Clinical pathology and recent follow-up study on gastric intraepithelial neoplasia and gastric mucosal lesions

Sun Sheng-bin*, Chen Zhi-tao*, Zhen Dan*, Huang Man-ling*, Xu Dan*, Zhang Heng*, Wang Ping*, Wu Jie*

*Department of Gastroenterology and Central Laboratory, The Central Hospital of Wuhan, Wuhan 430014, PR of China.

*Corresponding author:
Prof. Jie Wu, MD
Department of Gastroenterology and Central Laboratory, The Central Hospital of Wuhan Sheng Li Street 26, Wuhan 430014, Hubei Province, PR of China.
E-mail: wujie988@sina.com, Telephone: +86-27-82211566, Fax: +86-27-82811446
Abstract

Objectives Our aim was to explore the correlations between endoscopic gastric mucosal lesions and pathological gastric intraepithelial neoplasia, and to investigate outcomes of gastric intraepithelial neoplasia after various treatments. Methods A total of 18566 Chinese patients undergoing diagnostic gastroscopy, and biopsies were taken from every patients. Typing and grading of endoscopic and pathological diagnosis were performed. Among them, 130 cases of patients were given various treatments, including medication, endoscopic treatment and surgery. Three months later, re-gastroscopy was carried out, and biopsies were taken to evaluation the efficiency. Results There were 433 patients with GIN by initial pathological diagnosis. Among them, there were 367 LGIN and 66 HGIN, 348 cases accompanied with chronic gastritis, and 85 cases accompanied with localized foci. Eighty cases of Hp-positive patients with LGIN were given anti-Hp therapy. Three months later, re-gastroscopy was carried out and biopsies were taken. Our results showed that 45 cases of intraepithelial neoplasia disappeared with only chronic inflammation left. and also, 33 cases were given the original diagnoses and two cases developed into intraepithelial neoplasia of higher grade. Surgery was then performed, after that, one case of them was confirmed to have early gastric carcinoma, and the other case was diagnosed as advanced gastric carcinoma. Pathological examinations were carried out undergoing EMR or ESD treatment for 18 cases of patients with localized foci accompanied with LGIN. Results showed four cases of only chronic inflammation, 11 cases with original diagnoses maintained, and three cases of HGIN. Three months later, re-gastroscopy was carried out and biopsies were taken, the results revealed no intraepithelial neoplasia. Surgery and pathological examinations were performed for 32
cases of patients with HGIN. Our result showed that 15 cases maintained the original diagnoses, 12 cases of early gastric carcinoma and five cases of advanced gastric carcinoma. Three months later, re-gastroscopy was carried out and no relapse of foci was observed. **Conclusions** There were various endoscopic findings of gastric intraepithelial neoplasia, which occurred frequently in localized foci and atrophic gastritis. NBI magnifying endoscopy had a value of targeted biopsy. Meanwhile, GIN occurred frequently in patients with more severe pathological inflammations under endoscope, which also had certain correlations with intestinal metaplasia. After the treatment, parts of LGIN could be reserved. The effect of endoscopic resection on localized foci accompanied with LGIN was affirmative. However, the limitation of endoscopic biopsy should be fully understood, which might lead to the underestimation on the nature of foci.

**Key words:** gastric intraepithelial neoplasia; gastric mucosal lesions; pathology; follow-up; gastroscopy
Introduction

Gastric carcinoma is one of the most common malignant tumors. The diagnostic rate of early gastric carcinoma is still lower in Chinese population than that in Japan and Occident. Hence, gastric mucosal precancerous lesions are supposed to be a persistent focus for gastrointestinal endoscopy physicians. We previously reported [1] a preliminary study on the clinical pathology of low-grade gastric intraepithelial neoplasia (LGIN) in 2009. We present here a large and detailed study about clinical pathology and follow-up study on gastric intraepithelial neoplasia (GIN). Moreover, typing and grading of endoscopic and pathological were strictly performed via the narrow-band imaging (NBI) magnifying endoscopy. Besides, parts of medication, endoscopic and post-operative outcomes were analyzed, in anticipation of having a deeper understanding towards gastric intraepithelial neoplasia to guide the clinical work.

