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Research article

Histopathological staging of atrophic lesions of gastric mucosa

Yang-kun Wang [a], Ying-ying Li [b], Bin Wang [c], Dong-mei Ran [d], Chao-ya Zhu [e], Ping Li [f], Bo Jiang [g], Su-nan Wang [b,*]

[a] The Fourth People"s Hospital of Longgang District, Shenzhen, 518123, China
[b] Shenzhen Polytechnic University, Shenzhen, 518055, China
[c] Department of Radiation Therapy, Cancer Center, Shanghai Jiahui International Hospital, Shanghai, 200000, China
[d] Department of Pathology, Southern University of Science and Technology Hospital, Shenzhen, 518055, China
[e] Third Affiliated Hospital of Zhengzhou University, Shenzhen, 450052, China
[f] Department of Pathology, Peking University Shenzhen Hospital, Shenzhen, 518036, China
[g] Department of Pathology, No. 990 Hospital of the PLA Joint Logistics Support Force, Zhumadian, 463000, China

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ABSTRACT

Objective: To study the histopathological staging of atrophic lesions of the gastric mucosa.
Methods: Histology and immunohistochemistry were used to closely examine 2144 specimens of atrophic gastric mucosa that were taken from endoscopic biopsies.
Results: When the gastric mucosa epithelium is affected by infection, chemical stimulation, immune factors, genetic factors, and other factors, it may cause an atrophy of gastric mucosa epithelium and a decrease in the number of glands, intestinal metaplasia, hyperplasia of smooth muscle fibers, and atrophy of stem cells in the proliferative zone. In this study, we characterized the above lesions as atrophic lesions of the gastric mucosa. Based on the morphological and histological characteristics of the lesion, as well as the law of cell proliferation and transformation during its occurrence and development, we propose five stages. We also noted the onset age, gender correlation, and histopathological characteristics of each stage of gastric mucosal atrophies.
Conclusion: Understanding the pathological staging of gastric mucosal atrophy is essential for treating patients correctly and keeping track of changes in malignant cells. It is also very important in preventing the initiation of gastric cancer or from getting worse.

1. Introduction

Identifying precancerous mucosal lesions in gastric cancer, such as atrophic gastritis, intestinal metaplasia, and dysplasia, is a strategy for clinicians to reduce cancer-related mortality. The advances in image-enhanced endoscopy techniques and histological assessment have been proven crucial for the management of precancerous lesions [1–3]. The presence of gastric mucosal atrophy has been found to increase the risk of gastric cancer and is considered a precancerous lesion. Early detection may play a valuable role in tissue pathological risk assessment [4–6].. Recent literature reports that by observing changes in mucosal color through endoscopy, it is possible to differentiate between atrophic and non-atrophic gastric mucosa, increasing the color contrast of gastric mucosal atrophy

* Corresponding author. Sunan Wang Shenzhen Polytechnic University, Xili Lake, Xilihu Town, Nanshan District, Shenzhen, 518055, Guangdong, China.
E-mail address: mwangsunan@163.com (S.-n. Wang).

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[7,8]. The atrophy of gastric mucosa is one of the most common lesions worldwide across hospitals of all levels and can be considered a complex syndrome, mainly caused by *Helicobacter pylori* infection or autoimmune gastritis [9,10]. Histopathologically diagnosing intestinal metaplasia also implies diagnosing atrophic gastritis, as intestinal metaplasia often occurs with mucosal atrophy. Even if atrophy or metaplasia occurring with atrophy is not explicitly mentioned in clinical pathology reports, it is indeed accompanied by mucosal atrophy. Furthermore, mucosal atrophy represents an important stage with significant histopathological changes in the pathogenesis of gastric cancer [11–13]. Currently, there is still inadequate understanding of precancerous diseases, and risk stratification is also not ideal. Additionally, there is considerable disagreement in the literature regarding the definitions of atrophic gastritis, autoimmune gastritis, pernicious anemia, and gastric tumors, leading to confusion in clinical practice and research [14,15].

Previous studies have found histological changes in intraepithelial neoplasia caused by simple gastric mucosal atrophy, intestinal metaplastic atrophy, and atrophy [16]. When *Helicobacter pylori* infects the gastric mucosa it disrupts the proliferation of stem cells in the normal proliferative zone of the gastric mucosa. The histopathological features of *H. pylori* infection-led extensive segmental atrophy of lamina propria glands of the gastric mucosa have been previously described [17,18]. There are however, many types and histological changes in gastric mucosal atrophy. In this study, we explored the histomorphological features of the occurrence and progression of gastric mucosal atrophy. The histomorphological features, pathological stages, and histopathological diagnostic criteria of each stage were studied in the 2144 cases of gastric mucosal biopsy, which can help clinicians treat atrophic lesions accurately.

2. Data and methods

1. **Data:** Between September 2020 to September 2022, we enrolled 2144 patients with atrophic gastric mucosal lesions who were diagnosed by gastroscopy biopsy. The patients were from Foresea Life Insurance Guangzhou General Hospital, Southern University of Science and Technology Hospital, Peking University Shenzhen Hospital, The Third Affiliated Hospital of Zhengzhou University, and 990 Hospital of PLA Joint Service Support Force. There were 1316 males and 828 females. Among the cases of atrophic gastric

