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ORIGINAL RESEARCH

Immune Cell Crisis and Excess Histopathological Features During the Development and Progression of *H. pylori* Infection in the Gastric Mucosa

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Objective: To investigate immune cell crisis and excess histopathological features during the development and progression of *H. pylori* infection in the gastric mucosa.

Methods: One thousand two hundred and seventy-six cases of *H. pylori* infection were examined by endoscopic biopsy and endoscopic submucosal dissection (ESD) resection. The relationship between epithelial cells and immune cells and the pathological features of immune cell dysfunction and excess tissue were observed. The 1276 cases of mucosal biopsy of *H. pylori* infection and ESD resection were included. Among them, 39 were ESD excision and 1237 were gastric mucosal biopsy specimens. Among them, there were 896 cases of antrum infection, 274 cases of stomach body infection, and 106 cases of infection in antrum and body of stomach. Three to five pieces of mucosal tissue were extracted from each site. There were 789 males (61.8%) and 454 females (35.6%). There were 724 cases (56.7%) with age ≤60 and 552 cases (43.3%) with age >60.

Results: During the occurrence and development of *H. pylori* infection, there were not only spider-like vacuolar degeneration of surface epithelial cells, compensatory cervical mucous cell proliferation, proliferation disorder of stem cells in proliferating areas, and neoplastic proliferation of gastric mucosal epithelial cells, but also morphological changes of immune cells in the process of occurrence and development of *H. pylori* infection. First, neutrophils that rapidly respond and attack the infection; however, neutrophils quickly display functional deficiencies, forming mucosal erosion and micro-abscesses. Then, it enters a phase of immune cell crisis. The immune defense is adjusted. The rapid proliferation of lymphocytes leads to the formation of lymphocyte immunity and the formation of lymphocyte follicle-like structures. In this stage, the lesions are wide and deep, the duration is long, and the number of patients is large. Persistent *H. pylori infection* can result in abnormal proliferation and transformation of gastric mucosal epithelial cells and immune cells and gastric adenocarcinoma and MALT lymphoma.

Conclusion: Understanding the immune cell crisis and excess histopathological features during the occurrence and development of *H. pylori* infection is important for controlling the occurrence and development of gastric cancer and lymphoid system tumors via immune intervention.

Keywords: *Helicobacter pylori*, epithelial cells, immune cells, immunohistochemistry

Introduction

For a long time, the stomach was thought to be sterile because of the acid barrier. In 1983, Marshall and Warren discovered a spiral-shaped gram's vagina, *Helicobacter pylori* (*H. pylori*), which revolutionized the idea that the stomach was sterile.[1] The study found that this ancient pathogen has coevolved with humans for more than 60,000 years.[2] More

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than half of the world's population is infected with *H. pylori*, most of which are asymptomatic infections, and about 10% develop peptic ulcers, atrophic gastritis, gastric cancer, and MALT lymphoma.[3–6] The reason why *H. pylori* produces different symptoms after infecting the body is still unclear. More and more studies show that *H. pylori* strain, host, environment, and other factors jointly determine the occurrence and development of the disease.[7] Gastric flora, as an important part of the gastric microecological environment, maintains the balance of the gastric environment through various regulatory pathways. Once the structure of the flora changes, this balance is bound to be broken, which will lead to the production of diseases.[8] The World Health Organization has classified *H. pylori* infection as a carcinogen of gastric cancer, and it has become a trend to eliminate *H. pylori* through detection and treatment to prevent gastric cancer.[9–11] Our previous studies have found that *H. pylori* infection of gastric mucosa leads to disordered proliferation, with excess upward migration and insufficient downward migration, resulting in extensive segmental proliferation and atrophy of gastric mucosa, which is called the wave diagram of *H. pylori* infection proliferation and atrophy.[12] At the same time, our previous studies also proposed the histopathological stages and morphological characteristics of *H. pylori* infection.[13,14] However, the response of gastric mucosal immune cells to tumor cells mainly depends on their unique metabolic pathways, which are related to the type and function of immune cells.[15] However, it is not clear how immune cells compete when the gastric mucosa is infected by *H. pylori*. Therefore, in this study, endoscopic biopsy and ESD excised specimens of 1276 cases of *H. pylori* infection were collected. The immune cell crisis and excess histopathological features were investigated during the occurrence and development of *H. pylori* infection in gastric mucosa. Our study may be conducive to the precise treatment of *H. pylori* infection by clinicians and has important significance for controlling the occurrence and development of gastric cancer and lymphatic system tumors via immune intervention.

Materials and Methods

Materials

A total of 1276 cases of *H. pylori infection* were collected from June 2020 to June 2022. The histopathological diagnosis of *H. pylori* infection was performed by gastroscopic biopsy. Among them, 39 were ESD excisions and 1237 were gastric mucosal biopsy specimens. There were 896 cases in the antrum, 274 cases in the body of the stomach, and 106 cases of infection in the antrum and body of the stomach. About 3–5 pieces of mucosal tissue were extracted from each site. These cases were from the Fourth People's Hospital of Longgang District, Shenzhen Hospital of Peking University, Shenzhen Central Hospital of Bao'an District, Shenzhen Hospital of Southern Medical University, and The 990th Hospital of the Joint Logistics Support Force of the People's Liberation Army.

Methods

The specimens were fixed with freshly prepared 10% neutral buffered formalin solution (NBF) for 8h. And they were dehydrated, paraffin-embedded, sliced 4μm thick, stained by HE, and the tissue structure and cell morphology were observed by optical microscope. Furthermore, immunohistochemical and genetic tests were performed.

Immunohistochemical Staining

The En Vision two-step method is adopted. The paraffin from tissue sections was removed, and the tissue sections were hydrated and rinsed with distilled water. The sections are then placed in TBS for 10 minutes. Endogenous peroxidase was blocked with 3% hydrogen peroxide (H_2O_2) for another 25 minutes, then the sections were treated with TBS for 10 minutes. Each antibody (Hp, MUC5AC, CD3, CD20, ki-67; Roche Diagnostics (Shanghai) Ltd) was incubated with the sections at room temperature for 30 minutes. After washing in TBS for 10 minutes, the sections were incubated in EnVision. EnVision method is also called ELPS (enhance labeled polymer system) method. After the antigen–antibody reaction is bound, the second antibody is labeled with a polymeric compound (glucan) enzyme complex (EnVision complex), which binds to the first antibody and is then colored by the enzyme substrate. After another 10 minutes of washing in TBS, the sections were incubated for HRP type coagulated second antibody (Roche Diagnostics (Shanghai) Ltd) for 10 minutes. The sections were incubated with a colored substrate solution for 10 minutes and then rinsed with distilled water. The intensity was enhanced by DAB and redyed with hematoxylin. The gastric mucosa sections were

used as positive controls, while PBS buffers were used as negative controls to replace primary antibodies. The primary antibody (clone number: HpMX014) and working solution, as well as other related immunohistochemical reagents, are purchased from Roche Diagnostics (Shanghai) Ltd. The operation procedures follow the manufacturing instructions.