Materials and Methods

Subjects

Gastroscopy was performed in 18566 patients and continuous endoscopic mucosal biopsies were carried out from Central Hospital of Wuhan for this study from July 2007 to July 2012. Four biopsies were taken at sites with obvious inflammation or other types of foci, or two biopsies at gastric antrum would be taken in cases of no obvious foci. Typical gastric polyps, gastric ulcer, advanced gastric carcinoma, and various non-epithelial tumors under gastroscope were excluded. In this study, all the endoscopic diagnoses and pathological ones were made respectively by one experienced endoscopic physician and another experienced pathologist.
**Endoscopic typing and grading**

On the basis of gastroscopic characteristics, foci were classified as chronic gastritis type and localized foci type (without obvious inflammation surrounding mucosa). Typing and grading of chronic gastritis was determined according to the Criteria of Dalian Meeting of 2003 Chinese Society of Digestive Endoscopy. A retrospective diagnosis of atrophic gastritis was based on the pathological diagnosis. Superficial gastritis was divided into erythema type and reflux bile type according to endoscopic characteristics; erosive gastritis was divided into flat erosive type, isolated protuberant erosive type, and multiple protuberant erosive types. Meanwhile, when there were multiple lesions, the main lesion would be counted. In line with typing of early gastric carcinoma adopted in Japan, localized foci were classified as I polypoid type, II superficial type (IIa superficial elevated type, IIb superficial flat type, and IIc superficial depressed type), and III ulcerative type.

**Diagnosis by magnifying endoscopy**

A total of 136 patients with intraepithelial neoplasia were diagnosed by NBI magnifying endoscopy. The gastric pit patterns were divided into five types: type I round dot, type II linear, type III dendroid or en plaque, type IV villiform, and type V irregular. When multiple pit patterns coexist, the one with higher typing would be counted.

**Pathological grading of inflammation**

The grading was based on both degree of intensity and depth of invasion grading of...
chronic inflammatory cells. Mild inflammation: less chronic inflammatory cells localized in superficial mucosal layer, no more than one-third of mucous layer. Moderate inflammation: less intensive chronic inflammatory cells, more than one-third of mucous layer and reaching two-thirds. Severe inflammation: intensive chronic inflammatory cells, occupying the whole mucosal layer.

Pathological diagnosis of intraepithelial neoplasia

The diagnosis was determined according to WHO criteria (2000) [3].

Treatment and reexamination

Eighty cases of Hp-positive patients with LGIN were given anti-Hp therapy. The therapeutic schedule was orally taking Esomeprazole 20mg, Clarithromycin 0.5g, Amoxicillin 1.0g twice a day for one week in total. Three months after the treatment, re-gastroscopy was carried out and biopsies were taken at lesions the same as previous ones before treatment as much as possible. Eighteen cases of patients with localized foci accompanied with LGIN were given EMR or ESD and pathological examinations. Three months after the treatment, re-gastroscopy was carried out and biopsies were taken again. A total of 32 patients with high-grade gastric intraepithelial neoplasia (HGIN) were given surgery and pathological examinations. Three months after the treatment, re-gastroscopy was carried out.

Statistical analysis

Gastroscopic diagnosis and grading, pathological diagnosis and grading, and
reexamination results after treatment were collected as count data. The statistical analysis was done by SPSS 13.0 software. Continuous variables were reported as means±standard deviation (SD), and statistical comparisons were performed with the two-tailed, Student’s t-test and one-way anova analysis.