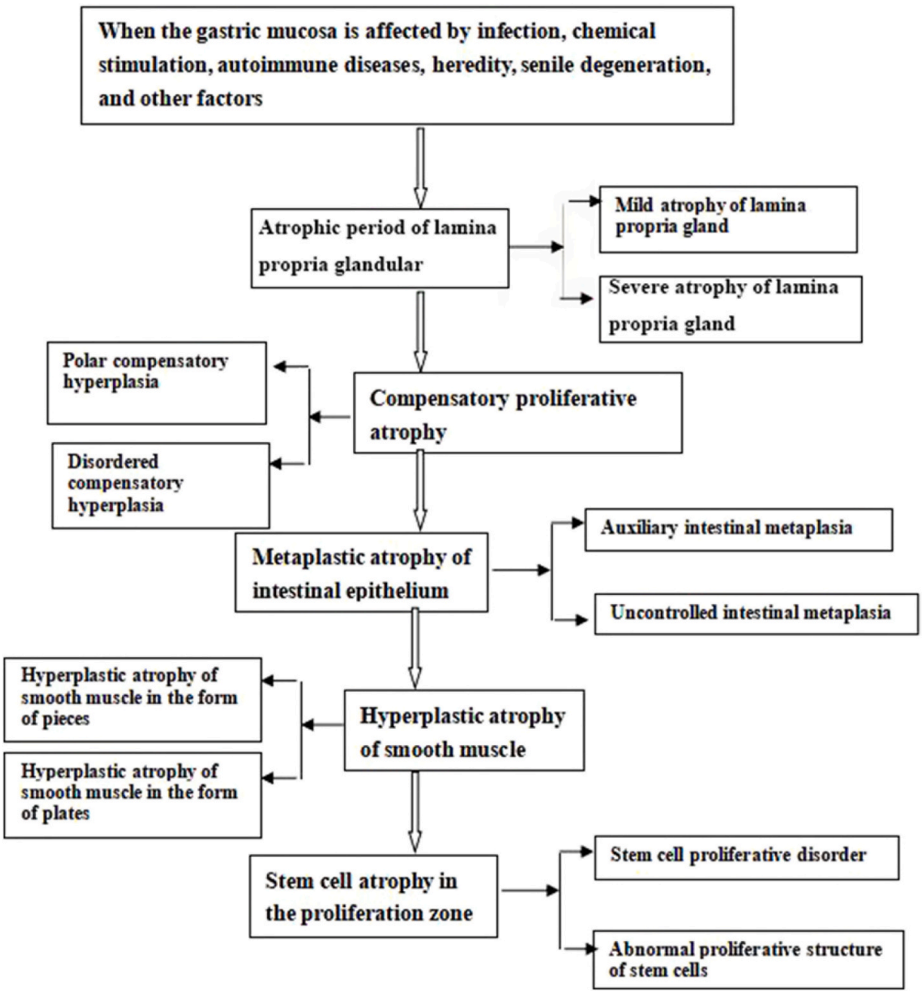

Fig. 1. Schematic diagram of the stages of gastric mucosal atrophy.

mucosal lesions, 748 were related to the esophagogastric angle, 735 related to the gastric antrum, 590 cases related to the gastric corpus, and 71 related to the gastric fundus.

2. **Methods:** In each case, four or five specimens from each section were collected endoscopically. The specimens were fixed with 10% neutral formalin, conventionally dehydrated, embedded in paraffin, sectioned into 4 μm thick sections, and underwent hematoxylin and eosin (H&E) and immunohistochemical staining.
3. **Immunohistochemical staining:** The EnVision two-step method was used.

After removing the paraffin, the sections were hydrated and rinsed with distilled water. Then, the sections were in placed tris-buffered saline (TBS) for 10 min. Endogenous peroxidase was blocked for another 5 min, and then, sections were treated with TBS for 10 min. The sections were incubated with the primary antibodies (MUC5AC, MUC2, MUC6, Desmin, p53, and ki-67) for 30 min at room temperature. The sections were incubated in EnVision™ after being rinsed in TBS for 10 min. After rinsing the sections in TBS, the secondary antibody was applied for 10 min. The chromogenic substrate solution was incubated for 10 min, and then rinsed with distilled water. The sections were colored with DAB and counterstained with hematoxylin. Positive controls were known gastric mucosal sections, and negative controls were phosphate-buffered saline (PBS) buffer instead of a primary antibody. The working solution was purchased from Fuzhou Maixin Biotechnology Development Co., Ltd., and the operation steps were followed as instructed in the kit [16].

4. **Statistical analysis:** The SPSS22.0 statistical software package was used for statistical analysis. The gender and age were analyzed using the chi-square test. $P < 0.05$ was statistically significant.

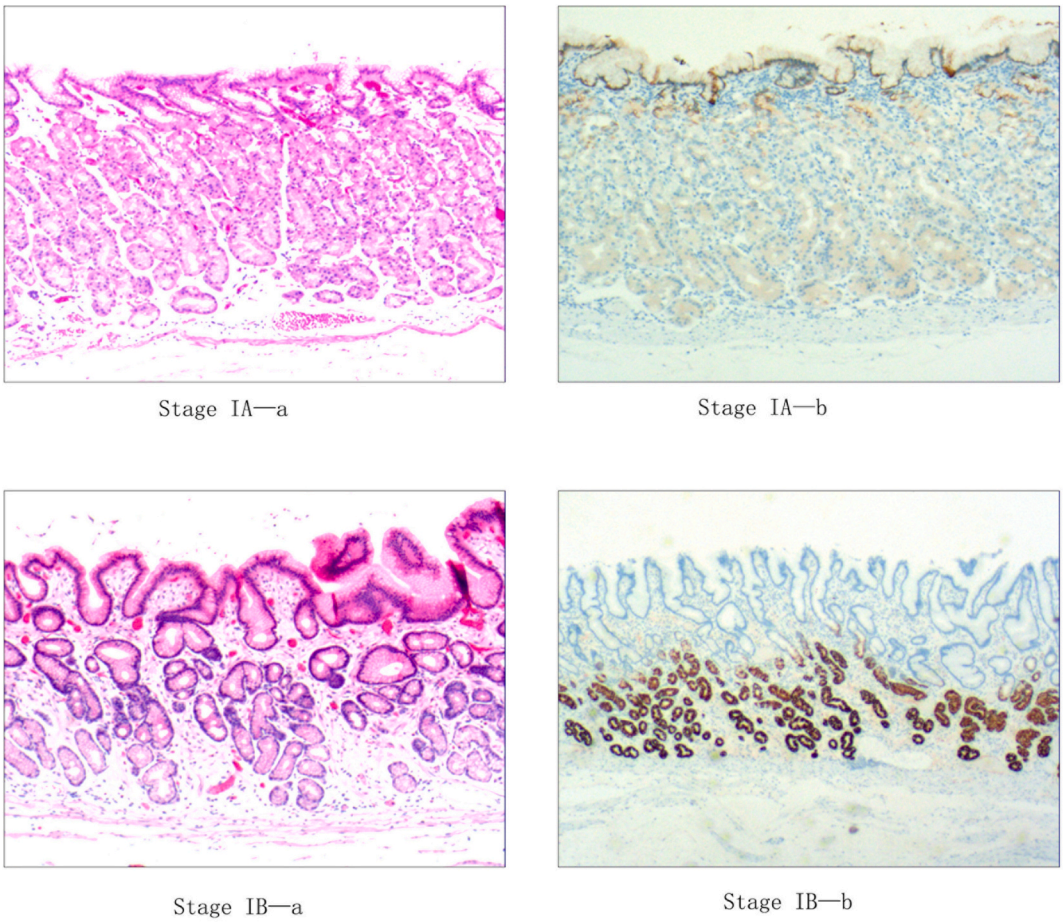

Fig. 2. Stage I—glandular atrophy of lamina propria. Stage IA—a: mild atrophy of lamina propria gland. The volume and number of lamina propria glands decrease. The number decreases by 1/3rd of the original glands, and the gastric fovea becomes shallower. H&E, × 100. b: positive for Muc5ac. The gastric fovea becomes shallower. EnVision method, × 100. Stage IB—a: The glands in the lamina propria atrophy decrease severely; the number of glands in the lamina propria decreases by more than 1/3rd of the original glands; the spaces between the glands are evidently widened. H&E, × 200. b: positive for MUC6. The glands of the gastric fundus reduce. EnVision method, × 100.