FISH Detection

Detection: t (11; 18) (q21; q21); t (1; 14) (p22; q32); t (3; 14) (p14; q32); t (14:18) (q32: q21).

Some cases were performed for the detection of MYC, BCL-2, and BCL-6. FISH procedures are carried out according to reported references[16–18] and regent instructions.

Statistical Analysis

SPSS22.0 statistical software was used for statistical analysis. The chi-square test was used for gender and age statistics, and the value of $P<0.05$ was considered statistically significant.

Result

Clinical Features

There were 789 cases (61.8%) of *H. pylori* infection in males and 487 cases (38.2%) in females. The incidence of Hp infection was 724 cases (56.7%) with age ≤60 and 552 cases (43.3%) with age >60, and the incidence of *H. pylori* infection was higher with age ≤60 than that with age >60, as shown in Table 1.

The Histomorphologic Changes the Relationship of Glandular Epithelial Cells and Immune Cells During the Occurrence and Development of H. pylori Infection

According to the histopathological features of gastric mucosal injury caused by *H. pylori* infection, as well as the degree and depth of gastric mucosal injury, it can be divided into 5 stages: Gastric mucosal surface epithelium covering mucous layer *H. pylori* infection stage; *H. pylori* infection stage of gastric mucosal surface epithelial cells; Stage of compensatory proliferation of *H. pylori* infected cervical mucous cells; *H. pylori* infectious lamina propria disease stage; *H. pylori* infectious abnormal proliferation and transformation stage. The histomorphologic characteristics of glandular epithelial cells and immune cells at each stage are shown in Figure 1.

Table 1 Relationship Between Age and Sex in the Occurrence and Development of *H. pylori* Infection

Type and stage	N (%)	Sex	Age
		Male (%), Female (%)	≤60 (%) >60 (%)
Gastric mucosal surface epithelium covering mucous layer *H. pylori* infection stage	18 (1.4)	11(61.1), 7(38.9)	10(55.6), 8(44.4)
Gastric mucosal surface epithelial cells *H. pylori* infection stage	124 (9.7)	78(62.9), 46(37.1)	73(58.9), 51(41.2)
H. pylori infectious compensatory cervical mucous cell proliferative stage	297 (23.3)	122(61.6), 76(38.7)	168(56.6), 129(43.4)
H. pylori infectious lamina propria lesion stage	576 (45.1)	353(61.3), 223(38.9)	329(57.1), 247(42.9)
H. pylori infectious abnormal proliferation and transformation stage	142 (11.1)	86(60.6), 56(39.2)	78(54.9), 64(45.1)
Low grade of *H. pylori* infectious intraepithelial neoplasia	78 (6.1)	47(60.3), 31(39.4)	43(55.1), 35(44.9)
High-grade intraepithelial neoplasia of *H. pylori* infection	36 (2.8)	22(61.1), 14 (38.9)	19(52.8), 17(47.2)
MALT lymphoma	4 (0.3)	3(75.0), 1(25.0)	3(75.0), 1(25.0)
Metastatic highly aggressive lymphoma	1 (0.1)	1(100.0), 0 (0)	1(100.0), 0(0.0)

