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TOPIC HIGHLIGHT

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Helicobacter pylori and skin autoimmune diseases

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Abstract

Autoimmune skin diseases are characterized by dysregulation of the immune system resulting in a loss of tolerance to skin self-antigen(s). The prolonged interaction between the bacterium and host immune mechanisms makes *Helicobacter pylori* (*H. pylori*) a plausible infectious agent for triggering autoimmunity. Epidemiological and experimental data now point to a strong relation of *H. pylori* infection on the development of many extragastric diseases, including several allergic and autoimmune diseases. *H. pylori* antigens activate cross-reactive T cells and induce autoantibodies production. Microbial heat shock proteins (HSP) play an important role of in the pathogenesis of autoimmune diseases because of the high level of sequence homology with human HSP. Eradication of *H. pylori* infection has been shown to be effective in some patients with chronic autoimmune urticaria, psoriasis, alopecia areata and Schoenlein-Henoch purpura. There is conflicting and controversial data regarding the association of *H. pylori* infection with Behçet's disease, scleroderma and autoimmune bullous diseases. No data are available evaluating the association of *H. pylori* infection with other skin autoimmune diseases, such as vitiligo, cutaneous lupus erythematosus and dermatomyositis. The epidemiological and experimental evidence for a possible role of *H. pylori* infection in skin autoimmune diseases are the subject of this review.

Key words: Autoimmune; Skin; *Helicobacter pylori*; Infection

Core tip: Epidemiological and experimental data now point to a strong relation of *Helicobacter pylori* (*H. pylori*) infection on the development of many autoimmune diseases. Eradication of *H. pylori* infection was shown to be effective in some patients with chronic autoimmune urticaria, psoriasis, alopecia areata and Schoenlein-Henoch purpura. There is conflicting and controversial data regarding the association of *H. pylori* infection with Behçet's disease, scleroderma and autoimmune bullous diseases. No data are available evaluating the association of *H. pylori* infection with vitiligo, cutaneous lupus erythematosus and dermatomyositis. A possible role of *H. pylori* infection in skin autoimmune diseases is the subject of this review.

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INTRODUCTION

The association between infection and autoimmunity has been progressively defined over the past 25 years.

Since *Helicobacter pylori* (*H. pylori*) identification in 1983, an increasing amount of knowledge has collected, with this pathogen having been directly involved in the pathogenesis of several dermatological diseases[1]. *H. pylori* is a widely prevalent microbe, with nearly 50% of the western world and over 80% of those living in developing countries infected[2]. The bacteria has the amazing ability to persist in infected individuals for many decades and have closely co-existed with humans at least since they first migrated out of East Africa approximately 60000 years ago[3]. Epidemiological and experimental data now point to a strong relation of *H. pylori* infection on the development of many extragastric diseases, including several allergic and autoimmune diseases[4].

The epidemiological and experimental evidence for a possible role of *H. pylori* infection in skin autoimmune diseases are the subject of this review.

IMMUNOMODULARY MECHANISMS OF *H. PYLORI* IN AUTOIMMUNE DISEASES

Various mechanisms have been proposed in an attempt to explain the extra intestinal autoimmune manifestations of *H. pylori* infections.

Autoimmune diseases are characterized by dysregulation of the immune system resulting in a loss of tolerance to self-antigens. The exact etiology for the majority of these diseases is unknown; however, complex process, including genetic predisposition, hormonal balance and environmental factors such as infectious agents are believed to play a pivotal role[4]. The inflammatory response to *H. pylori* infection can lead to the development of antigen-antibody complexes or cross-reactive antibodies resulting in autoimmunity[5]. *H. pylori* induced molecular mimicry can also result in both humoral and cell-mediated autoimmune reactions with the development of organ specific and systemic immunopathology[6].

Infection with *H. pylori* elicits a significant immunomodulation, that are typically triggered by chronic inflammation[7] and results in a primarily Th1 T-cell response, resulting in the production of interleukin (IL)-2 and interferon gamma[8]. This chronic infection is also characterized be higher local and systemic levels of proinflammatory cytokines such as tumor necrosis factor-α, IL-6, IL-10, and IL-8[9]. *H. pylori* chronic infection can also result in uncontrolled growth and proliferation of CD5+ B-cells, which produce polyreactive and auto-reactive IgM and IgG3 antibodies[10].

Several recent reports have implicated T regulatory cells (Tregs) and dendritic cells (DCs) with tolerogenic activity in mediating the systemic immunomodulatory effects of *H. pylori* infection[11]. Evidence for a functional role for Tregs and Treg-derived cytokines in promoting *H. pylori*-induced immunomodulation has been provided in experimental infection models[12,13]. Inducible Tregs, which are generated in the periphery are believed to initiate and maintain peripheral immune tolerance through the induction of anergy, deletion of autoreactive T-cells and the instruction and differentiation of inducible Tregs[14]. These tolerogenic DCs function by converting naive T-cells into FoxP3+ Tregs through antigen presentation in the absence of co-stimulatory signals or cytokines[14,15] and appears to play a central role in the induction and maintenance of *H. pylori*-specific immune tolerance and immunomodulation[16]. *H. pylori* also holds an ability to intensely reprogram DCs toward tolerogenicity by efficiently inducing FoxP3 expression in naive T-cells in a tumor growth factor (TGF)-β-dependent manner[17,18].