3. Results

1. **Clinical data:** There were 2144 biopsy specimens of the gastric mucosa; 1316 males (61.4%) and 828 females (38.6%). The average age of onset was ≤60 in 813 cases (37.9%) and >60 in 1331 cases (62.1%). Fig. 1 describes the association between onset age and gender.
2. **Definition of atrophic lesions of the gastric mucosa:** The normal gastric mucosa consists of three layers: epithelium, lamina propria, and muscularis mucosa. The thickness of the normal gastric mucosa in adults is as follows: gastric cardia:

0.7–1.1 mm, gastric fundus, 0.8–1.2 mm, gastric corpus: 0.9–1.3 mm, and gastric antrum: 1.0–1.5 mm [19]. When the gastric mucosa is affected by an infection, chemical stimulation, autoimmune diseases, heredity, senile degeneration, or other factors, it leads to atrophy of gastric mucosal epithelium, a decrease in the number of glands, intestinal metaplasia, hyperplasia of smooth muscle fibers, and atrophy of stem cells in the proliferation zone. All the lesions listed above are referred to as atrophic lesions of the gastric mucosa.

3. **Schematic diagram of the occurrence and progression of atrophic gastric mucosa:** When the gastric mucosa is affected by infection, chemical stimulation, autoimmune diseases, heredity, and senile degeneration, it leads to atrophic lesions
4. **Pathological staging and characteristics of gastric mucosal atrophic lesions:** Stage I, glandular atrophy of lamina propria (Fig. 2). In Stage IA, the lamina propria glands atrophied slightly. This is the start of gastric mucosal atrophy. It is primarily manifested by a drop in the quantity and volume of the lamina propria glands (Fig. 2 IAa). The specimens were positive for MUC5AC. The gastric fovea became lower (Fig. 2 IAb). Stage IB, severe atrophy of the lamina propria glands. More than 1/3rd of the glands in the lamina propria were lost, and the spaces between the glands grew larger (Fig. 2 IBa). The specimens were positive for MUC6. The glands of the gastric fundus gland decreased (Fig. 2 IBb). Stage II, compensatory proliferative atrophy (Fig. 3). Stage

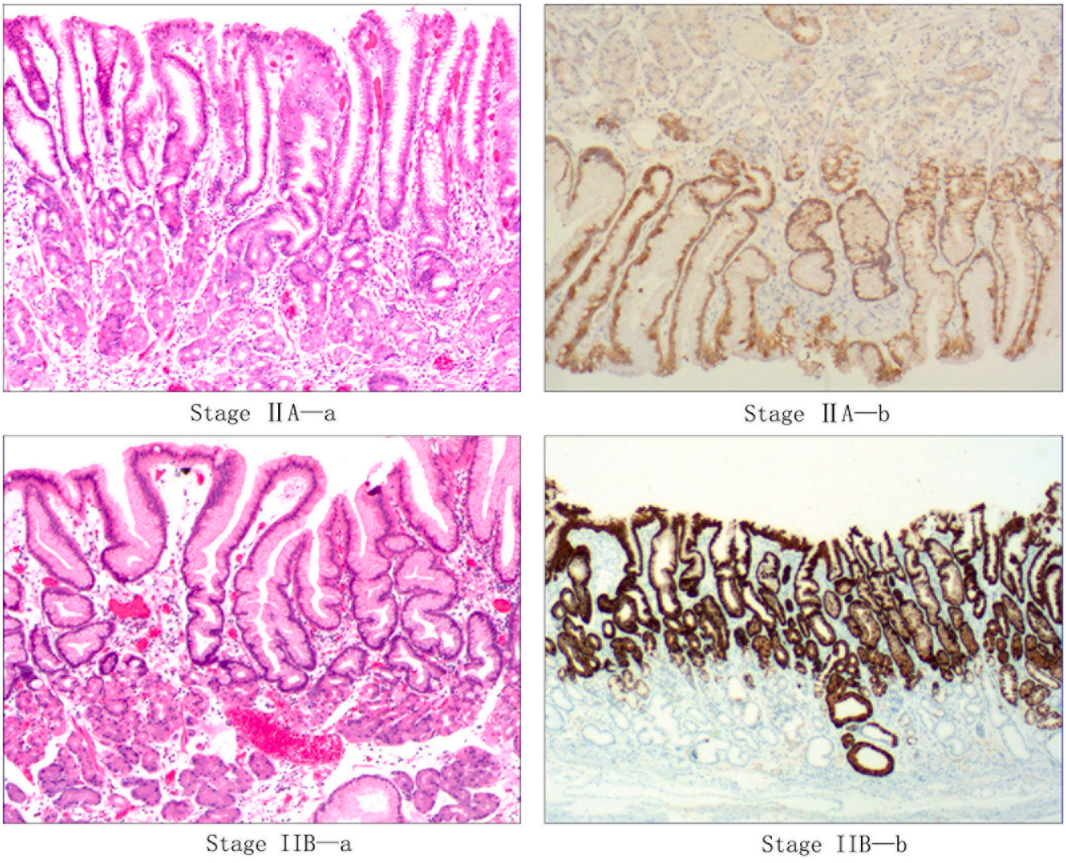

Fig. 3. Stage II—compensatory proliferative atrophy. Stage IIA—a: polar compensatory hyperplasia. The glands in the lamina propria decline. Stem cells and cervical mucous cells proliferate in the proliferative area. The surface epithelial cells proliferate in a unique papillary structure. H&E, × 200. b: positive for MUC5AC. The proliferated surface epithelial cells have a papillary structure. EnVision method, × 200. Stage IIB—a: Disordered compensatory hyperplasia. Surface epithelial cells feature a distinctive papillary proliferation. Glands of surface epithelial cells and cervical mucous cells appear in the glandular area of lamina propria. H&E, × 200. b: positive for MUC5AC. The surface epithelium appears in the glandular area of lamina propria. EnVision method, × 200.