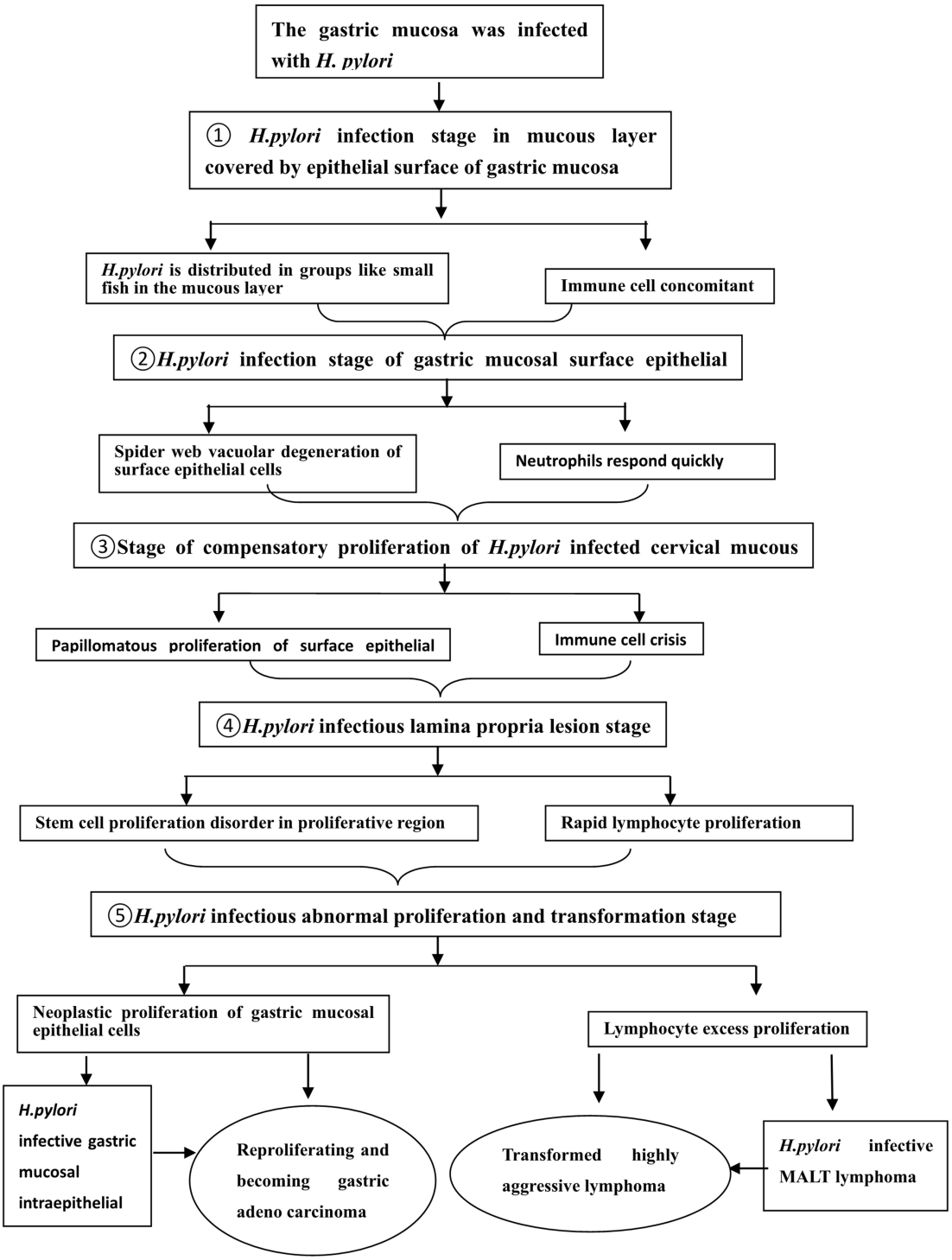

Figure 1 Flow draw. Immune cell crisis and excess during the development of *H. pylori* infection in gastric mucosa.

Histopathologic Characteristics of Glandular Epithelial Cells and Immune Cells During the Development and Progression of H. pylori Infection

Epithelial surface of gastric mucosa covered by mucous layer *H. pylori* infection stage: *H. pylori infection* begins mainly in the mucous layer covered by the epithelial surface of the gastric mucosa, also named as *H. pylori e*arly infection. The

surface covered by a mucous layer is the living environment of *H. pylori*, which is distributed in groups like small fish (Figure 2a). A few neutrophils were seen in the mucous layer (Figure 2b). Hp was positively expressed (Figure 2c).

H. pylori infection stage of gastric mucosal surface epithelial cells: *H. pylori* specifically and selectively adhered to the surface mucous cytoplasm and destroyed the cytoplasm of gastric surface epithelial cells. The cytoplasm presented spiderweb-like vacuolar degeneration, and finally, the cytoplasm was destroyed or left bare nucleus (Figure 3a). A small number of neutrophils, eosinophils, and lymphocytes infiltrated the superficial layer of lamina propria (Figure 3b). Hp was positively expressed (Figure 3c). Gastric mucosa *H. pylori* infectious compensatory cervical mucous cell proliferation stage: The destruction of surface epithelial cells accelerates the proliferation of stem cells in the deep stomach fovea to replenish surface epithelial cells. Therefore, upward migration was accelerated, resulting in compensatory proliferation of proliferating stem cells (Figure 4a). Lymphocytes, plasma cells, monocytes, macrophages, neutrophils, eosinophils, and almost all immune cells appeared in the superficial layer of lamina propria (Figure 4b). Hp was positively expressed (Figure 4c). Stages of *H. pylori* infection lamina propria lesion: Excessive upward migration and insufficient downward proliferation of proliferative regions resulted in disorders of stem cell proliferation (Figure 5a). This mainly results in the infiltration of a large number of lymphocytes, and the formation of lymphoid follicle-like structures (Figure 5b). Hp was positively expressed (Figure 5c). Abnormal proliferation and transformation stage of *H. pylori* infection: The abnormal proliferation and transformation of one or more gastric units occurred in the deep area of the gastric mucosa fovea, which was mainly located at the intersection of the fovea and the gastric gland, and showed transverse proliferation on the left and right sides. The glandular epithelial cells are arranged irregularly, with large nuclei, increased nucleo–plasma ratio, and enlarged and distinct nucleolus (Figure 6a). The proliferation of lymphatic follicles was prominent, the volume of lymphatic follicles increased, and cells proliferated in the marginal area outside the mantle area (Figure 6b). Hp was positively expressed (Figure 6c). Stages of *H. pylori* infectious intraepithelial neoplasia: *H. pylori* infectious intraepithelial neoplasia stage: Abnormal proliferation and transformation cells form tubular or branching structures, occupying almost the entire layer of the gastric mucosa (Figure 7a). The epidemic cells are still characterized by massive proliferation of lymphocytes (Figure 7b). The number of ki67 positive cells accounted for

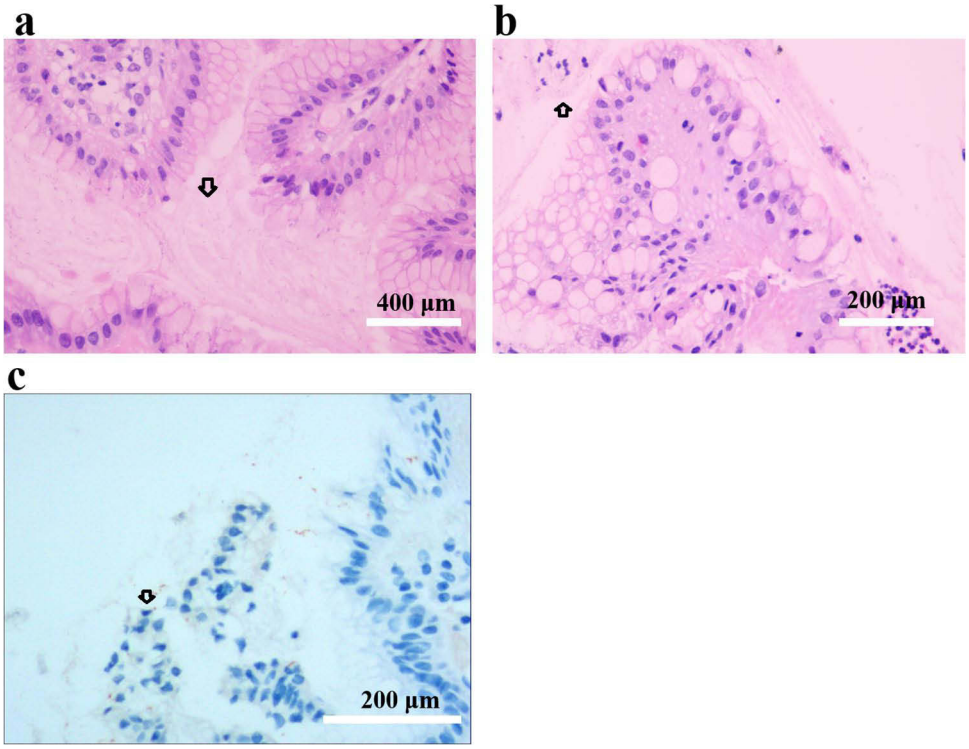

Figure 2 The epithelial surface of the gastric covered by mucosa mucous layer during *H. pylori* infection. (**a**) As shown by the arrows, the surface covered by mucous layer is the living environment of *H. pylori*, which is distributed in groups like small fish. (**b**) As shown by the arrows, few neutrophils were seen at this stage. (**c**) As shown by the arrows, Hp positive expression detected by En Vision method.