Results

gastroscopic and pathological diagnoses

Clinical features of the patients with various types of lesions under gastroscope accompanied with GIN were shown in Table 1. In all the patients, there were 435 patients with LGIN. Among them, LGIN was found in two cases of patients, who were excluded, with normal gastric mucosal biopsies. Accordingly, there were 433 cases of patients with an initial pathological diagnosis of GIN. Among them, there were 367 cases of LGIN, 66 cases of HGIN, 348 cases accompanied with chronic gastritis, and 85 cases accompanied with localized foci (Table 2). The age of patients with GIN ranged from 15 to 81 years old, with an average age of 49.25±18.57 years old. There were 235 males and 198 females. Endoscopic grading diagnoses of chronic gastritis for patients with GIN: 55 cases of grade 1, 172 cases of grade 2, and 121 cases of grade 3. Endoscopic characteristics of lesions: 58 cases of erythema type, 18 cases of reflux bile type, 74 cases of flat erosive type, 53 cases of isolated protuberant erosive type, and 106 cases of multiple protuberant erosive type.

Magnifying endoscopy typing
NBI magnifying endoscopy was carried out in 136 patients with GIN for diagnosis. Among them, there were 106 patients with LGIN and 30 patients HGIN. Results of gland secretory duct typing were shown in Table 3.

**Results of pathological inflammation**

Various degrees of pathological chronic inflammations were found in 435 cases of patients with GIN (Table 4).

**Results of treatments and follow-up**

Eighty cases of Hp-positive patients with LGIN were given anti-Hp therapy. Three months later, re-gastroscopy was carried out and biopsies were taken. Results showed that intraepithelial neoplasia disappeared in 45 cases with only chronic inflammation left. Besides, 33 original diagnoses were maintained and two cases developed into intraepithelial neoplasia of higher grade. After the surgery, one case of them was confirmed to be an early gastric carcinoma and the other case was diagnosed as an advanced gastric carcinoma (Table 5 and Figure 1). Pathological examinations were carried out after EMR or ESD treatment for 18 patients with localized foci accompanied with LGIN. Results showed four cases with only chronic inflammation left, 11 original diagnoses maintained, and three cases of HGIN. Three months later, re-gastroscopy was carried out and biopsies were taken at the wound. Finally, all results showed chronic inflammation or normal gastric epithelium, without intraepithelial neoplasia. Surgery and pathological examinations were performed for 32 patients with HGIN. Result showed 15 original diagnoses maintained, with 12 cases of early gastric carcinoma and five cases of
advanced gastric carcinoma. Three months later, re-gastroscopy was carried out and no relapse of foci was observed.

Discussion

GIN was a tumorous and non-invasive change \[^3\] and was a precursor lesion of carcinoma. It was not an inflammatory or hyperplastic change, and would occur together with inflammation, which could not exclude the possibility of coexisting carcinoma. LGIN was equal to primary mild and moderate atypical hyperplasia, and HGIN was equal to primary severe atypical hyperplasia and carcinoma in situ. Nevertheless, pervious atypical hyperplasia included neoplastic changes as well as reactive and hyperplastic changes, where the differences between these two concepts lay. All multiple gastric mucosal lesions, such as polyps, ulcer, tissues around gastric carcinoma, and etc., might be complicated with GIN. However, these lesions were typical and easily recognized under endoscope, and hence, it would not be easily missed. Moreover, pathological examinations and follow-up re-examination after treatments could be accepted easily by patients. This study was mainly for the most common chronic gastritis and localized flat type foci under endoscope. Although these two lesions were common, the pathological examinations and follow-up re-examination after treatments were prone to be neglected. Thus, it was of great importance to explore the correlations of lesions with GIN in anticipation of increasing the diagnostic rate of early gastric carcinoma.