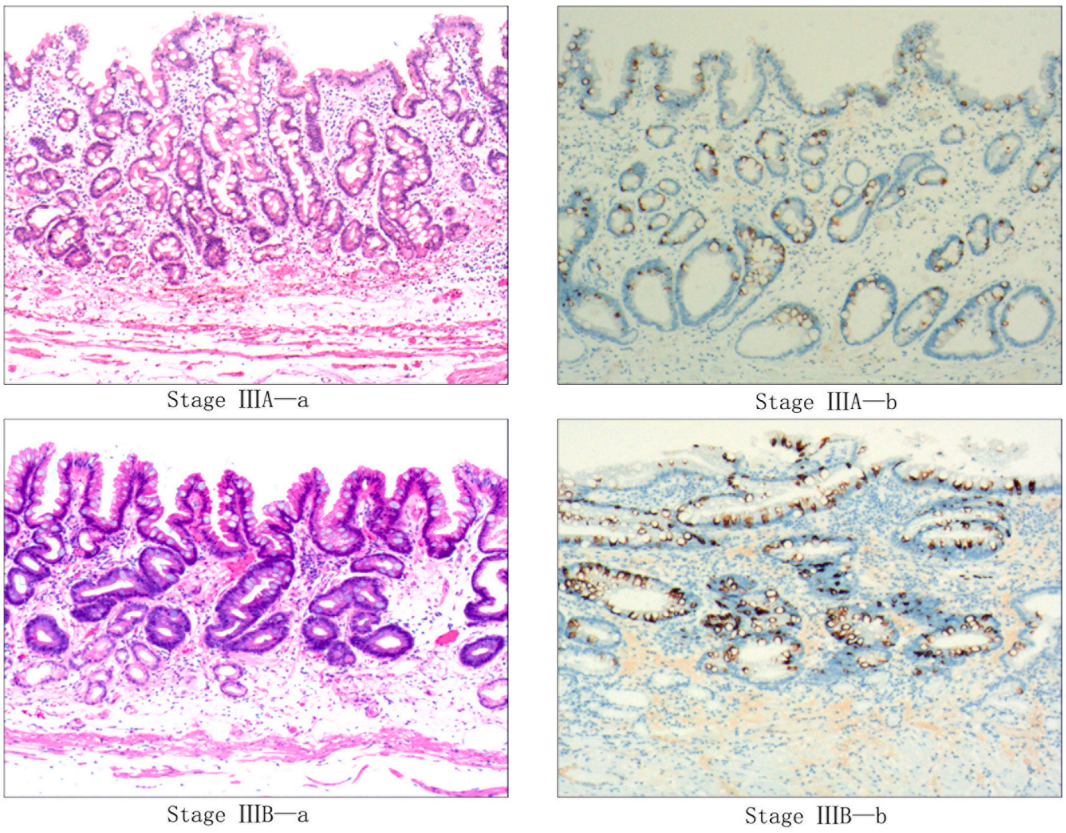

Fig. 4. Stage III—intestinal metaplastic atrophy. Stage IIIA—a: auxiliary intestinal metaplasia. This is primarily manifested by an atrophy of the lamina propria glands, which is accompanied by widespread intestinal metaplasia. H&E, × 200. B: positive for MUC2. Positive for intestinal metaplastic cells. EnVision method, × 200 b: Stage IIIB—uncontrolled intestinal metaplasia. This is characterized by atypical proliferative cells on one or both sides of the intestinal metaplastic cells, or by atypical hyperplastic glands near the intestinal metaplastic glands. At the same time, intestinal metaplastic cells show abnormal proliferation. H&E, × 200. b: positive for MUC2. Positive for intestinal metaplastic cells. EnVision method, × 200.

IIA, polar compensatory hyperplasia. While the pyloric gastric fundus glands decreased, stem cells and cervical mucous cells proliferated in the proliferative area, and surface epithelial cells proliferated in a distinctive papillary structure (Fig. 3 IIAa). The specimens were positive for MUC5AC. The proliferated surface epithelial cells showed a papillary structure (Fig. 3 IIAb). Stage IIB, disordered compensatory hyperplasia. This stage features the presence of surface epithelial cells and cervical mucous cells in the area of the pyloric gland and gastric fundus gland (Fig. 3 IIB a). The specimens were positive for MUC5AC. The surface epithelium appeared in the lamina propria glandular area (Fig. 3 IIB b). Stage III, intestinal metaplastic atrophy (Fig. 4). Stage IIIA, auxiliary intestinal metaplasia. This is primarily manifested by the atrophy of lamina propria glands, and is accompanied by a widespread intestinal metaplasia (Fig. 4 IIIAa). The specimens were positive for MUC2 and intestinal metaplastic cells (Fig. 4 IIIA b). Stage IIIB, uncontrolled intestinal metaplasia. Atypical proliferative cells on one or both sides of intestinal metaplastic cells or atypical proliferative glands surrounding the intestinal metaplastic glands were seen. Meanwhile, intestinal metaplastic cells also showed an abnormal proliferation (Fig. 4 IIIB a). The specimens were found to be positive for MUC2. The intestinal metaplastic cells were found to be positive (Figure IIIB b). Stage IV, hyperplastic atrophy of smooth muscle (Fig. 5). Stage IVA, smooth muscle proliferates in pieces. Smooth muscle fibers of various sizes and shapes were found in the lamina propria, sectioning, and surrounding glands. The smooth muscle at the base of the lamina propria penetrated in bundles, dividing the lamina propria glands into a nest-like structures of varying sizes (Fig. 5 IVA a). The specimens were positive for desmin. Hyperplastic smooth muscle fibers were present (Fig. 5 IVAb). In Stage IVB, smooth muscle proliferates like a plate. The hyperplastic smooth muscle extended from the muscular layer to the proliferative area of the mucosa. It made a unique muscular fiberboard with the muscular layer of the mucosa (Fig. 5 IVBa). The specimens were positive for Ki-67, and the proliferation zone was present (Fig. 5 IVBb). Stage V, stem cell atrophy in the proliferative zone (Fig. 6). In stage VA, the proliferation function of stem cells is disordered. The glands in the lamina propria of the gastric mucosa are extensively atrophied. The normal law or polarity of physiology changes, resulting in a disorderly proliferation (Fig. 6 VA a). The specimens were positive for Ki67. The proliferative zone disappeared, and the focal positive remained (Fig. 6 VAb). In stage VB, the proliferation structure of the stem cells was abnormal (see Table 1). In the proliferation zone, stem cells were consistently out of sync with the physiological regularity and polarity, which led to an abnormal structure of