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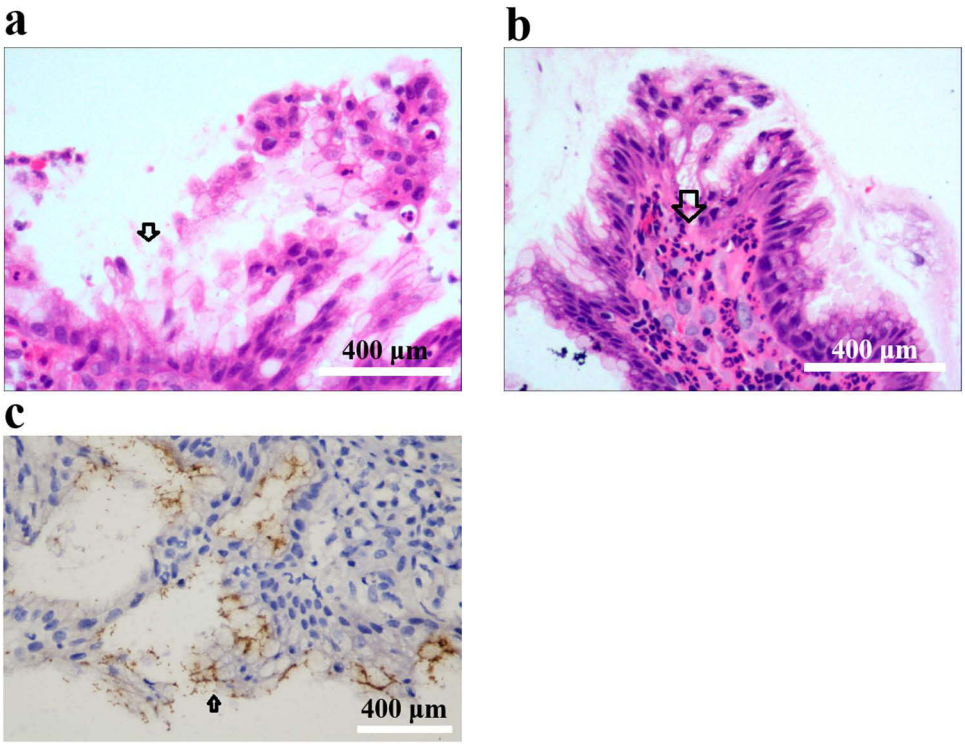

Figure 3 *H. pylori* infection stage of gastric mucosal surface epithelial cells: (**a**) As shown by the arrows, *H. pylori* adhered to the cytoplasm of surface mucous cells and selectively destroyed the cytoplasm of surface mucous cells. The cytoplasm of surface epithelial cells showed spiderweb-like vacuolar degeneration, and the cytoplasm was damaged. (**b**) As shown by the arrows, the superficial layer of lamina propria has an immune response, mainly neutrophil infiltration, and some eosinophils, forming microabscesses. (**c**) As shown by the arrows, Hp positive expression detected by En Vision method.

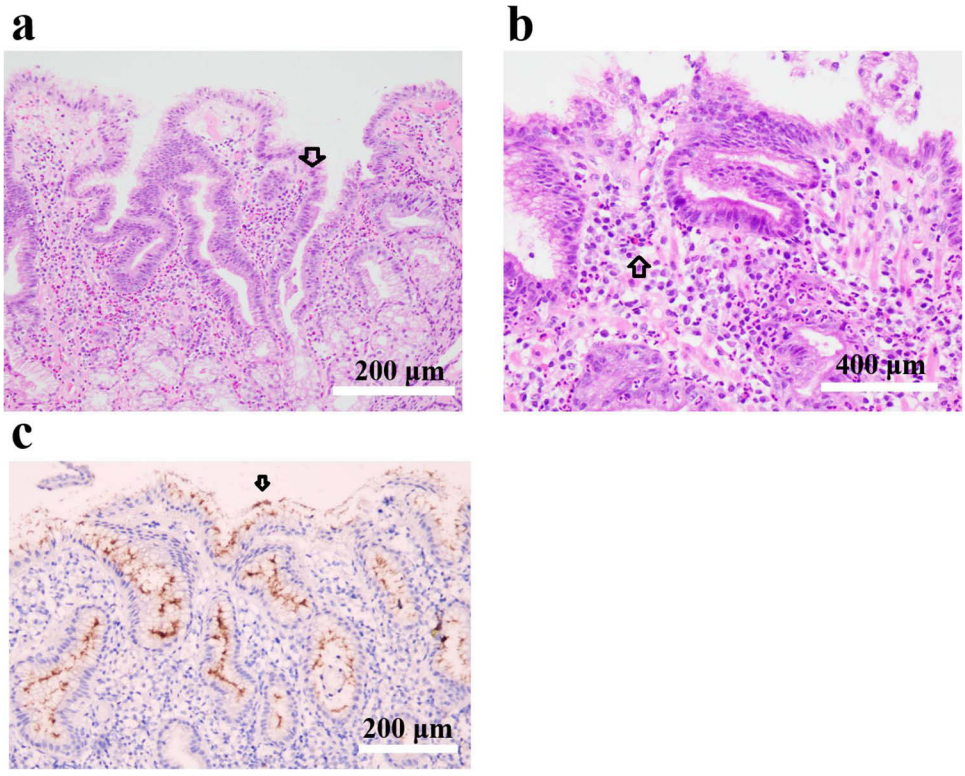

Figure 4 The compensatory proliferation of cervical mucous cells in *H. pylori* infection. (**a**) As shown by the arrows, compensatory cervical mucous cell proliferation, the nucleus becomes longer, and slightly heterotypic, nuclear chromatin increases, and small nucleolus can be observed in about 20% to 30% nucleus. (**b**) As shown by the arrows, lymphocytes, plasma cells, monocytes, macrophages, neutrophils, eosinophils, and almost all immune cells appeared in the superficial layer of lamina propria. (**c**) As shown by the arrows, Hp positive expression detected by En Vision method.