Based on these observations, it is now accepted; that the presence or absence of *H. pylori* infection may influence the risk of developing of several autoimmune conditions, include immune-mediated dermatological diseases[19].

H. pylori and chronic urticaria

Urticaria is widely regarded as a heterogeneous group of diseases that share a distinct skin reaction pattern, *i.e.,* the development of urticarial skin lesions[20]. Chronic spontaneous urticaria (CU) is defined as wheals arising spontaneously without any external physical stimuli and the disease lasts > 6 wk[20]. It is accepted that autoimmune mechanisms are involved in the pathogenesis of CU; and different pathogenic autoantibodies, namely causing a release of histamine, after reaction with IgE epitopes, or with the α-chain of FcεRI receptors, is considered[21]. Assessment of these autoantibodies in clinical practice is performed by the autologous serum skin test (ASST) and by immunoassay, while a positive ASST correlates with CU exacerbation[22]. The role of *H. pylori* infection in CU is still a matter of debate, although the association between CU and H. pylori has been found by some research groups[23-28].

The pathogenetic mechanisms by which *H. pylori* may induce urticaria are far from being clear and several hypotheses have been developed regarding the link with the bacteria and CU. The immunomodulatory role of *H. Pylori* infection in CU is a subject of intensive studies. For instance, IgG and IgA antibodies to 19-kDa *H. pylori*-associated lipoprotein was found to play a role in the pathogenesis of CU[29]. When IgA-, IgG-, and IgE- mediated immune responses against *H.pylori* antigens were analyzed, some bacterial immunoresponsive proteins were identified in cases of CU[30]. Moreover, *H.pylori* is causing excessive consumption of complement by specific antibodies produced against the bacterium, contributing to the pathogenesis of CU[31]. Generally, different strains of *H. pylori* may elicit different pathogenic responses[32]. In some cases specific IgE antibodies to *H. pylori* antigens have been described, both in active CU[33] and in complete remission after *H. pylori* eradication[34]. Significantly increased gastric juice eosinophil cationic protein (ECP) and gastric eosinophil infiltration were described in *H. pylori* infected CU patients[35]. Furthermore, *H. pylori* eradication results in a significant decrease in gastric juice ECP and gastric eosinophil infiltration only in CU patients[36]. CU is associated with a systemic in-

flammatory response, whereas the acute-phase response is manifested by increased circulating IL-6, which varies along with C-reactive protein changes and may be related to the urticarial activity[23].

The best evidence of *H. pylori* comes from studies investigating CU in which CU clinically improved in many patients with *H.pylori* infection after its eradication[24,37,38]. We recently observed that *H. pylori* eradication in CU patients, who are resistant to antihistamine medications, reduces clinical severity of CU through attenuation of low grade systemic inflammation[39].

Several studies evaluated a possible relationship between endoscopic gastrointestinal findings and CU using gastroduodenoscopy. In most patients with CU and *H. pylori* infection, endoscopic evaluation showed mostly mild to moderate gastric inflammation, but very few cases of gastric or duodenal ulcers were identified[29,35].

Recently, we described several cases of CU triggered by eradication of *H. pylori*[40]. Perhaps the systemic effects of the pathogen's eradication involve some kind of immunomodulation activating autoimmune mechanisms of CU[40].

Consequently, the recent critical appraisal of the 10 trials, utilizing the Grading of Recommendations Assessment, Development, and Evaluation approach, showed that the benefit of *H. pylori* eradication in patients with CU is weak and conflicting[41]. For this reason, a decision to proceed with this management should be considered carefully in the context of relative harms/burdens and benefits, as well as patient values and preferences[41].

H. pylori and psoriasis

Psoriasis is an autoimmune disease which affects 1%-3% of population[42]. Latest immunological studies have increased our understanding of the pathogenesis of psoriasis. Recently, it has been suggested that of *H. pylori* infection might be a triggering factor in psoriasis[43,44]. *H. pylori* infections were considerably more common in psoriasis patients than in healthy controls[43,45]. Several investigators reported cases in which psoriatic lesions cleared up following the eradication of *H. pylori* infections[45-47]. Further clinical and basic studies are needed to confirm this association and its pathophysiological mechanisms.

H. pylori and scleroderma

Over the last 20 years increasing evidence has accumulated to implicate infectious agents in the etiology of systemic sclerosis (SSc). The most recent research on the involvement of bacterial infections in the pathogenesis of SSc focuses *H. pylori*[48,49]. Several studies reported higher prevalence of *H. Pylori* infection in patients with SSc, than in healthy[50-51]. Moreover, most of the patients in these studies were infected with CagA strain of *H. pylori* as compared to infected controls. *H. pylori* infection was also associated with higher SSc activity[52]. At this time it is unclear, whether *H. pylori* eradication can improve the disease activity and skin involvement in SSc patients.