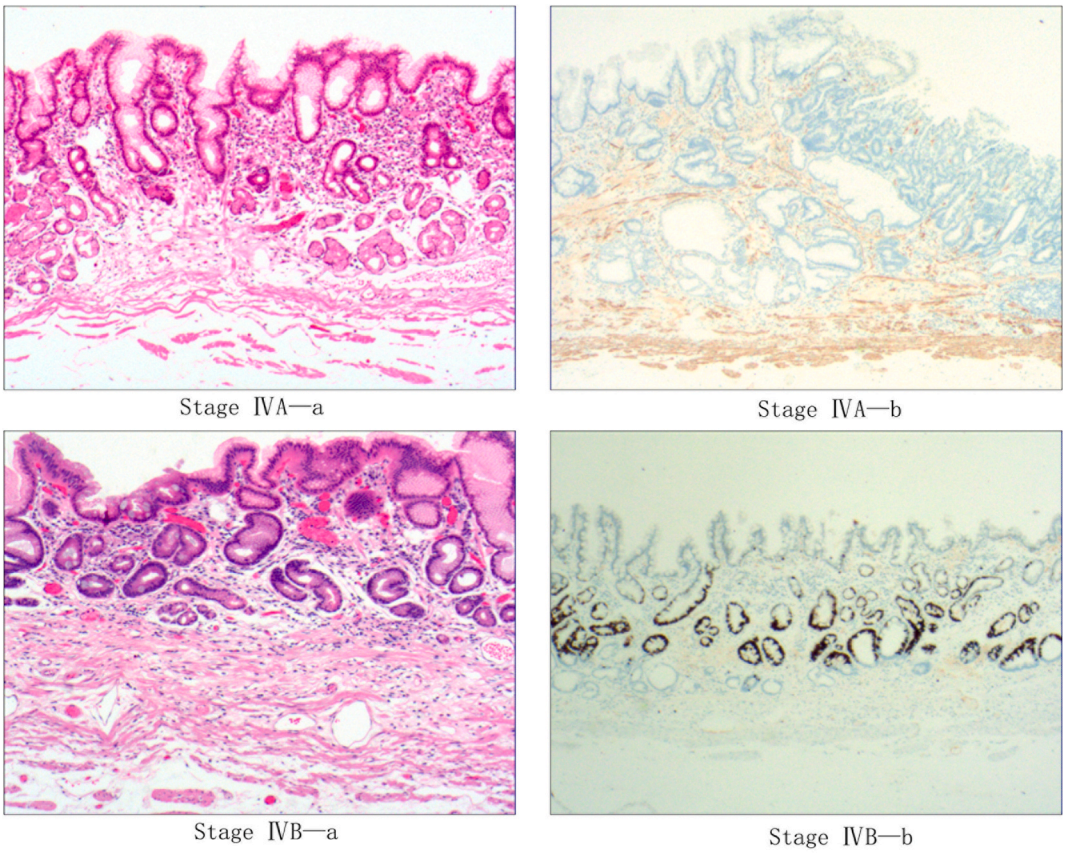

Fig. 5. Stage IV—hyperplastic atrophy of smooth muscle. Stage IVA—a: smooth muscle proliferates in pieces. Smooth muscle fibers of varying sizes and shapes show up in the lamina propria, sectioning, and surrounding glands in the lamina propria. The smooth muscle at the bottom of the lamina propria penetrates the lamina propria in bundles, dividing the lamina propria glands into nest-like structures of varying sizes. The smooth muscle at the bottom of lamina propria penetrates the lamina propria in bundles, dividing the lamina propria glands into a nest-like structures of varying sizes; H&E, × 200 b: positive for desmin. Hyperplastic smooth muscle fibers are present. EnVision method, × 100. Stage IVB—a: smooth muscle atrophy in the form of plates. Significant smooth muscle hyperplasia in lamina propria. In severe cases, the hyperplastic smooth muscle form a distinctive muscle fiberboard structure with hyperplastic muscularis mucosae from the mucosal muscular layer to the mucosal proliferative area. H&E, × 200. b: positive for ki-67. The proliferative zone is present. EnVision method, × 200.

proliferation. Its morphological characteristics mainly consist of cell atypia, mucosal structure disorder, and abnormal differentiation (Figure VBa). The specimens were positive for P53, and there was a multifocal positivity (Figure VBb). Table 2 shows how each stage can be diagnosed based on histopathology.

5. **Immunohistochemical staining results:** MUC2 was found to be negative in normal gastric mucosa but positive in intestinal metaplasia or intestinal malignancy. MUC5AC was found to be positive in the surface epithelium and cervical mucous gland of the normal gastric mucosa; MUC6 was found to be positive in the gastric fundus gland and pyloric gland of the normal gastric mucosa. The hyperplastic smooth muscle fibers were positive for desmin. Cell proliferation and transformation were indicated by the expression of the p53 protein. The high ki67 proliferation index was an important indicator of active cell proliferation.

4. Discussion

Gastric mucosal atrophy is defined as the loss of glands, and there is considerable variability among pathologists in assessing the severity of gastric atrophy. Each pathologist uses non-standardized methods to grade atrophy, with clinical pathology work typically categorizing atrophy as none, mild, moderate, or severe [20–22]. There are various types of mucosal atrophy and/or chronic atrophic gastritis, and the definitions of “gastric atrophy” and “atrophic gastritis” remain imprecise, contributing to confusion in histopathology [23–25]. Intestinal metaplasia is closely related to gastric cancer and is an important histological feature of patients with atrophic gastritis [26–28]. The severity of atrophic gastritis is closely related to the occurrence and development of gastric cancer. *Helicobacter pylori* infection leads to histopathological changes in gastric mucosal damage, which is also an important aspect in assessing the degree of gastric mucosal atrophy. Accurate evaluation of atrophic gastritis is crucial for interfering with disease progression and reversing gastric mucosal atrophy [29,30]. We suggest that there are shortcomings in this rating. Mucosal atrophy and/or chronic atrophic gastritis differ from glandular atrophy in more ways than one. There are also differences in cell morphology and tissue structure.