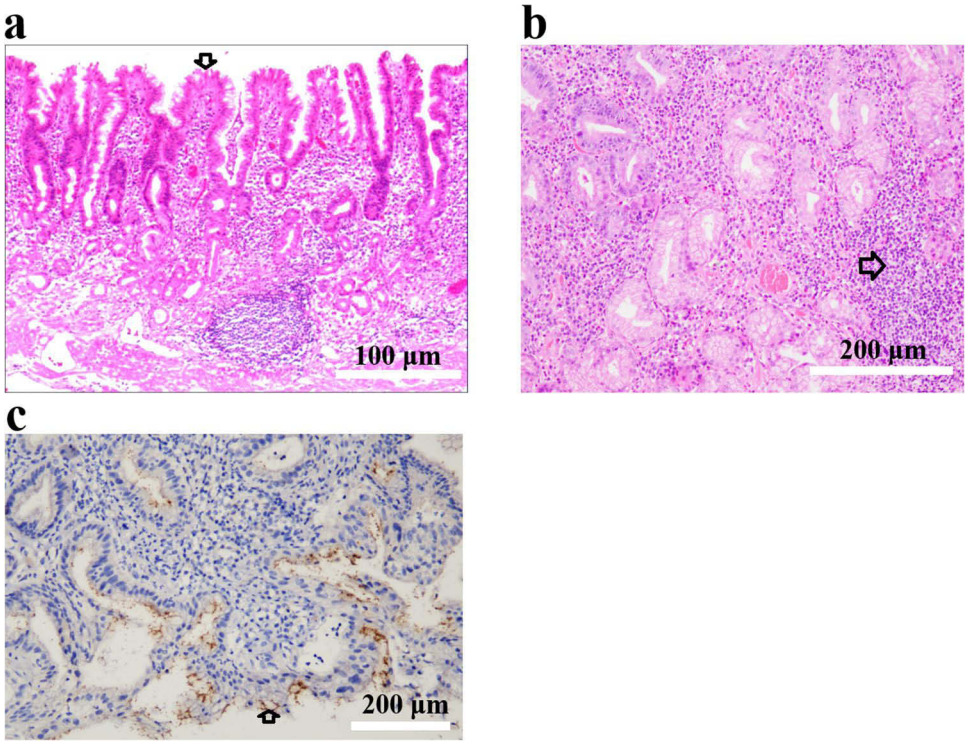

Figure 5 Lamina propria disease stage of *H. pylori* infection. (**a**) As shown by the arrows, upward migration of excess and compensatory proliferation of surface epithelial cells resulting in papillomatous hyperplasia. (**b**) As shown by the arrows, the infiltration of a large number of lymphocytes and the formation of follicle-like structures. (**c**) As shown by the arrows, Hp positive expression detected by En Vision method.

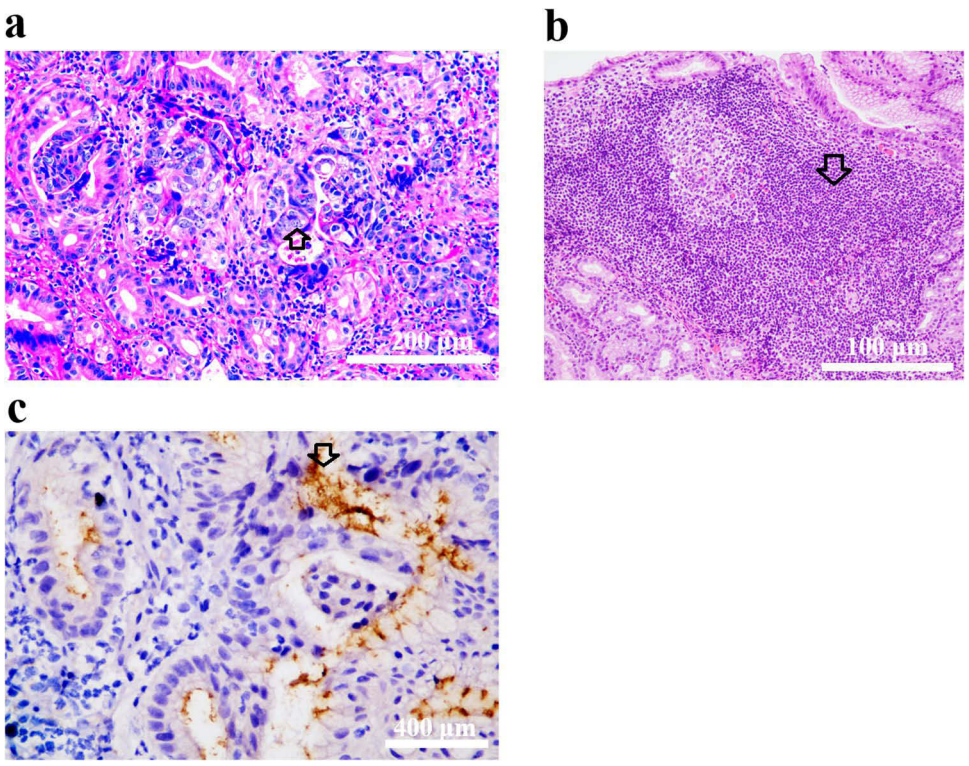

Figure 6 Abnormal proliferation and transformation of *H. pylori* infection. (**a**) As shown by the arrows, transformation of abnormal proliferation of multiple glandular ducts, large nuclei, increased nucleo–plasma ratio, and visibly enlarged nucleolus. (**b**) As shown by the arrows, the proliferation of lymphatic follicles was prominent, the volume of lymphatic follicles increased, and the cells in the marginal area outside the mantle area proliferated. (**c**) As shown by the arrows, Hp positive expression detected by En Vision method.