Other studies focused on a role of *H. pylori* infection in the development of Raynaud's phenomenon and Sjögren syndrome in SSc. At least, in primary Raynaud's phenomenon, eradication of *H. pylori* infection was associated with complete remission in some and with a reduction in symptoms in most of the treated patients[53,54].

Kalabay *et al*[55] explained the pathophysiologic association of *H. pylori* infection in SSc by the disturbed gastrointestinal motility in patients with SSc and *H. pylori* induced immune dysregulation, aggravating the course of SSc. Additional studies are necessary to elucidate the pathogenesis and confirm the association between *H. pylori* and SSc.

H. pylori and alopecia areata

Alopecia areata (AA) is an autoimmune T-cell mediated disease directed against the hair follicle, with an estimated lifetime risk of 1.7% among the general population[56]. While one group of investigators found higher prevalence of *H. pylori* infection in patients with AA[57], other studies failed to confirm this association[58,59]. However, recently a case of a 43-year-old man with an 8-mo history of AA of the scalp and beard and concomitant *H. pylori* infection was presented, with complete remission from AA after *H. pylori* eradication[60].

Further controlled trials are necessary to investigate the association between AA and *H. pylori* infection.

H. pylori and vasculitis

There is some evidence of an association of *H. pylori* infection with various vasculitides.

Behçet's disease (BD) is a multisystem inflammatory disorder characterized by recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions. The etiology of BD remains unknown, but epidemiologic findings suggest that an autoimmune process is triggered by an infectious or environmental agent in a genetically predisposed individual[61,62]. As for the most other autoimmune disorders, the Th1-type polarization is significant in BD[62] with increased numbers of activated γδ T lymphocytes[63].

A genetic susceptibility for both BD and *H. pylori* infection has been implicated by the fact that *H. pylori* infection is endemic in most of the countries in which BD is also highly prevalent[64].

While the prevalence of *H. pylori* IgG seropositivity was not significantly higher in the patients with BD compared to the controls, an eradication of *H. pylori* significantly decreased clinical manifestations of BD, such as oral, genital ulcerations and cutaneous lesions[65]. Other studies did not find differences in upper gastrointestinal endoscopy findings, prevalence and eradication rates of *H. pylori* between BD and control groups[66]. More trials are necessary to check the association between *H. pylori* and BD.

Schoenlein-Henoch purpura (SHP) is a leukocytoclastic vasculitis of small vessels and is characterized by IgA deposition in the affected tissues[67]. SHP is the most common vasculitic disorder affecting children, but is less common in adults[68]. Since 1995, when Reinauer *et al*[69]

first described the case of SHP and *H. pylori* positive gastritis; where after *H. pylori* eradication therapy, the clinical manifestations of SHP were resolved, several analogous case reports have been described[70-74]. In general, the relationship of *H. pylori* infection and SHP may be underestimated. Randomised controlled trials are necessary to confirm a relationship between *H. pylori* and SHP and to evaluate the usefulness of *H. pylori* eradication therapy in SHP.

H. pylori and autoimmune bullous diseases

Autoimmune bullous diseases (AIBD) are a heterogeneous group of disorders, which includes pemphigus, pemphigoid, epidermolysis bullosa acquisita, dermatitis herpetiformis, linear immunoglobulin A disease, and multiple autoimmune syndrome[75]. AIBD are characterized with a genetic predisposition, which promotes the production of auto-antibodies targeted against different components of the epidermal desmosome and hemidesmosome[76]. There are no published studies investigating the association between AIBD and *H. pylori*, though a contributing role of this pathogen in inducing bullous pemphigoid has been suggested by some authors[77]. Recently, Matsuo *et al*[78] reported on the remission of sublamina densa-type linear IgA bullous dermatosis after *H. pylori* eradication.

In a study looking at serological evidence of various infectious agents in patients with AIBD (Pemphigus and bullous pemphigoid), *H. pylori* IgG antibodies were reported to be more common in patients as compared to controls[79]. Clinical trials are necessary to confirm preliminary observations.

CONCLUSION

Autoimmune skin diseases are characterized by dysregulation of the immune system resulting in a loss of tolerance to skin self-antigen(s). The prolonged interaction between the bacterium and host immune mechanisms make *H. pylori* a plausible infectious agent for triggering autoimmunity. *H. pylori* antigens were found to activate cross-reactive T cells and induce autoantibodies production. Moreover, microbial heat shock proteins (HSP) play an important role of in the pathogenesis of autoimmune diseases because of the high level of sequence homology with human HSP.

Eradication of *H. pylori* infection has been shown to be effective in some patients with chronic autoimmune urticaria, psoriasis, alopecia areata and Schoenlein-Henoch purpura. There is conflicting and controversial data regarding the association of *H. pylori* infection with BD, scleroderma and autoimmune bullous diseases. No data are available evaluating the association of *H. pylori* infection with other skin autoimmune diseases, such as vitiligo, cutaneous lupus erythematosus and dermatomyositis. Epidemiological and clinical studies are necessary to investigate the association between *H. pylori* and these diseases.

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