In this study, continuous biopsies were taken. Namely, gastric mucosal biopsies were taken by the same endoscopic physician for patients, within the inclusion criteria, who underwent daily gastroscopy. Our results indicated that all kinds of endoscopic gastric
mucosal lesions could be complicated with GIN. In all the patients, the proportion of localized foci complicated with GIN was the highest, up to 35.71%, followed by atrophic gastritis and erosive gastritis, accounting for 9.26% and 4.93% respectively, and the remaining types accounting for less than 1%. In patients with chronic gastritis accompanied with various types of GIN, whether it was with LGIN or with HGIN, erosive gastritis was most common. In patients with chronic gastritis accompanied with LGIN, erosive gastritis accounted for 63.1% (188/298), whereas in those accompanied with HGIN, erosive gastritis accounted for 90% (45/50), which were far more than those with superficial, atrophic and hemorrhagic gastritis. In three characteristics of erosive gastritis lesions, multiple protuberant erosive types were most common, accounting for 45.5% (106/233). In current study, although there were only 30 cases of atrophic gastritis patients complicated with GIN, considering that there were only 324 cases of atrophic gastritis in total, the incidence of GIN was still higher. Above results indicated that enough importance on localized foci, erosive, and atrophic lesions, which might be related to the frequent occurrence of GIN, should be attached and the biopsies of these lesions should be taken in order to detect more precancerous lesions of gastric mucosa. In 85 cases of localized foci, 59 cases complicated with LGIN and 26 cases complicated with HGIN. Nonetheless, in 348 cases of chronic gastritis, 308 cases complicated with LGIN and 40 cases complicated with HGIN. By Fisher exact test, in localized foci, the incidence of HGIN was higher (P<0.01), indicating that we should attach more importance on pathological examination and follow-up of localized foci in order not to miss early gastric carcinoma. In the specific typing of localized foci accompanied with GIN, type IIa foci was most common, accounting for 63.5% (54/85), followed by type
I, type IIb, and type IIc, which was relatively less. Besides, considering that type III foci could easily be recognized, it was divided into ulcerative lesion. In our study, it was excluded and would not be discussed herein. It is worth noting that all kinds of gastroscopic changes including two cases of gastroscopic normal mucosa would be complicated with LGIN, which might suggest that all the patients who underwent gastroscopy should receive biopsy. We believed that the incidence of GIN for some endoscopic mucosal changes was lower than 1%. Based on China's national conditions, it was still difficult to carry out biopsy for all the patients.

In order to increase the ability to recognize lesions and to guide biopsy, some new optical technologies have been applied into the endoscopic diagnosis, such as narrow-band imaging, magnifying endoscopy, confocal endoscopy, and so on. In our study, NBI endoscopic diagnosis was used in foci of 106 cases of LGIN and 30 cases of HGIN to observe gland secretory duct openings on the mucosal surface. It was showed that villiform type was most common in LGIN, accounting for 55.7% (59/106), followed by dendroid type, accounting for 30.2% (32/106), and again irregular type, accounting for 6.6% (7/106). In HGIN, irregular type was most common, accounting for 83.3% (23/30) and followed by villiform type, accounting for 16.7% (5/30). No other types of gland secretory duct openings were found. Our results were basically consistent with literature reports [4], indicating that magnifying endoscopy has certain guidance values on the targeted biopsy of GIN foci. Particularly, the irregular type was closely related to HGIN, providing more help for the detection of HGIN. Although all these five types of pit patterns could exist in LGIN, villiform and dendroid types were the dominant ones, which were still helpful for targeted biopsy.
In the endoscopic inflammation grading for patients with chronic gastritis accompanied with GIN, there were not many cases of grade 1 while grade 2 and grade 3 accounted for 84.2% (293/348) in total, indicating that under endoscope, more severe inflammation would be more easily to be complicated with GIN. However, the correlation between inflammation and GIN still should be based on the pathological examinations. With the increase of degree of pathological inflammation, the comorbidity rate of GIN was higher. No matter it was LGIN or HGIN, their detection rates would increase with the increase of degree of pathological inflammation. In all the samples, the detection rate of intestinal metaplasia was 7.20% (1336/18566). In patients with intestinal metaplasia, the comorbidity rate of GIN was 10.4% (139/1336) while in all the GIN patients, the comorbidity rate of intestinal metaplasia was 32.0% (139/435), suggesting that there was certain relation between them and proving that GIN could be derived from gastric epithelium itself or gastric epithelium of intestinal metaplasia \[3\]. Correlations between above pathological inflammation and intestinal metaplasia and GIN were consistent with the pathogenesis of gastric carcinoma and the progression of tumors \[5\].

