se-
rologic features and survival in 1,012 Italian patients. Medicine
34. Crabtree JE, Peichl P, Wyatt J, Stachl U, Lindley J. Gastric inter-
leukin-8 and IGA IL-8 autoantibodies in Helicobacter pylori infec-
35. Peterson RA, 2nd, Hoepf T, Eaton KA. Adoptive transfer of sple-
nocytes in SCID mice implicates CD4+ T cells in apoptosis and
epithelial proliferation associated with Helicobacter pylori-in-
36. Peek RM, Jr, Fiske C, Wilson KT. Role of innate immunity in
Helicobacter pylori-induced gastric malignancy. Physiol Rev.
CD4+ T cells are associated with severe gastritis in Helicobacter
pylori-infected mice in the absence of CD4+ T cells. Infect Immun.
38. D'Elios MM, Amedei A, Manghetti M, Costa F, Baldari CT, Quazi AS,
et al. Impaired T-cell regulation of B-cell growth in Helicobacter
pylori-related gastric low-grade MALT lymphoma. Gastroenterol-
39. Theander E, Henriksson G, Ljungberg O, Mandl T, Manthorpe R,
Jacobsson LT. Lymphoma and other malignancies in primary Sjo-
gren's syndrome: a cohort study on cancer incidence and lympho-
40. Iwai H, Nakamichi N, Nakae K, Konishi M, Inaba M, Hoshino S,
et al. Parotid mucosa-associated lymphoid tissue lymphoma
regression after Helicobacter pylori eradication. Laryngoscope.
41. Walt RP. Regression of MALT lymphoma and treatment for Hel-