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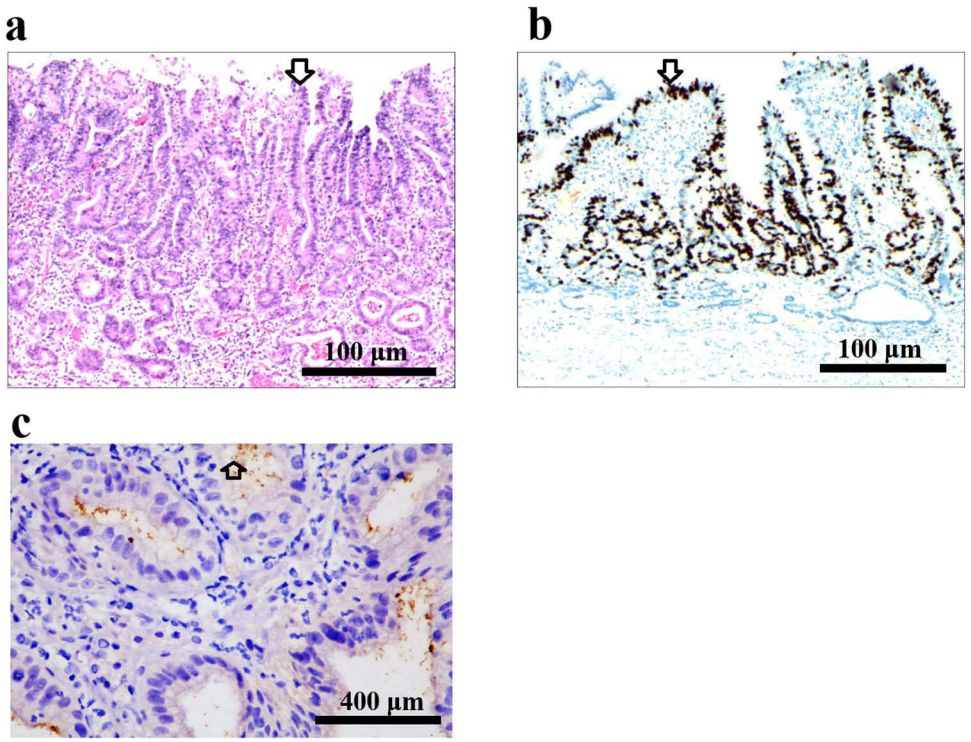

Figure 7 Stages of *H. pylori* infectious intraepithelial neoplasia. (**a**) As shown by the arrows, abnormal proliferation and transformation cells increased in number, expanded in area, and formed tubular or branching structures, occupying almost the whole layer of the gastric mucosa. (**b**). As shown by the arrows, ki67 positive cells accounted for 60%, which is detected by the En Vision method. (**c**). As shown by the arrows, Hp positive expression detected by En Vision method.

60% (Figure 7c). *H. pylori* infectious MALT lymphoma: Proliferating lymphocytes were distributed in multifocal lumps outside the intact mantle area and gradually spread to the interfollicular area to form diffuse proliferation (Figure 8a). The characteristics of immune cells showed abnormal proliferation and transformation (Figure 8b). Hp was positively expressed (Figure 8c). The diagnostic criteria for each stage are shown in Table 2.

Discussion

During the occurrence and development of *H. pylori* infection, in addition to spider-like vacuolar degeneration of surface epithelial cells, compensatory cervical mucous cell proliferation, proliferation disorder of stem cells in proliferating areas, and neoplastic proliferation of gastric mucosal epithelial cells, we proposed for the first time the morphological changes of immune cell invasion during the occurrence and progression of *H. pylori* infection. From early neutrophil concomitant, rapid neutrophil counterattack, neutrophil collapse, to the immune cell crisis period, the adjustment of immune defense, and then into the rapid proliferation of lymphocytes, it forms lymphocytic immunity. When a persistent *H. pylori* infection occurs, it can lead to abnormal proliferation and transformation of immune cells and the occurrence of MALT lymphoma. This study is of great significance for immunological intervention of the occurrence and controlling the development of gastric cancer and lymphatic system tumors.

Gastric surface mucous cells (gastric surface epithelial cells) secrete insoluble mucous containing a high concentration of bicarbonate, which covers the epithelial surface and plays an important protective role. Gastric mucosa self-protection mechanism: Gastric juice contains concentrated hydrochloric acid with strong corrosion, pepsin, and other proteins with the function of decomposition, while gastric mucosa is resistant to corrosion, mainly due to the presence of a mucus-bicarbonate barrier on its surface. The mucous layer covering the surface of gastric epithelium is 0.25–0.5 mm thick, which is mainly composed of insoluble mucous gel and contains bicarbonate. The mucus layer isolates the epithelium from pepsin, and the high concentration of bicarbonate makes the local pH = 7, which not only inhibits the activity of the enzyme but also neutralizes the infiltrated H+ to form carbonic acid (H_2CO_3). The latter is rapidly degraded into water (H_2O) and carbon dioxide (CO_2) by the carbonic anhydrase of gastric epithelial cells.[19,20] In