Eighty cases of Hp-positive patients with LGIN were given anti-Hp therapy. Three months later, both re-gastroscopy and pathological examination were carried out. Results showed that grades of both gastroscopic and pathological inflammations reduced obviously, indicating that anti-Hp therapy was effective. After the anti-Hp therapy, LGIN of 45 cases (56.3%) disappeared. Besides, two cases (2.5%) developed into HGIN and 33 cases (41.3%) had LGIN maintained. This suggested that a significant portion of LGIN could be recovered after treatment while a minority of LGIN would develop into HGIN, indicating that there was no necessity to worry about LGIN, but the importance of
treatment and follow-up on LGIN should be closely attached in order to increase the diagnostic rate of early gastric carcinoma. Meanwhile, it could be speculated from this result that HP might be involved in the pathogenesis of GIN. Animal experiments showed that HP infection and high salt diet were pathogenic factors of GIN, which also was consistent with the pathogenesis of gastric carcinoma. It is worth of noting that it was very difficult to distinguish and confirm whether the HGIN was developed from LGIN or it had already existed but was missed in initial biopsy. Considering that there were differences in the diagnoses made by different endoscopic physicians and pathologists, both endoscopic diagnoses and pathological ones were made respectively by the same experienced physician in this study. Literatures reported that the natural recovery rate of low-grade gastric intraepithelial neoplasia was 38% to 40% and the sustained rate was 19% to 28%. Besides, 0 to 15% cases developed into high-grade gastric intraepithelial neoplasia. Due to the short term of follow-up in this study, the outcome of LGIN still needed further long-term observation.

Pathological examinations were carried out after endoscopic resection for 18 cases of patients with localized foci accompanied with LGIN. Results confirmed that there were four cases of chronic inflammations, 11 original diagnoses being maintained, and three cases of HGIN. This indicated that LGIN could be reserved in short term. These three cases of HGIN were ascribed to the limitation of biopsy, which could not totally reflect the nature of foci. Three months after the endoscopic treatment, re-gastroscopy was carried out and no GIN was found by biopsy at the wound, demonstrating that the endoscopic resection of localized foci was fully effective. It should be noted that complete resection by endoscope was not only a therapeutic method but also a precise
diagnosis of localized lesions of gastric mucosa. With the rapid development of ESD technology, it brought about a good choice for both precise diagnosis and treatment strategy of GIN \[8\]. In this study, after surgery, there were 32 cases of patients with HGIN. Among them, only 15 original diagnoses were maintained and 17 cases were showed to be gastric carcinoma, indicating that the limitation of endoscopic biopsy might lead to the misjudgement of true nature of foci. Thus, for patients with HGIN, we should be vigilant and use multiple technologies, such as staining magnifying endoscopy, ultrasonic endoscopy, etc., to judge the depth of foci and to make a decision on which treatment method to choose. For foci being suspicious of submucosal invasion, surgery should be recommended. Relevant literatures showed that a majority of HGIN patients were with early or advanced gastric carcinoma \[9\]. In this study, the coincidence rate of diagnosis before and after the surgery seemed to be higher. We reckoned that this was mainly because gastric carcinoma patients with typical protruded type and ulcerative type had been excluded from this study.

To sum up, there were various endoscopic findings of gastric intraepithelial neoplasia, which occurred frequently in localized foci and atrophic gastritis. NBI magnifying endoscopy had a value of targeted biopsy. Meanwhile, GIN occurred frequently in patients with more severe pathological inflammations under endoscope, which also had certain correlations with intestinal metaplasia. After the treatment, parts of LGIN could be reserved. The effect of endoscopic resection on localized foci accompanied with LGIN was affirmative. Nevertheless, the limitation of endoscopic biopsy should be fully understood, which might lead to the underestimation on the nature of foci, especially on that of HGIN. Besides, various endoscopic findings should be
integrated and appropriate treatments should be adopted. In brief, the understanding of GIN should be strengthened and the importance of its follow-up should be attached to increase of level of diagnosis and treatment for gastric precancerous lesion and early gastric carcinoma.

Acknowledgements

This project was supported by grants from reaserch of Science and Technology of Wuhan (????).