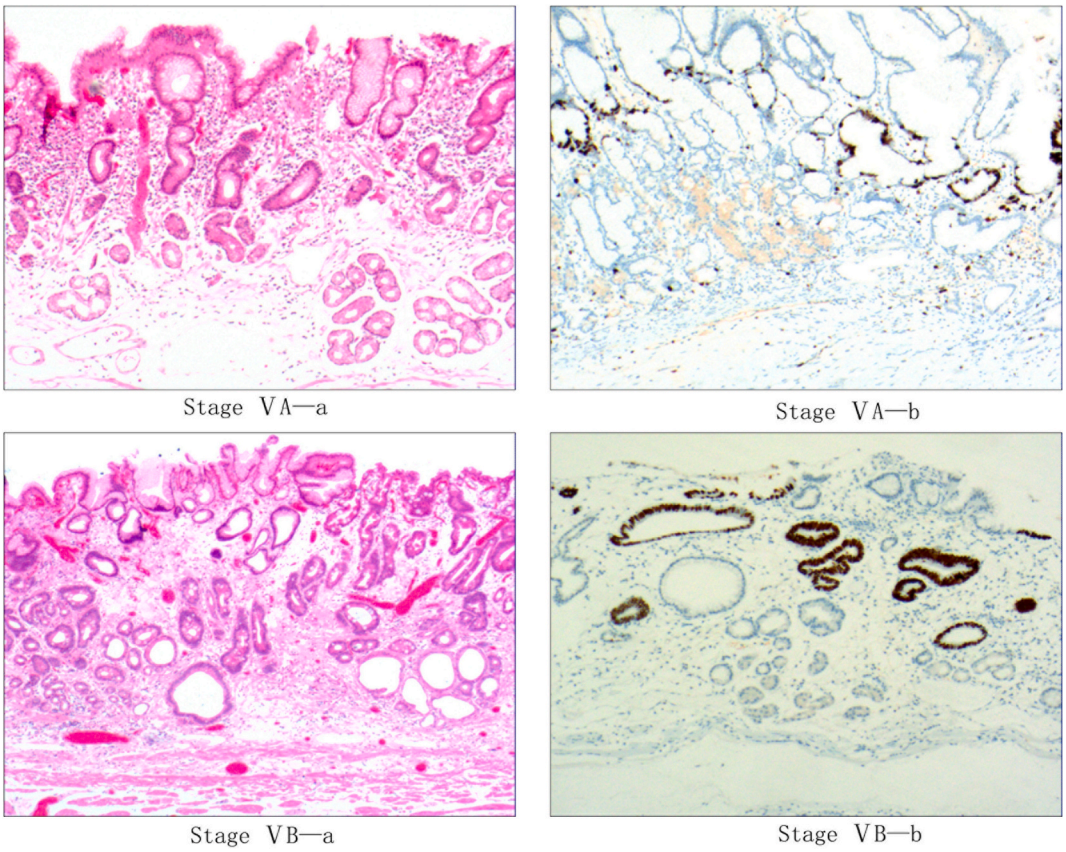

Fig. 6. Stage V—stem cell atrophy present in the proliferative zone. Stage VA—a: the proliferative function of the stem cells is disordered. The glands in the lamina propria of the gastric mucosa are extensively atrophied. The normal law or polarity of physiology changes, resulting in disorderly proliferation. H&E, × 200. b: positive for Ki67. The proliferative zone disappears, and the focal positive is present. EnVision method, × 200. Stage VB—b: abnormal proliferative structure of stem cells. a: the primary morphological features are cell abnormity, mucosal structural disorder, abnormal differentiation, varying cell sizes, and pleomorphic changes. H&E, × 200. b: positive for p53. There is a multifocal positivity. EnVision method.

Table 1
Association between onset age and gender of gastric mucosal atrophic lesions.

Staging	N (%)	Gender	Age
		Male/Female	≤60 , >60
Stage I glandular atrophy of lamina propria.	**927(43.2)**	**570(61.5),357(38.5)**	**335(66.1),592(63.9)**
Stage IA: mild atrophy of lamina propria gland.	588(63.4)	362(61.6),226(38.4)	214(36.4),374(63.6)
Stage IB: The glands in the lamina propria atrophy decrease severely	339(36.6)	208(61.4),131(38.6)	121(35.7),218(64.3)
Stage II compensatory proliferative atrophy.	**284(13.2)**	**170(59.9), 114(40.1)**	**111(39.1), 173(60.9)**
Stage IIA: polar compensatory hyperplasia.	229(80.6)	138(60.1),91(39.7)	90(39.3),139(60.7)
Stage IIB: Disordered compensatory hyperplasia.	55(19.4)	32(58.2), 23(41.8)	21(38.2), 34(61.8)
Stage III intestinal metaplastic atrophy.	**513(23.9)**	**314(61.2),199(38.8)**	**207(40.4),306(59.6)**
Stage IIIA: auxiliary intestinal metaplasia.	367(71.5)	226(61.6),141(38.4)	153(41.7),214(58.3)
Stage IIIB: uncontrolled intestinal metaplasia.	146(28.5)	88(60.3), 58(39.7)	54(37.0),92(63.0)
Stage IV hyperplastic atrophy of smooth muscle.	**276(12.9)**	**177(64.1),99(35.9)**	**106(38.4),170(61.6)**
Stage IVA: smooth muscle proliferates in pieces.	224(81.2)	143(63.8),81(36.2)	89(39.7),135(60.3)
Stage IVB: smooth muscle atrophy in the form of plates.	52(18.8)	34(65.4),18(34.6)	17(32.7),35(67.3)
Stage V stem cell atrophy present in the proliferative zone.	**144(6.7)**	**85(59.0),59(41.0)**	**54(37.5),90(62.5)**
Stage VA: the proliferative function of the stem cells is disordered.	91(63.2)	53(58.2),38(41.8)	35(38.5),56(61.5)
Stage VB: abnormal proliferative structure of stem cells.	53(36.8)	32(60.4),21(39.6)	19(35.8),34(64.2)
Total	2144	1316(61.4),828(38.6)	813(37.9),1331(62.1)

Table 2
Pathological staging and histomorphological features of gastric mucosal atrophy.