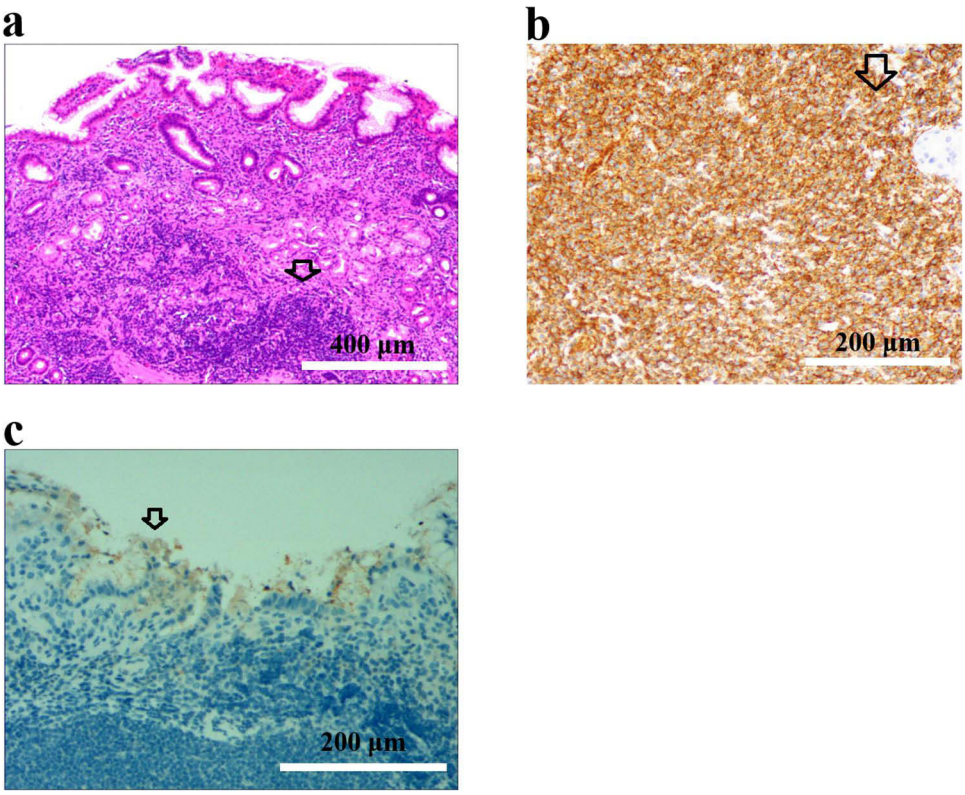

Figure 8 Gastric mucosa Hp infected MALT lymphoma. (**a**). As shown by the arrows, the proliferating lymphocytes were distributed in the marginal area outside the intact mantle area in multifocal lumpy distribution and gradually spread to the interfollicular area to form diffuse proliferation. (**b**). As shown by the arrows, the expression of CD20 is positive, which is detected by the En Vision method. (**c**). As shown by the arrows, Hp positive expression detected by En Vision method.

addition, the rapid renewal of gastric epithelial cells also enables the stomach to repair the damage in time. Normally, the amount of gastric acid secreted is in balance with the mucus-bicarbonate barrier. Alcohol, aspirin, *H. pylori* infection, and other factors can lead to excessive secretion of gastric acid or reduced mucus production, damage the barrier, and cause self-digestion of stomach tissues, resulting in gastritis or gastric ulcer.[21,22] In this study, it was found that the mucous layer covered by the surface of gastric mucosa was the adaptive environment for the survival of *H. pylori*. Especially in some areas where the mucous was increased, a large number of *H. pylori* were distributed in small fish-like groups in the mucous, which may also be the early stage of *H. pylori* infection. It is still unclear whether *H. pylori* can reside in the

Table 2 Histopathological Features of Glandular Epithelial Cells and Immune Cells During the Occurrence and Progression of *H. pylori* Infection

Stages	Characteristics of Glandular Epithelial Cells	Characteristics of Immune Cell
***H. pylori* infection stage of gastric mucosal surface epithelium covering mucous layer**	The beginning of *H. pylori* infection is colonized in the mucous layer covered by the epithelial surface of the gastric mucosa, also known as the initial stage of *H. pylori* infection. *H. pylori* is a spiral-shaped, flagellate, slightly aerobic gram-negative bacterium with a length of 2.5–4.0 μm and a width of 0.5–1.0 μm. It can be easily identified in HE stained sections. The mucous layer covered by the surface was adapted to the survival of *H. pylori* and distributed in groups like small fish.	No immune cells in the mucous layer, but a small number of neutrophils were observed when *H. pylori* is infected.

(*Continued*)

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Table 2 (Continued).

Stages	Characteristics of Glandular Epithelial Cells	Characteristics of Immune Cell
***H. pylori* infection stage of gastric mucosal surface epithelial cells**	*H. pylori* specifically and selectively adhered to the surface mucous cytoplasm and destroyed the cytoplasm of gastric surface epithelial cells. Histomorphology showed that the cytoplasm of the epithelial cells on the surface of the stomach was destroyed to different degrees, showing characteristic spiderweb-like vacuolar degeneration. Some leave only the bare nucleus and have separated from the tissue.	A small immune response begins in the superficial layer of the lamina propria. Mainly neutrophil infiltrates, and some eosinophils, with fewer lymphocytes. Histologically, mucosal erosion and microabscess were observed, namely neutrophil rapid attack.
***H. pylori* infectious compensatory cervical mucous cell proliferative stage**	Because the destruction of surface epithelial cells accelerates the proliferation of stem cells in the deep area of the stomach fovea, the surface epithelial cells are supplemented, and the compensatory proliferation of stem cells in the proliferative area is formed. At this stage, the compensatory proliferative cells are mainly cervical mucous cells, and gradually transition to surface mucous cells. This compensatory cervical mucous cell proliferation may have a small amount of *H. pylori*. Compensatory cervical mucous cell proliferation is cytologically characterized by elongated nuclei, slight atypia, increased nuclear chromatin, small nucleolus in about 20% to 30% of the nuclei, and 2 to 5 mitotic results/HPF. Reactive or compensatory hyperplasia is a benign hyperplasia that is not included in precancerous lesions.	Due to the mass death of a large number of neutrophils, lymphocytes, plasma cells, monocytes, macrophages, as well as neutrophils and eosinophils, almost all immune cells appeared in the superficial layer of lamina propria. At the same time, some immune cells showed vacuole-like degeneration, forming blocky and fuzzy basophilic cloud-like shape. This phase is called immune cell crisis.

mucous layer covered by the surface of gastric mucosa for a long time.[23] It has been reported that *H. pylori* is acquired in childhood, and once infected and untreated, people will carry this bacteria for decades or even a lifetime.[24] It has also been found that *H. pylori* infection can induce an adaptive response, which can increase the survival and proliferation of epithelial cells and reduce the renewal of most infected epithelial cells.[25] In this study, it was found that *H. pylori* specifically and selectively adhered to the surface mucous cytoplasm and destroyed the cytoplasm of gastric surface epithelial cells. When the cytoplasm of the epithelial cells on the surface of the stomach was destroyed, the morphology of the spiderweb-like vacuolar degeneration was formed, and some only left bare nuclei. In this study, this period was called *H. pylori* infection of gastric mucosal surface epithelial cells.