Competing interests

The authors declare that they have no competing interests

References


## Attached tables:

### Table 1 Various types of mucosal lesions complicated with GIN under gastroscope

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cases</th>
<th>Normal</th>
<th>Superficial</th>
<th>Erosive</th>
<th>Hemorrhagic</th>
<th>Atrophic</th>
<th>Localized foci</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total samples</td>
<td>18566</td>
<td>1806</td>
<td>10526</td>
<td>4722</td>
<td>950</td>
<td>324</td>
<td>238</td>
</tr>
<tr>
<td>GIN</td>
<td>435</td>
<td>2</td>
<td>76</td>
<td>233</td>
<td>9</td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>GIN/Total samples</td>
<td>2.34</td>
<td>0.11</td>
<td>0.72</td>
<td>4.93</td>
<td>0.95</td>
<td>9.26</td>
<td>35.71</td>
</tr>
</tbody>
</table>

### Table 2 Correspondence between gastroscopic findings and pathological characteristics in patients with intraepithelial neoplasia

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cases</th>
<th>superflcial</th>
<th>erosive</th>
<th>hemorrhagic</th>
<th>atrophic</th>
<th>LGIN</th>
<th>HGIN</th>
<th>Total</th>
<th>type I</th>
<th>type II a</th>
<th>type II b</th>
<th>type II c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accompanied with chronic gastritis (348 cases)</td>
<td>367</td>
<td>73</td>
<td>198</td>
<td>9</td>
<td>28</td>
<td>12</td>
<td>5</td>
<td>3</td>
<td>39</td>
<td>45</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td>Accompanied with localized foci (85 cases)</td>
<td>66</td>
<td>3</td>
<td>35</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>433</td>
<td>76</td>
<td>233</td>
<td>9</td>
<td>30</td>
<td>16</td>
<td>54</td>
<td>8</td>
<td>54</td>
<td>55</td>
<td>45</td>
<td>7</td>
</tr>
</tbody>
</table>

### Table 3 Typing by magnifying endoscopy

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cases</th>
<th>Round dot</th>
<th>Liner</th>
<th>Dendroid</th>
<th>Villiform</th>
<th>Irregular</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGIN</td>
<td>106</td>
<td>5</td>
<td>3</td>
<td>32</td>
<td>59</td>
<td>7</td>
</tr>
<tr>
<td>HGIN</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>25</td>
</tr>
</tbody>
</table>

### Table 4 Grading of pathological inflammation

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cases (%)</th>
<th>Mild inflammation</th>
<th>Moderate inflammation</th>
<th>Severe inflammation</th>
<th>With intestinal metaplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total samples</td>
<td>18566</td>
<td>12744</td>
<td>5028</td>
<td>794</td>
<td>1336</td>
</tr>
<tr>
<td>LGIN</td>
<td>369</td>
<td>174 (1.36)</td>
<td>146 (2.90)</td>
<td>49 (6.17)</td>
<td>125 (9.36)</td>
</tr>
<tr>
<td>HGIN</td>
<td>66</td>
<td>20 (0.16)</td>
<td>36 (0.72)</td>
<td>10 (1.26)</td>
<td>14 (1.05)</td>
</tr>
</tbody>
</table>

### Table 5 Gastroscopic findings and pathological changes after anti-Hp therapy in patients with LGIN

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cases</th>
<th>Gastroscopic inflammation grading</th>
<th>Pathological inflammation grading</th>
<th>Intraepithelial neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Before treatment</td>
<td>80</td>
<td>16</td>
<td>37</td>
<td>27</td>
</tr>
<tr>
<td>After treatment</td>
<td>80</td>
<td>44</td>
<td>28</td>
<td>8</td>
</tr>
</tbody>
</table>
Attached figures:

Figure 1a An elevated foci at greater curvature of the sinuses ventriculi. There is congestion on the surface and versicoloured macular changes around the mucosa. A low-grade gastric intraepithelial neoplasia was confirmed by the pathological examination.

Figure 1b This patient underwent a reexamination three months later. The surface of foci and surrounding mucosa were smooth while a high-grade intraepithelial neoplasia was revealed via pathological examination. An early gastric carcinoma was confirmed by pathological examination after surgery.