Type	Histological features
Stage I glandular atrophy of lamina propria.	
Stage IA: mild atrophy of lamina propria gland.	The structures of the proliferative areas in the deep part of the gastric fovea, the isthmus of the gastric gland, and the glandular neck are usually normal. There is a decrease in the number of glands in the lamina propria (pyloric gland/gastric fundus gland/cardiac gland), the volume of glands becomes smaller, and the spaces between the glands widen. There is no obvious atypical change in the cytological morphology of the lamina propria gland. Less than 1/3rd of the glands in the lamina propria are lost. This stage is commonly observed in senile degeneration, which is caused by slowing normal physiological migration in the proliferative zone.
Stage IB: The glands in the lamina propria atrophy decrease severely	The structures of the proliferative areas in the deep part of the gastric fovea, the isthmus of the gastric gland, and the glandular neck are normal. There is a decrease in the number of glands in the lamina propria (pyloric gland/gastric fundus gland/cardiac gland), the volume of glands becomes smaller, and the spaces between the glands widen. Furthermore, there is hyperplasia of collagen fibers in the glandular stroma of lamina propria, a significant increase in lymphocytes and plasma cells, and there are a small number of smooth muscle fiber bundles. The cytological morphology of the lamina propria gland shows no obvious atypical changes. More than 1/3rd of the glands in the lamina propria are lost. Clinically, in addition to senile degeneration, it is seen due to the impact of chemical stimulation, autoimmune diseases, genetics, and other factors.
Stage II compensatory proliferative atrophy.	
Stage IIA: polar compensatory hyperplasia.	When the gastric mucosa is affected by infection, chemical stimulation, autoimmune diseases, genetics, and other factors, it leads to a decrease in the pyloric gland/gastric fundus gland, hyperplasia of interstitial fibrous tissue and smooth muscle fibers, and inflammatory lesions. Then, the upward migration of the gastric fovea deep area, gastric gland isthmus, and cervical mucous cells increases, resulting in compensatory hyperplasia. Histologically, it is mainly the hyperplasia of surface epithelial cells that form distinctive papillary hyperplasia, usually 0.3–0.6 mm in height. The hyperplastic glands and cells continue to maintain normal polarity, hence it is also called polar compensatory hyperplasia.
Stage IIB: Disordered compensatory hyperplasia.	In persistent polar compensatory hyperplasia, there is a significant decrease in the number of glands in lamina propria (pyloric gland/gastric fundus gland/cardiac gland); stem cells and cervical mucous cells proliferate more significantly in the proliferative area; the surface epithelial cells show a distinctive papillary proliferation, usually 0.5–1.2 mm in height. At the same time, there is a proliferative disorder in the deep area of the gastric fovea, gastric gland isthmus, and glandular neck. The main manifestation is that the glands of surface epithelial cells and cervical mucous cells appear in the lamina propria gland (pyloric gland/gastric fundus gland/cardiac gland), which is the morphological feature of this stage. It is also called disordered compensatory hyperplasia.
Stage III intestinal metaplastic atrophy.	
Stage IIIA: auxiliary intestinal metaplasia.	When the gastric mucosa is infected, primarily in case of *H. pylori* infection, the stem cells in the proliferative area differentiate into intestinal epithelial cells, forming intestinal metaplasia. The focus of early intestinal metaplasia is mainly on the gastric fovea, forming a micro-intestinal metaplasia focus. Then, it gradually develops to the surrounding gastric area, forming a widespread intestinal metaplasia. When the intestinal metaplastic cells account for more than 30% of the total glands; intestinal metaplasia area is more than 3 gastric areas (1 gastric area is 2–6 mm), or intestinal metaplasia foci are present in multiple gastric areas; meanwhile, the glands of lamina propria glands (pyloric gland/gastric fundus gland/cardiac gland) become smaller and their number decreases. This is referred to as auxiliary intestinal metaplastic atrophy. At this stage of intestinal metaplasia, the cells are mature and reactive and non-atypical. It is also known as defensive reactive hyperplasia.
Stage IIIB: uncontrolled intestinal metaplasia.	When the gastric mucosa is consistently affected by infection, chemical stimulation, and other factors, accompanied by intestinal metaplasia, the stem cells proliferate and transform in the deep part of the gastric fovea, gastric glandular isthmus, and glandular neck. While the nuclei of the proliferative gastric mucosal epithelial cells get bigger and longer, they grow to be 1–2 times the size of normal nuclei. These nuclei have mild atypia and more chromatin, about 20%–50% of them have small to medium-sized nucleoli. However, because intestinal metaplastic cells are also derived from stem cells in the proliferative areas, intestinal metaplastic cells also show abnormal proliferation. Histologically, this is manifested by atypical proliferative cells on one or both sides of intestinal metaplastic cells or atypical proliferative glands around the intestinal metaplastic glands. This is called uncontrolled intestinal metaplasia. Furthermore, the glands of lamina propria (pyloric gland/gastric fundus gland/cardiac gland) become smaller and the number decreases. It is called uncontrolled intestinal metaplastic atrophy.
Stage IV hyperplastic atrophy of smooth muscle.	
Stage IVA: smooth muscle proliferates in pieces.	Smooth muscle hyperplasia in the form of pieces: smooth muscle fiber bundles in various sizes and shapes show up in the lamina propria, sectioning, and surrounding the pyloric gland/gastric fundus gland. The mucosal layer at the bottom of the lamina propria begins to penetrate the lamina propria in the form of smooth muscle fiber bundles, dividing the lamina propria glands into a nest-like structures of varying sizes. In this stage, mild compensatory proliferation of stem cells and cervical mucous cells can be seen in the proliferative areas of the deep part of the gastric fovea, the isthmus of the gastric gland, and the glandular neck. Intestinal metaplasia may occur in local areas.
Stage IVB: smooth muscle atrophy in the form of plates.	Persistent smooth muscle hyperplasia in fragments result in significant hyperplasia of smooth muscle in lamina propria. This refers to the smooth muscle hyperplasia from the mucosal muscular layer to the mucosal proliferative area. The hyperplastic smooth muscle and mucosal muscular layer together, form a distinctive muscular fiberboard-like structure with a thickness of 0.6–0.9 mm. In this stage, the mild compensatory proliferation of stem cells and cervical mucous cells can be seen in the proliferative areas of the deep part of gastric fovea, the isthmus of the gastric gland, and the glandular neck. Intestinal metaplasia may occur in local areas.

(*continued on next page*)

Table 2 (*continued*)

Type	Histological features
Stage V stem cell atrophy present in the proliferative zone.	
Stage VA: the proliferative function of the stem cells is disordered.	Persistent atrophy of gastric mucosa can impair stem cell proliferation in the proliferative zone. While the proliferative areas do not sufficiently migrate upward, they result in the reduction of the gastric foveolar epithelium. However, the proliferative areas do not sufficiently migrate downward, resulting in extensive atrophy of the lamina propria glands of the gastric mucosa. Lastly, stem cells are stopped from moving up from the top of the gastric fundus gland to the deep part of the gastric fovea. Changes in the polarity or normal physiological law of cell proliferation in the area between the top of the gastric fundus gland and the deep part of the gastric fovea result in disorderly proliferation.
Stage VB: abnormal proliferative structure of stem cells.	In the proliferation zone, stem cells are consistently out of sync with physiological regularity and polarity. This leads to an abnormal structure of proliferation. Its morphological characteristics mainly include cell atypia, mucosal structure disorder, and abnormal differentiation. Cell atypia: the cells are of varying sizes and show pleomorphism. The proportion of the nucleus and cytoplasm grows. Mucosal structure disorder: the normal three-layer structure of gastric mucosa (epithelium, lamina propria, and muscularis mucosa) disappears. Abnormal differentiation: the basophilia of the cells grows; the secretory function of the cells reduces; the mucous cells, main cells, and parietal cells cannot be distinguished.