Normally, the cervical mucus cells of the gastric mucosa are few, located on the top of the fundus gland, and often wedged between other cells. They are derived from neck stem cells with active nuclear division, and the main function of mucous neck cells is mucosal proliferation and regeneration. The cervical mucous cells are continuous and similar to the small concave epithelium. The cells are columnar, but irregular in shape, with fewer mucous particles in the cytoplasm. The nucleus is flat, located at the base of the cell matrix, and there are many mucogen particles above the nucleus, and its secretion is soluble acidic mucus. It can produce acidic glycoprotein, which is different from the neutral mucus secreted by the concave epithelium.[26,27] The histomorphology in this study showed that when the surface epithelial cells were damaged during *H. pylori* infection, stem cells proliferated in the deep stomach fovea to supplement the surface epithelial cells, forming compensatory proliferation of stem cells in the proliferative region. It is mainly the cervical mucous cells that gradually accelerate the transition proliferation to the distribution area of the surface mucous cells, forming a wide proliferation area. In cytology, mitosis is active, increasing in cell size and number. The feature of compensatory hyperplasia in this period is physiological hyperplasia, which is reversible and is called repair hyperplasia change.

This means that after aggressive drug treatment for the eradication of *H. pylori* infection, it is complete recovery. The immune cells in this period are characterized by the mass death of a large number of neutrophils, followed by the appearance of lymphocytes, plasma cells, monocytes, macrophages, as well as neutrophils and eosinophils in the superficial layer of the lamina. This is called an immune cell crisis.

After *H. pylori* infection, the stomach body and gastric antrum are prone to atrophy of gastric mucosa and intestinal metaplasia.[28,29] Especially when *H. pylori* infection cannot be controlled or eradicated in time, there is a deep area of stomach fovea. The proliferation of cells in the isthmus of the gastric gland and the upper part of the glandular neck led to excessive upward migration and insufficient downward proliferation of the proliferating regions, resulting in the proliferation of stem cells. The compensatory proliferation of surface epithelial cells results in the formation of papillary or adenomatous hyperplasia; insufficient downward proliferation results in atrophy of the fundus/pyloric gland.[30] Our previous studies also found that *H. pylori* infectious lamina propria lesions of a large number of patients had with wide range of depth and long duration, and were not easy to eradicate during drug treatment.[12] This study also found that the characteristics of immune cells at the stage of *H. pylori* infection lamina propria lesions were as follows: due to the wide range, depth, and long duration of the lesions at this stage, immune cells made defensive adjustments and formed an immune defense dominated by lymphocytes. It is mainly the infiltration of a large number of lymphocytes and the formation of lymphoid follicle-like structures. There are some plasma cells, monocytes, macrophages, and so on. This is called lymphocytic immunity or rapid lymphocyte proliferation.

Gastric cancer is the third leading cause of cancer death in the world, and *H. pylori* infection is associated with most cases of gastric adenocarcinoma and the vast majority of non-cardiac gastric adenocarcinoma.[31,32] The best way to prevent gastric cancer or reduce the incidence of gastric cancer is to eradicate *H. pylori* infection of gastric mucosa.[33,34] Our previous studies found that *H. pylori* infection continued to occur and develop, and abnormal proliferation and transformation of one or more gastric units occurred in the deep fovea of the gastric mucosa. It is mainly located at the intersection of the fovea and gastric gland, showing lateral proliferation on the left and right sides, which is called abnormal proliferation and transformation.[13,14] This study also found that there are two types of abnormal proliferation and transformation, one is the abnormal proliferation and transformation of gastric mucosal epithelial cells; the other is the proliferation and transformation of immune cells. The abnormal proliferation and transformation of epithelial cells were characterized by irregular arrangement of glandular epithelial cells, large nuclei, increased nucleo–plasma ratio, enlarged and obvious nucleolus, and milky-white spherical bodies in the nucleus. Both are important precancerous lesions. It is characterized by pathological hyperplasia and is irreducible. The following is the *H. pylori* infective intraepithelial neoplasia stage, which finally developed into gastric adenocarcinoma. The proliferation and transformation of immune cells: at the beginning, a large number of lymphocytes proliferate in the gastric mucosa, forming lymphoid follicles; some of the lymphoid follicles are closely connected; the reduction of mucosal glands is replaced by proliferative lymphoid tissue, called immune cell surplus. Subsequently, proliferating lymphoid follicles appeared, and the proliferating lymphocytes outside the mantle were distributed in multifocal patches, gradually spreading to the interfollicular region.[35,36] Proliferating lymphocytes are small to medium in size, with slight atypia, slightly irregular nuclei, and relatively abundant cytoplasm, similar to central cells, which form diffuse proliferation. At the same time, it invades the glands of the gastric mucosa and destroys the follicular dendrite network structure in the center of the follicle, which is called the follicular infiltration phenomenon of proliferating lymphocytes, namely gastric MALT lymphoma. Immunophenotype: diffuses strong positive expression of CD20 and CD79a, and the presence of molecular genetic t (11; 14)(q13; q32) chromosome translocation. In addition, this study found that MALT-transformed highly aggressive lymphoma occurred in a small number of cases, and gastric MALT lymphoma underwent clonal proliferation of lymphatic follicles, and then differentiation and proliferation led to lymphocyte transformation, that is MALT-transformed highly aggressive lymphoma stage. The transformation is the transformation area of diffuse large B-cell lymphoma.

In summary, in addition to spider-web-like vacuolar degeneration of surface epithelial cells, compensatory cervical mucous cell proliferation, proliferation disorder of stem cells in proliferating areas, and neoplastic proliferation of gastric mucosal epithelial cells, the morphological changes of immune cells fighting with *H. pylori* infection during its occurrence and development have been proposed. We explored the transition from early neutrophil concomituation,

rapid neutrophil counterattack, and neutrophil collapse, to the immune cell crisis phase, the adjustment of immune defense, and then into the rapid proliferation of lymphocytes to form lymphocytic immunity. Persistent *H. pylori* infection leads to abnormal proliferation and transformation of immune cells, resulting in MALT lymphoma. This study is of great significance for controlling the occurrence and development of gastric cancer and lymphatic system tumors, as well as immunological intervention. The mechanism of transformation of *H. pylori* infection into gastric cancer and lymphoid system tumor during its occurrence and development remains to be studied by follow-up of large cases and molecular biology.

Study Approval Statement

This study conformed to the ethical guidelines of the Declaration of Helsinki as reflected in a priori approval by the human research committee of Shenzhen Polytechnic University.

Consent to Participate Statement

The written informed consent was acquired from each patient.

Disclosure

The authors declare that they have no competing interests in this work.

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