Mucosal atrophy, intestinal metaplasia, and the amount of cell proliferation and transformation are not synchronous. Gastric mucosal atrophy is not caused by chronic gastritis, or rather, gastric mucosal atrophy is not always accompanied by gastritis. This study found that continuous gastric mucosal atrophy can lead to functional disruption of proliferative zone stem cell proliferation. On one hand, insufficient upward migration of the proliferative zone results in a decrease in the gastric pit epithelium; on the other hand, inadequate downward migration of the proliferative zone leads to extensive atrophy of the intrinsic glandular layer of the gastric mucosa. This ultimately results in the obstruction of stem cell upward migration from the top of the gastric gland to the depths of the gastric pit; and changes in the normal physiological regulation or polarity of stem cell proliferation from the top of the gastric gland to the depths of the gastric pit, leading to a state of disordered proliferation. At the same time, continuous proliferation of stem cells in the proliferative zone disrupts the normal physiological regulation and polarity of proliferation. This is manifested morphologically by cell atypia, mucosal structural disorder, and abnormal differentiation. Cell atypia: Cells vary in size, exhibit pleomorphism, and have an increased nuclear-to-cytoplasmic ratio. Mucosal structural disorder: The normal three-layer structure of the gastric mucosa, including the epithelial layer, the intrinsic layer, and the mucosal muscle layer, is disrupted. Abnormal differentiation: Cells show increased alkalinity, reduced secretory function, and an inability to differentiate between mucous cells, chief cells, and parietal cells.

Histopathological staging of atrophic lesions of the gastric mucosa is based on the cellular morphology and histological characteristics of the lesions, as well as the law of cell proliferation and transformation during the occurrence and development. Stage I—glandular atrophy of lamina propria. This is a change in the early stages of gastric mucosal atrophy. It is imperative to find out the cause, control it as early as possible, reduce inflammatory stimulation, and maintain the balance of gastric acid secretion and the mucus-bicarbonate barrier. This stage is commonly observed in senile degeneration, which is caused by slowing normal physiological migration in the proliferative zone. Some severe atrophies of the lamina propria gland are caused by chemical stimulation, autoimmune diseases, genetics, and other factors. Stage II—compensatory proliferative atrophy. The proliferation of surface epithelial cells forms a distinctive papillary proliferation. Infection is the main cause. Stage III—intestinal metaplastic atrophy. Early intestinal metaplasia, or auxiliary intestinal metaplasia, is a defensive reactive hyperplasia. It is a mature, reactive cell that is usually caused by *H. pylori* infection. However, uncontrolled intestinal metaplastic atrophy is different, and the atypia of cells should be closely followed up. Stage IV—hyperplastic atrophy of smooth muscle. The hyperplastic atrophy of smooth muscle in the form of plates and pieces suggests that the injury is irreparable, and that the onset time is extended. Stage V—stem cell atrophy in the proliferation zone. This indicates a prolonged onset time of atrophic lesions of gastric mucosa, irreversibility, and a high risk of cancer. Clinicians need to understand the histological features and pathological staging of gastric mucosal atrophic lesions to treat them correctly and keep track of how malignant cells change. It is very important for preventing and stopping gastric cancer from getting worse.

In this study, we examined 2144 cases of atrophic lesions of the gastric mucosa. Endoscopic biopsy specimens were studied using histomorphology and immunohistochemistry. We then proposed the histopathological staging and morphological features of atrophic lesions of the gastric mucosa. Accordingly, an endoscopic biopsy of gastric mucosal atrophic lesions should include at least 4 specimens. It is even more important that the clinicopathological examination report includes information about the morphological features and pathological stages of gastric mucosal atrophic lesions. The results of this study revealed that gastric mucosal atrophic lesions can be divided into five stages ranging from mild to severe: glandular atrophy of lamina propria, compensatory proliferative atrophy, intestinal metaplastic atrophy, hyperplastic atrophy of smooth muscle, and stem cell atrophy in the proliferative zone. The histopathological and immunophenotypic characteristics of atrophy in different stages were analyzed. The findings of this study on the histomorphological features, immunophenotype, and pathological staging of the occurrence and progression of gastric mucosal atrophic lesions offer a new perspective at how early gastric cancer develops.

5. Conclusion

A total of 2144 cases of gastric mucosa biopsy were collected in this study, observing the histological morphology of gastric mucosal atrophic lesions in endoscopic biopsy specimens, as well as immunohistochemical detection. In this study, in addition to the histopathological features of intrinsic glandular atrophy, compensatory hyperplastic atrophy, intestinal metaplastic atrophy, and smooth

muscle hyperplastic atrophy of the gastric mucosa, we also identified the atrophy of proliferative zone stem cells. Continuous gastric mucosal atrophy can lead to functional disruption of proliferative zone stem cell proliferation. On one hand, insufficient upward migration of the proliferative zone results in a decrease in the gastric pit epithelium. On the other hand, inadequate downward migration of the proliferative zone leads to extensive atrophy of the intrinsic glandular layer of the gastric mucosa. We also found that continuous gastric mucosal atrophy can disrupt the normal physiological regulation and polarity of proliferative zone stem cells, leading to abnormal proliferative structures. The formation of abnormal proliferative structures is mainly characterized by cell atypia, mucosal structural disorder, and abnormal differentiation. The 5 histopathological stages proposed in this study, along with the morphological characteristics of each stage, facilitate precise treatment and tracking of malignant cell transformation, providing new insights into the formation of early gastric cancer.

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Ethics approval and consent to participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of No. 990 Hospital of the PLA Joint Logistics Support Force. A written informed consent was obtained from all participants.

Data availability

Data will be made available on request

CRediT authorship contribution statement

Yang-kun Wang: Writing – original draft, Funding acquisition, Conceptualization. **Ying-ying Li:** Writing – original draft, Data curation, Conceptualization. **Bin Wang:** Software, Resources. **Dong-mei Ran:** Resources, Formal analysis. **Chao-ya Zhu:** Resources, Data curation. **Ping Li:** Formal analysis, Data curation. **Bo Jiang:** Resources, Data curation. **Su-nan Wang:** Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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